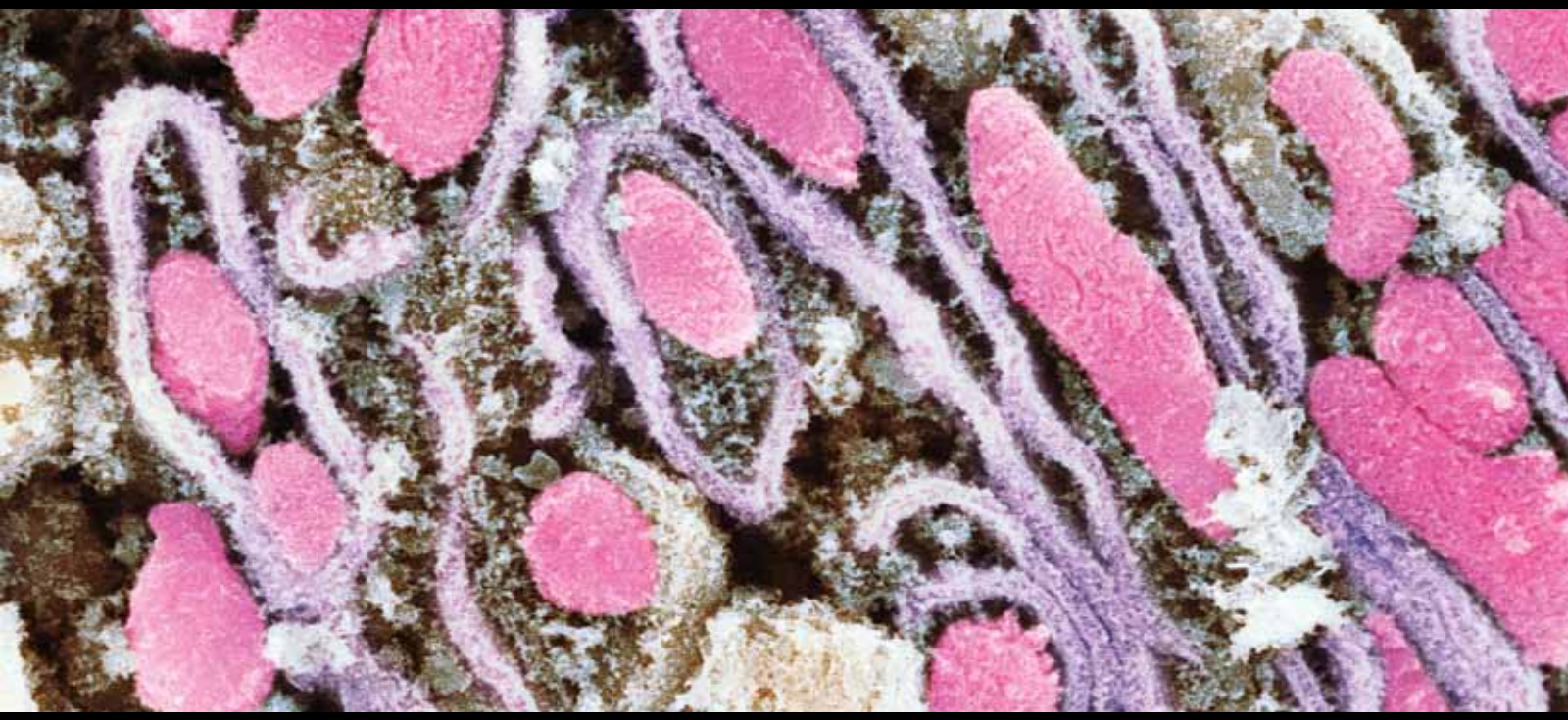
International Journal of Nephrology

Peritoneal Dialysis

Guest Editors: Hulya Taskapan, Olof Heimburger, Cengiz Utas, and Paul Tam



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Editorial Board

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 218974, 1 page
doi:10.4061/2011/218974

Editorial

Peritoneal Dialysis

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Received 31 January 2012; Accepted 31 January 2012

Since the introduction of continuous ambulatory peritoneal dialysis by Moncrief and Popovich in 1976, the number of patients treated with peritoneal dialysis has continuously increased. Today, approximately 200 000 patients are treated with peritoneal dialysis (PD), and the growth is particularly rapid in many Asian countries.

Compared to hemodialysis, PD has been reported to be associated with similar patient survival (or even better during the first months) as well as better quality of life. Therefore, the PD first concept has been adopted in Hong Kong and Thailand. In this special issue about PD, K. Chaudhary et al. discuss the evidence for use of this concept. Then, the benefits and problems with use of PD in the rapidly growing diabetic population are discussed by A. Rocha and coworkers. Quality of life in PD patients is reported by M. Moreiras-Plaza et al., whereas P. Theofilou discusses socioeconomic factors and psychological problems such as depression and anxiety in patients with CKD.

Three further articles discuss different complications in PD patients: peritonitis (by M. OtsRosenberg et al.), calcific uremic arteriolopathy (by N. New and coworkers), and C. Kennedy et al. report a case series of patients with pleuroperitoneal leak, a rare but troublesome complication.

Other four papers deal with the function of the peritoneal membrane as a dialyzing membrane. L. Oliveira and A. Rodrigues report on the impact of previous renal replacement therapy on the membrane function, whereas S. Mizuiri et al. report on the importance of peritoneal effluent markers and their relation to epithelial to mesenchymal transition, which is thought to be an important part of pathogenetic process causing long-term changes in the peritoneum. Finally, N. Jiang et al. report on the impact of a supplemented low-protein diet on peritoneal membrane transport characteristics, whereas A. W. D. Stavenuiter et al. report on the effect of different peritoneal fluid components on the membrane in a rat model.

The guest editors wish to thank all authors for their valuable contributions. Without their efforts, this special issue would not have been possible.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 914849, 10 pages
doi:10.4061/2011/914849

Review Article

Peritoneal Dialysis in Diabetics: There Is Room for More

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Received 26 February 2011; Revised 5 July 2011; Accepted 15 August 2011

Academic Editor: Olof Heimburger

End stage renal disease diabetic patients suffer from worse clinical outcomes under dialysis-independently of modality. Peritoneal dialysis offers them the advantages of home therapy while sparing their frail vascular capital and preserving residual renal function. Other benefits and potential risks deserve discussion. Predialysis intervention with early nephrology referral, patient education, and multidisciplinary support are recommended. Skilled and updated peritoneal dialysis protocols must be prescribed to assure better survival. Optimized volume control, glucose-sparing peritoneal dialysis regimens, and elective use of icodextrin are key therapy strategies. Nutritional evaluation and support, preferential use of low-glucose degradation products solutions, and prescription of renin-angiotensin-aldosterone system acting drugs should also be part of the panel to improve diabetic care under peritoneal dialysis.

1. Diabetes Mellitus as a Leading Cause of End-Stage Renal Disease

End-stage renal disease (ESRD) can be considered a health epidemic involving considerable human and financial resources [1, 2]. The number of patients with ESRD is increasing in the world due to aging populations, longer life expectancy, increasing access to renal replacement therapies (RRT), and higher incidence of diabetes mellitus (DM) and hypertension. Nowadays, dialysis is the dominating therapy to prevent death from uremia, in large part because donor kidneys are in short supply, and thus, the survival of these patients is still a major concern [3]. According to the United States Renal Data System (USRDS), in 2008, the adjusted rate of prevalent ESRD cases rose 1.9%, to 1.699 per million population (pmp), with 547.982 patients under treatment. The prevalent dialysis population increased 3.6%, reaching 382.343 patients and has grown 34.7% since 2000 [4]. Among these amazing numbers, DM is present as the leading cause of ESRD in the USA and most other countries. After a dramatic increase in the incidence rate of ESRD due to diabetes, peaking in 2006 at 160 pmp, this rate fell 3.2% and 1.5% in the following two years, reaching 153 pmp in 2008, but still corresponding to 43% of all incident patients [4].

Although their survival is still much worse than that of nondiabetic counterparts, mainly because of the preexisting severely compromised cardiovascular conditions, between 1994–1998 and 1999–2003, the 5-year diabetic patients survival improved 15.3% in hemodialysis (HD) and 27.1% in peritoneal dialysis (PD), reaching 29% and 27%, respectively [4]. In Europe, diabetes as the cause of ESRD averaged 124 pmp. In the cohort 1999–2003, the unadjusted 1-, 2- and 5-year survival of patients on RRT was 80.8% (95% CI: 80.6–81.0), 69.1% (95% CI: 68.9–69.3), and 46.1% (95% CI: 45.9–46.3), respectively. Survival of incident diabetic patients either in HD and PD was the lowest and around 30% by 5 years [5].

2. Potential Benefits of Peritoneal Dialysis in Diabetics

Global benefits of home therapy [6, 7] and mainly slow sustained ultrafiltration (UF) conferred by PD [8] are particularly important in diabetic uremic patients. Even before the dialysis stage, most diabetic patients with ESRD have multiple cardiovascular and metabolic complications. Because of the rapid and intermittent removal of solutes and water and the extracorporeal circulation inherent to

HD, it can frequently be associated with dialysis-induced hypotension, coronary ischemia, and arrhythmia [9], possibly leading to a worsening cardiovascular status in these patients [10]. A recurrent circulatory stress is postulated as a cause of important deleterious effects of standard schedules of HD [11]. On the contrary, PD avoids aggressive fluid shifts offering a better hemodynamic tolerance. It deserves to be mentioned that HD-induced myocardial stunning is identified as a new aspect of cardiovascular disease (CVD) in chronic kidney disease (CKD) [12, 13], while PD is not associated with such complications [14]. In addition, the lack of a need to create an arteriovenous fistula, which increases cardiac load, accelerating heart failure, may also be a potential benefit of PD in diabetic patients [10]. The preservation of the vascular network, usually frail in these patients, and sparing diabetic patients from the serious complications of vascular access thrombosis and infections are certainly underestimated but crucial arguments favoring PD in diabetics.

PD also protects patients from the HD-induced recurrent regional ischemia that may lead to increased endotoxin translocation from the gut. Resultant endotoxemia is associated with systemic inflammation, markers of malnutrition, cardiac injury, and reduced survival. Circulating endotoxemia was most notably documented in those patients with the highest CVD, and a sharp increase was observed after initiation of HD [15].

Besides, residual renal function (RRF) loss threatens patient survival both in HD and PD [16]. Diabetes is also a risk factor for faster RRF decline [17]. However, PD might confer more RRF protection [18–22] in this group of risk patients. Moist et al. showed that the risk of RRF loss was 65% lower in PD patients than in HD [23]. Furthermore, they showed that the selection of HD as the dialysis modality and diabetic nephropathy were predictors of RRF loss. Thus, the approach of "PD first" appears to be a rational way to maximize the maintenance of RRF in diabetics, while simultaneously avoiding instrumenting a frail vascular capital and exposing patients to the risk of aggressive fluid shifts. On the other hand, RRF preservation and the consequenced higher elimination of advanced glycated proteins may overcome the risk of glucose degradation products (GDP) accumulation as a deleterious effect of PD in diabetics.

Other potential advantages can still be mentioned. Fewer episodes of progressive diabetic retinopathy were observed in the PD patients, also fewer events of hemorrhagic retinopathy, and this is probably related to a more stable hemodynamic status and a lack of exposure to heparin. In a Japanese study that evaluated the progression of retinal lesions in diabetic patients either on HD or PD treatment, no patients in the PD group showed worsening of diabetic retinopathy during a 1-year observation period, compared to approximately 20% of HD patients [24].

Concerning insulin therapy, the advantages of intraperitoneal insulin administration include a higher physiological effect of insulin in patients with diabetic nephropathy during continuous ambulatory PD (CAPD) or automated PD (APD) treatment. Major fluctuations of blood glucose, hyperinsulinemia, and the formation of insulin antibodies can be minimized. In the final analysis, a better adjustment of blood glucose levels results [25]. However, there are pros and cons of various forms of insulin administration therefore, this might not be a sound argument for PD by itself. The reduction in insulin requirement is most pronounced compared with subcutaneous administration when insulin is instilled into the empty abdominal cavity, but if insulin is instilled with dialysis solution, there are losses of activity due to adsorption to the plastic surface of delivery systems [25]. Besides, bioavailability of intraperitoneal insulin might differ according to the solution bag used [26]. Importantly, hepatic subcapsular steatosis may be a complication associated with intraperitoneal insulin [27]. As part of other general PD benefits that also address diabetics, further aspects can be added. PD also allows good hemoglobin targets maintenance at lower erythropoietin doses, with both clinical and economic advantages [28]. Patients on PD also have a lower risk of contracting certain blood-borne diseases, like hepatitis C, which constitutes another advantage of this modality. In a report by Pereira and Levey, the prevalence of antiHCV antibodies in patients on dialysis was significantly lower in PD than in HD patients [29]. Additionally, PD is associated with lower rates of delayed graft function after transplantation [30, 31], possibly due to lower risk of hypotension and hypervolemia particularly relevant in diabetic patients prone to hemodynamic intolerance. Table 1 summarizes these general and specific PD benefits in diabetic patients.

3. Controversy on Survival Data

Despite the substantially equivalent survival in diabetic patients either on HD or on PD [32] and the good reasons for initially offering PD to this group, only a small and decreasing proportion of diabetics receive PD [33, 34]. There is not any *a priori* first-choice dialytic treatment modality for these patients, and the decision to adopt HD or PD should be made on medical grounds and, above all, on the wishes of the individual patients. Whichever the modality, diabetics suffer from further clinical complications. A number of earlier studies documented varied results, some already beneficial to PD in diabetic patients in spite of addressing a remote PD era with less therapy resources, others showing possible lower benefit from PD regimens in older diabetics [35–40]. A long-term PD favorable study, which included more than 400 patients, showed that the best survival occurred in nondiabetic patients on PD, the survival rate of diabetic patients on PD was equal to that of nondiabetic patients on HD, and diabetic patients on HD had the worst survival rate [10]. Subgroup analysis in specific populations might, however, alert for lower benefits or even increased mortality risk in older diabetic patients in PD modality [41].

Vonesh et al. systematically reviewed six large-scale registry studies and three prospective cohort studies that compared mortality among ESRD patients receiving HD versus PD, conducted in the US, Canada, Denmark, and The Netherlands. Generally, PD was associated with equal or better survival among nondiabetic patients and younger diabetic patients in all four countries, while among older

Table 1: Potential benefits and risks of PD in the treatment of diabetic patients.

General PD benefits	Specific PD benefits in diabetics	PD risks in diabetics
(1) Home-based continuous therapy	(1) Sustained daily ultrafiltration	(1) Fluid overload
(2) Advantages in lifestyle	(2) Better preservation of residual renal function	(2) Aggravated dysregulated metabolic response to glucose
(3) Avoids vascular access related infections	(3) Vascular capital preservation	(3) Hyperinsulinemia
(4) Avoids recurrent circulatory stress	(4) Avoids peripheral and coronary steal syndromes	(4) Central obesity
(5) Avoids myocardial stunning	(5) Fewer episodes of hypotension	(5) Dyslipidemia
(6) Fewer episodes of blood-borne disease	(6) Better blood pressure control	(6) Peritoneal albumin losses
(7) More liberal diet (in spite of fluid and Na restriction)	(7) No need for systemic anticoagulation	(7) Peritoneal infection
(8) Control of anemia with lower doses of erythropoietin	(8) Fewer episodes of progressive retinopathy	(8) Membrane fast transport status
(9) Lack of pain from needle puncture	(9) Feasibility of elective intraperitoneal insulin	
(10) Lower rate of delayed renal graft function		

diabetic patients, results varied by country. Among older diabetics, the Canadian and Danish registries found no difference in survival between PD and HD, while in the US, HD was associated with better survival only in diabetics aged 45 and older [42]. A more recent Dutch study reported that the survival advantage for PD compared with HD patients decreases over time, with age and in the presence of diabetes as primary disease [43]. Among 139 diabetic PD patients studied during a mean followup of 28.2 ± 21.8 months, Fang et al. found 1-, 2-, 3-, and 5-year patient survival rates of 91%, 76%, 66%, and 47%, respectively [44]. These outcomes were better than those reported by USRDS for incident diabetic PD patients (85.7%, 67.9%, 52.5%, and 26.0%, respectively), and the data reported by CORR (86.4%, 53.6%, and 31.3% at 1-, 3-, and 5-year). Diabetic patients had a significantly poorer survival rate than did nondiabetics, both in the group younger than 65 and in those patients aged 65 or older [44]. Two recent studies also showed higher mortality and hospitalization rates in diabetic versus non diabetic PD patients. The presence of more morbidity factors at starting PD and a higher rate of previous cardiovascular events in diabetic patients may explain part of this risk [45, 46]. Added reasons for the reported worse outcome might be the variations in fluid homeostasis and corporal composition in diabetic patients, as fluid overload is the main cause of death in ESRD dialysis patients, and fluid control is potentially more difficult in PD diabetic patients [47]. Adjusted therapy is mandatory since results might differ according to treatment skills and policies. Besides, differences of some months of survival might be statistically significant but not clinically relevant. In fact population-averaged survival curves comparing adjusted PD and HD survival for US Medicare patients (1995–2000), showing that adjusted median life expectancy in HD is 35.1 months and in PD 33.8 months, are such an example [42].

More recent cohorts safely support PD prescription for diabetic patients, demonstrating similar long-term patient survival in both modalities and that DM *per se* should not be a barrier to PD [48]. Instead, the higher mortality rate in diabetic PD patients, in particular among female patients, was mainly attributable to concurrent morbidity such as CVD and protein-energy wasting, together with low RRF [49]. PD is more beneficial as the initial modality of dialysis for ESRD patients. Older patients with diabetes and patients without diabetes may switch modality to HD or undergo kidney transplantation in 1-2 years' time; long-term PD is viable in younger patients with diabetes [50].

4. Peritoneal Dialysis Risks in Diabetics

Glucose and insulin homeostasis are altered in CKD patients even in the early stages of renal disease. Metabolic syndrome is usually defined as a cluster of risk factors—obesity, high blood pressure, insulin resistance, and dyslipidemia—that are involved in development of CKD or are a consequence of it. It is argued that uremic patients treated with PD have a higher risk for deregulated metabolic response because of increased glucose absorption, with hyperglycemia prevalence greater than 50% comparing to 20% in HD patients [51]. It was also found that metabolic syndrome is a potent risk marker for adverse CV outcomes in nondiabetic patients on PD [52]. Notably, 60–80% of glucose-containing PD solution instilled into the peritoneal cavity is absorbed, corresponding to daily intake of 100–300 g glucose. This continuous glucose absorption modulated also by uremic toxicity and factors related to PD fluid bioincompatibility may indeed lead to aggravation of hyperglycemia, obesity and hyperlipidemia. Al these factors trigger the production of reactive oxygen species (ROS) and induce an inflammatory cascade that includes blocking insulin action and normal lipoprotein metabolism as recently revised [53]. Waist circumference is not a correct parameter to evaluate obesity due to the presence of the Tenckhoff catheter and potential residual peritoneal dialysate inside the abdominal cavity; however

the use of body mass index (BMI) is also a biasing factor. Increased body mass due mainly to fat has a different prognostic meaning than body mass related to more muscle. PD patients with a high BMI associated with high muscular mass seem to have a survival advantage, compared with those with high BMI but low muscular mass that have an enhanced risk of cardiovascular death [54].

It is well established that PD patients frequently gain weight (fat mass), especially during the first year of PD therapy and particularly if they have diabetes or have a high BMI at initiation. However, several groups have not found any association between glucose absorption and weight gain. However the application of icodextrin solution may be a better option to alleviate excessive fat gain over time for patients on PD with studies revealing a significantly lower percentage of fat mass during the first 36 months ($P < 0.05$) [55]. Factors associated with the higher percentage of fat mass gain over time on PD were age, diabetes, gender (female) and nonicodextrin group (all, $P < 0.01$, generalized estimating equation). Wang and his/her group also found that genetic factors play an important role in the accumulation of fat mass in PD patients (uncoupling protein 2 exon 8 insertion/deletion polymorphism) [56]. Concerning to hyperglycemia diagnosis and glycated hemoglobin levels, important factors must be mentioned, because deregulation of sugar levels, associated with glucose-containing solutions, has important non linear implications for the patients. It has been documented that after 18 months of followup of 269 nondiabetic PD patients, HbA1c was the significant risk factor for all-cause mortality after relating variables were adjusted (HR: 4.114; 95% CI: 1.426–11.872; $P = 0.009$). Moreover, high HbA1c (HR: 3.892; 95% CI: 1.273–11.959; $P = 0.026$) and low HbA1c (HR: 1.179; 95% CI: 1.160–1.198; $P = 0.039$), with middle HbA1c group as the reference, also significantly predicted for mortality in these patients [57]. However, PD patients had lower HbA1c values than those without CKD with the same average glucose level, suggesting that HbA1c underestimates the glucose level in these patients. This underestimation might be secondary to the use of erythropoietin, meaning that a larger proportion of circulating erythrocytes have not been around long enough for sufficient glycosylation of hemoglobin. It was shown that a greater predictive value is achieved with the use of glycated albumin which measures glycemic control over the preceding 2 weeks and is not affected by serum albumin concentrations [58]. Furthermore, PD patients are never truly fasting because they continuously absorb glucose from the PD solution. So it is important to consider the limitations of both HbA1c and home glucose monitoring in PD patients before one makes therapeutic decisions. However, our goal is to achieve an HbA1c of <7% [59], taking into account that strict glycemic control based in such parameter might be hazardous in individual patients [60].

Blood glucose measurements in patients receiving icodextrin must be done with a glucose-specific method to avoid interference by maltose, a metabolite of icodextrin.

Glucose dehydrogenase pyrroloquinoline quinone or glucose dye oxidoreductase-based methods must not be used. Results inconsistent with clinical suspicion of hypoglycemic coma should be retested with another testing system [61, 62]. Therapy must also be adjusted according to PD regimens aiming for glucose sparing prescriptions. Diabetic patients have a minimal increase in insulin requirement after initiation of PD *per se*, but the dosage of insulin increases markedly after exposure to hypertonic glucose solution [63]. A study of risk factors for high glucose use in PD patients showed that patients with DM, high BMI, and low RRF were more likely to require a high glucose load for PD therapy, especially during the first 3 years. After that, DM was the only significant factor associated with the need for higher glucose load [64]. One of the implications associated with hyperglycemia is the activation of the thirst mechanism with problems in managing fluid balance. Devolder et al. evaluated volume status with multifrequency bioimpedance (body composition monitoring, bioimpedance analysis (BIA)) in PD and HD patients revealing in multivariate models that diabetes and being under PD are associated with increased extracellular water (ECW) volume [65]. In turn, fluid overload implies use of more hypertonic bags negatively impacting glycemic control and peritoneal integrity, therefore creating a vicious circle. A baseline fast transport status can also be present in diabetics which will oblige careful therapy adjustment [66]. Peritoneal membrane exposed to higher content of GDP present in PD solutions is impaired by several mechanisms. First, GDP activates an inflammatory process promoting neoangiogenesis and consequently fast transport proprieties in the face of a progressive increase in peritoneal permeability. As a result of the inflammation, profibrotic factors are generated, such as transforming growth factor beta, leading to peritoneal fibrosis and accelerated loss of UF, ultimately leading to possible technique failure in diabetic patients on PD [10].

It is well known that diabetics have impaired antibacterial defenses and the risk of dying from an infection increases with worse glycemic control. It was demonstrated that GDP rich solutions accelerate leucocyte apoptosis and adversely affect the peritoneal defense [67]. However, neither peritonitis episodes nor other PD related infections have been observed to be more common in diabetic than in nondiabetic patients [47]. Several articles report, notwithstanding the risks presented, no difference in technique survival between diabetics and nondiabetic dialysis group of patients [49]. Clinicians should however be most concerned about nutritional and volume status of PD diabetic patients, which impact on patient survival. The etiology of malnutrition is multifactorial (acidosis, insulin resistance, inflammation, dialysate protein losses) and delayed gastric emptying associated with autonomic nervous system dysfunction is considered to be a significant factor. Dialysate volume in the peritoneal cavity was initially appointed as having a negative effect on gastric emptying. But in clinical practice its removal was not associated with any noticeable improvement. A study designed to estimate the direct influence of indwelling dialysate in the peritoneal cavity on gastric emptying, in patients treated with CAPD, determined by dynamic abdominal scintigraphy have shown no significant differences between those with and without indwelling dialysate. However, gastric emptying is markedly impaired

in CAPD patients compared to healthy subjects indicating that other factors are responsible for the development of gastropathy in these patients, suggesting a gastric motility test with an empty peritoneal cavity [68]. A recent report, using an extracellular mass/body cell mass ratio (ECM/BCM ratio) as a marker of malnutrition, revealed that for every 10% increase of it, the relative risk of death was increased by about 35%, demonstrating that bioimpedance-derived enrollment ECM/BCM ratio was an independent predictor of long-term survival in PD patients [69]. Paniagua and his group studied the role of N-terminal fragment of B-type natriuretic peptide (NT-proBNP) as a predictor of mortality in ESRD patients. Showing that NT-proBNP levels and ECW/total body water (TBW) were correlated with several inflammation, malnutrition, and myocardial damage markers, they proved that NT-proBNP might be an added reliable predictor of death risk independently of the effect of dialysis modality [70].

Multifrequency BIA also enabled documenting that ECW adjusted for height was similar in diabetic and nondiabetic patients, but the ratio of ECW to TBW was greater for diabetics [71]. Additionally, a prospective study that evaluated heart failure in long-term PD patients concluded that diabetes and left ventricular mass and volume index were significant predictors of new-onset heart failure [72]. On the other hand the status of peritoneal fast transport, if inadequately managed, is also associated with worse outcomes and diabetes has been associated with a higher proportion of fast transport status. Icodextrin and APD can adequately support these patients. However there is concern about peritoneal protein leak during continuous PD procedure [73], because although correlated with volume overload and inflammation, it is largely an independent predictor of mortality [74]. Increased large-pore protein loss may reflect the severity of underlying CVD, portending a poor prognosis for these patients. Peritoneal protein clearance and not peritoneal membrane transport status predicts survival in contemporary PD patients [75]. Additionally higher daily peritoneal protein clearance when initiating PD was independently associated with peripheral arterial disease, a possible new marker of systemic endothelial dysfunction [76]. Last but not least, there are concerns about PD modality and transplantation outcomes. Analysis of the risk factors for development of posttransplant DM (PTDM) was performed with respect to pre-transplant dialysis modality. A total of 137 (6.8%) patients developed PTDM; 7% in the HD group and 6.5% in the PD ($P = 0.85$). In the multivariate analysis, age, BMI, rejection episodes and use of tacrolimus were identified as independent risk factors for its development. Adjusted analysis confirmed that pre-transplant dialysis modality does not have an impact on the subsequent development of PTDM [77]. Likewise, PD prior to simultaneous-pancreas-kidney transplantation is not associated with increased incidence of intra-abdominal infection compared to HD [78]. As described, PD may provide several advantages for diabetic patients, while risks should also be taken into account to optimize therapy (Table 1).

5. Strategies to Improve Outcomes

Throughout this paper we have emphasized the importance of preservation of RRF attending to the advantage in controlling fluid balance and solute clearance, protecting patient life. This task force should be pursuit both before and after dialysis induction. Early nephrology referral is an important measure for improved long-term clinical outcome in type II diabetics on maintenance PD [79]. Indeed attending an options class predialysis was associated with more frequent selection of home dialysis, fewer tunneled HD catheters and lower mortality risk during the first 90 days of dialysis therapy [80]. Considering the timing of dialysis, there is however no benefit from an early start. A retrospective analysis of patients, entering the USRDS database from January 1, 1995 to September 30, 2006 was carried out, sorting patients into groups by estimated glomerular filtration rate (eGFR) at dialysis initiation. In this total incident population ($n = 896,546$), 99,231 patients had an early dialysis start (eGFR >15 mL/min per 1.73 m2) and 113,510 had a late start (eGFR $\leq$ 5 mL/min per 1.73 m2). The first group had increased risk of mortality, while the late start was associated with reduced risk of mortality [81]. In another study planned early initiation of dialysis (eGFR was 10.0 to 14.0 mL/min) in patients with stage V CKD in comparison with later stage (eGFR was 5.0 to 7.0 mL/min) was not associated with an improvement in survival or clinical outcomes. During a median followup period of 3.59 years, 152 of 404 patients in the early-start group (37.6%) and 155 of 424 in the late-start group (36.6%) died (HZ with early initiation, 1.04; 95% CI, 0.83 to 1.30; $P = 0.75$) [82]. An individualized strategy leveling indication and risk for dialysis induction in diabetics is mandatory. Dedicated and multidisciplinary care is than essential to offer the best treatment and the adequate control of cardiovascular risk factors: diet, exercise and weight control. Adequate patient education, and support with dietitian, podologist, endocrinologist and frequent monitorization are very important. One of the limitations is severe visual or functional impairment, necessitating the involvement of a relative. Experience has demonstrated that even blind patients can perform the technique properly, although it might oblige individualized and more prolonged training. Elective assisted PD might be considered in patients with less autodialysis capacity. There are multifactorial interventions that may additionally improve the survival of diabetic PD patients.

New PD solutions with low GDP are promising in reducing the risk of CVD in these patients, by preserving RRF, optimizing volume control, and possibly reducing local and systemic inflammation.

A study comparing the use of balance, a neutral pH, low GDP solution to conventional one, during 12 months, revealed a lower degree of systemic inflammation. The Balance group had a superior profile of PD effluent markers of mesothelial cell mass marker and inflammation [83].

As a glucose sparing policy, the use of 1 bag of icodextrin or amino-acid (AA) solution daily may reduce the glucose load by 15–30%. In addition, icodextrin use was significantly associated with a reduced risk of death

(HR, 0.40; 95% CI, 0.28 to 0.58; $P < 0.001$) in a recent retrospective investigation. AA-containing dialysate has been used to compensate for a low dietary protein intake but clinical benefits have not been consistently demonstrated because these solutions can induce an anabolic response in malnourished patients on CAPD only if enough calories are ingested simultaneously. Dialysis solutions containing a mixture of AAs and glucose in appropriate proportions can serve as a source of both proteins and calories. Although the metabolism of intraperitoneal AAs causes the generation of hydrogen ions and urea, acid-base homeostasis can be preserved using dialysis solutions with a buffer content of 40 mmol/L [84]. Additionally, calcium exposure through PD solution plays a role in the progression of arterial stiffness, which may be related to increased vascular calcification [85], therefore individualized low calcium solutions should be prescribed. Most importantly icodextrine has a role in diabetic patients' PD treatment: as Paniagua et al. state, in a study of 12 months, the use of icodextrin allows in the early phase (6 months), reduction in ambulatory blood pressure (ABP) and left ventricular end diastolic diameter. These changes correlated with changes in body fluids. In the late phase (12 months), a trend towards baseline values in ABP was seen. It was argued that changes in inferior vena cava diameter and in low-frequency R-R variability spectral analysis suggest that icodextrin increases circulating blood volume and sympathetic tone, probably by accumulation of icodextrin metabolites in the bloodstream and improvement in diabetic neuropathy as a result of lower peritoneal glucose absorption [86].

The benefits of icodextrin use in diabetic patients were also supported by the same investigators in a prospective, randomized controlled trial, comparing it with conventional glucose solutions. These authors showed that icodextrin significantly reduces ECW volume, thereby leading to a significant reduction in both systolic and diastolic blood pressure. Moreover, they demonstrated that icodextrin, reduces blood glucose concentration, a finding that was accompanied by a concomitant reduction in insulin dosage. Furthermore, a particularly finding was that icodextrin was associated with a delay in the decline of eGFR and urine volume over a 6-month observation period [87]. So icodextrin, besides its elective indication in fast transporters, gathers a group of potential benefits in diabetic PD patients: increase in UF volume with better blood pressure control; increase in solute clearance; better glycemic control with fewer requirements for insulin; and better preservation of RRF.

A bimodal solution based on the mixing of glucose (2.6%) and icodextrin (6.8%), during a 4-month prospective intervention period, showed that net UF and peritoneal sodium removal during the long dwell was about 2-fold higher than baseline. Therefore a combined crystalloid and colloid PD solution might be useful as a glucose-sparing strategy for volume control in high-transport APD diabetic patients [88]. Low-GDP solutions also are advocated, if financial constraints are not superimposed: in vitro and ex vivo studies clearly support better biocompatibility of these solutions. Notwithstanding, in the clinical field it was mainly RRF the parameter that showed to be protected by using these solutions. In a multicenter approach, 80 patients were randomized to treatment with a PD fluid containing low levels of GDP or standard PD fluid for 18 months. Data revealed a significant difference in monthly RRF change and twenty-four-hour urine volume decline, demonstrating a significant benefit concerning preservation of RRF and urine volume of using a PD fluid with low GDP levels [89]. The previously mentioned inflammatory cascade, activated by GDP is mediated by renin-angiotensin-aldosterone system (RAAS), constitutively expressed in peritoneal mesothelial cells, and ROS. So it is postulated that use of angiotensin converting-enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) helps, not only to preserve RRF in ESRD patients, but also to maintain peritoneal membrane integrity longer in PD patients. Thus, these classes of drugs should be the first choice for antihypertensive therapy [59]. Antioxidants, namely N-acetylcystein, might also support preservation of peritoneal membrane function by the same mechanism [50] but need further evidence. Table 2 resumes strategies that potentially will improve clinical outcomes in PD diabetic patients.

6. Our Clinical Experience of PD in Diabetic CKD

In our centre, by carrying out a prospective registry based study of 432 adult incident patients admitted during 25 years in a PD university program (11640 months at risk), we compared clinical outcomes of PD treatment on diabetic versus nondiabetic counterparts. At baseline analyzed groups were identical concerning mean age, proportion of older patients, gender, previous RRT and reason for PD; diabetic had lower RRT vintage (33(15–99) versus 75(23–125) months; $P = 0.05$). Patient survival was significantly lower in diabetic, when compared to nondiabetic: 89%, 77%, 67%, 52% versus 93%, 86%, 79%, 71%, at 1, 2, 3, and 4 years, respectively ($P < 0.0001$). However, technique survival was similar between diabetic and nondiabetic: 84%, 74%, 66%, 51% versus 87%, 79%, 66%, 57%, at 1, 2, 3, and 4 years, respectively (P = NS). Our results compare favourably with international reports: In EDTA registry report 2008 [5], diabetic patient survival was 73% by 2 years; in the French PD registry diabetic patients lower three-year patient and technique survival was reported as 59% and 34%, respectively for patients aged 50–60 years [90].

On multivariate analysis including in the model diabetes, older status, PD after HD and PD after transplant, DM was an independent predictor for patient mortality (HZ 2.3; CI 1.5–3.7) but not for technique failure (HZ 1.3; CI 0.9–1.9). A lower proportion of diabetics received a renal graft during the followup (19% versus 32%; $P = 0.016$). Among the reasons for transfer to HD, UF failure/underdialysis was similar between groups (26% versus 22%, P = NS), a higher proportion of dropout was observed in diabetic due to loss of autonomy for the technique (23% versus 5%, $P = 0.004$). The global peritonitis rate was similar between the diabetic and their counterparts: 0.53 versus 0.61 ep./pt.y (P = NS).

Table 2: Strategies to improve clinical outcomes in PD diabetic patients.

Strategies	Practice
(1) Opportune nephrology referral	More than 3 months before dialysis initiation, ideally when GFR ≤ 30 mL/min
(2) Residual renal function protection	Avoidance of dye studies, nonsteroidal antiinflammatory drugs (including cyclooxygenase-2 inhibitors), aminoglycosides, and extracellular fluid depletion
(3) Control of cardiovascular risk factors	Diet counseling and promotion of physical activity to avoid obesity; pharmacologic therapy for hypertension atherogenic dyslipidemia, dysglycemia and prothrombotic state (ACE inhibitors, AII receptor antagonists, B blockers, statins, and aspirin)
(4) Patient education and multidisciplinary support	Group discussion and individual consultation (booklets, video, and interview) promotion of hometherapy and transplantation (both renal and renopancreatic) glycemic control optimization foot care and peripheral vascular evaluation ophthalmologist followup
PD specific strategies	
(5) Skilled volume evaluation and control	Panel of clinical evaluation (blood pressure, weight, and edemas), biomarker (pro BNP) and multifrequency BIA (longitudinal trends of body composition) high-dose furosemide fluid, and sodium restriction elective use of icodextrine and APD
(6) Preferential use of low GDP solutions, glucose sparing regimens, and individualized low calcium solutions	Avoidance of hypertonic bags use Bi/tri compartment bag solutions (low GDP) individualized low Ca solutions prescription "PEN" regimen: physioneal; extraneal; dianeal; "NEPP" regimen: 1 amino acid exchange, 1 icodextrin exchange, and 2 glucose bicarbonate/lactate exchanges as options
(7) Nutritional evaluation and support	Assessed by a panel: subjective global assessment (SGA), protein equivalent of nitrogen appearance (nPNA), serum albumin and lipid profile, multifrequency BIA diet counseling by nutritionist
	Enteric supplements (protifar as protein supplement) peritoneal supplement (nutrineal once day)
(8) Preferential use of RAAS acting drugs	ACEI and ARB as first antihypertensive drugs possible protective effects in peritoneal membrane status
(9) Optimize technique survival and opportune transfer to HD	International recommendations on peritoneal access management and prophylactic measures individualized training and retraining peritonitis rate systematic control and quality assessment individualized APD prescription depression assessment and specific management routine annual peritoneal membrane evaluation

The global hospitalization rate was significantly higher in diabetics than in nondiabetics: 1.39 versus 0.84 ep./pt.y ($P = 0.004$). In our study, PD proved to be an effective long term RRT option in diabetics, without a higher rate of technique failure, UF failure or peritonitis. DM was however associated with higher mortality, higher autonomy loss, and higher hospitalization rate, enhancing the need for investigation and control of comorbidities with potential negative impact on these parameters.

7. Conclusion

Diabetes is among nephrological causes of ESRD that are associated with the worst diagnosis. Independently of the renal replacement therapy patient survival is limited and exposed to higher rate of complications and hospitalizations. PD however, offers a cluster of advantages in diabetic patients: besides amenable better life-style the modality avoids vascular access complications in patients with frail vascular capital, protects RRF, and allows higher hemodynamic stability with less myocardial stress and stunning, with slower progressive retinopathy. The disadvantages can be overcome by adequate care, glucose-sparing PD regimens, optimization of volume control and other protective measures like RAAS acting drugs and antioxidants to prolong the best quality of care while on PD. P. Cotovio and A. Rocha contributed equally to this paper.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 685457, 6 pages
doi:10.4061/2011/685457

Clinical Study

Previous Renal Replacement Therapy Time at Start of Peritoneal Dialysis Independently Impact on Peritoneal Membrane Ultrafiltration Failure

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Received 28 February 2011; Revised 5 July 2011; Accepted 8 August 2011

Academic Editor: Olof Heimburger

Background. Peritoneal membrane changes are induced by uraemia per se. We hypothesise that previous renal replacement therapy (RRT) time and residual renal function (RRF) at start of peritoneal dialysis impact on ultrafiltration failure (UFF). *Methods*. The time course of PET parameters from 123 incident patients, followed for median 26 (4–105) months, was evaluated by mixed linear model. Glucose 3.86% solutions were not used in their standard therapy. Sex, age, diabetes, previous RRT time, RRF, comorbidity score, PD modality and peritonitis episodes were investigated as possible determinants of UFF-free survival. *Results*. PET parameters remained stable during follow up. CA125 decreased significantly. Inherent UFF was diagnosed in 8 patients, 5 spontaneously recovering. Acquired UFF group presented type I UFF profile with compromised sodium sieving. At baseline they had lower RRF and longer previous time of RRT which remained significantly associated with UFF-free survival by Cox multivariate analysis (HR 0.648 (0.428–0.980), $P = 0.04$) and (HR 1.016 (1.004–1.028), $P = 0.009$, resp.). UFF free survival was 97%, 87% and 83% at 1, 3 and 5 years, respectively. *Conclusions*. Inherent UFF is often unpredictable but transitory. On the other hand baseline lower RRF and previous RRT time independently impact on ultrafiltration failure free survival. In spite of these detrimental factors generally stable long-term peritoneal transport parameters is achievable with a 5-year cumulative UFF free survival of 83%. This study adds a further argument for a PD-first policy.

1. Introduction

Peritoneal membrane ultrafiltration failure (UFF) is a relevant long-term complication menacing peritoneal dialysis (PD) [1]. It has been reported to lead to technique failure in a rate of 1.7% [2] to 13.7% [3]. Peritoneal morphological changes seem to be related to dialysis solutions, bioincompatibility, and to infections. Uremic milieu per se may also contribute to peritoneal changes since both submesothelial fibrosis and vascular changes are already present in uremic patients, before dialysis induction. The median thickness of the submesothelial compact collagenous zone was 50 micron for normal subjects, but was 140 micron for uremic predialysis patients, 150 micron for patients undergoing hemodialysis, and 270 micron for patients undergoing PD [4]. Honda et al. concluded that the average peritoneal thickness was increased in uremic patients and progressively thickened as the duration of peritoneal dialysis prolonged, while the lumen/vessel diameter ratio was lower in uremia than normal and progressively decreased as the duration of peritoneal dialysis was prolonged [5]. Thus, the effect of uremia on the baseline and time dependent profiles of peritoneal membrane function deserves further studies. It is a continuous bystander in dialysis patients only more recently introduced in PD animal models [6], but often excluded from UFF analysis [7].

Currently, the determinants of small solutes, proteins, and water transport across the peritoneal membrane, as well as their evolution during PD therapy, are still a matter of debate. Recently, some mechanisms involved in acquired UFF have been identified but less is known about the role

of previous renal replacement therapy time in this issue. Moreover, early UFF is still an unexplained phenomenon.

A fast transport status is the primary mechanism of UFF and it is sometimes documented as an inherent condition whose clinical impact has been debated [8–11] but early UFF still remains often unexplained [7, 12]. Later during PD, loss of glucose osmotic conductance might add to the process of acquired UFF, with a disproportionally more severe compromise of free water transport [13]. Additionally, it is known that peritoneal fibrosis is induced by PD solutions but uraemia per se is also a fibrogenic factor [14]. Residual renal function and precious renal replacement therapy time at PD start are clinical variables that reflect the cumulative uremia stage.

We aim to identify relevant clinical determinants of early and acquired UFF, focusing on the independent impact of previous renal replacement therapy time and residual renal function at start of PD. Its eventual independent impact may strengthen PD prescription as a first renal replacement therapy option.

2. Patients and Methods

We prospectively studied 123 consecutive peritoneal dialysis incident patients enrolled at Hospital Santo António PD Unit since 1st January 2001. All patients were free of hypertonic 3.86% glucose solutions. Standard prescription included low-GDPs solutions; median glucose concentration exposure was 1.65% (range 1.36%–2.27%) and 40% used icodextrin. Age, diabetes, previous renal replacement therapy time (RRT), baseline residual renal function (RRF) quantified as glomerular filtration rate (GFR mL/min/1.73 m^2)—based on 24 hrs urine collections with determinations of creatinine and urea, Davies comorbidity score, automated PD, and peritonitis events were investigated as possible determinants of baseline or late UFF. All patients performed baseline and yearly 3.86%-peritoneal equilibration tests (PETs), being followed for median 26 (4–105) months: D/P creatinine, D/D0 glucose, sodium sieving, and peritoneal ultrafiltration (UF) were analyzed, and UF failure was defined as a net UF lower than 400 mL after a 4-hour dwell with 3.86%. PET; CA125 appearance rate was also calculated after 4 hours of PET dwell.

The time course of PET parameters was explored by repeated measurements mixed linear model analysis with SPSS software.

Clinical and laboratory parameters considered to be possible determinants of UFF were investigated and its impact on UFF-free survival was studied by using Cox multivariate analysis. Investigation was made both in the whole cohort and in the subgroup after excluding patients admitted after renal graft failure.

3. Results

The investigated patients had a mean age of 48 ± 15 (20–82) years and female predominance (62%). Twenty-three patients (18.7%) were diabetic, thirty (24.4%) were anuric and the majority of them (59%) were on APD. Fifty-four patients (43.9%) had been on previous renal replacement therapy (RRT) for a median time of 63 months (2–410): 30.9% after hemodialysis (HD) and 13.0% after renal transplant failure (RT).

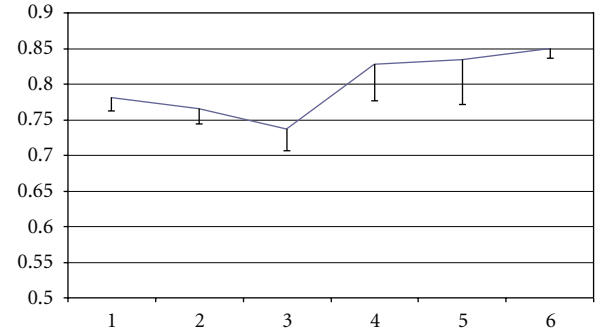

Figure 1: PET 3.86% D/P creatinine means by time (years on PD) estimated by repeated measurements mixed model analysis (P = NS).

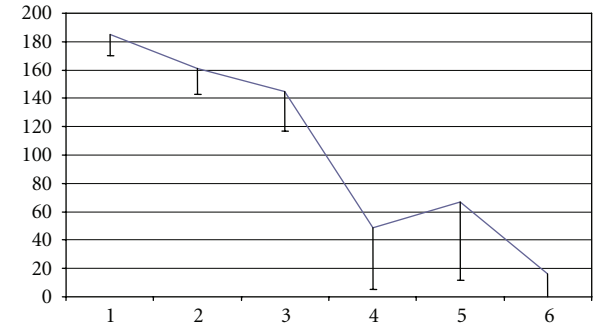

Figure 2: Effluent CA125 U/min means by time (years on PD) estimated by repeated measurements mixed model analysis (P = 0.009).

3.1. Time Course of Peritoneal Membrane Function. By repeated measurements mixed model analysis, it was shown that small solute, UF, and sodium-sieving parameters remained essentially stable during the followup. A U-shaped curve of D/P creatinine was documented, but this variation with time did not attain significance (Figure 1). CA125 decreased progressively (P = 0.009) (Figure 2), mainly in late UFF patients. The same profile was documented in the subgroup of patients after excluding those admitted after renal graft failure (D/P creatinine U-shaped curve though P = ns; for Ca125 parameter P = 0.015).

3.2. Inherent and Acquired Ultrafiltration Failure. UFF was documented in 15 patients: eight patients (6.5%) showed baseline ultrafiltration failure (UFF) while seven patients (5.7%) developed acquired UFF. Notably, five patients completely recovered from baseline UFF.

Sex, age, diabetes, comorbidity score, baseline RRF, and previous RRT did not differ significantly between baseline UFF group and the other patients (Table 1). D/P creatinine

Table 1: Comparison between inherent (baseline) UFF group and baseline-stable patients (categorical data as number (percentage) compared by Fisher's exact test; continuous data presented as median (25%–75% interquartile range), compared by Mann Whitney U-test).

	Baseline UFF $N = 8$	Baseline stable group $N = 115$	P
Sex (male) (N; %)	3 (37.5%)	44 (38.3%)	1
Diabetes (N; %)	1 (12.5%)	22 (19.1%)	1
Age	44 (38–66)	47 (35–60)	0.64
Comorbidity score (≥2)	1 (12.5%)	30 (26%)	0.76
Baseline GFR mL/min	4.2 (2.2–6.2)	4.8 (0–7.4)	0.90
RRT time (months)	0 (0–1.9)	1.7 (0–41)	0.32
PET parameters			
D/P creatinine	0.76 (0.65–0.81)	0.77 (0.66–0.86)	0.74
D/D0 glucose	0.25 (0.21–0.28)	0.29 (0.25–0.3)	0.12
PET drainage	2200 (2100–2287)	2800 (2600–2900)	<0.0001
D/P Na 60	0.90 (0.86–0.93)	0.87 (0.85–0.89)	0.057
Dip Na	0.028 (0.001–0.076)	0.050 (0.022–0.073)	0.21
Ca125 U/min	143 (67–350)	136 (85–241)	0.89

of inherent UFF group and other patients was similar (0.74 ± 0.11 versus 0.75 ± 0.13, $P = 0.74$). Also sodium sieving did not differ significantly between the groups (D/P Na60 0.90 ± 0.038 versus 0.87 ± 0.034, $P = 0.057$), although a trend was noticed.

On the other hand, the acquired UFF group presented type I UFF profile with clearly compromised sodium sieving (D/P creatinine was 0.83 ± 0.10 versus 0.72 ± 0.12, $P = 0.035$ and D/PNa60 0.92 ± 0.028 versus 0.87 ± 0.034, $P = 0.010$) (Table 2). They had significantly lower baseline RRF ($P = 0.009$) and longer previous RRT time ($P = 0.003$) (Figure 3).

3.3. Ultrafiltration Failure Free Survival

3.3.1. UFF-Free Survival Was 97%, 87%, 83% at 1, 3, 5 Years (Figure 4). Baseline lower RRF and longer previous RRT were independently associated with lower UFF-free survival by Cox multivariate analysis (Table 3). Sex, age, diabetes, APD modality, and peritonitis did not significantly impact on UFF-free survival. After excluding patients admitted after graft failure ($n = 13$), RRT time remained independently associated with UFF (B 0.023 Exp(B) 1.023 (1.007–1.040) $P = 0.006$) as also baseline GFR (mL/min) (B-0.447 Exp(B) 0.64 (0.412–0.993) $P = 0.047$).

4. Discussion

Our study highlights that residual renal function and previous cumulative renal replacement therapy time, in a contemporary PD population-free of hypertonic 3.86% glucose solutions exposition, independently impact on ultrafiltration-failure-free survival. This study therefore adds a new argument for a PD-first policy as a strategy to improve technique survival.

Additionally it documented that important membrane functional changes occur already from start of PD. Measuring peritoneal transport characteristics is an approach which gives objective and reproducible information on peritoneal performance and possible etiological factors of UFF [15]. A fast transport status however, either alone or in combination with other alterations in membrane function, remains the most common underlying mechanism of UFF. We indeed showed that acquired UFF group presented type I UFF profile with compromised sodium sieving. UFF in long-term PD is most often due to a combination of a rapid disappearance of the osmotic gradient, together with an impairment of transcellular water transport (TCWT) [13]. But the activity of water channels is dependent and limited by the crystalloid osmotic pressure [16] which our methodology did not allow to be calculated, being a limitation for characterization of the late stage UFF. In spite of that we were able to document free water transport compromise by the indirect sign of decreased sodium sieving. For this reason, we are now measuring the actual UF and effluent sodium after 60 min dwell followed by effluent reinfusion and completion of standardized 4-hour 3.86% PET which allows evaluation of both free water and standardized small solute transport [17]. Finally, back filtration of fluid through the capillaries and fluid reabsorption from the peritoneal cavity into tissues and lymphatics is a recognized mechanism of UF failure and accounts for approximately 25% of the cases of UF dysfunction, but only investigational methods with tracer macromolecules hard to apply in a clinical ward are able to evaluate this.

More relevant to our study was to highlight that baseline UFF is prevalent but often transitory and not predicted by baseline clinical variables according to previous investigations [7–12]. Many aspects of early stage transport changes and mechanisms indeed remain to be understood. While lymphatic absorption cannot be excluded as a cause of early UFF, the evolution of patients recovering ultrafiltration capacity does not support such etiology. We can speculate that although no significant changes were documented in small solute transport at baseline between the groups with and without UFF, membrane structural changes induced

Table 2: Comparison between acquired UFF group and stable patients (categorical data as number (percentage) compared by Fisher's exact test; continuous data presented as median (25%–75% interquartile range), compared by Mann Whitney U-test); Δ Ca125 is the variation between last evaluation in the followup and baseline effluent CA125 U/min levels.

	Acquired UFF $N = 7$	Stable group $N = 108$	P
Sex (male) (N; %)	5 (71.4%)	39 (36.1%)	0.104
Diabetes (N; %)	0 (0%)	22 (20.4%)	0.343
Age	39 (34–45)	48 (35–60)	0.179
Comorbidity score (≥2)	2 (28.5%)	28 (25.9%)	0.203
RRT time (months)	77 (13–147)	0 (0–33)	0.003
Baseline GFR mL/mn	0 (0–3.6)	5.1 (1.37–7.4)	0.009
APD (Yes)	5 (71.4%)	61 (56.5%)	0.697
Peritonitis (Yes)	7 (100%)	61 (56.5%)	0.040
Peritonitis (n)	3 (1–4)	1 (0–2)	0.008
PET parameters			
D/P creatinine	0.78 (0.75–0.94)	0.71 (0.64–0.81)	0.037
D/D0 glucose	0.24 (0.18–0.30)	0.30 (0.30–0.34)	0.021
PET drainage	2300 (2250–2400)	2800 (2600–2900)	<0.0001
D/P Na 60	0.92 (0.88–0.95)	0,88 (0.85–0.89)	0.007
Dip Na	0.028 (−0.007–0.054]	0.048 (0.021–0.071)	0.16
Ca125 U/min	23 (10–28)	163 (86–227)	<0.0001
Δ Ca125	−52 (−79–−13)	0 (−29–53)	0.004

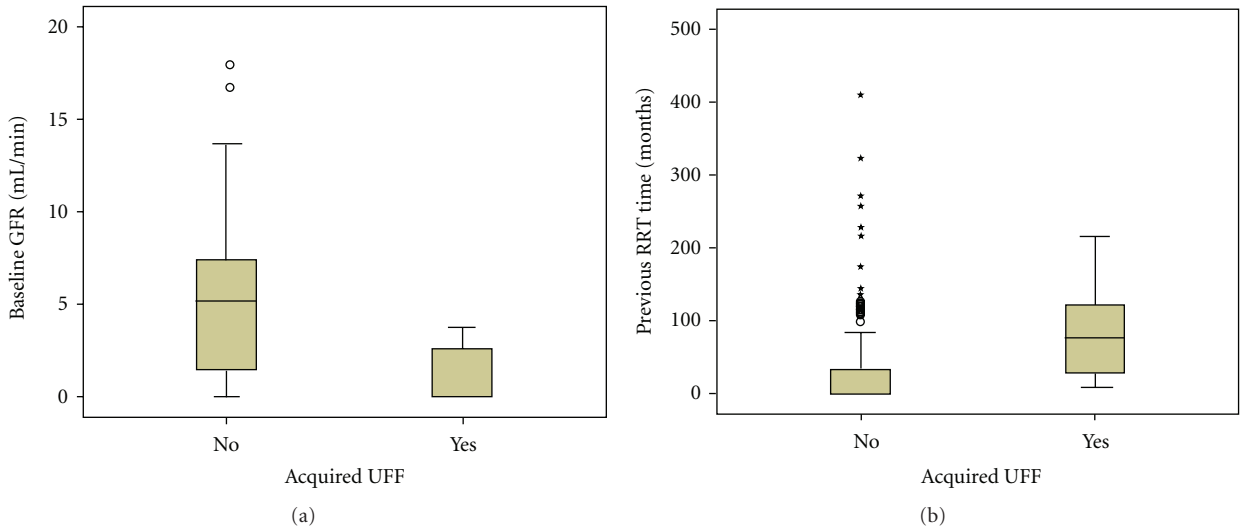

Figure 3: Comparison between acquired UFF patients and preserved UF group: acquired UFF group had significantly lower baseline residual renal function ($P = 0.009$) and longer previous renal replacement therapy ($P = 0.003$).

by uremia per se namely interstitium fibrosis might justify the marginal compromise of sodium sieving. This indeed gives lumped information and is not only dependent on an increase of diffusive mass transport coefficients for small solutes, but also on a decrease of the glucose osmotic conductance (number and function of aquaporins, number and diameter of small pores) and on reduction of ultrafiltration coefficient of the peritoneal membrane (role for the interstitium changes).

Interestingly, we found a U-shaped curve of D/P creatinine in the followup, already previously reported by our group and others [8, 13, 18] though not attaining statistical significance in this contemporary cohort. The early phase of D/P creatinine normalisation may express an adaptive process whose mechanisms are unclear but may include early recruitment or vasodilation of vessels mediated by vasoactive mediators, many of them secreted by mesothelial cells. Therefore, in some of our patients a transitory fast transport status may explain the inherent UFF. In other patients, the causes of such baseline UFF are not clear, pointing to the complexity of peritoneal membrane time-dependent functional changes. The risk phase with clinical

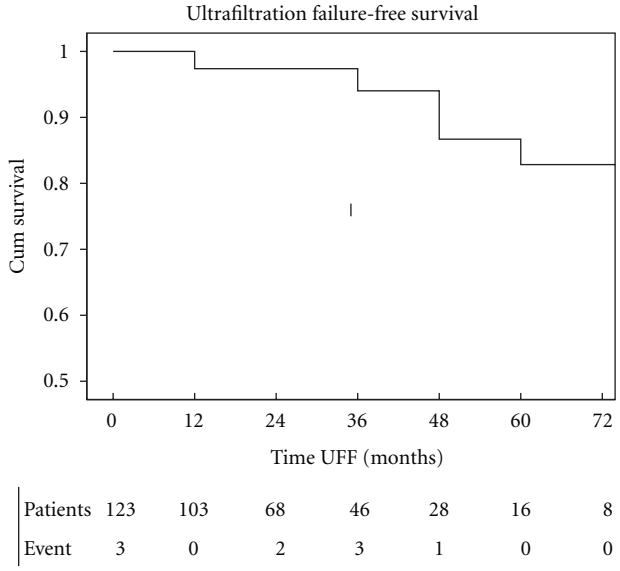

Figure 4: UFF-free survival rate was 97%, 87%, 83% at 1, 3, 5 years.

Table 3: Multivariate Cox proportional hazard analysis of variables significantly associated with UFF-free survival. Sex, age, diabetes, APD, and peritonitis did not significantly impact on UFF-free survival.

	B	Exp(B) (95% CI)	*P*
Baseline GFR (mL/min)	−0.434	0.648 (0.428–0.980)	0.040
RRT time (month)	0.016	1.016 (1.004–1.028)	0.009

Cox regression; status acquired UFF.

impact may be documented by the late increasing side of the U-shaped curve, with decreasing mesothelial cell mass as a marker of structural changes that go along with UFF and sodium sieving compromise. Again we highlight the importance of routine membrane monitorization also including an accessible and affordable structural marker—CA125 effluent appearance rate [19].

However, our global population presented stability in the transport rates for small molecules and sodium sieving over time. This is in accordance with previous publications where small-solute transport parameters were found to be increased only in long-term patients [20], but happily, in disagreement with the gloomier reports of sustained and inexorable increase of D/P creatinine over time, already from the start [21]. On the other hand, uremia and baseline GFR as its surrogate, is indeed an important bystander not usually taken into account in peritoneal membrane changes investigation. We identified it here as a clinical variable that independently impacts on UFF-free survival. This clue deserves further investigation but suggests that uremia may be crucial to explain acquired peritoneal membrane changes, and although it has not been associated with baseline transport characteristics may modulate membrane time-dependent profile [4–6].

As a limitation of our study, we did not control for a panel of pharmacological agents shown experimentally to modulate membrane structure, namely, renin angiotensine system inhibitors and erythropoiesis stimulating agents [22, 23]. However, since the use of these agents is massive in our PD patients, it is not presumed to change our results.

In spite of some controversy [18], our study also showed that the influence of peritonitis on the development of UFF seems to be limited. It has been found that patients with a history of peritonitis were not different from patients without a previous peritonitis episode in terms of D/P ratio and mass transfer area coefficient of low molecular weight solutes, lymphatic absorption rate, transcapillary ultrafiltration, and net ultrafiltration [24]. Only clusters of peritonitis or peritonitis episodes that occur later in PD have been described as causing a decrease in UF [25].

Considering the link between comorbidity and peritoneal transport, data is controversial. Some papers document that systemic inflammation associated with comorbid diseases and elevated interleukin- (IL-) 6 level may induce vasodilation and neoangiogenesis in peritoneal membrane [26]. We did not find any association between morbidity and higher transport rates, like others [27], nor comorbidity score was predictive of UFF.

As a structural marker, effluent cancer antigen 125 can be used reflecting mesothelial cell mass and cell turnover in stable, noninfectious PD patients. Its decrease with the duration of PD, described previously [28], is consistent with the reported cell loss observed in peritoneal biopsies. Such profile of effluent CA125 appearance rate is therefore more likely a sign of damage to the peritoneum than a causative factor of UF by itself. It can be interpreted as an additional prognostic sign, adding to the changes of D/P creatinine and effluent IL-6 [29].

In conclusion, this paper documents early-stage peritoneal membrane changes with transitory cases of inherent ultrafiltration capacity failure dissociated from small-solute transport, whose mechanisms remain unclear. On the other hand, lower baseline RRF and previous longer RRT were associated with acquired UFF in our population. In spite of these detrimental factors, we found generally stable long-term peritoneal transport parameters with 5 years 83% cumulative UFF-free survival. By highlighting the importance of previous cumulative RRT time and baseline RRF concerning peritoneal membrane function status these results support a PD-first strategy in the integrated renal replacement treatment plan.

Conflict of Interests

The authors declared that there is no conflict of interests.

Acknowledgments

The authors are grateful to Professor Denisa Mendonça for statistical advice, to Dr. Antonio Cabrita, Dr. MJ Carvalho, and nurse Olivia Santos for patient recruitment and management.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 526753, 4 pages
doi:10.4061/2011/526753

Case Report

Pleuroperitoneal Leak Complicating Peritoneal Dialysis: A Case Series

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Received 6 March 2011; Revised 6 June 2011; Accepted 14 June 2011

Academic Editor: Hulya Taskapan

Pressure related complications such as abdominal wall hernias occur with relative frequency in patients on peritoneal dialysis. Less frequently, a transudative pleural effusion containing dialysate can develop. This phenomenon appears to be due to increased intra-abdominal pressure in the setting of congenital or acquired diaphragmatic defects. We report three cases of pleuroperitoneal leak that occurred within a nine-month period at our institution. We review the literature on this topic, and discuss management options. The pleural effusion resolved in one patient following drainage of the peritoneum and a switch to haemodialysis. One patient required emergency thoracocentesis. The third patient developed a complex effusion requiring surgical intervention. The three cases highlight the variability of this condition in terms of timing, symptoms and management. The diagnosis of a pleuroperitoneal leak is an important one as it is managed very differently to most transudative pleural effusions seen in this patient population. Surgical repair may be necessary in those patients who wish to resume peritoneal dialysis, or in those patients with complex effusions. Pleuroperitoneal leak should be considered in the differential diagnosis of a pleural effusion, particularly a right-sided effusion, in a patient on peritoneal dialysis.

1. Introduction

Peritoneal dialysis (PD) is a well-established means of renal replacement therapy. A Tenckhoff catheter is electively inserted into the peritoneal cavity before PD starts. After a healing period of at least two weeks, PD training begins. In our centre, 500 ml volumes are used for the first two days of training and titrated upwards, based on body surface area, over a two-week period.

In our centre, there are 35–40 patients on PD at any one time. Approximately 2 patients join our program per month, and a similar number exit the program due to transplantation, switch to haemodialysis, or death. Patients starting PD in our unit use standard dextrose-based, lactate-buffered dialysate. If infusion pain is a problem, bicarbonate/lactate buffered dialysate is used instead. A daytime icodextrin-based dialysate dwell is often required in patients with little residual renal function for extra ultrafiltration. Icodextrin is a hyperosmolar glucose polymer.

The main complications of PD are either infectious, such as peritonitis and exit site infections, or pressure related, such as abdominal wall hernias and gastrooesophageal reflux. Less frequently, a pleural effusion containing dialysate can develop. This phenomenon appears to be due to increased intraabdominal pressure in the setting of congenital or acquired diaphragmatic defects. The incidence rate of pleuroperitoneal leak development is thought to be less than 2% in newcomers to peritoneal dialysis [1]. We report three cases of pleuroperitoneal leak that occurred within a nine-month period at our institution. This corresponded to a 12% incidence rate amongst newcomers to PD in that calendar year (25 newcomers). Prior to that, there had been no cases in our department for over 10 years [2]. We review the literature on this topic and discuss management options.

2. Case 1

A 35-year-old Philipino female presented to our unit with advanced chronic kidney disease, secondary to medullary

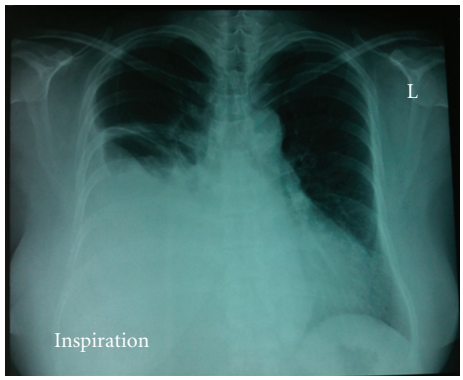

Figure 1: Chest radiograph at presentation.

Table 1: Biochemical results.

	Pleural fluid	Serum
pH	7.64	7.38
Albumin (g/dL)	<15	32
HCO3—(mmol/L)	30.1	28
LDH (iu/L)	<50	474
Glucose (mmol/L)	12.1	5.2
Amylase (iu/L)	<10	40

cystic kidney disease, which was diagnosed many years earlier in the Philipines. She had no significant heart disease. One year later, she was approaching end-stage kidney disease and a Tenckhoff catheter was inserted. Training for PD began four weeks later, using standard dextrose-based solutions.

She presented after four days of PD training with dyspnoea. She was otherwise well and was afebrile. Blood tests and ECG were unchanged. She had clinical evidence of a large, rightsided pleural effusion. This was confirmed on a chest radiograph (Figure 1). A diagnostic aspirate was performed and yielded serous fluid. The pleural fluid biochemistry was consistent with a transudative process (Table 1). The high-pleural-fluid-serum-glucose ratio confirmed the clinical suspicion of a pleuroperitoneal leak.

The pleural effusion resolved over a number of days with conservative management and the maintenance of a dry peritoneal cavity. A follow-up chest radiograph was normal (Figure 2). In accordance with patient preference, PD was discontinued. Haemodialysis (HD) access was established and HD is ongoing one year later.

3. Case 2

A 38-year-old Romanian female was admitted acutely with symptomatic uraemia. Her background was significant for minimal change disease, diagnosed in 2001 in Romania. She had received two courses of heavy immunosuppression for this and was then lost to follow up. She had no known heart disease. Her renal ultrasound showed small, shrunken kidneys, which confirmed the suspicion of advanced chronic kidney disease.

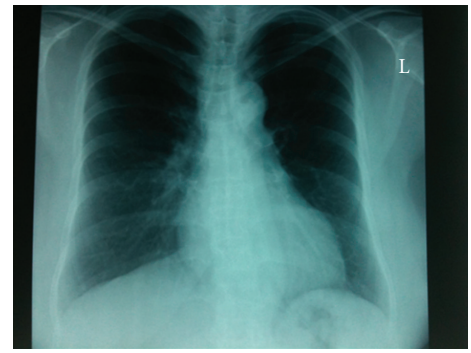

Figure 2: Follow-up chest radiograph.

Table 2: Biochemical results.

	Pleural fluid	Serum
pH	7.55	7.37
Albumin (g/dL)	<15	39
HCO3—(mmol/L)	29	32
LDH (iu/L)	<50	379
Glucose (mmol/L)	8.6	6.1

Acute HD was initiated but, as the patient's preference was for PD, a Tenckhoff catheter was inserted. Five weeks later, PD training began. Her target PD prescription consisted of four cycles of two litre exchanges with standard dextrose-based standard solution. She was also prescribed one icodextrin-based dwell by day.

After six days of PD training, she presented with dyspnoea that was exacerbated by infusing dialysate. She had no other systemic symptoms. She was seven kg above her dry weight and had clinical evidence of a rightsided pleural effusion and pedal oedema. Her electrocardiogram (ECG) and routine blood tests were unchanged. As she appeared volume overloaded, she had three litres of isolated ultrafiltration, using her central venous catheter. Her diuretic regime was maximized and she was discharged.

Despite these interventions, she presented several days later with worsening dyspnoea. A chest radiograph confirmed a large rightsided pleural effusion. Again, she had 3 litres of isolated ultrafiltration. With this, she developed bad cramping. Therapeutic thoracocentesis was performed, with the removal of 1.2 litres of serous fluid. This led to marked clinical and radiological resolution of the pleural effusion.

Although the initial presumed diagnosis was volume overload, the high pleural fluid glucose relative to the serum glucose confirmed the presence of a pleuroperitoneal leak (Table 2). In accordance with patient preference, PD was discontinued and the Tenckhoff catheter was removed. HD is ongoing without complication.

4. Case 3

A twenty-four-year-old Irish male with a background history of congenital deafness, intellectual impairment and repair of a posterior urethral valve initially presented to the paediatric

Table 3: Biochemical results.

	Pleural fluid	Serum
pH	7.23	7.36
Albumin (g/dL)	28	29
HCO3—(mmol/L)	20	26
LDH (iu/L)	2816	614
Glucose (mmol/L)	<0.6	4
Amylase (iu/L)	<10	32

nephrology services with nephrotic syndrome. A renal biopsy revealed secondary focal segmental glomerulosclerosis and significant tubuleinterstitial fibrosis. Following introduction of Renin-Angiotensin-Aldosterone system blockade, his proteinuria was controlled.

Despite this, his chronic kidney disease progressed. Ten years later, he was approaching end-stage kidney disease. A Tenckhoff catheter was inserted without complication. Six weeks later, PD training was initiated. A bicarbonate/lactate buffered solution was used to avoid infusion pain, which he would be unable to verbalise. The following months were complicated by dialysis-associated pericarditis that resolved with intensive haemodialysis for a number of weeks. His baseline PD prescription consisted of seven cycles of two litre exchanges with 1.36% dextrose solution. He was also prescribed an icodextrin-based daytime dwell.

Five months later, he was admitted with clinical and radiological evidence of a large, rightsided pleural effusion with pleural thickening. The exact duration of the effusion was unclear as he was unable to verbalise symptoms. It was thought to have developed over weeks given the apparent absence of symptoms and the degree of pleural thickening. A chest radiograph four months earlier showed normal lung fields.

He was afebrile and systemically well. His serum biochemistry and haematology were unchanged and his inflammatory markers were not raised. ECG and echo were normal. A diagnostic pleural aspirate was performed under ultrasound guidance. This yielded serous fluid and also identified numerous loculations within the collection.

The pleural fluid biochemistry was atypical for that seen with pleuroperitoneal leak (Table 3). However, as the patient was so well clinically, and numerous pleural fluid cultures were sterile, it was felt that the effusion was not related to infection. It was also felt that the effusion was not due to volume overload given the degree of loculation within the effusion and the absence of other clinical signs of volume overload. The low pleural fluid glucose and high lactate dehydrogenase (LDH) were difficult to interpret as the sampled fluid was walled off within a loculation, probably for many weeks. A clinical diagnosis of pleuroperitoneal leak was made and PD was discontinued.

The effusion did not resolve with drainage of the peritoneal cavity, and a chest drain was inserted. This drained minimal serous fluid due to the highly loculated nature of the effusion. A second drain was inserted and intrapleural alteplase administered. This drain became dislodged and was replaced by a third drain with further intrapleural alteplase administration. At this point, however, a chest radiograph confirmed persistence of the large, loculated effusion with a small pneumothorax and a thick pleural rind.

Video-assisted thorascopic surgery with decortication was performed. A rapid postoperative recovery ensued and the postoperative chest drains were removed without event. A chest radiograph six weeks later showed a well-expanded right lung, without effusion or pleural abnormality. HD is ongoing without complication.

5. Discussion

The first description of a pleuroperitoneal leak causing a pleural effusion in a PD patient was in 1967 [3]. Since then, several reports have estimated the incidence of this complication; the largest report estimated an incidence of 1.6% [1].

It is thought that congenital or acquired communications between the pleura and peritoneum underpin this problem. This had been demonstrated both in scintigraphy [4] and in autopsy specimens with localized absence of diaphragmatic muscle fibres [5]. The raised intraabdominal pressure with dialysate infusion, in a patient with such a communication, promotes the translocation of dialysate into the pleural space.

An increased incidence of pleuroperitoneal leak is seen in patients with polycystic kidney disease [6]. This is probably related to the increased intraabdominal pressure in these patients and, therefore, higher pleuroperitoneal pressure gradients [6]. There is also a generalized connective tissue weakness in this condition that may contribute to inherent diaphragmatic weakness [6]. Patients with previous peritonitis are also at higher risk of developing this condition. This is probably due to a weakening of diaphragmatic tissue during peritonitis [7].

The timing of this complication varies from days to years after the initiation of PD. Half of cases occur within one month of starting PD [3]; these probably represent patients with congenital diaphragmatic defects. Those cases that occur later probably represent those with acquired diaphragmatic defects. Patients typically present with dyspnoea, although a significant proportion are asymptomatic [3]. Clinical examination reveals a pleural effusion that is usually rightsided [3]. Presumably the preponderance of rightsided cases is due to diaphragmatic protection by the heart on the left.

Pleural effusions are broadly divided into transudative and exudative effusions. Transudative effusions develop when systemic factors affect the pleural Starling forces, as seen, for example, in congestive cardiac failure. Exudative effusions develop when local factors influence the formation of pleural fluid, as seen in malignant effusions. Light's criteria are applied to the pleural and serum biochemistry to make the distinction between a transudate and an exudate [8]. An effusion is an exudate if the pleural-fluid-to-serum-protein ratio is >0.5 or the pleural-fluid-to-serum-LDH ratio is >0.6 [8]. Pleuroperitoneal leaks typically cause transudative effusions with low LDH and low cell count [5].

The differential diagnosis of a pleural effusion in a dialysis patient is extensive. Transudative pleural effusions

due to volume overload or congestive cardiac failure are relatively common in this population. In PD patients, such effusions would typically be managed by increasing the dialysate volume and tonicity to increase ultrafiltration. However, this can exacerbate the problem if the effusion is due to a pleuroperitoneal leak.

This highlights the importance of the pleural fluid glucose measurement. In the absence of loculation, a high pleural fluid to serum glucose concentration gradient is a very sensitive and specific test for diagnosing a pleuroperitoneal leak [9]. The ratio of pleural fluid to serum glucose is dynamic, and varies depending on the type of fluid instilled, the volume and the contact time. However, a positive gradient is highly suggestive of a pleuroperitoneal leak [9]. This is due to the presence of hypertonic, usually dextrose-based, dialysate in the pleural space—a "sweet hydrothorax" [10]. Atypical biochemistry can be seen when the fluid has been in the pleural cavity for a prolonged period and has been partially reabsorbed by lymphatics, as seen in Case 3.

Other diagnostic tests are less practical and include Technetium-99m labelled peritoneal scintigraphy [4] and computed tomography (CT) with intraperitoneal dye [11].

In terms of management, emergency large volume thoracocentesis is occasionally required [3]. However, most cases of pleuroperitoneal leak are initially managed by drainage of the peritoneal cavity [3]. Temporary HD may be required, especially for those with minimal residual renal function. Many patients choose to remain on HD in the long term and, therefore, formal repair of the diaphragm is not required.

For those that wish to return to PD, there are a number of management options. One group advocates early diaphragmatic repair and continuation of peritoneal dialysis [12]. In this case, thorascopic diaphragmatic repair was performed using absorbable polyglycolic acid felt, and fibrin glue [12].

Most advocate temporary discontinuation of PD. This allows resolution of the effusion and, in some cases, healing of the diaphragmatic defects. A trial of low-volume PD two–six weeks later is successful in a significant proportion of cases [13].

Recurrent hydrothorax necessitates either a permanent switch to haemodialysis or definitive management of the pleural-peritoneal communication. Chemical pleurodesis via an intercostal drain has been used in several cases with success [13]. Agents used include tetracycline, blood and fibrin glue. This method had relatively high rates of success, with 48% of patients resuming long-term PD after pleurodesis in one large systematic review [13].

Video-assisted thorascopic surgery, with direct visualization of the diaphragmatic defect and suture repair, has shown much promise in recent times for the management of this condition [13, 14]. Using this approach, 88% of patients in one study successfully resumed long-term PD without recurrence [13].

The three cases described above highlight the variability of this condition in terms of timing, symptoms, and management. Pleuroperitoneal leak should be considered in the differential diagnosis of a pleural effusion, particularly a rightsided effusion, in a patient on peritoneal dialysis.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 742196, 5 pages
doi:10.4061/2011/742196

Review Article

Bioincompatible Impact of Different Peritoneal Dialysis Fluid Components and Therapeutic Interventions as Tested in a Rat Peritoneal Dialysis Model

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Received 24 March 2011; Accepted 1 June 2011

Academic Editor: Hulya Taskapan

Peritoneal dialysis (PD) is associated with functional and structural changes of the peritoneal membrane. In this paper, we describe the impact of different factors contributing to peritoneal incompatibility of PD fluid installation including presence of a catheter, volume loading, and the PD fluid components itself. These factors initiate recruitment and activation of peritoneal immune cells such as macrophages and mast cells, as well as activation of peritoneal cells as mesothelial cells in situ. We provide an overview of PD-associated changes as seen in our rat PD-exposure model. Since these changes are partly reversible, we finally discuss therapeutic strategies in the rat PD model with possible consequences of long-term PD in the relevant human setting.

1. Factors Contributing to Functional and Structural Changes in an Experimental Rat PD Model: Introduction

Peritoneal dialysis (PD) is a therapy used to replace kidney function in end-stage renal disease patients. The therapy is based on the ability of the peritoneal membrane to function as a dialysing membrane, allowing exchange of solutes and waste products between the PD fluids (PDFs) and the circulation. Dialysis fluid is instilled in the peritoneal cavity via a permanent catheter. PDFs contain an osmotic agent, mostly glucose, which facilitates fluid movement from the bloodstream to the peritoneal cavity leading to removal of metabolic waste products and water. Continuous removal of waste products achieved using PDs, results in improved well-being of patients. In contrast, in haemodialysis, waste products accumulate between two dialysis treatments. Furthermore, patients on PD have increased mobility compared to haemodialysis since PD can be done at home, and moreover, PD is less expensive.

However, drawbacks of PD include the risk of peritonitis and peritoneal membrane damage upon exposure to PDF. The latter induces inflammation, angiogenesis, and fibrotic changes. In this paper, we describe the usefulness of a rat PD exposure model in defining the impact of PDF components in this process. Finally, we will discuss interventions in this model and the possible clinical implications for long-term PD.

2. PD-Related Changes as Observed in a Rat PD-Exposure Model

The efficacy of PD depends on the structural and functional integrity of the peritoneum, that is, the inner surface of the abdominal wall (parietal peritoneum), omentum, and mesentery (visceral peritoneum). The peritoneum consists

Table 1: The degree of contribution by extrinsic (catheter, uremia) and intrinsic (fluid) factors on the peritoneum in rats.

Peritoneal changes	Extrinsic factors		Intrinsic factors		
	Catheter	Uraemia	(Lactate) Buffer	Buffer + Glucose	Buffer + Glucose + GDP
Ultrafiltration failure	−	±	±	+	++
Angiogenesis	±	±	±	+	++
Fibrosis	−	−	−	+	++
Mesothelial regeneration	−	−	+	++	++
Effluent cell number	−	−	−	+	+
Omental mast cells	−	±	+	+	++
Omental milky spots	−	−	+	+	++

GDP = glucose degradation products.
Peritoneal changes are scored from no (−), weak (±), and moderate (+) to very strong alterations (++) compared to control rats.

of a mesothelial cell (MC) monolayer and underlying connective tissue interstitium comprising extracellular matrix (ECM), blood vessels, fibroblasts, and innate immune cells.

In our rat PD-exposure model, we use normal renal function, no omentomectomy, and no addition of heparins during PD-exposure or addition of antibiotics [1]. We have shown that several weeks of PD results in a loss of MCs and denuded areas in the mesothelial layer [2]. Liver imprints of rats show increased mesothelial cell density, indicating mesothelial regeneration [3, 4]. Among the mesothelial cells, vimentin-positive, spindle-like-shaped cells are found indicating the process of epithelial to mesenchymal transition (EMT; [5]). Changes also take place in the submesothelial interstitium, and ECM thickness is significantly increased upon PD [6–8].

Significantly higher numbers of leukocytes are found in the effluents of PD-treated animals compared to nontreated animals. Although the percentage of macrophages and lymphocytes does not change, an exchange of mast cells and eosinophils for neutrophils is seen after PD treatment [7, 9]. Increased numbers of activated macrophages are seen in mesentery and omentum upon PD [5], including accumulations around vessel networks in the omentum, known as milky spots [7, 10]. In a steady state, milky spots occupy a small percentage of the total surface area of the omentum, whereas after PDF exposure, this increases dramatically [3, 11]. Throughout the peritoneal tissues, new blood vessels and lymphatics [7] are formed. Angiogenesis leads to a large effective surface area exchange, contributing to ultrafiltration loss [12]. Furthermore, the thickened submesothelial fibrotic layer counteracts osmotic pressure further, reducing efficacy of exchange [13].

In summary, loss of mesothelium and induction of inflammation and angiogenesis are typical morphologic features seen in long-term PD which in part contribute to fibrotic changes, ultimately leading to technique failure.

In this paper, we discuss the changes that occur upon PD in our rat PD-exposure model. This model, as described above, shows similar changes upon long-term exposure to PDF fluid as patients on CAPD. For example, thickening of the submesothelial compact zone, degeneration of the MC layer, loss of microvilli on residual MC, and increased vessel numbers are also observed in biopsies from patients on long-term PD, as in detail described by Williams et al. [14]. In addition, Devuyst et al. recently reviewed the similarities between mice, rats, and humans regarding a.o. peritoneal transport, aquaporins, and net UF after long-term PD exposure [15].

3. Causes of PD-Induced Peritoneal Membrane Changes

Several factors can contribute to PD-related changes, including the presence of the catheter, uraemia, peritonitis, and instillation of the volume loading of PDF itself. Moreover, different components of the PDF, including the used buffer (low pH), glucose concentration, and glucose degradation products (GDPs) generated during heat sterilisation, influence peritoneal inflammation (as reviewed by Schilte et al. [2] and summarized in Table 1). The presence of only the catheter itself already induces PD-related morphological changes such as increase in angiogenesis and thickness of ECM, as well as slight effect on total effluent cell numbers [9, 16]. Morphologic and inflammatory parameters of rats treated with PDF via a peritoneal catheter are significantly increased compared to rats treated via intraperitoneal needle injections (blood vessels, ECM thickness, and total cell count).

Volume loading is already a second inflammatory trigger. Zareie et al. showed that instillation of lactate buffer without glucose or GDPs already resulted in increased cell influx, mesothelial regeneration, angiogenesis, and increased number of milky spots although it not significantly enhanced fibrosis [7, 9]. Moreover, they showed that the addition of glucose to the buffer-induced angiogenesis and mesothelial regeneration, and induced fibrosis as well as cell influx even further. Finally, the presence of GDPs enhanced all mentioned peritoneal changes, apart from cell influx and mesothelial regeneration, even further. Besides, GDPs, advanced glycation end products (AGEs) formed by heating of glucose, contribute to the toxicity of PDF [17].

It has become increasingly clear that more biocompatible PDFs (bicarbonate/lactate buffer, reduced concentration of glucose and GDPs) induce less damage and decrease impaired ultrafiltration when compared with conventional PDF [2, 6, 8, 17].

In addition, supplementing PDF with aminoguanidine, which scavenges GDPs and prevents AGE formation, resulted in less mesothelial denudation [18], reduced fibrosis, and less angiogenesis in omentum and parietal peritoneum, but not in mesentery [19] as shown in our own rat PD-exposure model.

Apart from intrinsic factors as PDF composition, other factors have been suggested to contribute to PD-related tissue remodelling (Table 1). Animal studies have shown the increase in vascular network as a result of uraemia in non-PD-treated animals. Although differences between uremic and nonuremic rats were found in control animals (no PD), there is no longer a prominent effect of uraemia during PD therapy [4, 20].

In contrast, peritonitis episodes always significantly contribute to peritoneal changes by inducing mesothelial damage, a massive inflammatory response, and increased vascularisation of peritoneal tissue leading to impaired membrane function [12, 21, 22].

4. Peritoneal Rest and Reversibility

Activation of peritoneal cells, mediators, and pathways, results in functional and structural changes of peritoneal membranes in long-term PD. Some of these changes can be reversed by peritoneal rest. The reversibility of both morphological and functional alterations in the peritoneal membrane by peritoneal rest has been shown in animal studies [23, 24].

Peritoneal rest of more than 4 weeks restored ultrafiltration capacity as well as peritoneal permeability for glucose and total protein [23, 24]. Moreover, the thickness of the parietal peritoneum was reduced, and omental and mesenterial vessel density was restored [23, 24]. Furthermore, peritoneal rest reversed the increased mast cell density and milky spot response and recovered PD-induced mesothelial damage [24]. These data suggest that PD-induced changes in the peritoneal membrane are reversible after peritoneal rest, at least in the rat model. We therefore foresee future therapies focusing on the prevention and reversibility of these changes as shown below. Moreover, this may have major implications for therapeutic clinical interventions in preventing the PD-induced changes in long-term PD.

5. Therapeutic Interventions in the Rat PD Model

Recent reviews of our group have shown that the rat PD model is also ideally to test anti-inflammatory therapeutic interventions [2, 25].

Heparin has been mentioned as a regulator in inflammation, but the addition of unfractionated or low-molecular weight heparin was not able to counteract the PD-fluid-induced changes in our rat PD model [5], but in an editorial, the usefulness was highlighted [26].

Recently, we could show that Sunitinib inhibits angiogenesis in our rat PD model, and so the usefulness of inhibitors in the field of angiogenesis can have important functional implications [27]. Moreover, the usefulness of Celecoxib as inhibitor of Cox-2 and the inflammation cascade has been discussed [28] and indeed in our rat PD model, we could demonstrate an effect on angiogenesis and functional ultrafiltration, but not on clear inflammation markers [29]. These two interventions so in part show some positive results, but future experiments should determine if no side effects of Celecoxib are seen, when used in a clinical setting (as presently is investigated in our institute) and whether the reduction of angiogenesis by Sunitinib really results in better ultrafiltration.

It must be mentioned that macrophages are thought to play a key role in the inflammatory process, as earlier discussed [2]. More recently, it was shown that the discrete balance between the so-called proinflammatory M1 macrophages and alternatively activated M2 macrophages might determine the outcome in inflammation in PD [30] as has also been shown for macrophages in wound healing [31] and oncology [32, 33].

Finally, molecules as bone morphogenetic protein-7 (BMP-7) and the vitamin D analogue paricalcitol have been shown to be important in inhibiting peritoneal and renal fibrosis [34, 35]. BMP-7 also was shown to prevent peritoneal damage in our PD-exposure model [36], and preliminary data on paricalcitol also show a clear effect in our PD rat model [37]. These observations should be investigated more deeply and mechanistically in the in vivo animal model, since they offer opportunities for therapeutic clinical interventions in the near future.

6. Summary and Conclusion

In long-term PD, the catheter, uraemia, peritonitis, and permanent exposure to PDF (volume loading, glucose, and GDP's) result in morphological and functional changes of the peritoneal membranes. In part, the ultrafiltration loss seen in PD patients is caused by the bioincompatibility of PDF. Novel PDFs offer an improvement in biocompatibility, and further development of biocompatible fluids will lead to better preservation of the peritoneal membrane. Especially therapeutic interventions on angiogenesis, fibrosis, and inflammation are thought to be promising strategies in preventing ultrafiltration failure. We therefore foresee a combination therapy using more biocompatible fluids along with specific inhibitors involved in peritoneal inflammation/angiogenesis/fibrosis to be the most effective approach in future PD to prevent PD-induced changes and which will be beneficial for PD patients.

Acknowledgment

This work was supported by Grant no. C09.2331 of the Dutch Kidney Foundation.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 528685, 8 pages
doi:10.4061/2011/528685

Review Article

Assessment of Health-Related Quality of Life: The Cinderella of Peritoneal Dialysis?

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Received 6 February 2011; Accepted 6 May 2011

Academic Editor: Hulya Taskapan

The studies of quality of life (QoL) are becoming increasingly interesting in clinical setting because their findings have implications for making decisions on resource allocation and health policies. The assessment of health-related QoL is especially directed to patients with chronic illnesses that cause progressive deterioration and limitations, and consume the bulk of financial resources for health. Among these chronic kidney disease and, more specifically the renal replacement therapy, is an important condition. Due to the diagnostic and therapeutic advances, we see a gradual increase both in the number of the dialysis population and its age, which leads to a growing interest in the study of these patients' QoL, as evidenced by more than one thousand articles published on this subject.

1. Definition of Quality of Life

Quality of life is a difficult variable to define. We distinguish two basic characteristics in the concept of QoL: subjectivity and multidimensionality. Subjectivity should be distinguished because the QoL is a unique perception for each individual, which reflects the patient's self-assessment about their own health, defined by medical and nonmedical aspects of their lives. In fact, patients use the possible negative impact or treatment side effects for the evaluation of any medical intervention. Therefore, the success or failure of a medical intervention is the QoL acquired or recovered after it, in spite of success or technical failure of the procedure itself. Moreover, QoL is a multidimensional concept that comprised not only aspects directly related to health but also other nonmedical aspects, but the autonomy, the retention of employment, the impact on family relationships, the economic resources, and many other life circumstances are connected as well.

Many definitions have been proposed for an individualized, dynamic, and multifaceted concept. Thus, it has been defined as "the value assigned by an individual per year of life, modified by the social disadvantage, the perception, the functional status, or deficiencies due to illness, treatment or accident", while the WHO definies it as: "the perception that individual makes about his position in life, within its cultural context and value system, and related to its goals and vital objectives." Perhaps one of the rough and clear definitions referred to QoL is "the measure resulted from the physical, mental, and social well-being, such as is perceived by each individual." The medical and nonmedical factors are both related: the illness, as well as having an impact on the physical area of a person, has impact on the personal psychological state and his social relations. So we use the term health related quality of life, which could have been formally defined as "The extent to which one's usual or expected physical, emotional and social well-being is affected by a medical condition or its treatment." The concept of health related-quality of life (HRQOL) covers the impact of the disease or medical actions on the physical symptoms, functional status, and mental and social functioning [1–3].

2. Quality of Life and Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD) has a great impact on HRQOL [4–7]. Symptoms appear and induce substantial changes in lifestyle from the early stages of the disease to the substitution treatment such as hemodialysis (HD), peritoneal dialysis (PD), or renal transplantation (RT). CKD is invariably associated with decreased HRQOL, and there is a correlation between the magnitude of the effect on HRQOL and glomerular filtration rate. The most affected HRQOL areas are work and leisure, family life, and sleep and rest. Although an adequate treatment of patients during the predialysis stage may slow the progression of CKD and that is recognized as an important factor of morbidity and mortality (and therefore of HRQOL) of kidney patients, the start of dialysis treatment is the patients' turning point in their concept of quality of life. They go from a situation of "normal life" (often idealized) to a state of "mortal danger" or "life without health" that requires dialysis to stay alive. There are several aspects that affected patients will feel altered.

(i) *The Well-Being.* The repetition and frequency of dialysis procedure constantly reminds one of the disease, favouring self-analysis that exaggerates physiological phenomena. On the other hand, decreased sexual desire and activity (present in up to 50% of patients) are experienced as a sign of advanced age and interfere with relationships. Finally, dietary restrictions are perceived (and therefore often ignored) as the deprivation of the last "pleasure" that patients keep.

(ii) *Body Image.* Issues like skin colour, body odour, loss of urinary function, sexual impotence, internal arteriovenous fistula or peritoneal catheter presence, scars, or abdominal distension help patients to perceive their bodies negatively and with inferiority feeling. And these feelings will limit the social and family relationships, encouraging introversion.

(iii) *Autonomy.* The frequency of dialysis (either HD or exchange sessions in PD) interferes and limits the lifestyle of patients. On the other hand, inferiority feelings facilitate physical deterioration, passivity, neglect, and dependency, often enhanced by the good-intentioned help from patient's family and social environment.

(iv) *The Mental Attitude.* Anxiety is always in the background due to daily contact with the disease and the risk of death. And that anxiety leads to distress, somatisation, obsessive attitudes, depression, aggression, and so forth.

Today, due to scientific and medical advances, patients survive with problems that were deadly time ago, but this survival is often associated with various degrees of disability, causing dependence and a greater need of both medical and social care. The progressive aging of the dialysis population and greater comorbidity is a fact, and the close relationship between HRQOL and mortality score confirms the importance of including quality-of-life markers in the clinical management of patients. Moreover, now patients not only have an expectation to survive but also expect to achieve a certain level of well-being.

3. Measuring Instruments for HRQOL Assessment

As most of the components of HRQOL cannot be observed directly, to quantify this so broad and "confused" term we need measuring instruments such as HRQOL questionnaires. These instruments involve both subjective and objective measures. The subjective assessments involve any aspect of patients' health status that comes directly from the patient without interpretation of the response by a health care provider. The objective assessment of patient status is needed to evaluate the impact of health on quality of life and formulate clinical intervention strategies [1, 3, 4, 7]. The dimensions usually measured by HRQOL questionnaires are

(i) physical function: mobility, self-care, and work,

(ii) emotional Function: well-being, satisfaction, depression, and anxiety,

(iii) social function: social support, family, and social relationships,

(iv) cognitive function: ability to reason, think, concentrate, and remember,

(v) other general or specific symptoms: sleep disturbance, sexual function, energy/vitality, pain, life satisfaction, body image, and so forth.

HRQOL questionnaires were designed and validated for specific populations and cultures, and therefore they need to be adapted to the language and culture in which it will be used, preserving the semantic content and thus leading to the equivalence between the two populations. This process of adaptation must be made according to scientific standards and has a complex but validated methodology. Therefore, the use of free translations of the original questionnaire is considered improper. It is often preferable to use a HRQOL questionnaire adapted to a new one, because in this way not only studies can be made to compare large groups, but also this use will be faster and cheaper.

HRQOL instruments are used for three main purposes: to discriminate between patients with better and worse HRQOL at one time, to assess how much the quality of life has changed between two different time points, and to predict future HRQOL from a current measurement. For accomplishing these purposes, the questionnaires must meet certain requirements to ensure valid and reliable clinical data [1, 3]. These requirements are the following.

(i) *Viability.* The best questionnaire will be useless if its implementation is difficult, costly, and complex for both patient and health professionals. This is why aspects such as simplicity, brevity and clarity of the questions, and ease of completion and correction must be valued.

(ii) *Reliability.* It indicates the degree to which a measurement is free from random error and refers to the degree

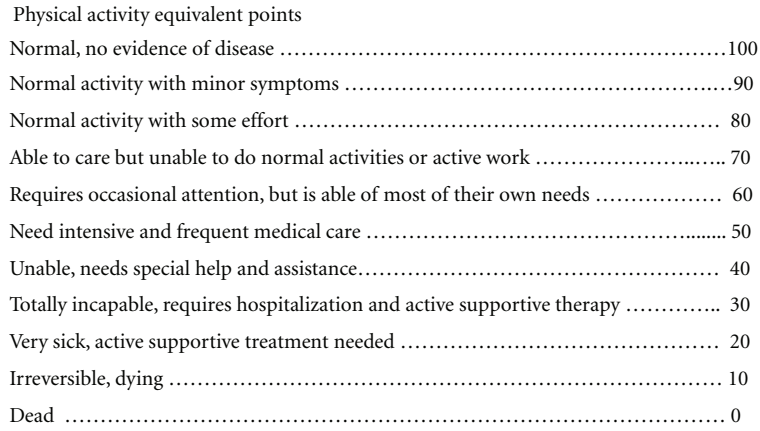


Figure 1: Karnofsky scale physical.

to which they can reproduce the results obtained under constant conditions, even in an extended series of repeated assessments. In addition, it refers to the homogeneity of items comprising the questionnaire.

(iii) *Coverage.* The questionnaire should include all basic dimensions that are important to members of the patient population and susceptible to being affected, positively or negatively, by interventions.

(iv) *Validity.* It measures only what they claim to measure.

(v) *Sensitivity to Change.* It shows the ability to detect and reflect true changes or differences in patient health.

(vi) *Clinical Significance.* The definition of "minimal clinical important difference", which is the rate of change in score of HRQOL questionnaire that should make the medical treatment, will be implanted.

(vii) *Reproducibility.* It shows stability over time, with little variation between intra- and interobservations.

(viii) *Internal Consistency.* All questions in one dimension (physical, emotional, etc.) measure the same concept.

The HRQOL questionnaires can be generic or disease-specific. Generics questionnaires can be broadly used in different diseases and patient groups because they cover a wide range of dimensions of HRQOL, while the disease-specific questionnaires are designed for a population or a disease including the most relevant dimensions for patients affected by a particular condition. Disease-specific instruments are more sensitive to clinical changes but do not allow HRQOL comparisons among patients with different pathologies. The most comprehensive assessment of HRQOL includes an assessment of both generic and disease-specific questionnaires [8].

4. HRQOL Measurement Instruments in Nephrology

The *Generic questionnaires* most commonly used in nephrology are the following.

(i) *The Short Form-36 (SF-36)*. It is a short form of HRQoL scoring system with 36 items forming eight multi-item scale measuring physical functioning, role of physical, bodily pain, general health, vitality, social functioning, and role of emotions and emotional health [7, 9]. It is one of the most commonly used HRQOL questionnaires used in CKD patients with or without maintenance dialysis therapy.

(ii) *Nottinghan Health Profile*. It consists of 38 items to measur 6 dimensions and is widely used because of its simplicity [10].

(iii) *Sickness Impact Profile (SIP)*. It comprises 136 items to measure 12 dimensions [11].

(iv) *The Karnofsky Scale*. It was initially designed for cancer patients and is an ordinal scale ranging from a score 100 (normal state) to 0 (dead) which focuses exclusively on physical functioning and on role of limitations imposed by physical health [12] (see Figure 1).

(v) COOP-WONKA Charts [13] (see Figure 2).

(vi) The Squedule for Evaluation of Individual Quality of Life (SEIQOL). It is an established instrument that seeks to asses QoL on the basis of the domains that patients feel important [5, 7].

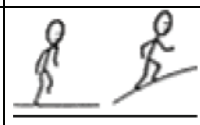
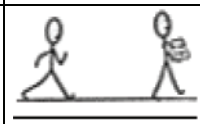
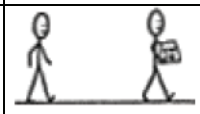
The *specific questionnaires* mostly used for kidney patients are the following.

(i) *Kidney Disease Quality of Life Questionnaire (KDQOL)*. It includes the SF-36 as the generic core, supplemented with multi-item scales targeted at particular concern of patients with CKD and on dialysis [7].

Physical fitness

During the past 4 weeks

What was the hardest physical activity you could do for at least 2 minutes?

Very heavy (for example) - Run, at a fast pace - Carry a heavy load upstairs or uphill		1
Heavy (for example) - Jog, at a slow pace - Climb stairs or a hill moderate pace		2
Moderate (for example) - Walk, medium pace - Carry light load level ground		3
Light (for example) - Walk, medium pace - Carry light load level ground		4
Very light (for example) -Walk, at a slow pace or not able to walk - Wash dishes		5

(a)

Feelings

During the past 4 weeks

To what extent have you been bothered by emotional problems such as feeling anxious, depressed, irritable or downhearted and sad?

Not at all		1
Slightly		2
Moderately		3
Quite a bit		4
Extremely		5

(b)

Daily activities

How difficult has it been for you to do of your usual activities or tasks, both inside and outside the house because of your physical and emotional health?

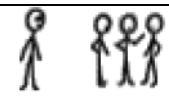
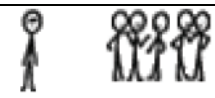
No difficulty at all		1
A little bit of difficulty		2
Some difficulty		3
Much difficulty		4
Could not do		5

(c)

Social activities

During the past 4 weeks

Has your physical and emotional health limited your social activities with family, friends, neighbors, or groups?

Not at all		1
Slightly		2
Moderately		3
Quite a bit		4
Extremely		5

(d)

Figure 2: Continued.

Change in health

How would you rate your overall health now compared to 4 weeks ago?

Much better	++	1
A little better	+	2
About the same	=	3
A little worse	-	4
Much worse	--	5

(e)

Overall health

During the past 4 weeks

How would you rate your health in general?

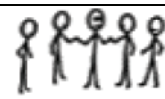
Excellent		1
Very good		2
Good		3
Fair		4
Poor		5

(f)

Social support

During the past 4 weeks

Was someone available to help you if you needed and wanted help? For example if you
- felt very nervous, lonely, or blue
- got sick and had to stay in bed
- needed someone to talk to
- needed help with daily chores
- needed help just taking care of yourself

Yes, as much as I wanted		1
Yes, quite a bit		2
Yes, some		3
Yes, a little		4
No, not at all		5

(g)

Pain

During the past 4 weeks

How much bodily pain have you generally had?

No pain		1
Yes, mild pain		2
Mild pain		3
Moderate pain		4
Severe pain		5

(h)

Figure 2: Continued.

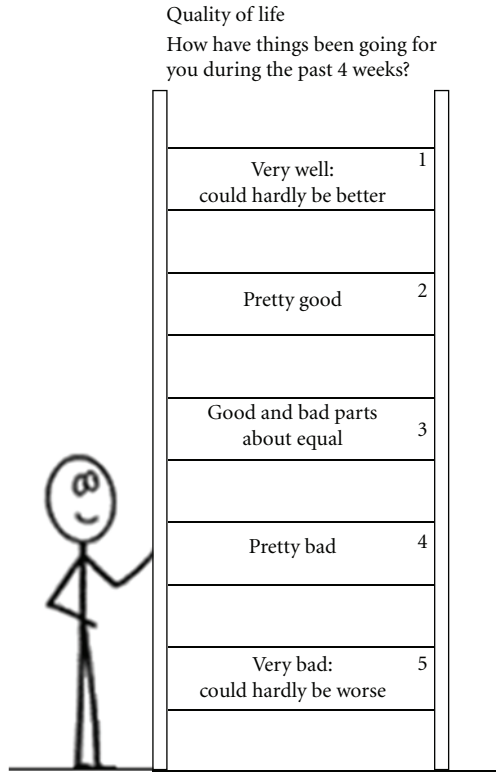


Figure 2: Example of COOP/WONCA charts.

(ii) *KDQOL-SF.* It is a short form of KDQOL that consists of the SF-36 plus a small set of 43 kidney-disease-targeted items. It is the most commonly used.

(iii) *Parfrey Test.* It is a Specific test for patients on hemodialysis and consists of 24 items distributed in two dimensions (physical and emotional) [14].

There is not a specific questionnaire for patients on peritoneal dialysis.

5. HRQOL Studies and CKD

Early HRQoL studies conducted in CKD were published for more than 20 years. Initially served to analyze the quality of life of uremic patients compared with the general population, showing in general lower scores in patients with CKD. The following studies focused on comparing patients on dialysis (any modality) and renal transplant, confirming a better HRQOL in the last, coming to score similar as to that of healthy populations. Most recent studies focus on the hemodialysis population (largest) and those technique and treatment factors that may influence morbidity and mortality of patients.

So, KDQOL-SF has been used in HEMO and DOPPS studies [15, 16]. The HEMO study is randomized multicenter prospective one, which studies the effect of CKD and hemodialysis treatment on quality of life. The DOPPS (Dialysis Outcomes and Practice Patterns Study) is a prospective, multicenter study over a population of 10,000 patients that found an independent relationship between the physical dimension score of the SF-36 and hospitalization and mortality; this relationship was not shown in the mental dimension. The opposite results, however, were observed in the Spanish multicenter study, CALDIVIA, in which the mental dimension was the score that predicted hospitalization and mortality. The CHOICE Health Experience Questionnaire, which has 5 ESRD-specific domains (diet, freedom, body image, dialysis access, and symptoms) added to 8 generic domains in the SF-36 and 8 additional generic domains, is an instrument for measuring heath-related quality of life for patients with ESRD designed to evaluate the effectiveness of alternative dialysis modalities and prescriptions [17].

In general, most of HRQoL studies are observational and do not appreciate the change in HRQOL scores after interventions to improve health status.

6. HRQOL Studies and Peritoneal Dialysis

There are few, and most of them are comparative with haemodialysis, so many of the differences between the two populations reflect different policies for inclusion of patients on peritoneal dialysis [18–21]. Patients who are on peritoneal dialysis for the first time and by own choice tend to have better clinical state (physical, emotional, autonomous, social) maintain longer residual clearance, with the clinical implications that it supposes. Fewer jobs compare manual

and automated peritoneal dialysis. Although *a priori* the automated mode (DPA) should have better HRQOL scores both for the technical characteristics and for the patient's autonomy, this has not been confirmed in recent reviews in which automated peritoneal dialysis has not been shown to provide a relevant improvement in HRQOL compared to manual mode, except in a greater availability of free time [22–25].

Among the studies comparing different modalities of dialysis therapy, we highlight the NECOSAD Study Group's [20] that analyzes the effect of starting dialysis with haemodialysis or peritoneal dialysis modalities on survival adjusted for quality of life, the meta-analysis of Cameron et al. [21] that studies HRQOL of patients undergoing different types of renal replacement therapy and the Diaz-Buxo's [19] report analyzing quality of life in hemodialysis and peritoneal dialysis patients.

Comparing the two types of peritoneal dialysis, we can outline the Van Biesen et al.'s [22] serie and the recent one of Michels et al. that did not find significant differences between the HRQOL in manual or automated peritoneal dialysis, as will as the De Wit et al.'s [23] report which shows only a slight improvement in mental health in patients on automated peritoneal dialysis and the Bro's study in which patients on APD had improved social and family issues and worse scores in the section on sleep.

7. Practical Applications of the Study of HRQOL for PD Patients

From the various studies about HRQoL conducted in different populations of kidney patients, factors with a proven to relationship and affecting the quality of life were identified. Thus, it is shown that the improvement of various parameters of the quality of life of patients was achieved with a better hematocrit. Other factors whose relationship has been confirmed are the predialysis control, the tolerance to dialysis procedure, the psychological situation, and finally sex and age. Treatment of depression, pain, and sleep disorders and changes in the regimen of dialysis therapy have been suggested to have positive effects on HRQOL.

It is obvious that it would be much easier for everyone to translate the results of therapeutic measures of HRQOL to specific therapeutic manoeuvres, but unfortunately, and due to the peculiarities of the concept of quality of life, that is not possible. Many times, the subjective factors, derived or not from actual physical situations, determine the self-concept of quality of life of patients. That is why the results of the questionnaires should be analyzed carefully and thoroughly, dedicating to the discussion with the patient the necessary time to carry out actions aimed at improving the deficient aspects. A recent paper focuses on this subject suggesting that these tests could be applied as a nurse-led case management programme [26].

The measurable parameters (hematocrit, KTV, albumin, etc.) are not always the only ones on which we must depend, and responses to questionnaires of HRQOL can focus on what is more important for the patients. Here are some simple measures applicable to peritoneal dialysis that can benefit many aspects assessed with HRQOL questionnaires.

(i) *Body Image.* A lower insertion of a shorter peritoneal catheter makes it easily concealable even under swimwear; reducing the exchange volume as much as adequacy permits; avoiding the premature loss of residual renal function; giving instructions about skin care and oral hygiene.

(ii) *Physical State.* Controlling the anaemic status, the nutrition, and the possible associated diseases (digestive, vascular, cardiac); starting dialysis sequentially.

(iii) *Work and Social Life.* Accommodating as much as possible the schedules of peritoneal exchanges to the usual scheme of patient's life; offering automated peritoneal dialysis; facilitating alternative schedules of treatment or guidelines for the various social contingencies that may arise.

(iv) *Mobility and Hospital Dependence.* Minimizing hospitalization, spacing periodic controls (telemedicine), facilitating telephone contact, and cooperating with home care services.

(v) *The Self-Care.* Avoiding overload the patients with a "hospitalary method" for their daily care that will constantly remind them of their illness, but without letting them feel abandoned; seeking alternatives to a possible lack of infrastructure to perform the technique: involving the family only just to discourage the feeling of dependency or disability; using the minimum number of exchanges that adequacy permits.

(vi) *The Emotional State.* Maintaining a fluid dialogue between caregiver and patient; discussing all aspects of nephrology treatment; resolving doubts and problems, looking for extrarenal situations that may interfere with the perception of well-being; stopping the progress of any depressive state.

(vii) *Diet.* Reducing as much as possible the diet restrictions ("a little bit of everything, a lot of anything") and making that patient see the reason for the limitations indicated; giving menu suggestions, dietary supplements where necessary, or oral moisturizers to reduce the thirst sensation.

(viii) *Sex, Sleep, and Pain.* Asking patients directly and openly about these issues and trying to alleviate them (and not considering them as "inevitable disease's consequences").

8. Final Comments

After almost 20 years from implementation, HRQOL questionnaires are not used routinely, perhaps because its usefulness is not known, not only in the field of research (analysis after pharmacological or therapeutic interventions, cost-effectiveness assessment of new technologies) but also in the clinical setting (descriptive analysis of population, like

a parameter of clinical quality). K-DOQI Guidelines 2000 recommend, in form of opinion, the periodic assessment of HRQOL of patients in any of the stages of CKD and in the specific population on peritoneal dialysis. Instruments recommended are the SF-36, KDQOL, and COOP-WOKA sheets, advising to always use the same one to improve data analysis over time.

For practical purposes, and while experience is not acquired in handling and interpretation, the Karnofsky scale and CCOP-WONCA sheets are easily applicable instruments: the time spent in filling them is little, they are attractive to patients and easy to evaluate, and their use lights clinical aspects that otherwise would be ignored.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 261040, 5 pages
doi:10.4061/2011/261040

Clinical Study

Effluent Markers Related to Epithelial Mesenchymal Transition with Adjusted Values for Effluent Cancer Antigen 125 in Peritoneal Dialysis Patients

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Received 27 January 2011; Accepted 26 April 2011

Academic Editor: Hulya Taskapan

Objectives. Epithelial mesenchymal transition (EMT) is important for peritoneal deterioration. We evaluated the association between peritoneal solute transport rate (PSTR) and effluent markers related to EMT with adjusted values for effluent cancer antigen 125 (CA125). *Methods*. One hundred five incident peritoneal dialysis (PD) patients on PD for 25 (12–68) months with biocompatible solutions were included in the study. Fast peritoneal equilibration test was used to evaluate PSTR. Effluent hepatocyte growth factor (HGF), bone morphogenic protein-7 (BMP-7), vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), and CA125 at 4 h were measured. *Results*. Patients with dialysate/plasma creatinine $\geqq$0.82 showed significantly higher effluent HGF (240 versus 133 pg/mL, $P < .001$), VEGF, IL-6, and IL6/CA125 levels than the others but no significant differences in effluent HGF/CA125, BMP-7, and BMP7/CA125 were observed. *Conclusion*. Increase in the effluent HGF levels as a compensatory mechanism is a marker of peritoneal deterioration, but controversy remains regarding adjusted value for CA125.

1. Introduction

Resident fibroblasts and infiltrating inflammatory cells are considered to be the main entities responsible for structural and functional alterations in the peritoneum, but recent findings have demonstrated that new fibroblastic cells can arise from the local conversion of mesothelial cells by epithelial-to-mesenchymal transition (EMT) during the inflammatory and repair responses that are induced by peritoneal dialysis (PD) [1]. EMT of peritoneal mesothelial cells is associated with angiogenic stimuli and altered transport through common initiating growth factors and inflammatory cytokines [2, 3]. Hepatocyte growth factor (HGF) and bone morphogenic protein-7 (BMP-7) ameliorate high-glucose-induced EMT of the peritoneal mesothelium [4, 5].

As it is not possible to perform repeated peritoneal biopsies, the search for effluent markers of peritoneal damage and EMT is clinically important. However, the clinical significance of HGF and BMP-7 effluent levels with regard to these conditions remains unclear. It has also been reported that dialysate growth factor levels should be measured relative to the mesothelial cell mass, for example, relative to the level of cancer antigen 125 (CA125) [6, 7]. We evaluated the association between peritoneal membrane transport rate and the expression of effluent markers related to epithelial mesenchymal transition (HGF, BMP-7, vascular endothelial growth factor (VEGF), and interleukin-6 (IL-6)) with adjusting the levels of these markers relative to the effluent CA125 concentration in patients on PD.

2. Subjects and Methods

2.1. Patient Selection. From December 2007 to December 2010, all incident PD patients, aged between 20 and 69, who were being treated at our unit were enrolled in the study ($n = 116$). The patients had been on continuous ambulatory peritoneal dialysis (CAPD) with dual-chamber bags, neutral-pH, and low-GDP glucose-based solutions for more than

6 months and had been clinically stable and peritonitis-free for at least 3 months before the study. Patients on automated peritoneal dialysis (APD) and patients who had received glucose polymer-based peritoneal dialysis solution were also included the study, but they were switched to CAPD with dual-chamber bags, neutral-pH, and low-GDP glucose-based solutions the day before the study. None of the subjects were on PD with conventional acidic PD solutions. The exclusion criteria included severe systemic disease, malignancy, and patients with elevated serum CRP levels. All eligible 105 incident PD subjects were included for this study, and 11 patients were excluded. The ethics committee of Toho University School of Medicine approved this study, and informed consent was obtained from all subjects.

2.2. Study of Peritoneal Transport Kinetics and Effluent Markers. The study was performed cross-sectionally, and on the night before the study, all patients were asked to undergo PD using 2.5% glucose PD solution with a 10 h dwell time. After the dialysis fluid had drained completely, a standard fast peritoneal equilibration test (fast PET) was performed. The drainage volume and ultrafiltration volume were recorded at 4 h.Dialysate to plasma creatinine values (D/P creatinine) and effluent glucose were measured at 4 h, and effluent samples were taken at 4 h and immediately stored at −70°C until they were used to measure HGF, BMP-7,VEGF, IL-6, and CA125.

2.3. Measurement of Effluent Markers. The concentrations of CA125 and IL-6 in the effluent were measured using a chemiluminescent enzyme immunoassay with appropriate kits (Fujirebio, Tokyo, Japan) [8, 9]. The concentrations of VEGF, HGF, and BMP-7 were measured with commercially available immunoenzymometric assays according to the manufacturer's instructions (VEGF and HGF were measured with ELISA kits from Quantikine R & D Systems, Minneapolis, Minn, USA and BMP-7 was measured with an ELISA kit from RayBiotech Inc., Peterborough, UK).

2.4. Statistical Analysis. The data were not in the normal distribution, and nonparametric tests were performed in all analyses. The data are expressed as median values and 25% to 75% interquartile ranges (IQR). Differences between two groups were assessed by the Mann-Whitney U test. Differences considered to be associated with diabetes were assessed using the chi-square test. A P value less than .05 denoted the presence of significant difference.

3. Results

The clinical characteristics and the results of the fast PET in the subjects are shown in Table 1. The median (IQR) age was 55 (44–64) years old, and the median (IQR) PD duration was 25 (12–68) months for all patients. The patients were subdivided into two groups according to their peritoneal transport characteristics to allow statistical evaluations to be performed: the patients with high peritoneal transport rate (D/P creatinine $\geqq$ 0.82) and the "others" (D/P creatinine < 0.82).

Table 1: Clinical characteristics and the results of the fast peritoneal equilibration test.

Group	Patients with high transport rate	Others
n	14	91
Age (years old)	58 (44–68)	55 (46–64)
Diabetics	8/14	22/91
Duration of PD (months)	10 (7–11)**	32 (15–75)
Urine volume (mL/day)	400 (175–624)	100 (0–875)
Drainage volume (mL)	2120 (1963–2260)**	2370 (2265–2450)
D/P creatinine	0.90 (0.87–0.96)**	0.71 (0.60–0.75)
Dialysate glucose (mg/dL)	596 (469–668)**	834 (718–948)
Serum albumin (g/dL)	2.70 (2.69–2.98)**	3.40 (3.03–3.78)

Data are medians with 25 and 75% interquartile ranges in parentheses.
PD: peritoneal dialysis; D/P creatinine: dialysate to plasma creatinine level.
*P < .05 compared with others; **P < .001 compared with others.

There were significant differences between the two groups with regard to the duration of PD (P < .05) and serum albumin levels (P < .001). Furthermore, prevalence of diabetes was higher in the patients with high transport rate than the others, although the difference was not statistically significant (P = .08).

Effluent markers and effluent markers-to-effluent CA125 ratio in patients with high transport rate and others are shown in Table 2. Significantly higher effluent HGF, VEGF, and IL-6 levels were found in the patients with high transport rate compared to the others. No differences were observed in the effluent BMP-7 or CA125 levels between the two groups. With regard to effluent markers-to-effluent CA125 ratio, there was a significant difference only in effluent IL-6/CA125 levels between two groups. No significant differences were observed in effluent HGF/CA125, BMP-7/CA125, and VEGF/CA125 levels between two groups.

4. Discussion

It was reported that solute transfer increases and ultrafiltration declines with time during peritoneal dialysis treatment [10] and that a high transport status is observed after 6 years dialysis treatment and subsequently develops into encapsulating peritoneal sclerosis [11–13]. In contrast with previous reports [10–13], the patients with high transport rate in our study had not undergone PD treatment for a longer period than the other group. Differences between the PD solutions might partly explain the different results since all our patients were treated with new biocompatible solutions whereas the patients in previous reports were treated with conventional nonbiocompatible solutions. However, the patients with high peritoneal transport rate in our study showed a higher prevalence of diabetes and hypoalbuminemia, as reported previously [14–16].

Table 2: Effluent markers and effluent markers-to-effluent cancer antigen 125 ratio in patients with high transport rate and others.

Group	Patients with high transport rate	Others
n	14	91
Effluent HGF (pg/mL)	240.0 (197.5–319.3)***	133.0 (107.0–216.0)
Effluent HGF/CA125 (pg/U)	19.0 (10.8–33.2)	13.7 (8.0–25.9)
Effluent BMP-7 (pg/mL)	8.3 (7.4–9.4)	7.5 (4.8–9.1)
Effluent BMP-7/CA125 (pg/U)	0.6 (0.5–0.8)	0.6 (0.3–1.2)
Effluent VEGF (pg/mL)	33.0 (29.0–34.0)**	25.0 (20.0–31.0)
Effluent VEGF/CA125 (pg/U)	2.5 (1.7–3.7)	2.3 (1.4–3.7)
Effluent IL-6 (pg/mL)	23.8 (13.9–35.1)*	11.6 (6.7–24.0)
Effluent IL-6/CA125 (pg/U)	1.9 (1.3–2.2)*	1.1 (0.6–1.8)
Effluent CA125 (U/mL)	13.3 (7.6–18.9)	11.1 (6.3–20.0)

Data are medians with 25 and 75% interquartile ranges in parentheses.
HGF: hepatocyte growth factor, BMP-7: bone morphogenic protein-7, VEGF: vascular endothelial growth factor, IL-6: interleukin-6, CA125: cancer antigen 125.
*$P < .05$ compared with others, **$P < .01$ compared with others, ***$P < .001$ compared with others.

EMT of mesothelial cells is associated with high peritoneal transport [17]. There is emerging evidence that the mesenchymal conversion of mesothelial cells is an important mechanism for the failure of peritoneal membrane function [18–20]. High levels of glucose, glucose degradation products, a low-PD solution pH, inflammation, and angiotensin II are responsible for the production of transforming growth factor β (TGF-β) and VEGF, which induce EMT, by mesothelial cells [1]. TGF-β is a key regulator of EMT [1, 20]; however, the measurement of TGF-β is not easy because of its low concentration in dialysis effluent fluids [6]. In addition, it is not clear whether measuring the amount of TGF-β protein in peritoneal fluid, in which it is mostly found in an inactive state, that is, bound to a latency-associated protein, is reflective of the tissue levels of active TGF-β [6, 21] and a previous study found no differences in TGF-β at any time in a comparison of patients treated with low-GDP solution and patients treated with high-GDP solutions [6]. VEGF was found to be locally produced in the peritoneal tissue of patients undergoing peritoneal dialysis, and effluent VEGF was found to be correlated with solute transport but not the TGF-β1 level [22, 23].

IL−6 is a cytokine involved in the acute-phase inflammatory reaction, and dialysate IL-6 levels and VEGF concentrations are associated with a high peritoneal solute transport rate [24]. It has also been reported that HGF and BMP-7 ameliorate high-glucose-induced EMT in the peritoneal mesothelium [4]. Furthermore, it was reported that measuring the dialysate VEGF, level relative to the effluent CA125 level revealed a significant association with EMT, whereas unadjusted levels of the growth factor did not [6]. Thus, we studied the relationship between peritoneal transport characteristics and effluent HGF, BMP-7, VEGF and IL-6 levels and their values relative to the effluent CA125 concentration, focusing on EMT in patients being treated with PD using new, biocompatible PD solutions.

Consistent with previous reports, VEGF and IL-6 levels were significantly different between patients with high transport rate and others [24]; however, effluent HGF levels showed bigger difference in these two groups in our study. We considered that using a low-GDP, neutral-pH, dual-chamber bag PD solution also causes EMT since high glucose itself induces EMT in cultured human peritoneal mesothelial cells [4]. According to previous studies, it is conceivable that the mesothelial cells of patients with high transport rate undergo EMT and display decreased production of HGF and BMP-7. However, in our study, the high transport rate group showed increased effluent HGF concentrations. HGF is a heterodimeric molecule composed of a 69 kDa alpha subunit and a 34 kDa beta subunit (Entrez Gene ID: 3082). Its peritoneal permeability is expected to be poor, and so the HGF protein detected in the effluent may be produced locally. Yu et al. demonstrated that human peritoneal mesothelial cells constitutively synthesized HGF [4]. In a previous study, high-glucose-induced EMT in the peritoneal mesothelium was reversed by HGF treatment, suggesting a link between decreased HGF expression and EMT in human peritoneal mesothelial cells [4]. HGF also prevented peritoneal fibrosis in a rat model of EPS [25]. However, Rampino et al. showed that treatment with high-dosage HGF (50 pg/mL) and the HGF released during peritonitis in humans may facilitate repair through mesothelial cell growth, but may also contribute to peritoneal fibrosis including cell detachment, fibroblast-like phenotype changes, and collagen synthesis [26]. These findings suggest that an antifibrotic effect of HGF may be dosage dependent with variable therapeutic dosages that depend on experimental conditions and types of animal model. We considered that unexpected increase in the HGF levels has been proposed as a compensatory mechanism in patients with high peritoneal transport rate. High effluent HGF may be a marker of peritoneal deterioration since high HGF levels coexist with high peritoneal transport rate.

In contrast with Szeto et al.'s report [27], no difference in BMP-7 was demonstrated by the difference in D/P creatinine in our study. Their results showed that the PD effluent BMP-7 level displayed a significant correlation with the change in the D/P creatinine level but was not significantly correlated with the D/P creatinine level at 4 or 52 weeks in new PD patients. However, we only studied the D/P creatinine level in incident CAPD patients at one time point, which may account for our different results. We consider that it is difficult to interpret EMT using measurements of effluent BMP-7 concentrations taken at one time point alone.

The number or mass of mesothelial cells could affect the levels of intraperitoneal growth factors in CAPD patients.

It was reported that the CA125 levels in peritoneal effluent were higher in patients treated with low-GDP solution than in those treated with conventional solution [28]. Do et al. observed differences in dialysate-VEGF/CA125 levels between the low- and high-GDP groups during the initial 12 months, but did not observe any difference in the unadjusted VEGF concentration [6]. From our data, patients with high transport rate displayed higher HGF, VEGF, and IL-6 levels. While, effluent HGF/CA125, and VEGF/CA125 levels were not significantly different between patients with high transport rate and others. Furthermore, IL-6/CA125 effluent level did not show a stronger relation with D/P creatinine than unadjusted IL-6. Breborowicz reported that CA 125 does not a good index of the number of mesothelial cells or their functional properties, because the amount of CA125 released from mesothelial cells is not only depend on the number of cells, but also on their properties, age of cell donor, and environmental factors [29]. We consider that the effluent concentrations of growth factors should be measured relative to mesothelial mass integrity and that the CA125 effluent level may not be a suitable surrogate marker for this purpose.

Our study has certain limitation. The small number of the patients in the high transport group and shorter duration of the PD in this group may affect the results. In conclusion, increase in the effluent HGF levels as a compensatory mechanism is a marker of peritoneal deterioration, but controversy remains regarding the adjustment of markers for CA125.

Conflict of Interests

The authors declare that there is no conflict of interests.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 982854, 9 pages
doi:10.4061/2011/982854

Review Article

Calcific Uremic Arteriolopathy in Peritoneal Dialysis Populations

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Received 1 March 2011; Revised 11 April 2011; Accepted 14 April 2011

Academic Editor: Hulya Taskapan

Calciphylaxis or calcific uremic arteriolopathy is an infrequent complication of end stage kidney disease. It is characterized by arteriolar medial calcification, thrombotic cutaneous ischemia, tissue necrosis often leading to ulceration, secondary infection and increased mortality rates. Current, multimodality treatment involves local wound care, well-controlled calcium, phosphate and parathyroid hormone levels and combination therapy with sodium thiosulfate and hyperbaric oxygen therapy. This combination therapy may be changing the historically poor prognosis of calcific uremic arteriolopathy reported in the literature. Peritoneal dialysis is considered a risk factor based on limited publications, however this remains to be proven. Clinical presentation, diagnosis, pathogenesis and treatment of calcific uremic arteriolopathy in these patients are no different from other patients manifesting with this condition.

1. Introduction

Calcific uremic arteriolopathy (CUA), commonly referred to as calciphylaxis, is an uncommon but increasingly recognized disorder associated with high morbidity and mortality. Although the disorder was first reported in 1898 [1], the term calciphylaxis was coined by Selye in 1962 as a condition of systemic hypersensitivity induced by a sensitizing agent that resulted in metastatic calcification in various organs analogous to anaphylaxis [2].

It is characterized by tender plaques or nodules with violaceous discoloration associated with severe pain that is often refractory to standard analgesia [3]. Historically, CUA has been associated with significant morbidity including debilitating pain, surgical resections, and amputations. More than 50% die within one year of diagnosis, usually due to superimposed sepsis [4]. Approximately 1–4% patients with chronic kidney disease (CKD) manifest CUA, and a recent report estimates a prevalence of 4% in patients with end-stage kidney disease (ESKD) [5]. The pathogenesis of CUA is poorly understood; however, many putative risk factors such as female gender, hyperphosphatemia, hypercalcemia, high calcium phosphorous product [6], use of calcium containing phosphate binders, and hypercoagulable states are reported [6, 7]. Nonuremic CUA is also reported, mostly in the context of primary hyperparathyroidism, malignancy, alcoholic liver disease, or connective tissue diseases [8]. Mineral abnormalities that are postulated in CUA are often absent in these patients suggesting that various factors play a role in its pathogenesis. Peritoneal dialysis (PD) is shown to be a risk factor for CUA in one prospective cohort [9] but has not been subsequently substantiated adequately. Further, the exact mechanism of presumed increased incidence of CUA in PD patients is not well described and in one report was attributed to the use of calcium containing phosphate binders [10]. The introduction of early aggressive therapy with sodium thiosulfate (STS) and hyperbaric oxygen therapy (HBO), in addition to local wound care, calcium, phosphate, and parathyroid hormone (PTH) control, is hoped to improve the

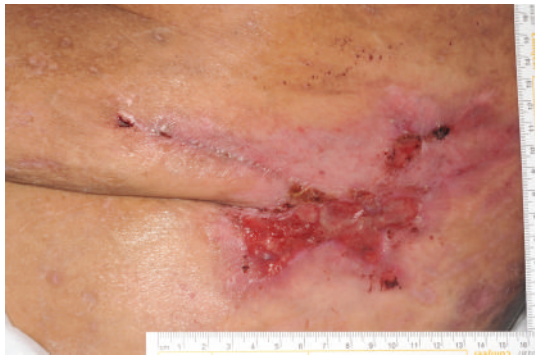

Figure 1: CUA lesion on the lateral abdominal wall with early ulceration, surrounding erythema and induration.

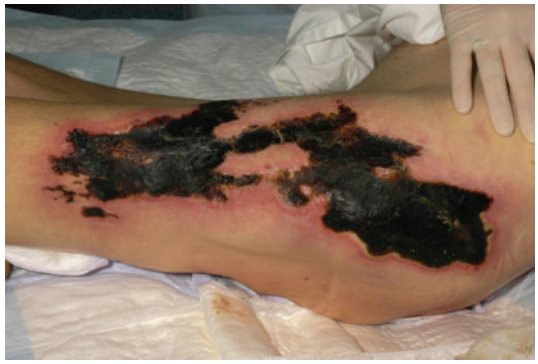

Figure 2: Large CUA lesion of the proximal lower limb with necrotic ulceration.

very poor outcome of this debilitating condition. The aim of this paper is to study the clinical features, pathogenesis and management of CUA in PD patients.

2. Clinical Presentation

CUA is now a well-described entity in the nephrology literature in both hemodialysis (HD) and PD patients. A spectrum of disease has been described (Table 1), most likely representing a continuum dependent on both the underlying severity and the duration of disease.

Early lesions present with localized erythema, skin induration, and associated pain and tenderness, as documented in the cases identified by Fine and Zacharias [10]. Untreated, these lesions tend to progress to become painful plaques with violaceous discoloration and formation of a central eschar. Progression leads to central ulceration (Figure 1) with an expanding border of necrosis (Figure 2) invariably associated with intense pain requiring, and often resistant to, high doses of opioids. Severity of disease has been proposed to correlate with high mortality rate and likely treatment failure.

The distribution of the lesions predominantly involves the lower limbs and the abdomen. Upper extremity [13, 14], breast [13], penis, vulva [16], and cardiac and pulmonary [17] involvement have also been documented. Some authors suggest a distal distribution, in comparison with more proximal, portends a better prognosis [16]. However, this has not been proven.

Radiological investigations support but not confirm the diagnosis. Plain radiographic films of involved soft tissue may demonstrate areas of calcification representative of small vessel calcification. Standard mammography technique of involved soft tissue increases the sensitivity of imaging and is more sensitive than high-resolution-computed tomography [18]. The characteristic mesh-like pattern of arterioles demonstrated in CUA using a mammographic technique was not present in a long-term HD patient when CUA was absent [18].

Histological diagnosis remains the gold standard although it is often avoided for fear of poor wound healing and exacerbating associated ulceration [9]. Histopathologic features are small and medium vessel involvement with circumferential wall calcification involving both the medial and intimal layers. There may be associated intimal hyperplasia with partial obliteration of the vessel lumen. Acute or chronic panniculitis with a relative absence of inflammatory cells is a frequent feature [16]. Fibrin thrombi are often noted and are in close proximity to epidermal and dermal necrosis. Necrosis can extend into the subcutaneous tissue.

3. A Local Cohort of Peritoneal Dialysis Patients with CUA

A retrospective chart analysis from 2007 to 2010 identified 5 PD patients treated for CUA within our centre (Table 2). This represents an annual incidence of 0.97%, with one patient excluded due to referral from outside our local treatment population. An additional 4 HD patients in our centre were identified, not included here, with an annual incidence of 0.75%. Patient characteristics were similar to those documented in the literature (Table 1). Three of five were male, all with hypertension and two with ischemic heart disease. Only one had diabetes and none treated with therapeutic anticoagulation with either heparin or warfarin. Hyperphosphatemia was universal, while two of the five also had hypercalcemia at presentation. Time-averaged phosphate and calcium levels were not available. The average calcium-phosphate product was 5.46 $mmol^2/L^2$. There was a wide range in parathyroid hormone levels (PTH). Of note is a 28-years old female with ESKD secondary to lupus nephritis with suppressed PTH and intact parathyroid glands. Similar presentations have been noted previously with underlying SLE and normal or suppressed PTH [19, 20].

All our patients presented with ulcerative lesions. The margins of ulceration were biopsied and examined by a pathologist who was blinded to clinical severity (Figure 3.) There was no association between the size of involved vessel, maximal degree of luminal narrowing, associated changes including: ulceration, epidermal necrosis, panniculitis, fat necrosis, thrombosis, calcification (septal, lobular, or both), and outcome. Despite patients presenting with ulcerative lesions, outcomes were better than expected from the literature. We suggest the better outcomes are due to a multimodality approach with STS and HBO.

Table 1: CUA cases in PD population described within the literature.

Patient numbers, patient characteristics	PD duration	Clinical presentation	CCa^{2+} (mmol/L)	PO_4^- (mmol/L)	PTH (ng/L)	Treatment	Outcome	Reference
$n = 54$ most female diabetics	> 2 months	73% subcutaneous plaques 95% lower legs (95% bilateral) 5% abdomina l wall	n/a	n/a	n/a	Parathyroidectomy ($n = 6$) Change to HD ($n = 13$) Steroid therapy ($n = 19$)	5 improve 11 improve 3 die within 3 month8 improve 8 no change	[11]
$n = 169$ female HTN, IHD, renal calculi, osteoarthritis, graves thyroid disease, osteoporosis	3 months	Unilateral right calf violaceous lesion 1.5 inch, progressing to bilateral indurated lesions calf and thighs	2.22	2.10	109	D/C caltrate, calcitriol start sevelamer prednisolone STS (IV)	Resistant to all but STS, with improved pain in 2 weeks, and reduced lesion size in 8 weeks	[12]
$n = 126$ female 2 failed transplant not on calcium salts	4 years	Violaceous lesions progressing in 6 weeks to ulcerations of left proximal arm and bilateral thigh	2.4	1.77	89	Prior parathy-roidectomy, initially STS (IV) 2 months STS (IP) 4 months	STS(IV) response but D/C due to N&V. STS(IP) no response and died from sepsis	[13]
$n = 153$ female Moroccan obese, IDDM, IHD, CVA	3 years	Redness right breast progressed to ulcerate Further progressed to bilateral breast and fingertip ulceration. Further progression to thigh	2.7	2.0	1376	Parathyroidectomy mastectomy STS—although very late	Poor response to all. Poor wound healing. Died from sepsis	[14]
$n = 117$ male Afro-American Wegener's granulomatosis (receiving cyclophosphamide and prednisolone) previous warfarin (right atrial thrombus)	3 years	Erythema and swelling bilateral metatarsals, progressed to necrotic feet and fingers, with scintigraphy evidence of widespread disease	2.42	2.68	321	D/C caltrate Sevelamer preexisting Aluminium commenced STS (IV) 3 months HBO Change to HD	Pain relief with STS but lesions progress. HBO did not halt Proceed to bilateral BKA. Change to HD 5x/week and disease healed	[15]

PD: peritoneal dialysis, CCa^{2+}: corrected calcium, PO_4^-: phosphate, PTH: parathyroid hormone, *n*: number, HD: hemodialysis, HTN: hypertension, IHD: ischemic heart disease, D/C: discontinue, STS: sodium thiosulphate, IV: intravenous, IP: intraperitoneal, N&V:, nausea and vomiting, IDDM: insulin-dependent diabetes mellitus, CVA: cerebrovascular accident, HBO: hyperbaric oxygen therapy, and BKA: below knee amputation.

4. Risk Factors

Although many authors have proposed potential risk factors in CUA, its low frequency has restricted analysis design to retrospective case control studies with only one prospective study reported in the PD population [11]. Females are disproportionately represented with Zacharias documenting 75% of cases being female, compared with 53% females in the background PD population [10]. Female predominance has also been observed in HD populations [7]. Diabetes is another potential risk factor in patients with a frequency of 67% in CUA, compared to 29% in PD patients without CUA [9]. This association is not confirmed in the HD population [7].

Fine reported a link between PD and increased risk of CUA with a reported incidence of approximately 4% during

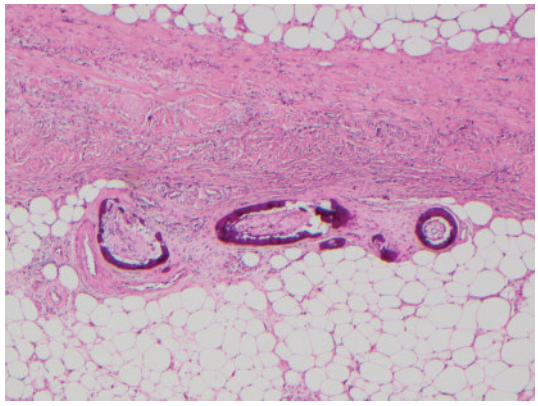

Figure 3: Characteristic biopsy specimen of CUA demonstrating circumferential calcification of small blood vessels with narrowing of the vascular lumen.

the late 1990s, but with a declining incidence during the last decade [9]. However, the literature reports a similar incidence of 4.1% within a HD population [21]. Single-centre studies report the proportion of PD suffering CUA to be higher than the HD population [9]. Supporting the notion of dialysis modality being a contributing factor is the reported therapeutic response in CUA with a change from PD to HD. Reasons for this remain unclear although the constant high levels of phosphate in PD, in comparison with the fluctuations seen in HD, may contribute.

Use of calcium containing phosphate binders during the months preceding CUA onset was suggested to contribute to the incidence in PD patients [10] with the observation of decreasing incidence following the introduction of non-calcium containing phosphate binders [9]. It must be noted that these observations were not controlled for hyperphosphatemia. Hyperphosphatemia was identified as the only significant risk factor in a HD population although the small sample size of nineteen limited the power of this study [7].

Retrospective case-controlled cohort analyses have identified numerous other potential risk factors, including time on dialysis [7], obesity [22], and warfarin use [23], in the development of CUA.

5. Pathogenesis

The molecular biology of intimal and medial vascular calcification is a subject currently attracting considerable interest in the literature and is particularly pertinent to the ESKD population where widespread large vessel, that is, arterial, calcification is common [24]. Small and medium arteriolar vessel calcification, as seen in CUA, is much less common. In the absence of data in CUA, the molecular biology is presumed to be similar [3, 24]. Identifying the stimulus for the development of CUA, and how it selects patients, remains elusive. However, it is unlikely to be a single injury but rather the sum of a variable combination of multiple processes. Pathophysiological mechanisms of established CUA remain largely theoretical. The emergence of possible treatment modalities has sparked interest in research into identification of these mechanisms. Hans Selye [2] hypothesized a "two-hit" mechanism for CUA in a rat model, whereby sensitization with either vitamin D or intact endogenous parathyroid hormone would prime the animal for the development of "calciphylaxis" when injected with either iron preparation or egg white compound.

Disordered mineral metabolism of the calcium, phosphate, and parathyroid axis is almost universally assumed to play a role in CUA. An association between osteoporosis or osteopenia and vascular calcification has been well documented [24], although this is restricted to large vessel calcification. Available literature does not confirm a causative relationship between disordered mineral metabolism and CUA, possibly due to heterogeneity and lack of well powered prospective studies.

Hyperphosphatemia induced vascular smooth muscle cell (vSMC) mineralization and transition from contractile smooth muscle to an osteochondrogenic phenotype expressing osteopontin, Cbfa-1/Runx2, alkaline phosphatase, and osteocalcin in *in vitro* studies (Figure 4) [24]. Similar expression markers have been identified in human CUA biopsy samples [25]. Long-term exposure to hypercalcemia at levels similar to that seen in ESKD-induced mineralization of cultured human smooth muscle cells [26]. Hypercalcemia induced increased expression of the type III sodium dependent phosphate cotransporter, Pit-1 [26]. In the presence of both hyperphosphatemia and hypercalcemia mineralization was dramatically enhanced.

The final common pathway of the varying mechanisms is the expression of nuclear factor κ-B (NFκB), a nuclear transcription factor, through the complex interaction of receptor activator of NFκB (RANK), its ligand (RANKL) and antagonist to the ligand, osteoprotegerin (OPG) [27]. Increased expression of NFκB promotes extraosseous mineralization and decreases osseous mineralization. OPG underexpression results in osteoporosis and vascular calcification, while increased expression results in an osteopetrosis phenotype [27]. The therapeutic mechanism of bisphosphonate therapy in CUA may be explained by its inhibition of the RANK/RANKL interaction [27]. This pathogenic mechanism does not, however, explain the higher incidence in the female and obese populations, where oestrogen, in the former, and leptin, in the later, increase OPG levels resulting in an expected protective effect.

Other proteins have been implicated in vascular calcification in the ESKD population. Fetuin-A or alpha-Heremans-Schmid glycoprotein (ASHG) has been demonstrated to inhibit ectopic calcification in knockout mice [28]. ASHG levels have been demonstrated to be low within both HD [29] and PD populations. Interestingly, low ASHG levels were also shown to be a predictor of mortality and cardiovascular death [28]. A second protein, matrix Gla protein (MGP) has been shown to regulate medial calcification, which develops spontaneously in knock-out mice [30]. MGP requires vitamin K as an activating cofactor, thereby providing a mechanism of involvement for warfarin, by depleting vitamin K. Supporting the role of these two proteins is the observation of low MGP and ASHG levels in a HD population, with a negative correlation to time-averaged phosphate levels [31].

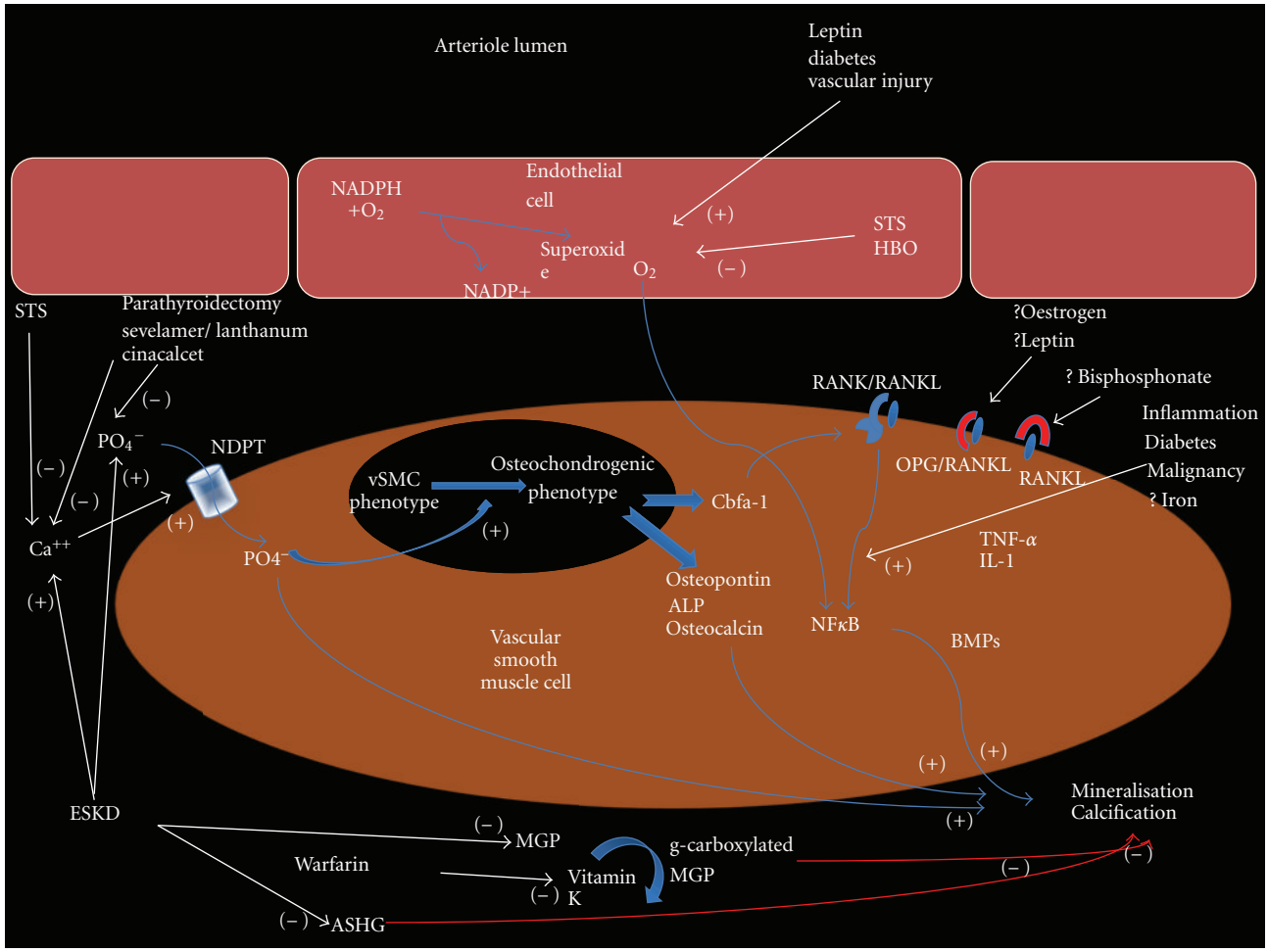

Figure 4: Schematic representation for the pathogenic mechanisms of CUA development and the potential sites of action for therapeutic intervention, where (+) indicates augmentation and (−) indicated inhibition; STS, sodium thiosulfate; HBO, hyperbaric oxygen; PO_4^-, phosphate; Ca^{++}, calcium; NDPT, sodium-dependent phosphate cotransporter (Pit-1); vSMC, vascular smooth muscle cell; Cbfa-1, core-binding factor alpha 1; NFκB, nuclear factor κ−B; RANK(L), receptor activator of NFκB (ligand); OPG, osteoprotegerin; TNF-α,tumour necrosis factor alpha; IL-1 interleukin 1; BMP, bone morphogenic protein; ESKD, end-stage kidney disease; MGP, matrix G1a protein; ASHG, α-2 Heremans-Schmid glycoprotein.

Iron deposition may also be involved in the development of CUA. Farah identified iron deposition in all the analyzed biopsy specimens of their series of CUA [32]. Eleven had iron deposited within the affected vessel wall and iron around the vessel wall only in the twelfth [32]. No iron deposits in areas unaffected by CUA were seen in any biopsies. Whether iron deposition is a cause, a consequence, or an unrelated association remains to be determined. Calcific narrowing of small and medium vessels provides the milieu for additional processes that may ultimately culminate in the development of CUA [27]. Associated thrombosis can develop secondary to low blood flow rates through narrowed arteriolar lumens [27]. Ahmed proposes a second mechanism, whereby vSMCs sloughed into the lumen aggregate to form thrombus [33]. Local small and medium vessel luminal thrombus in addition to vessel lumen narrowing, promotes ischemia and secondary necrosis. Systemic procoagulant states may also increase the risk of CUA development through enhanced thrombus development.

Local and systemic inflammatory mediators are thought to potentiate the development of CUA. Chronic dialysis and diabetes are known to be associated with increased levels of proinflammatory mediators, such as tumor necrosis factor alpha, Interleukin-1 and Interleukin-6 which can result in endothelial disruption promoting local thrombosis and necrosis in addition to potentiation of NFκB stimulating further vessel calcification [3, 27]. Such mechanisms may explain the possible increased risk of CUA in diabetic populations and with local minor trauma such as with insulin and erythropoietin injections.

6. Treatment of CUA

6.1. General Measures

6.1.1. Local Wound Care. There is some evidence to support surgical debridement of the wounds [27, 34]. The opposing point of view is that debridement can increase the extent of

Table 2: CUA cases within our local PD population.

Patient characteristics	PD duration	Clinical presentation	CCa^{2+} (mmol/L)	PO_4^- (mmol/L)	PTH (ng/L)	Treatment	Response to treatment
79 yo female ESRD (? cause) HTN, IHD, PVD, dyslipidemia, depression	9 years CAPD	Painful bilateral foot ulceration	2.64	2.16	598	D/C calcium carbonate and calcitriol Started cinacalcet and aluminium OHSTS (IV) 3 monthsIntensive PD—change to HD	With STS and change to HD lesions resolvedDied 7/12 after resolution of lesions. Withdrawal of HD for functional decline
67 yo male ESKD (FSGS) IHD, HTN, dyslipidemia, OSA, BPH, GORD	7 months CAPD	Painful red violaceous ulceration right calf: Multiple indurated lesions on thighs and bilateral calf	2.42	2.61	1386	Started cinacalcet. Parathyroidectomy and STS (IV) 6 months commenced at same time. Caltrate and calcitriol not stopped due to hungry bone	Complete resolution of lesions including ulceration. Died 18 months later with ischemic CCF not for intervention
75 yo male ESKD (DM/ obstructive) DM, IHD, dyslipidemia, CVA, GORD, HTN, gout	7 months CAPD	Ulcerations right anterior lower leg, initially presumed DM ulcers	2.73	1.73	132	D/C calcium carbonate. Started sevelamer, cinacalcet, aluminium OHHBO + pamidronate + Intensive PD STS (IV) 5 weeksPD changed to HD while on STS	No response to change in phosphate binders. Pain relief gained while on STS but no wound healing. Ulcers began to heal off STS after HD initiated. Died secondary to sepsis
74 yo male ESKD (ADPKD) PVD, HTN, gout, ex-smoker	3 years CAPD	Painful ulceration of left shin, superimposed infection	2.45	2.28	38	Prior Parathyroidectomy. STS (IP) 12 weeks + HBO for 5 days. PD changed to HD after 2nd PD peritonitis	Complete response was documented. STS complicated by 2 episodes PD peritonitis and was D/C
28 yo female ESKD (SLE) AIHA, Epilepsy, HTN	27 months CAPD	4 painful ulcerating lesions left lower leg medial and posterior	2.42	1.90	8.54	Started sevelamer. STS (IP) 3 months −25 g was reduced to 12.5 g for nausea. HBO 30 treatments	Complete response, with durability to 2 years. Remaining on PD

PD peritoneal dialysis, CCa^{2+} corrected calcium, PO_4^- phosphate, PTH parathyroid hormone, ESRD (aetiology), HD haemodialysis, HTN hypertension, IHD ischemic heart disease, PVD peripheral vascular disease, CAPD continuous abdominal PD, D/C discontinue, STS sodium thiosulphate, IV intravenous, IP intraperitoneal, OSA obstructive sleep apnoea, AIHA autoimmune hemolytic anemia, DM diabetes mellitus, CVA cerebrovascular accident, and HBO hyperbaric oxygen therapy.

the nonhealing ulcer surface. The use of antibiotics is limited to obvious bacterial infection rather than colonization.

6.1.2. Nutrition. CUA is most often painful and associated with depression which both impact the nutritional state. Necrotic tissues reduce appetite, possibly through the release of cytokines. Adequate analgesia with nonsteroidal anti-inflammatory drugs and opioids without significantly affecting quality of life is important, as is supportive psychotherapy.

6.1.3. Cessation of Warfarin. Warfarin inhibits matrix GLA metalloproteinases, thus promoting vascular calcification. Based on this molecular mechanism, stopping warfarin with vitamin K reversal has become a common practice despite scant clinical evidence [23]. Substitution with low molecular weight heparin (LMWH) is a reasonable long-term management strategy, where anticoagulation is mandated. Therapeutic bridging from warfarin to LMWH with monitoring of Factor Xa levels is performed in those with mandated therapeutic anticoagulation. Conditions such as atrial fibrillation necessitate and individualized decision, recognizing traditional risk benefit ratios demonstrated in the general public cannot be generalized to the dialysis population [35]. Management is determined by the balance of risk of stroke or thrombosis, ability to administer and monitor LMWH,

patient preferences and risk of LMWH, including the cumulative risk of precipitating new CUA lesions through endothelial damage from subcutaneous injections [3].

6.2. Vitamin K Administration. Regular administration of Vitamin K has not been investigated. Through the γ–carboxylation of MGP, Vitamin K administration may have a therapeutic benefit [36] although likely small.

6.3. Lowering the Calcium Phosphorus Product

6.3.1. Substitution with Non-Calcium Containing Phosphate Binders Like Sevelamer and Lanthanum Carbonate May Be Beneficial [27, 37]. Change of dialysis prescription to: intensified PD, extended hours of HD or daily HD has been shown to be beneficial in some patients [38]. Changing to HD from PD has been trialed in the past with dramatic improvement in some patients and not in others [11].

6.3.2. Reduction of Elevated PTH Levels. The relationship of CUA with hyperparathyroidism is best seen in the nonuremic population [8]. There are also reports of ulcer healing, pain relief and survival benefit in patients on dialysis with CUA and hyperparathyroidism who undergo parathyroidectomy [39]. Medical treatment of hyperparathyroidism with cinacalcet, a relatively recent option, was reported to be beneficial [40]. Our local practice is surgical parathyroidectomy in the presence of uncontrolled hyperparathyroidism, that is, hormone levels greater than seven to nine times the upper limit of reference range (CARI guidelines [41]). Cinacalcet is used in those who are not surgical candidates.

6.4. Emerging Treatment Options

6.4.1. Sodium Thiosulfate (STS). STS acts as a chelating agent for calcium and iron and also as a potent antioxidant resulting in decreased vasospasm and pain along with solubilization and decalcification of the deposits [42, 43]. STS can be given orally [40], intravenously (IV) [12] or intraperitoneally (IP) [13]. There is no consensus on the best dosing schedule and STS is given at varying regimes, including 7.5 g/week orally [40], 12.5 g [44] to 25 g IV or IP three times a week. Intravenous STS can cause abdominal cramping, nausea, vomiting, and diarrhea if infused rapidly [45]. Acidosis and hypocalcemia have been reported [46]. We used STS in all our PD patients with CUA. In three patients, we administered STS IV and converted them to HD. However we left the last two patients on PD and administered 12.5 g of STS in 2 litres of the long dwell dialysate, three times a week. One patient developed bacterial peritonitis after one week of therapy, which was treated according to the International Society of Peritonitis Dialysis guidelines and continued on IP STS and PD. Two months later, he presented again with culture negative peritonitis raising the possibility of chemical peritonitis. He also developed tremors and we stopped IP STS due to concern over STS causing these side effects. The second patient received STS IP for 3 months uneventfully and there was a complete healing of skin lesions. The optimum dose and duration of treatment with STS is yet to be determined.

6.4.2. Hyperbaric Oxygenation Therapy (HBO). This modality is increasingly used for its benefits of better tissue oxygenation, improved angiogenesis, and enhanced phagocytic activity and bactericidal action in tissues with CUA and hypoxemia driven injury [47]. Ulcers heal in 40% to 75% of treated patients [48, 49]. Reported side effects are barotrauma, reversible myopia and neurological complications from oxygen toxicity [50]. Logistical constraints may limit its use as HBO may not be available in all centers, necessitating transfer of patients to a unit with such facilities.

6.4.3. Combination Therapy. Aggressive therapy with a combination of all these modalities, including HBO and STS, in early lesions is likely to promote healing through multiple pathways [47]. Treatment using this approach in our PD population resulted in healing of skin lesions of all cases despite aggressive presentations.

6.4.4. Bisphosphonate Therapy. Bisphosphonates have an anti-inflammatory action and inhibit osteoprotegerin mediated calcification [51]. Despite bisphosphonates current product information contraindication in ESKD, case reports have document benefit with their use in CUA [52, 53]. Data to guide safe dosing of bisphosphonate therapy in ESKD is absent, hence routine use in this population cannot be recommended.

Due to increasing success with combination therapy of STS and HBO, our unit reserves bisphosphonate use for last line therapy. The decision to use bisphosphonate should include the bone metabolism status; however, the high mortality in CUA often supervenes a concern of later development of adynamic bone disease. The emergence of more accurate markers of bone turnover such as C-telopeptide and N-terminal propeptide of collagen type I may better guide our use in the future but would require investigation prior to routine use.

7. Conclusions

The clinical features of CUA in PD patients, the diagnosis, and possible pathogenetic mechanisms are comparable to other patient groups with CUA. The risk association of PD with CUA requires confirmation. Aggressive therapy with combination STS and HBO, in addition to general measures, may reduce morbidity and mortality in PD patients with CUA. Treatment of CUA in PD patients does not differ from other patient groups except for the intraperitoneal route of administering STS.

Further prospective studies are needed to clearly identify the risk factors, to describe the pathophysiology, in particular the differences from atherosclerosis seen in large arteries, and to define and standardize therapy. Adequately powered randomized studies will be difficult to conduct due to the low incidence of disease and the high associated mortality causing hesitancy and ethical consideration in randomization to

a control group. Recently, international CUA registries have been established to promote knowledge of CUA and progress therapeutic strategies:

(i) Germany: Calciphylaxie Register, International Collaborative Calciphylaxis Network (http://www.calciphylaxie.de/),

(ii) USA: Calciphylaxis Registry, KU Medical Center, University of Kansas (http://www2.kumc.edu/calciphylaxisregistry/),

(iii) UK: UK Calciphylaxis Registry, International Collaborative Calciphylaxis Network (http://www.calciphylaxis.org.uk/).

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 542704, 6 pages
doi:10.4061/2011/542704

Clinical Study

Low-Protein Diet Supplemented with Keto Acids Is Associated with Suppression of Small-Solute Peritoneal Transport Rate in Peritoneal Dialysis Patients

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Received 27 February 2011; Accepted 1 May 2011

Academic Editor: Hulya Taskapan

Objective. We investigate whether low-protein diet would show benefits in suppressing peritoneal transport rate in peritoneal dialysis (PD) patients. *Methods.* This is a supplemented analysis of our previously published trial, which randomized 60 PD patients to receive low- (LP: dietary protein intake of 0.6–0.8 g/kg/d), keto-acid-supplemented low- (sLP: 0.6–0.8 g/kg/d with 0.12 g/kg/d of keto acids), or high- (HP: 1.0–1.2 g/kg/d) protein diet and lasted for one year. In this study, the variations of peritoneal transport rate were assessed. *Results.* While baseline D/P_{cr} (dialysate-to-plasma concentration ratio for creatinine at 4 hour) and $D/D0_{glu}$ (dialysate glucose at 4 hour to baseline dialysate glucose concentration ratio) were similar, D/P_{cr} in group sLP was lower, and $D/D0_{glu}$ was higher than those in the other two groups ($P < 0.05$) at 12th month. $D/D0_{glu}$ increased ($P < 0.05$), and D/P_{cr} tended to decrease, ($P = 0.071$) in group sLP. *Conclusions*. Low-protein diet with keto acids may benefit PD patients by maintaining peritoneum at a lower transport rate.

1. Introduction

Since peritoneal equilibration test (PET) was introduced in 1987 [1], high transporters have been reported to show poor clinical outcomes [2, 3], which are due to fluid overload [4], inflammation [5], or malnutrition [6], and so forth. Peritoneal characteristics were determined by several factors including genetic factors, peritoneal membrane anatomy, effective surface area, age, and uremia, which contribute to the heterogeneity of peritoneal membrane function at the onset of PD [7–10]. Except those inherited high transporters, it was observed that peritoneal transport rate increased with the time of treatment on PD [7]. During the PD process, repeatedly exposure to inflammatory stimuli such as glucose-based solutions and peritonitis episodes may lead to persistent increase of peritoneal transport rate [11].

Many studies explored methods to prevent patient from to be high transporters, thus preserve peritoneal function. Recently, an interesting study found that a strict low-protein diet (0.37 ± 0.05 g/kg/d) during the predialysis period may suppress peritoneal transport rate at induction of PD [12]. However, it is unknown whether low-protein intake during PD would show benefits on peritoneal transport rate maintenance. Since the current PD guidelines recommend high-protein intake of no less than 1.2 g/kg ideal body weight (IBW)/day [13], very few clinical practice could answer this question. Based on what we have found in our recent published paper [14, 15], DPI of 0.6–0.8 g/kg/d resulted in neutral nitrogen balance, maintained good nutritional status, and improved plasma amino acids pattern in PD patients if together with keto acid during 12 months of followup. We, therefore, further assessed the effect of dietary intervention

on peritoneal transport rate by analyzing PET results at baseline and 12th month in the original PD cohort.

2. Methods

2.1. Study Design. The study population and methodology have been previously described in detail [14, 15]. Briefly, 60 PD patients with residual renal function (urine output ≥800 ml/d or eGFR ≥2 ml/min/1.73 m^2) who fitted the inclusion criteria were enrolled and randomized to low- (LP: DPI of 0.6–0.8 g/kg IBW/d), keto-acid-supplemented low- (sLP: DPI of 0.6–0.8 g/kg IBW/d with keto acids of 0.12 g/kg IBW/d, Ketosteril; Fresenius Kabi Co., Ltd., Beijing, China), or high- (HP: DPI of 1.0–1.2 g/kg IBW/d) protein group in the original study. The total energy intake (TEI), including both from diets and PD glucose [16], was prescribed as 35 kcal/kg IBW for patients below 60 years of age and 30 kcal/kg IBW for the rest.

During the 12 months of followup, 7 patients dropped out, thus, 53 patients finished the study (18 in group LP, 18 in group sLP, and 17 in group HP) and were analyzed in the present study. PET was performed at baseline and 12th month as described by Twardowski et al. [1] using 2 liters of 2.5% dextrose solution for a 4-hour dwell. The dialysate-to-plasma concentration ratio for creatinine at 4 hours (D/P_{cr}) and dialysate glucose at 4 hours to the baseline dialysate glucose concentration ratio ($D/D0_{glu}$) were calculated. D/P_{cr} was used to classify the patients as high, high average, low average, or low transporters [1]. The estimated peritoneal glucose exposure was calculated from the dialysis prescription as described by Davies et al. [17]. For example, for a patient dialyzed by 4∗2 L exchanges (2∗1.5%, 1∗2.5%, and 1∗4.25%), daily peritoneal glucose exposure would be 2∗30 + 1∗50 + 1∗85 = 195 g.

During followup, angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin II receptor blockers (ARBs) were applied to all the patients to control hypertension. Amino acids and other nutritional supplements were avoided, and aminoglycosides were forbidden for patients with residual renal function when infection occurred during followup.

2.2. Statistical Analysis. Results are presented as mean ± SD or median (interquartile range). Differences across groups were assessed by ANOVA or Kruskal-Wallis test as appropriate. Post hoc analysis was done using methods of Student-Newman-Keuls (S-N-K) for ANOVA or Dunnett's T3 for Kruskal-Wallis test. Comparisons between time periods were performed using paired t-test or Wilcoxon's paired test. Comparisons of numeration data were performed using the Chi-square test. A P value <0.05 was considered statistically significant. All analyses were carried out with SPSS 11.0 for windows statistical software (SPSS Inc., Chicago, Ill, USA).

3. Results

3.1. Baseline Data. Baseline data of the 53 patients were shown in Table 1. Briefly, there were no significant differences in any of the assessed parameters between the groups, except that C-reactive protein (CRP) level was slightly higher in group sLP than group LP (7.8 [3.0–15.0] versus 3.0 [1.0–4.2] mg/l, $P < 0.05$).

3.2. Dietary Compliance and Comorbidities. As we previously reported [14], DPI differed significantly during the whole period between group sLP and the others ($P < 0.05$). Group LP achieved a significantly lower protein intake than group HP in months 6 and 10. TEI was similar among the three groups during the study ($P > 0.05$).

During the study, 8 peritonitis episodes occurred in the 53 patients (2 in group LP, 4 in group sLP, and 2 in group HP, $P = ns$). While CRP level at baseline was slight higher in group sLP than group LP, it was similar among the three groups at 12th month (LP: 3.1 [3.0–3.2] mg/l, sLP: 3.1 [3.1–3.9] mg/l, and HP: 3.2 [3.1–6.4] mg/l, $P = ns$).

3.3. Peritoneal Transport Rate. Figure 1 shows data of D/P_{cr} and $D/D0_{glu}$ in the three groups at baseline and 12th month. While baseline D/P_{cr} and $D/D0_{glu}$ were similar among the three groups, at 12th month in group sLP, D/P_{cr} was significantly lower (sLP: 0.59 ± 0.09, LP: 0.70 ± 0.09, and HP: 0.66 ± 0.12, $P < 0.05$) and $D/D0_{glu}$ was higher (sLP: 0.49 ± 0.08, LP: 0.42 ± 0.06, and HP: 0.43 ± 0.11, $P < 0.05$) than the other two groups.

During 12 month followup, $D/D0_{glu}$ increased ($P < 0.05$), and D/P_{cr} intended to decrease ($P = 0.071$) in group sLP. Changes of both D/P_{cr} and $D/D0_{glu}$ in group sLP were more noticeable than the other two groups during followup ($\Delta D/P_{cr}$: sLP: −0.04 [−0.13, 0.05], LP: 0.04 [−0.06, 0.14], and HP: 0.03 [−0.02, 0.12], $P < 0.05$; $\Delta D/D0_{glu}$: sLP: 0.05 [0.01, 0.10], LP: −0.03 [−0.11, 0.06], and HP: −0.04 [−0.10, 0.05], $P < 0.05$).

Table 2 shows distribution of peritoneal transport rate classified by D/P_{cr} among the three groups. At baseline, all of three groups showed similar peritoneal transport rate distribution ($P = 0.559$). At 12th month ($P = 0.175$), the peritoneal transport rate distribution in group sLP showed a borderline difference from group LP ($P = 0.060$), and HP ($P = 0.088$), which indicated that fewer patients in group sLP, had higher peritoneal transport rate after 12 months followup.

3.4. Dialysis Dose and Glucose Exposure. As shown in Table 3, baseline PD dosage and PD glucose exposure were equal among the three groups. During followup, patients in both groups LP and HP tended to increase their PD dosage, while those in group sLP kept stable. PD glucose exposure in both group LP and HP increased significantly (LP: 100 ± 31 to 114 ± 27 g/d; HP: 110 ± 25 to 129 ± 37 g/d, $P < 0.05$ for both), while in group sLP it kept stable (sLP: 107 ± 18 to 109 ± 22 g/d, $P > 0.05$), which in turn leads to markedly lower glucose exposure in group HP than group sLP at 12th month ($P < 0.05$).

4. Discussion

In this supplemented analysis of a prospective randomized trial, we found that in stable PD patients, low-protein diet

Table 1: Baseline data of the 53 PD patients, grouped according to the diet that they asre randomized to.

	Group LP ($n = 18$)	Group sLP ($n = 18$)	Group HP ($n = 17$)
Age (year)	52.5 ± 13.7	56.3 ± 11.5	50.4 ± 12.3
Gender (male : female)	6 : 12	9 : 9	10 : 7
Diabetic nephropathy (yes/no)	1/17	1/17	1/16
BMI (kg/m^2)	21.1 ± 2.1	22.3 ± 3.0	22.2 ± 3.3
Height (cm)	161.8 ± 8.1	163.7 ± 7.7	164.2 ± 6.1
Kt/V_{total}	2.4 ± 0.6	2.2 ± 0.3	2.4 ± 0.4
PD duration (month)	5.6 (1.3–14.2)	11.8 (3.8–20.9)	5.5 (1.3–14.2)
Urine protein (g/d)	0.7 (0.4–1.5)	0.7 (0.5–1.3)	1.0 (0.4–1.4)
Urine volume (ml/d)	1444 ± 460	1153 ± 409	1208 ± 378
e-GFR ($ml/min/1.73\,m^2$)	4.3 ± 2.4	3.7 ± 2.2	4.5 ± 2.4
Ultrafiltrational volume (mL/d)	0 (−240, 200)	130 (70, 610)	300 (−150, 425)
Serum CRP (mg/l)	3.0 (1.0–4.2)	7.8 (3.0–15.0)*	3.1 (2.8–6.4)
Serum albumin (g/l)	36.1 ± 3.2	37.4 ± 4.2	38.3 ± 2.8

Note: $^*P < 0.05$, compared with group LP. PD: peritoneal dialysis; BMI: body mass index; e-GFR: estimated glomerular filtration rate, calculated as an average of the creatinine and urea clearances by 24-hour urine; CRP: C-reactive protein.

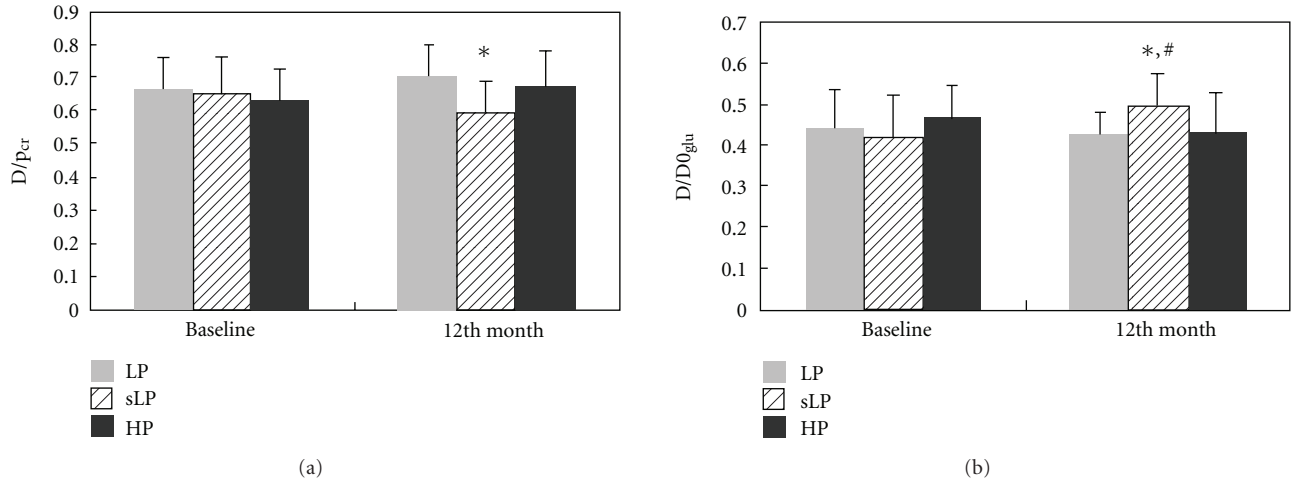

Figure 1: Peritoneal equilibration test (PET) results in the 53 PD patients, grouped according to the diet that they are randomized to during 12 month followup. (a) shows D/P_{cr} (dialysate-to-plasma concentration ratio for creatinine at 4 hours). (b) shows $D/D0_{glu}$ (dialysate glucose at 4 hours to baseline dialysate glucose concentration ratio). $^*P < 0.05$, compared with the other two groups. $^{\#}P < 0.05$, compared with baseline.

supplemented with keto acids seemed to impact peritoneal characteristics. Indeed, after 12 months of followup, patients on supplemented low-protein diet showed declined D/P_{cr} and elevated $D/D0_{glu}$ compared with patients on either high-protein diet or low-protein diet alone.

As peritoneal membrane function of solute clearance and water removal is the basic rationale of PD therapy, preservation of peritoneal function is critically important. It is generally accepted that avoidance of repeated peritonitis and control of inflammation are favorable to peritoneal transport rate maintenance [5, 18]. Blockades of the rennin-angiotensin-aldosterone system could mitigate peritoneal inflammation and fibrosis, thus preserve peritoneum function [19]. Some studies also found that residual renal function could contribute to peritoneal function maintenance [5]. However, there are certain amount of publications reporting the elevated transport rate with the time on PD [7]. According to recent reports, the increasing use of automated PD [20] and icodextrin-based PD solutions [21] could partly overcome problems caused by fluid overload and improve the clinical outcome among high transporters. Continuous ambulatory peritoneal dialysis (CAPD) by dextrose solutions is, however, the most widely used PD form in developing countries such as China. Thus, studies on suppressing peritoneal transport rate are still highly warranted.

Low-protein diet has been advised for predialysis patients as it shows effects in controlling uremic symptoms, retarding renal function loss [22, 23], and postponing the initiation of dialysis [24] by lowering the requirements for renal nitrogen clearance and/or reducing proteinuria [25, 26]. Low-protein diet among predialysis patients may suppress peritoneal transport rate at induction of PD which was

Table 2: Comparison of peritoneal transport rate distribution classified by D/P_{cr} among the 3 groups at baseline and 12th month.

	Group LP ($n = 18$)		Group sLP ($n = 18$)		Group HP ($n = 17$)	
	Baseline	*12th month*	*Baseline*	*12th month*	*Baseline*	*12th month*
H	1	4	2	0	0	1
HA	9	7	7	6	8	9
LA	8	7	9	9	7	6
L	0	0	0	3	2	1

Table 3: Changes of PD dose and PD glucose exposure in the 53 PD patients, grouped according to the diet which they are randomized to during 12 month followup.

		Group LP ($n = 18$)	Group sLP ($n = 18$)	Group HP ($n = 17$)
PD dose (L/d)	*Baseline*	6.0 ± 1.5	6.7 ± 1.2	6.8 ± 1.2
	12th month	6.4 ± 1.1	6.7 ± 1.2	7.2 ± 1.0
PD glucose exposure (g/d)	*Baseline*	100 ± 31	107 ± 18	110 ± 25
	12th month	$\mathbf{114 \pm 27}^{\#}$	$\mathbf{109 \pm 22}$	$\mathbf{129 \pm 37}^{*,\#}$

Note: $^{*}P < 0.05$, compared with group sLP. $^{\#}P < 0.05$, compared with baseline.

recently reported by Hasegawa et al. [12]. In the present study, we further confirm that low-protein diet during PD therapy benefits patients regarding peritoneum preservation. The exact mechanisms to explain this phenomenon are not clear. One possible explanation is that low-protein diet is associated with decreased expression of fibrotic factors such as transforming growth factor-beta (TGF-β) [27]. In fact, we found that compared with the patients in group sLP, those in the other two groups increased their PD dose and exposed to more hypertonic solutions during 1 year of followup. The increment use of bio-incompatible solution was reported to stimulate the releasing of fibrotic or inflammatory factors [28] and resulted in increased peritoneal transport rate [29]. Secondly, uremia itself may also impact peritoneal transport rate [30]. Low-protein diet reduces uremic wastes such as urea, phosphate, and so forth, in either predialysis patients [24] or PD patients [14], and, in turn, protects peritoneal membrane. On the other hand, the beneficial effects of residual renal function on peritoneal function maintenance have been reported by different studies [5, 31]; therefore, better preservation of residual renal function in group sLP [14] seems to be another explanation supporting current results.

In addition, there are several other factors which may be also involved in. It is well known that peritonitis episodes [18] and inflammation [5] play an important role in the increment of peritoneal permeability. Interestingly, patients in group sLP maintained peritoneal membrane function better during 12 months of followup in our study, even though their baseline CRP level was significantly higher than others. The potential role of keto acids in peritoneum preservation cannot be completely excluded in group sLP. Furthermore, high transporters usually have greater albumin loss through peritoneal cavity [32], which is conceptually analogous to microalbuminuria in diabetic patients [33]. Though the present study did not investigate peritoneal protein loss; however, we observed the decrement of urine protein output in patients receiving keto-acid-supplemented low-protein diet. The prescription of sLP may also suppress peritoneal protein leakage in these patients.

There are several limitations in the present study that need to be discussed. Firstly, the sample size of the study was relatively small, and data of peritoneal transport rate as only available on two time points, lack of data on protein loss and TGF-β levels in dialysate, as it is only a supplemented analysis for our previous study. Secondly, the patients in group LP did not manage their DPI consistently to the prescribed range. Thus, we cannot differentiate in current study whether beneficial effect on peritoneal function comes from low-protein diet or the use of keto acid. Nevertheless, our data provides a new clue for peritoneum preservation among PD patients.

In summary, our results showed that low-protein diet (DPI of 0.6–0.8 g/IBW kg/d) supplemented with keto acids may benefit PD patients by maintaining peritoneum at a lower transport rate.

Conflict of Interests

Qiang Yao is now employed by Baxter Healthcare.

Acknowledgments

The study is supported by research grants from Shanghai Municipal Education Commission (jdy10070), Shanghai Jiaotong University School of Medicine (YZ1037), Renji Hospital (RJPY10-014), and Baxter, China. The authors thank Ms Aiping Gu, Ms Chunhua Hu, and Miss Yiqian Cang for their kind assistance.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 239515, 5 pages
doi:10.4061/2011/239515

Review Article

In Peritoneal Dialysis, Is There Sufficient Evidence to Make "PD First" Therapy?

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Received 19 January 2011; Revised 6 April 2011; Accepted 20 April 2011

Academic Editor: Hulya Taskapan

Since its introduction more than 3 decades ago, the use of peritoneal dialysis (PD) has increased greatly due to its simplicity, convenience, and low cost. Advances in technique, antibiotic prophylaxis, and the introduction of newer solutions have improved survival, quality of life, and reduced rate of complications with PD. In Hong Kong, approximately 80% end-stage renal disease (ESRD) patients perform PD; in others, that is, Canada, Australia, and New Zealand, 20%–30% patients use PD. However, in the United States, the annual rate of prevalent patients receiving PD has reduced to 8% from its peak of 15% in mid-1980s. PD as the initial modality is being offered to far less patients than hemodialysis (HD), resulting in the current annual incidence rate of less than 10% in USA. There are many reasons preventing the PD first initiative including the increased numbers of in-center hemodialysis units, physician comfort with the modality, perceived superiority of HD, risk of peritonitis, achieving adequate clearances, and reimbursement incentives to providers. Patient fatigue, membrane failure, and catheter problems are other reasons which discourage PD utilization. In this paper, we discuss the available evidence and provide rationale to support PD as the initial renal replacement modality for ESRD patients.

1. Introduction

Over half million Americans were undergoing renal replacement therapy (RRT) for ESRD at the end of year 2008. In-center Hemodialysis (HD) and home PD are the two common forms for dialysis therapy. Only about 8% of patients with ESRD are receiving PD as RRT in the United States compared to Canada and Europe, where PD is much more common [1]. The percentage PD patients has declined significantly from the peak of 15% in the mid-eighties to 5.8% in 2007 [1]. There are numerous factors contributing to the low incidence and prevalence of PD in this country [2, 3]. Concerns regarding achievement of adequate clearance with PD, especially in patient with no residual renal function and a perception of better patient survival on HD compared to PD amongst US nephrologists impact selection of dialysis modality. Risk of infectious complications, specially PD peritonitis and catheter-related problems contribute to the selection bias. Systemic factors such as the easy accessibility to HD, financial incentives, and ownership of dialysis units, including units owned by large dialysis organization (LDOs), as well as physician education and exposure to PD during training also play an important role in the selection of RRT for ESRD patients. Strategies to prevent peritonitis, ultrafiltration failure, managing catheter-related complications, and improving adequacy of dialysis as well as education of patients and medical staff may all help with increasing PD utilization.

2. Why PD before HD?

Along with improved survival, other long-term goals of ESRD patients are to improve quality of life, preserve residual renal function, and reduce morbidity. Many young ESRD patients will likely receive PD, HD, and renal transplantation at different points over their lifetime. Better survival on PD compared to HD during first two years of dialysis treatment is one of the compelling reasons to start patient on PD first. In the last decade, infection-related complications are higher and appear to be increasing in HD patients, whereas such complications are steadily declining in PD patients [1]. Preservation of residual renal function and vascular access

sites, lower cost of therapy, convenience of home therapy, a flexible schedule, and increased freedom from the patient's perspective are other reasons to offer PD as the first choice modality.

3. Survival Advantage

Comparisons of mortality outcomes in HD and PD patients in studies have yielded conflicting results. Vonesh et al. analyzed the Medicare data of 398,340 patients initiating dialysis between 1995 and 2000. They showed survival differences between HD and PD varied substantially according to the underlying cause of ESRD, age, and level of baseline co morbidity. The adjusted mortality rates were either the same or higher for HD as compared to PD in most patient groups except in older diabetic patients [4]. Heaf and colleagues reported survival benefit for PD during the first two years of dialysis treatment from the Danish Terminal Uremia registry data [5]. Similar survival benefits were reported from Canadian cohort of dialysis patients initiating dialysis between 1990–1994 [6]. However, among CHOICE cohort, Jaar et al. reported no difference in the mortality risk during first year but significantly higher mortality risk for patients undergoing PD relative to HD during second year [7]. The CHOICE study has been criticized for collection of data after dialysis initiation, recruitment bias and data analysis. Mehrotra et al. examined the US Renal Data System (USRDS) for secular trends in survival among patients treated with HD and PD on day 90 of ESRD (HD 620, 020 patients; PD 64 406 patients) in three 3-year cohorts (1996–1998, 1999–2001, and 2002–2004) for up to 5 years of follow up. Authors reported higher risk of death seen with PD in earlier cohorts which improved with time and there was no significant difference in the risk of death for PD and HD patients for the 2002–2004 cohorts during 5-year followup. Subgroups analysis based on age, diabetes status, and baseline comorbidity showed greater improvement in survival among patients treated with PD relative to HD at all follow-up periods [8]. In a separate study of 66,381 PD patients, comparing 1996–1998 cohorts to 2002–2004 cohorts, the risk of death and switch to HD were 45% and 38% lower, respectively, in the later cohort [9]. Researchers compared mortality rates between patients treated with PD and HD (including home HD) using data from 27,015 patients in the Australia and New Zealand Dialysis and Transplant Registry. Overall mortality rates were significantly lower during the 90- to 365-d period among those being treated with PD at day 90 (adjusted hazard ratio [HR] 0.89; P .001) [10]. Five-year survival on dialysis has improved significantly in last one decade. However, survival probabilities were improved more for patients on PD compared to HD. For incident patients on hemodialysis or peritoneal dialysis, survival probabilities in 1998–2002 were 7.2 and 14.8 percent higher, respectively, than in 1993–1997 [1]. The improvement in survival for diabetics was 12.9 and 21.8 percent for HD and PD, respectively. Similarly for patients with hypertension, the improvement was 4.0 and 13.2 percent for HD and PD, respectively [1]. In contrast to a common belief that survival on PD is inferior as compared to HD, the converse is actually the case for most patient groups, particularly in the first few years of dialysis. Although the rates of native AVF are lower in PD patients, it has not translated into inferior survivals and it would be prudent to protect the veins of a PD patient specially those who are not a transplant candidate [11].

4. Preservation of Residual Renal Function

Residual renal function (RRF) is clinically important as it contributes to adequacy of dialysis, quality of life, and mortality in dialysis patients. Rate of decline in RRF is a more powerful prognostic factor than baseline RRF associated with all-cause mortality in PD patients [12]. Loss of RRF reduces small and middle molecular weight toxin clearance, decreased erythropoietin synthesis and increase sodium, phosphorus, and water retention [13]. These can lead to anemia, malnutrition, congestive heart failure, cardiac hypertrophy, atherosclerosis, vascular, and valvular calcification; and overall increase in cardiovascular morbidity and mortality [13]. In a study Moist et al. showed that PD had 65% lower risk of loss of RRF compared to HD during first year of RRT in incident ESRD patients [14]. Maintenance of RRF has shown direct correlation with patient survival. In a prospective observational study involving 231 chronic PD patients, Wang and colleagues reported 50% reduction in all-cause mortality and cardiovascular death for every 1 ml/min increase in residual GFR [15]. It is imperative to periodically measure both the delivered dose of PD and RRF and make necessary adjustments to the dialysis prescription as RRF is lost. Efforts to maintain RRF with use of biocompatible PD solutions and treatment with ACE inhibitors should be considered [16].

5. Lower Infection and Hospitalization Rates

After cardiovascular disease, infection is the most common cause of death in dialysis patients accounting for 33 deaths per 1000 patient years in the USRDS cohort of 2001–2003 [1]. In a single-center observational cohort of dialysis patients ($n = 181$; HD 119 and PD 62) from 1999 to 2005, as expected only HD patients had bacteremia (0.16/year) and PD patients had peritonitis (0.24/year), the investigators however did not find any difference ($P = .24$) in the rates of overall infection between HD and PD patients [17]. According to USRDS data from 2007, the rates of admission for bacteremia/septicemia were 1.5–2.3 times higher in HD patients reaching 102 per 1000 patient years compared to 66.7 per 1000 patient years in PD patients [1]. Comparing HD to PD as initial RRT modality, HD patients are at twice as higher risk of hospitalization from septicemia than PD patients. In another longitudinal cohort of incident dialysis patients with seven years of followup, the adjusted risk of death from septicemia was almost double in HD patients compared to PD patients (9.79 versus 4.81, $P < .01$) [18]. Since the introduction of twin bags and Y set system and use of "flush before fill" technique, the rates of PD peritonitis have gone down significantly over the last few years. Use of Gentamicin cream application at exit site reduces the

occurrence of both S Aureus and gram negative infections, including pseudomonas, and should be applied as a best practice [19].

6. Quality of Life and Patient Satisfaction

PD offers home-based therapy, thus there is no need to go to dialysis unit three times per week and no time spending in dialysis unit. Most PD patients pay visit to see their physician once a month. PD offers a flexible schedule with opportunities to travel and participate in other activities. Patient satisfaction is better amongst PD patients as compared those on HD [20]. In CHOICE cohort researchers surveyed 736 new dialysis patients from 37 centers regarding their satisfaction with treatment. Patients receiving PD were much more likely than those receiving HD to give excellent ratings of dialysis care overall and significantly more likely to give excellent ratings for each specific aspect of care rated. The differences between peritoneal dialysis and hemodialysis patient satisfaction persisted even after adjustment for patient age, race, education, health status, marital status, employment status, distance from the center, and time since starting dialysis [21].

7. Better Graft Survival in Transplant Patient

It would be preferable to start ESRD patients waiting for renal transplant on PD; especially ones with live donors. In a case-control study the incidence of delayed graft function was less, and the drop in serum creatinine was faster in continuous ambulatory peritoneal dialysis (CAPD) patients compared to HD patients. No differences in surgical complications or infections were observed between CAPD and HD patients [22]. One study reported high graft thrombosis with PD and high acute rejection episodes in HD patients but overall graft survival was similar [23]. While another study reported that the choice of pretransplant dialysis modality did not influence waiting time for transplant or the results of transplantation [24]. A study from the United States suggested that the use of PD immediately before transplantation predicts a 3% lower risk for graft failure ($P < .05$) and 6% lower risk for recipient death ($P < .001$). Better recipient and graft survival was noted when patient received at least 50% of their pretransplant RRT time as PD [25].

8. Economic Issues

Per Center for Medicare and Medicaid, the cost difference between HD and PD was $13,900 in 2001. Though the costs of both modalities have increased over years, the difference in cost has also increased to $20,000 in 2009 [1]. Per person, per year cost for HD was $73,008 versus $53,446 for PD [1]. Until recently in the US, there was a fixed "composite rate" for dialysis-related services and in addition providers were also reimbursed for "injectable" medications (such as erythrocyte stimulating ages, intravenous iron, and vitamin D analogues) on an "as used" basis. On an average, PD patient uses less intravenous medications than in-center HD patient which contributes to higher cost of HD.

Shih et al. evaluated the impact of initial dialysis modality choice and subsequent modality switches on Medicare expenditure in a 3-year period involving 3423 patients with new initiation of dialysis. After adjusting for patient characteristics, the annual Medicare expenditure was significantly lower for patients with peritoneal dialysis as the initial modality (56,807 dollars versus 68,253 dollars) ($P < .001$). "Peritoneal dialysis, with at least one switch" and "hemodialysis, with at least one switch" had a lower or similar annual expenditure of $66,639 and $72,335, respectively [26]. In a recent cost comparison study of 463 dialysis patient with 12% of PD patients, the rate of hospitalization was less in PD patients compared to HD patients in the year following initiation of dialysis and had significantly lower health care cost over 12 month period. ($173,507 versus $129,997, $P = .03$) [27].

9. Achieving Solute Clearance

As with HD, the clearance of small solutes has been thought to be an important predictor of survival in PD patients. The Canada-USA (CANUSA) study examined the relationship between dialysis adequacy and mortality, hospitalization, and technique failure in PD patients. According to this study results, a decrease of 5 L/1.75 m^2 in creatinine clearance per week was associated with a 7% increase in relative risk of death. Also, a decrease of 0.1 units Kt/V per week was associated with a 5% increase in the relative risk of death. Based on these results, NKF-DOQI guidelines suggested a weekly Kt/V of 2.0 and weekly creatinine clearance of 60 L/1.73 m^2 for PD patients. These Kt/V and creatinine clearance were difficult to achieve in large and anuric patients. However, the CANUSA study assumed that renal and peritoneal clearances were similar and additive [28]. The ADEMEX study showed that increasing peritoneal small solute clearance achievable in clinical practice did not improve survival in PD patients [29]. In a study from Hong Kong, Lo et al. showed that there was no difference in outcome for patients with Kt/Vurea maintained above 2.0 versus Kt/Vurea between 1.7 and 2.0 [30]. Reanalysis of CANUSA data showed no association between peritoneal clearance and the relative risk of death. Based on these results, the 2006 NKF-DOQI guidelines suggested a minimum weekly Kt/Vurea target of 1.7 for PD. These lower adequacy targets are easier to achieve in practice and have not translated in inferior outcomes.

10. Adequate Ultrafiltration and Volume Control

Inability to achieve adequate ultrafiltration and failure to maintain volume homeostasis is another cause of technique failure in PD patients. Prevalence of ultrafiltration failure is reported to be between 1.7% and 13.7% [31]. Failure to follow fluid and dietary sodium restrictions necessitates use of more hypertonic solution to achieve adequate ultrafiltration. Use of hypertonic glucose solution can lead

to hyperglycemia, weight gain, and hyperlipidemia. Furthermore, chronic exposure to hypertonic solutions which degrade into AGEs may alter peritoneal membrane transport characteristics, converting a low transporter into high transporter [32]. In two different PD cohorts—one from Netherlands and one from Japan—failure of ultrafiltration was the biggest reason for withdrawal from CAPD [33, 34]. However, in these both cohorts the major modality was CAPD and Icodextrin was not used. Icodextrin is a glucose polymer that may be used as an osmotic alternative to dextrose in PD solutions. In a Japanese cohort of greater than 7000 patients, Kuriyama et al, showed that the dropout rate in patients who used Icodextrin (8.9%), was significantly lower than those using dextrose (14.5%), ($P < .0001$) [35]. Newer biocompatible solutions without dextrose, and having a more physiologic pH have been associated with better preservation of peritoneal membrane; however, most human studies done with biocompatible solutions had short followup duration and clear evidence of benefit is lacking [36, 37]. Mechanical complications like catheter malposition or malfunction are also known to cause failure of ultrafiltration. Many causes of catheter malfunction such as occlusion by bladder or bowels can be corrected with use of laxatives or emptying the bladder. Obstruction due to clots can be dislodged with injecting heparinized saline; and if unsuccessful, by instillation of TPA or urokinase in the catheter. Common mechanical problems of omental trapping, adhesion formation, and so forth can be corrected through laparoscopic means by performing omentopexy, adhesiolysis, resection of epiploic appendices, colopexy, and so forth [38].

11. Education Is Important

Adequate understanding and education of patient and nephrologists are key to improve utilization rates of PD. In dialysis centers with limited knowledge and experience in performing PD, the recommendation "PD first" can lead to poor outcomes. Along with the education of physicians and medical staff, patients with chronic kidney disease approaching ESRD should be educated about kidney failure and renal replacement therapies. The National Pre-ESRD Education Initiative involved 15,000 patients from 932 referring nephrologists between 1997 and 2001. Upon completion of the program 55% chose hemodialysis, while 45% chose peritoneal dialysis, suggesting important influence of predialysis education on selection of modality of treatment [39].

Low prevalence of PD leads to inadequate exposure of in-training fellows to this modality. This in turn leads to vicious cycle in which uncomfortable nephrologists not offering PD to their patient and further reducing its use. To offset these concerns, the training programs must provide fellows adequate exposure to PD. Programs with limited access should offer fellows elective rotation in centers with larger PD population and have a core curriculum for PD including text and visual aids.

In conclusion, there is sufficient evidence to support the initiative of PD first and with improving PD techniques, greater use of biocompatible solutions, improved patient and physician education, and the bundling of dialysis services, providers will be more receptive towards the PD first initiative.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 470426, 4 pages
doi:10.4061/2011/470426

Research Article

Peritoneal Dialysis Penetration and Peritonitis Rate at a Single Centre during Last Decade

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Received 31 January 2011; Revised 6 April 2011; Accepted 19 April 2011

Academic Editor: Paul Tam

Peritoneal dialysis (PD) has been intensively offered at our centre to patients (pts) with end-stage renal disease (ESRD) from 2000, and the number of PD pts was noticed to raise. We aimed to analyse the PD population from the aspect of penetration and peritonitis rate during eleven years. Cumulative number of new RRT pts was 378 during the study period. We found high PD penetration rate: 53% (range 32–72%). The rate of peritonitis was as high as 9.8 during first study years, but it has declined progressively last year being 29.1 by September 2010 and 21.7 by December 2010. Most cases of peritonitis were due to gram-positive pathogens. We have demonstrated steady high single-centre PD penetration rate and improvement of management of patients during last decade probably because of the result of better pts education and a continued dedication of the staff.

1. Introduction

Penetration of peritoneal dialysis varies widely across the world. It ranges from about 80% in Hong Kong and Mexico to few percentage points in the United States and some developing countries [1–5]. Peritoneal dialysis appears to have some excellent properties as a first-line renal replacement therapy (RRT) [6]. The use of dialysis and transplantation as complementary therapies for RRT is well established in our country. RRT data at December 31, each year have been reported regularly to European Dialysis and Transplantation Association Registry [7] and detailed epidemiologic data available in Annual Report of Kidney Diseases in Estonia 2009 [8]. According to reports, the incidence and prevalence of RRT patients in our country remains lower than that reported from the other European countries. The incidence of RRT has a decreasing tendency during last three years in the country being 62.7 pmp at day 91 in 2008 [7]. Peritoneal dialysis (PD) was introduced to the clinical practice already 17 years ago at our university hospital which is the second largest centre in the country. Since 2000, after structural changes at our centre when nephrology division was connected with dialysis unit, we started to intensively offer PD treatment to every patient with end-stage renal disease (ESRD) without contraindications for PD, and the number of PD patients raised sharply. The number of peritoneal dialysis patients have been the highest in the country compared with other centres [8]. According to the Annual Report PD, patients formed 47% from dialysis prevalence patients at Tartu University Hospital at the end of 2009, whereas the percentage was lower in other centres: 21% at West-Tallinn Hospital and 44% at North-Estonia Regional Hospital [8]. Peritonitis remains a significant problem in peritoneal dialysis. It is the leading cause of technique failure in peritoneal dialysis. Therefore, we aimed to analyse our PD population in a single-centre cohort study with respect to penetration and peritonitis rate during last decade.

2. Materials and Methods

The report is based on retrospective data from patient's records, and comparable whole country data were obtained from Annual Report of Kidney Diseases 2009. PD penetration rate was defined as the percentage of new patients on PD in relation to all new dialysis patients each year. PD penetration rate, peritonitis rate, and microbiology of peritoneal fluid have been analysed for all pts in our program since 2000. In conjunction with epidemiological research study in the country, we recently expanded the

data set where individual RRT patients data together with clinical performance indicators (CPI) at the end of each year have been collected and analyzed beside the basic RRT epidemiological data collection. In the current investigation, we demonstrate our single centre PD patients CPIs that characterize anaemia, calcium phosphate, and lipids mean patients group levels. The following biochemical parameters (using the Hitachi 912 Analyzer until 2004 and COBAS INTEGRA 800 after 204) were studied: serum creatinine (S-Crea, μmol/L), serum albumin (S-Alb, g/L), C-reactive protein (CRP, mg/L), serum-ionized calcium (S-i-Ca, mmol/l), serum total calcium (S-total Ca, mmol/L), and serum phosphate (S-P, mmol/L). Studied lipid profile was the following: serum total cholesterol (S-Chol, mmol/L), serum HDL cholesterol (S-HDL chol, mmol/L), serum LDL cholesterol (S-LDL chol, mmol/L), and serum triglyceride (TG, mmol/L). Parathyroid hormone (PTH, pmol/L) levels were determined by immunoanalyzer IMMULITE 2000 using chemiluminescence method. Haemoglobin (Hgb g/L) levels were measured by photometric method. Peritonitis was defined as turbid fresh dialysis effluent containing polynuclear leukocyte cell count higher than 100/mm^3. Peritonitis rate was calculated as number of peritonitis episodes per number of patients-months. For the isolation of the organisms, blood culture media was used (BACTEC Microbiological Culture Analyzer). Two thirds of patients were on Baxter DUO connection system, and one third of patients remained on Fresenius stay-safe system.

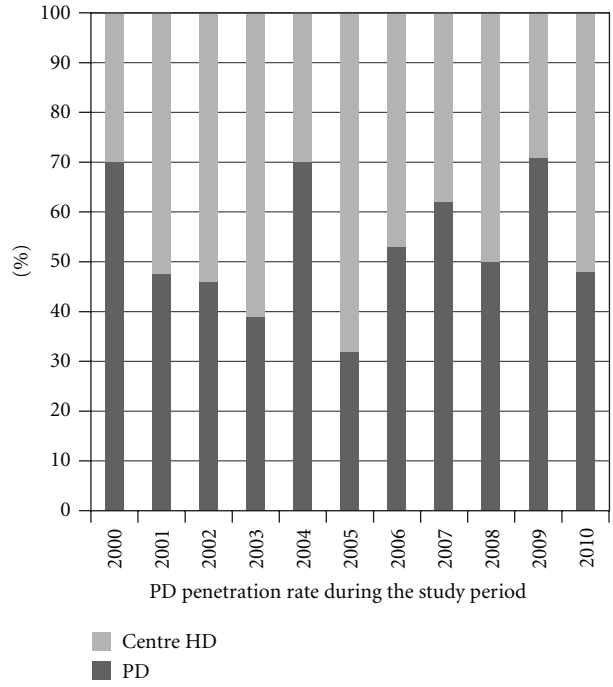

Figure 1: Peritoneal dialysis penetration rate at the Tartu University Hospital 2000–2010.

3. Results and Discussion

The retrospective study was carried out at the Department of Internal Medicine of Tartu University. Cumulative number of new RRT patients in our centre who started peritoneal dialysis between January 2000 and December 2010 was 378. Mean age of all incidence dialysis patients was 58.8 years in 2010 with male predominance of 57%. Demographic data are comparable with country RRT incidence data showed in Annual Report of Kidney Diseases 2009. According to the Report, the mean age of incidence patients was 60.5 years, percentage of males 58%. Diabetes is the main cause of ESRD in new dialysis patients in Estonia [8]. Table 1 shows the main causes of ESRD patients at our centre and comparable data of whole country. Because of small numbers, our centre incidence patients diabetes diagnosis percentage differs from year to year being still high every year.

Figure 1 showed the percentage of mean peritoneal dialysis penetration rate which was 53% (range 32–72%) in our centre during the eleven year-study period. With these results, we demonstrate a steady peritoneal dialysis penetration rate during long period. In our opinion, this is because of better patients education and a continued dedication of the staff. It is important that patients and nurses are well educated in the practice of peritoneal dialysis. Similarly, in other long-term studies, many centres report higher penetration rate after essential improvement of local skills [1–3].

Clinical and laboratory data are demonstrated in Table 2. Results show that many of our peritoneal dialysis patients have overweight, increased inflammatory status, hypoalbuminemia and dyslipidemia. Inflammation and dyslipidemia accelerate atherosclerosis and are often present in peritoneal dialysis patients [9, 10]. Normal range of haemoglobin according to guidelines [11] was found in our study patients.

Arterial calcification is common in adults with chronic kidney disease and progresses with time. On the other hand, peritoneal calcification, one of the major complications, can develop in peritoneal dialysis patients [12]. Therefore, the management of secondary hyperparathyroidism and avoidance of peritonitis should be important aims of the treatment. We found that, although, calcium and phosphate levels were almost in normal range, mean PTH was increased in our patients (Table 2). We conclude that further improvement of the management of mineral metabolism and secondary hyperparathyroidism as well as body composition measurements and calcification diagnostics are needed at our centre to avoid serious complications described by many authors [12–15].

Peritonitis remains a major complication in patients undergoing peritoneal dialysis and remains a major cause of patients discontinuing peritoneal dialysis and switching to haemodialysis. However, technique survival at year 1 has been almost 100% at our center during last years. Because of short period and small numbers survival, data are not included and will be shown separately. Our study analyzed peritonitis rate and pathogens responsible for the peritonitis. The incidence of peritoneal dialysis-related peritonitis was as high as 1 episode every 9.8 months in 2004, but it has progressively declined during the last years being 29.1 in September 2010 and 21.7 at the end of the year (Table 3).

Table 1: Aetiology of chronic kidney disease in dialysis incident and prevalent patients at Tartu University Hospital during 2008–2010 and in Estonia in 2009.

	Incident RRT pts at TUH, N (%)	Incident PD pts at TUH, N (%)			Prevalent PD patients in Estonia, N (%)*			Incident RRT pts at TUH, N (%)	Prevalent PD patients at TUH, N (%)
Diagnosis	2010	2008	2009	2010	2008	2009	2010	2009	2009
Diabetes mellitus	4 (14)	4 (25)	9 (33)	1 (7)	6 (22)	13 (32)	7 (20)	30	24 (33)
Hypertension	5 (17)	0 (0)	5 (19)	2 (14)	4 (15)	8 (20)	5 (15)	14	18 (25)
Glomerulonephritis	5 (17)	2 (12)	3 (11)	2 (14)	5 (19)	6 (16)	6 (18)	13	6 (8)
Chronic pyelonephritis	7 (24)	5 (32)	4 (14)	5 (37)	6 (22)	8 (20)	8 (23)	19	12 (16)
Polycystic kidney disease	2 (7)	2 (12)	1 (4)	2 (14)	3 (11)	1 (2)	2 (6)	3	3 (4)
Other	6 (21)	3 (19)	5 (19)	2 (14)	3 (11)	4 (10)	6 (18)	21	10 (14)

* Data from Annual Report of Kidney Diseases in Estonia 2009.
Abbreviations: TUH, Tartu University Hospital; RRT, renal replacement therapy; PD, peritoneal dialysis; N, number.

Table 2: Clinical and laboratory mean data in prevalent peritoneal dialysis patients group at the end of year 2010.

Variables	PD pts group mean	SD*	Min	Max
Patients total **n = 34**				
BMI (kg/m^2)	28.8	1.1	19	43.6
Haemoglobin (g/L)	113.4	2.6	94	157
S-creatinine (μl/L)	705.5	45.6	316	1112
S-albumin (g/L)	34.3	0.9	19	42
C-reactive protein (mg/L)	9.5	1.5	1	32
S-ionized calcium (mmol/L)	1.2	0.0	1.0.	1.4
S-total calcium (mmol/L)	2.4	0.0	1.7	2.8
S-phosphate (mmol/L)	1.8	0.1	0.6	4.4
PTH (pmol/L)	52.2	10.9	1.6	197
S-total cholesterol (mmol/L)	5.7	0.2	3.0	7.8
S-HDL cholesterol (mmol/L)	1.2	0.1	0.6	1.8
S-LDL cholesterol (mmol/L)	3.9	0.2	1.9	6.2
S-triglycerides (mmol/L)	1.9	0.2	0.8	5.4

* SD- standard deviation.

Table 3: Peritonitis rate at Tartu University Hospital.

Year	2004	2006	2008	2010*	2010
Pts total nr	42	46	45	42	45
Pts nr at the end of the year	29	34	27	35	34
Treatment months	354	303	409	408	500
Peritonitis nr	36	19	19	14	23
Peritonitis rate (episodes/nr pts-months)	9.8	16	21.5	29.1	21.7
Peritonitis rate (episodes/pts-year)	1.2	1.3	1.8	2.4	1.8

* January–September 2010.

Table 4: Etiology of peritonitis at Tartu University Hospital.

Pathogen	2009-2010, N (%)	2006-2007, N (%)
Coagulase-negative staphylococci	21	15
Staphylococcus aureus	11	10
Streptococci	2	6
Gram-positive rod-shaped bacteriae	5	3
Enterococci	4	2
Enterobacteria	7	3
Acinetobacter baumannii	1	0
Pseudomonas aeruginosa	0	1
Yeasts	2 (3%)	0
Gram-positive organisms	43 (74%)	36 (84%)
Gram-negative organisms	8 (14%)	4 (9%)
Culture-negative peritonitis	5 (9%)	3 (7%)
Total	58 (100%)	43 (100%)

The improvement that we noticed between 2004 and 2006 may be the result of change in the connection systems at that time. Currently, during last years, almost two thirds of patients were on Baxter DUO connection system and one third of patients remained on Fresenius stay-safe system.

Many centres have been reported that, over time, the microbiology at those institutions has been changing [16]. We cannot confirm this because the aetiology of peritonitis have been similar many years. Table 4 demonstrates that coagulase-negative staphylococcus has been the most common pathogen during 2006–2010 followed by *Staphylococcus aureus*. In two effluents in 2009 and three in 2010, more than one pathogen was isolated. Thus, most cases of peritonitis were due to Gram-positive pathogens, accounting around 35% of all peritonitis episodes, and Gram-negative infections were presented with a variety of different organisms, predominantly *E. coli*.

4. Conclusions

This is a first report on long-term peritoneal dialysis experience at a single centre in Estonia. We have demonstrated

steady high single-centre peritoneal dialysis penetration rate and declining tendency of peritonitis rate after essential improvement of local skills.

Acknowledgments

The authors thank Maie Pikkmaa, Pirgit Palk, Siiri Mesikepp, Elviira Seppet, Eino Sinimäe, Külli Kõlvald, and Kristi Veermäe.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 514070, 6 pages
doi:10.4061/2011/514070

Research Article

Depression and Anxiety in Patients with Chronic Renal Failure: The Effect of Sociodemographic Characteristics

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Received 24 January 2011; Accepted 31 March 2011

Academic Editor: Hulya Taskapan

"Do the sociodemographic characteristics relate to the levels of depression and anxiety in patients with chronic renal failure in Athens?" The study investigated in a group of renal disease patients differences referring to self-reported mental health, depression, and anxiety, after controlling for gender, age, education, and marital status. Patient-reported assessments included General Health Questionnaire (GHQ-28) of Goldberg, Center for Epidemiological Studies Depression Scale (CES-D), and State-Trait Anxiety Inventory (STAI I & II) of Spielberger. Female patients reported higher scores in the *trait anxiety* measure. Elder patients reported higher scores in the GHQ-28 subscale of *social dysfunction* and in the CES-D *depression* scale, while less educated patients presented higher scores in the GHQ-28 subscales of *anxiety/insomnia* and *severe depression*. Divorced/widowed patients presented higher scores in the *severe depression* subscale. Findings provide evidence that sociodemographic variables, like being older, less educated, and divorced/widowed, relate to a more compromised mental health.

1. Introduction

Populations facing chronic illness have been reported to have poorer quality of life (QoL) and mental health, including higher levels of depression [1–5]. In this context, health services for ill-health populations, including chronic renal failure (CRF), have drawn attention to promotion of mental health issues [6–10]. It is worth noting that CRF is a disease with serious effects on the patients' QoL, negatively affecting their social, financial, and psychological well-being [11–14].

Regarding differences between the main methods of renal replacement therapy, that is haemodialysis (HD) and peritoneal dialysis (PD), HD patients have been found to experience more depressive symptoms than PD [9, 11]. Depression may be linked to the HD treatment modality, since the patient has to be continually connected to the haemodialysis machine during dialysis and so experience significant restrictions in independent living [10]. In addition, the rate of reported suicide in HD is higher, while a substantial number of deaths resulting from dietary violations could also be accounted for as suicide [10].

Furthermore, HD patients are reported to face psychosocial problems, which can contribute to conflictions between themselves and their medical carers. Such findings could be attributed in part to the stressful conditions in the HD treatment modality, including frequent visits and prolonged waiting time in the dialysis unit [12]. Regarding psychological dimensions in end-stage renal disease (ESRD), it seems that PD patients are better adjusted than HD. This may be due to the peritoneal treatment modality offering increased autonomy and control, flexibility in everyday life and the dietary regime, and fewer social restrictions [14]. PD patients have been found to report better QoL ratings in specific areas like "perceived ability to travel," "financial concerns", "restriction in eating and drinking," and "dialysis access problems" [12]. Furthermore, PD patients have indicated more positive ratings in several disease QoL domains, for example, less kidney disease burden, and being more encouraged and satisfied with care [12–14].

Regarding the effect of sociodemographic variables on patients' mental health, gender is reported to have an effect; so female patients present higher scores of depression and trait anxiety and lower scores in positive affect [15–18]. Male patients are reported of having more social activities and interests and better QoL [15, 19, 20].

Table 1: Sociodemographic characteristics of the sample (N = 144).

	Male N = 86 (59.7%)	Female N = 58 (40.3%)
Age (years)		
Mean (SD)	59.90 (16.88)	61.84 (11.68)
Marital status		
Single	18 (20.9%)	7 (12.1%)
Married	65 (75.6%)	42 (72.4%)
Divorced/Widowed/ Roommate	3 (3.5%)	9 (15.5%)
Total	86 (100%)	58 (100.0%)
Education		
Elementary	29 (33.7%)	33 (56.9%)
Secondary	35 (40.7%)	21 (36.2%)
University	22 (25.6%)	4 (6.9%)
Total	86 (100.0%)	58 (100.0%)

Further, older patients present lower levels of physical well-being and higher scores of depression [17, 21–28]. Regarding the effect of socioeconomic status, patients in the lower range face many problems, including poorer mental and general health and lower social well-being [29, 30], whereas higher economic and educational level is associated with higher health-related QoL [19, 31]. Concerning marital status, being married is related to better physical well-being as well as emotional health [26].

In spite of the fact that several papers on mental health referring to patients with CRF have been published, the studies investigating the role of sociodemographic variables on mental health issues are limited, and the produced findings are frequently controversial. The aim of this study was to investigate in a total sample of chronic renal disease patients differences referring to self-reported mental health, depression, and anxiety after controlling for gender, age, levels of education, and marital status. These differences were also investigated in the groups of HD and PD patients separately.

The main hypothesis is that being male patient, younger, more educated, and married relates to a better mental health with less depressive and anxiety symptoms.

2. Materials and Methods

A sample of 144 patients was recruited from three general hospitals in the broader area of Athens, consisting of 84 patients (58.3%) undergoing in-centre haemodialysis (HD) and 60 patients (41.7%) in continuous ambulatory peritoneal dialysis (CAPD/PD). The rate of response was very high, reaching 99%. Thus, the total sample includes almost all patients of these three units, consisting of 86 males (59.7%) and 58 females (40.3%), with a mean age of 60.6 years ± 14.9. Participants were Greek adults having signed a consent form for participation. All subjects had been informed of their rights to refuse or discontinue participation in the study according to the ethical standards of the Helsinki Declaration in 1983. Ethical permission for the study was obtained from the scientific committees of the hospitals. The period of the questionnaires given to the patients was between November 2007 and March 2008, while the study took place between October 2007 and June 2008. Full descriptive data of the sample are presented in Table 1.

The subjects (HD, PD) were selected according to the following criteria:

(1) diagnosis of end-stage renal disease,

(2) current HD or PD treatment,

(3) age above 18,

(4) native language, Greek,

(5) volunteer participation and signed consent form.

Measurements were conducted with the following instruments

(1) *General Health Questionnaire* (GHQ-28) version is a widely used self-report measure designed to detect psychiatric problems in general settings [32], which has been standardized in Greek populations [33]. It includes four subscales: (a) *somatic symptoms,*(b) *anxiety/insomnia,* (c) *social dysfunction,* and (d) *severe depression.* Higher scores indicate a worse general condition of health.

(2) *Center for Epidemiologic Studies Depression Scale* (CES-D) is a 20-item self-report measure of depression [34, 35]. According to Fountoulakis et al. [36], it is suggested that for Greek populations a value above 9.03 is indicative that a subject can be classified as depressed [36].

(3) *State-Trait Anxiety Inventory* (STAI I/STAI II). It consists of 20 items referring to self-reported state anxiety and 20 items to trait anxiety [37]. The instrument is standardized in Greek populations [38]. Higher scores indicate the presence of state and trait anxiety.

3. Results

The values of the two gender groups were found to pass the normality distribution, with the use of Kolmogorov-Smirnov Z test. Investigating gender differences, female patients tended to report higher scores in the GHQ-28 subscale of *severe depression* (P = .05) (Table 2). No statistically significant differences were found in *depression* measured by CES-D (Table 2). It is noteworthy that regarding this scale, with the use of the above-suggested cutoff point, both male and female patients present higher values and can be considered as depressed (M = 11.94 and 14.32, resp.). Further, women presented significantly higher scores than men in *trait anxiety* measured by STAI II.

Concerning age, statistically significant differences were found between younger (<45 years) and older patients (>45 years). Specifically, older patients reported a significantly higher level of *social dysfunction* and *depression* (Table 3).

Table 2: Mean scores ± SD of GHQ-28 health subscales, depression and state-trait anxiety. Independent samples t-test demonstrating differences between men and women.

	($N = 86$) Men $M \pm$ SD	($N = 58$) Women $M \pm$ SD	P value
GHQ-28 subscales			
Somatic symptoms	1.73 ± 0.50	1.87 ± 0.60	NS**
Anxiety/insomnia	1.66 ± 0.60	1.78 ± 0.72	NS
Social dysfunction	2.20 ± 0.43	2.35 ± 0.51	NS
Severe depression	1.35 ± 0.55	1.62 ± 0.86	.05*
Total score	1.74 ± 0.41	1.91 ± 0.58	NS
CES-D			
depression	11.94 ± 10.73	14.32 ± 12.56	NS
STAI I			
state anxiety	28.77 ± 7.11	32.39 ± 12.22	NS
STAI II			
trait anxiety	33.30 ± 7.85	38.21 ± 10.14	.01*

*$P < .05$; $N = 144$.
**NS: not significant.

Table 3: Mean scores ± SD of GHQ-28 health subscales and depression. Independent samples t-test demonstrating differences between the two categories of age.

	($N = 24$) Age (<45 years) $M \pm$ SD	($N = 120$) Age (>45 years) $M \pm$ SD	P value
GHQ-28 subscales			
Somatic symptoms	1.76 ± 0.55	1.79 ± 0.55	NS**
Anxiety/insomnia	1.81 ± 0.63	1.69 ± 0.65	NS
Social dysfunction	2.04 ± 0.45	2.30 ± 0.46	.01*
Severe depression	1.35 ± 0.36	1.48 ± 0.75	NS
Total score	1.74 ± 0.37	1.82 ± 0.51	NS
CES-D			
Depression	6.62 ± 3.24	13.58 ± 11.89	.00*

*$P < .05$; $N = 144$.
**NS: not significant.

Table 4: Mean scores ± SD of GHQ-28 health subscales. Independent samples t-test demonstrating differences between the two categories of education.

GHQ-28 subscales	($N = 87$) Years of education (<9) $M \pm$ SD	($N = 57$) Years of education (>9) $M \pm$ SD	P value
Somatic symptoms	1.81 ± 0.55	1.74 ± 0.54	NS**
Anxiety/insomnia	1.82 ± 0.69	1.54 ± 0.54	.01*
Social dysfunction	2.30 ± 0.49	2.20 ± 0.43	NS
Severe depression	1.57 ± 0.79	1.29 ± 0.50	.01*
Total score	1.88 ± 0.53	1.70 ± 0.41	.03*

*$P < .05$; $N = 144$.
**NS: not significant.

Regarding education, less educated patients (<9 years) reported significantly higher scores in the *anxiety/insomnia* and *severe depression* subscales as well as in the *total GHQ-28 score* (Table 4).

As far as marital status is concerned, divorced/widowed patients presented significantly higher scores in the GHQ-28 subscale of *severe depression* compared to singles and married (Table 5).

In the group of HD patients, females reported worse mental health with more *somatic symptoms* (2.04 ± 0.57, $P = .04$) and *social dysfunction* (2.46 ± 0.54, $P = .05$). Females also reported more *trait anxiety* (39.45 ± 7.73, $P = .04$) in comparison to males. With regards to age and marital status, older (>45 years) and divorced/widowed HD patients presented higher level of *depression* (12.90 ± 13.96, 35.50 ± 4.95, $P = .02$). On the contrary, married HD patients reported better mental health (1.84 ± 0.49, $P = .01$), measured by GHQ-28 questionnaire.

In the group of PD patients, females presented more *state anxiety* (33.55 ± 10.28, $P = .02$). Concerning age, older (>45 years) PD patients presented more *somatic symptoms* (1.72 ± 0.53, $P = .03$) and *social dysfunction* (2.25 ± 0.40, $P = .03$) as well as more *depression* (13.96 ± 10.69, $P = .00$).

4. Discussion

Investigating the relationship of sociodemographic variables to mental health, female patients tended to evaluate less favourably their general condition of health and mental health as measured by GHQ-28. The tendency was to report being more *depressed* endorsing more suicidal thoughts than men. This finding is in agreement with several studies on chronic diseases, presenting female patients feeling more depressed than males [15–18]. However, when gender differences were investigated in another measure of depression using the CES-D scale, they were not significant. Both genders in this scale presented a higher level than that found in normal populations and should be considered as depressed according to Fountoulakis et al. [36]. A possible explanation regarding the differential results in the GHQ-28 and the CES-D scales is that although the two measures may be comparable regarding parts of their content, actually they measure different aspects of depression. Namely, the GHQ-28 *severe depression* subscale includes items on suicidal thoughts, which are not included in the CES-D scale. Thus, although men and women in our sample reported being depressed, they seemed to differ regarding the degree of endorsed suicidal ideas, and so we may suggest that women indicated more symptoms of "suicidal depression." Further, female patients reported being more *anxious* in comparison to males. This finding is also in agreement with several studies indicating that women present a higher prevalence of trait anxiety [15, 18]. As in the above case of measures of depression, differential values were observed between the

STAI II and the GHQ-28 *anxiety/insomnia* subscale. In this case, gender differences were found in the STAI II scale, as women reported higher levels of trait anxiety—a rather longstanding condition—while differences were not found in the GHQ-28 respective subscale. It is noteworthy that although these scales may present some content overlap, they do not measure the same dimensions of anxiety (e.g., the GHQ-28 *anxiety/insomnia* subscale includes items on sleep problems which are not included in the STAI II scale). It is suggested that both depression and anxiety measures need to be multiple as they are useful addressing different dimensions of the clinical entity.

Regarding age, although the differences found were generally expected, they were also illuminating as older patients reported falling behind in social activities and interests, and being more socially restricted and depressed. These findings are in agreement with several studies indicating that older patients present lower levels of physical well-being and higher levels of depression [17, 21–28].

Regarding differences in relation to education, end-stage renal disease (ESRD) patients with less than nine years of education seemed to evaluate their mental health in a more negative way and reported suffering from higher levels of *anxiety/insomnia* and *severe depression*. In overall, patients with lower socioeconomic profiles or lacking in education (which is generally taken as an indicator of social status) are reported in the literature facing problems in their psychological well-being, social relationships, and general health [19, 29–31].

In respect to marital status, divorced/widowed patients, compared to singles and married, evaluated less favourably their mental health and reported a higher level of *depression* with suicidal thoughts. On the basis of these findings, married patients seem to experience a better QoL. Similar evidence in the literature indicates that the status of marriage in these patients may be significantly correlated to an enhanced physical well-being and emotional health [26].

Investigating the effect of sociodemographic variables on the mental health of two groups separately, interesting and important findings are observed. More specifically, in the group of HD patients, females seem to face many difficulties in their mental health with more *somatic symptoms* and *social dysfunction*. Females also present more *trait anxiety* in comparison to males. With regards to age and marital status, older (>45 years) and divorced/widowed HD patients appear more depressive. On the contrary, married HD patients evaluate their mental health positively.

In the group of PD patients, females present more *state anxiety*. Concerning age, older (>45 years) PD patients have more *somatic symptoms*, restrictions in their social life, and more *depression*.

These results provide useful indications that certain variables referring to the patient's sociodemographic profile may affect favourably or unfavourably his/her mental health. The findings support evidence in the literature indicating that sociodemographic factors may to some extent contribute to the explanation of mental health and QoL [39–41]. According to Sprangers et al. [42], independent of the kind of illness, being female, older, less educated, and living without a partner is connected with a lower QoL. This is an important reference which shows the strong relation between specific sociodemographic factors and QoL. With regards to the main hypothesis of the study, it is recognized that being male patient, younger, more educated, and married relates to a better mental health with less depressive and anxiety symptoms, giving in this way emphasis to the importance of family and high educational level. Consequently, our research hypothesis is confirmed.

Table 5: Mean scores ± SD of GHQ-28 health subscales. One-way ANOVA showing differences among singles, married, and divorced/widowed.

GHQ-28 subscales	($N = 25$) Single $M \pm$ SD	($N = 108$) Married $M \pm$ SD	($N = 11$) Divorced/ Widowed $M \pm$ SD	P value
Somatic symptoms	1.91 ± 0.54	1.74 ± 0.54	1.94 ± 0.57	NS**
Anxiety/ insomnia	1.74 ± 0.60	1.70 ± 0.65	1.76 ± 0.78	NS
Social dysfunction	2.29 ± 0.38	2.24 ± 0.48	2.44 ± 0.52	NS
Severe depression	1.32 ± 0.32	1.41 ± 0.66	2.19 ± 1.14	.00*
Total score	1.82 ± 0.38	1.77 ± 0.49	2.08 ± 0.64	NS

* $P < .05$; $N = 144$.
**NS: not significant.

In overall, our findings provide evidence which can be useful to health professionals and managers of health services offered to patients with CRF. Tailored interventions can be developed to support female but also male patients, those who are older, less educated, living alone, depressed, and anxious, in an effort to address issues of compromised mental health.

Concerning limitations in the study, it is noted that patients were recruited from three renal units and were a convenience sample. Thus, it was not possible to have an adequate control on demographic or clinical variables. Evidence provided by the results of this study can be further extended by the control of the above variables and the use of even larger samples. Limitations may also include the lack of pre-ESRD data as well as the fact that we did not investigate the effect of duration of disease and treatment on patients' mental health.

5. Conclusions

The main focus of the present study was to examine in a group of chronic renal disease patients differences referring to self-reported mental health, depression, and anxiety, after controlling for gender, age, levels of education, and marital status.

In the present study, our hypothesis is confirmed, that is being male, younger, more educated, and married appeared to have a favorable effect on several aspects of the patients' mental health.

Acknowledgments

The author would like to thank the patients for their participation in the study and acknowledge the support given by the health professionals and the administration personnel of the dialysis participating units.

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