Encapsulating Peritoneal Sclerosis in the Netherlands
A study on incidence, risk factors and clinical consequences

MARIO KORTE

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Encapsulating Peritoneal Sclerosis in the Netherlands
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Een studie naar incidentie, risicofactoren en klinische consequenties

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Every beginning is only a sequel, after all
and the book of events is always open halfway through.

Wislawa Szmborska

CONTENTS

Chapter 1

Introduction

PERITONEAL DIALYSIS

Patients with chronic renal failure have an accumulation of extracellular fluid and waste products (uremic toxins) which are normally excreted by the kidney. There are different renal replacement therapies, which can partially correct these abnormalities. Peritoneal dialysis (PD) is one of these modalities. Since the introduction of continuous ambulatory peritoneal dialysis (CAPD) in 1976 [1], the use of PD has increased steadily and is now used worldwide. On January 1st 2009, 6292 patients were on dialysis in The Netherlands, of which 18.1 % (n=1139) were on PD (source:RENINE www.renine.nl).

In PD the peritoneal membrane is used as a dialyzer membrane. By gravity a sterile dialysis solution is instilled in the peritoneal cavity via an intra-abdominal catheter. Through a combination of diffusion and convection waste products and fluid are transported between the peritoneal capillaries and the dialysis fluid. After a few hours an equilibration is reached, and the effluent is drained. In the regular CAPD scheme, this cycle is performed 4 times a day for 4 hours with a long night dwell.

Dialysis solutions contain varying concentrations of glucose in order to provide an osmotic gradient necessary for the transport and removal of excess body water. The glucose is absorbed by the peritoneal capillaries, which leads to a decrease of the osmotic gradient. In the early nineties icodextrin was introduced as a new dialysis fluid. This is a glucose polymer derived from starches, which is absorbed slowly by the capillaries. Therefore it is very effective for ultrafiltration, particularly in long dwells [2]. Although, the side effects of icodextrin appear to be limited, sterile peritonitis due to icodextrin has been reported [3].

Normal peritoneum comprises different components; a thin layer of mesothelial cells and a submesothelial layer with vessels and fibroblasts. The inner abdominal wall is lined with a parietal membrane, where as a visceral membrane covers the intestines. Continuous exposure to dialysis solutions and other exogenous factors results in changes of the peritoneal membrane. In long term PD there is mesothelial denudation, the submesothelial layer becomes thicker and new vessels develop [4].

The 5-years survival of the PD population is approximately 50 % [5]. The main reasons of mortality are cardiovascular disease, infections and malnutrition. The reports on the survival of PD and hemodialysis (HD) patients are somewhat conflicting. Some reports showed comparable mortality rates of PD and HD patients [6-7]. There are also reports that show a slightly increased survival in the first years of renal replacement therapy of PD compared to HD [8-9]. This may be explained by the improved preservation of renal residual function in PD patients, which is an independent predictor of mortality [10-11].

Despite the fact that both patient and technique survival improved during the decades, the number of patients on PD is decreasing. In the Netherlands the proportion of dialysis patients on PD was 31.3% in 2002 and this decreased to 18.1% in 2010 (source: RENINE database). The reason for this decline is not completely understood but appears to be a worldwide

phenomenon [12-13]. It is probably because of multiple reasons; increasing transplantation numbers, reimbursement issues, lack of education and the fear of complications. Furthermore, the ESRD patient eligible for PD, is getting older. Subsequently, the likelihood of being able to perform PD without extra support decreases.

The main complications of PD are peritonitis, access related complications, hernias, ultrafiltration failure and encapsulating peritoneal sclerosis (EPS).

ENCAPSULATING PERITONEAL SCLEROSIS

One of the most feared complications of PD is encapsulating peritoneal sclerosis (EPS). Gandhi *et al.* was one of the first to describe EPS [14]. Five patients were described who were treated with PD during several years. At laparotomy a thick tissue covering the peritoneum was found. Subsequent microscopical investigation showed extensive formation of fibroconnective tissue. In the following years the diagnosis was reported more often with different names such as abdominal cocooning and sclerosing encapsulating peritonitis (SEP). The current name is more appropriate given its chronic non-inflammatory appearance at presentation. The prevalence varied from 0.7% in Australia [15], 2.5 % in Japan [16] to 3.3 % in a single center study from the UK [17]. In the past EPS was predominantly described and investigated in Japanese literature. Encapsulating peritoneal sclerosis (EPS) appeared to be a life threatening complication of peritoneal dialysis (PD) with a mortality rate as high as 50%. The majority of deaths occurred during the first year after the diagnosis.

The diagnosis of EPS is difficult, mainly because a uniformly used definition is lacking. The international society for peritoneal dialysis (ISPD) was the first to make a definition of this complication [18]. The ISPD stated that EPS is a clinical syndrome with signs of intermittent and persistent or recurring complaints of gastro-intestinal obstruction, with macroscopic and/or radiological confirmation of sclerosis, calcification, peritoneal thickening or encapsulation of the intestines.

Even though this definition of EPS is not specific, the presence of a disturbed intestinal function, such as the clinical symptoms of partial or total obstruction, is essential for the diagnosis. The complaints may progress to severe abdominal pain, vomiting, anorexia, malnutrition, weight loss, and the development of an abdominal mass. The chronic and insidious nature of this developing clinical syndrome is specific for EPS [16]. As a consequence, EPS is often recognized in a late stage.

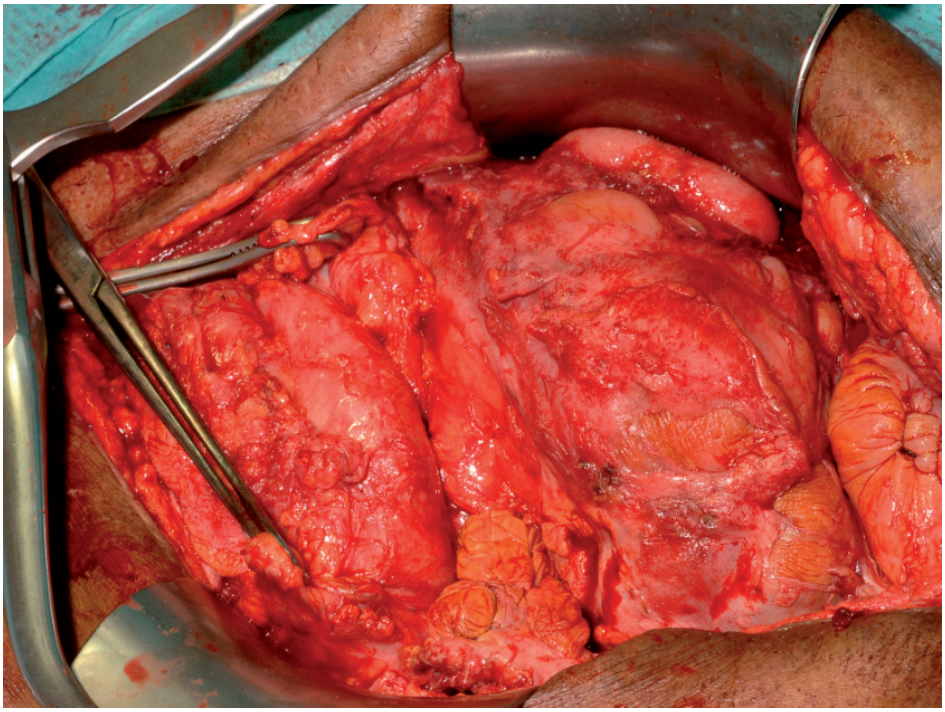
Macroscopic inspection at laparotomy shows extensive peritoneal changes with a thickened brownish peritoneum with adhesions, which partially cover the intestines. In later stages there is a total encapsulating of the intestine with a dense sclerotic cover. Because of this thickened

fibrous membrane, it leads to the impression of an abdominal cocoon. An example is depicted in figure 1.

Although much basic research is done with respect to peritoneal remodeling, clinicians still struggle with various issues and questions concerning EPS. For instance, there is the notion of an increased incidence of EPS in the Netherlands. In addition, the risk factors for EPS have been poorly investigated and may have changed over time. These are important issues as both patient and doctor should be informed on the risk of EPS prior to the initiation and during PD treatment. Finally, there are no clear guidelines for diagnosing and treating EPS. Specifically the diagnostic tools to recognize the early stages of EPS development are lacking.

In this thesis these clinical relevant aspects of EPS are addressed.

Figure 1 | EPS at laparotomy



This patient with a history of PD had developed complaints of intestinal obstruction. At laparotomy there is a clear fibrotic and thickened membrane covering the bowel. There are also extensive adhesions.

HYPOTHESIS AND OUTLINE OF THE THESIS

In ***chapter 2*** we explored the current knowledge on EPS. The last decade more attention has been focused on this complication. This attention mainly concerned the possible increase of incidence, new diagnostic tools and the therapeutical management of EPS. Recent

developments led to a debate on an arbitrary expiry date for PD because of the risk of EPS. To investigate the disease various registries have recently been initiated.

In the years 2004-5 it was our distinct empirical impression that EPS was increasing in incidence. This observation appeared to be shared by other nephrologists in the Netherlands. Given the impressive clinical spectrum this caused concerns and led to a diminished enthusiasm to start PD as an initial choice for renal replacement therapy.

In the first part of the thesis the possible increase in incidence will be explored. Therefore we initiated an investigation in the university hospitals of Rotterdam and Utrecht. This is described in ***chapter 3.1***. In this initial report the EPS patients in these centers were investigated, as was the hypothesized increasing incidence of EPS in the period 1996-2006.

After the first report it could be hypothesized that in addition to PD duration, there might be novel independent risk factors associated with EPS and its increased incidence. This was more thoroughly investigated in a case-controlled multicenter study, in which eight large Dutch centers participated. This study is described in ***chapter 3.2***. This study was intended to investigate the EPS incidence in a larger cohort. The chosen log linear statistical model enabled us further to investigate the hypothesis that besides PD duration other novel independent risk factors, as age, dialysis solutions, peritonitis, kidney transplantation and ultrafiltration failure are associated with EPS and its increased incidence.

There is a great need for early detection of EPS in patients. This is hampered by the insidious nature of the disease. Patients slowly develop intermittent abdominal complaints, but the differential diagnosis at the time of considering EPS is extensive. Additionally, the radiological establishment of EPS with abdominal CT scanning is not useful in early screening. In ***chapter 4*** it was hypothesized that using Il-6, as a regulatory cytokine and CA125 as a marker for mesothelial cell mass, both measured in effluent, might have a predictive value for EPS. The ultrafiltration capacity was also taken into account. This hypothesis was retrospectively investigated in EPS patients in whom longitudinal equilibration tests were done.

Currently there is no consensus on therapeutical management of EPS. Nutritional status is important. Surgery with extensive adhesiolysis is recommended, but this is rarely performed in Western Europe. There are anecdotal reports on the positive effect of tamoxifen in EPS, but there is a lack of controlled studies concerning tamoxifen. In ***chapter 5*** it was hypothesized that tamoxifen may result in lower mortality in treated patients. We performed a retrospective study in the multicenter EPS study to investigate whether tamoxifen was associated with an improved survival in these patients.

EPS in general has a high mortality, but the impact of the recently described post-transplantation EPS on mortality after kidney transplantation is yet unknown. We hypothesized that

post-transplantation EPS has a considerable impact on mortality of transplanted PD patients. We performed a study investigating this issue, which is described in ***chapter 6***. Using the national transplantation database and the RENINE database, it is investigated what the mortality is of post-transplantation EPS and how this influences the survival of transplanted PD patients.

In ***chapter 7*** the results of the studies are summarized and discussed in general.

It is known that with new findings more questions and possible explanations concerning etiology arise. In ***chapter 8*** some of the possible future questions on EPS and post-transplantation EPS, in particular are explored. In the first part of this chapter the developed initiative for the EPS registry is described. In the second part some future recommendations, pathophysiological hypothesis and possible research initiatives are described.

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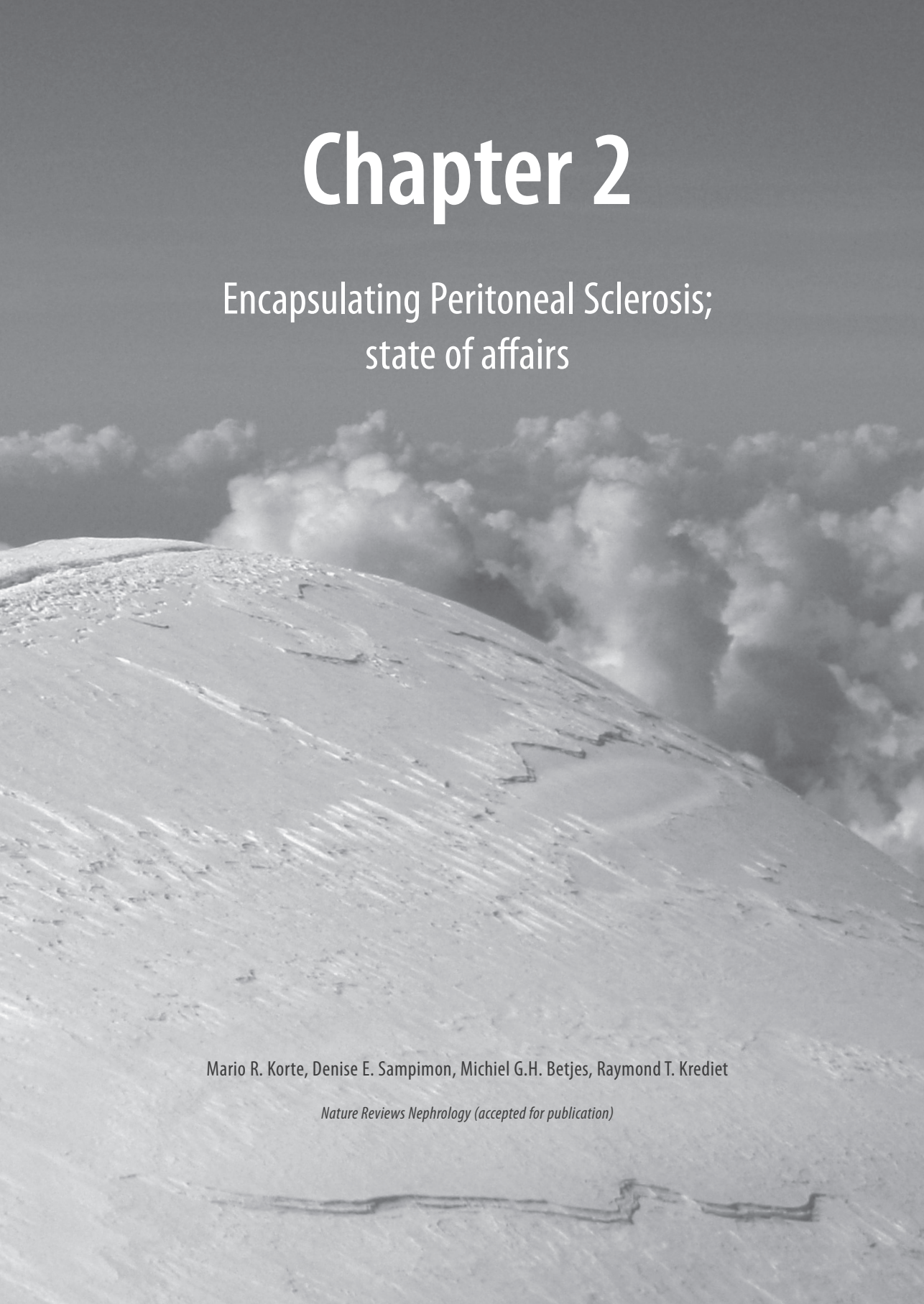
Chapter 2

Encapsulating Peritoneal Sclerosis; state of affairs



Mario R. Korte, Denise E. Sampimon, Michiel G.H. Betjes, Raymond T. Krediet

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INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) is the most severe complication of long-term peritoneal dialysis (PD). A fibrous cocoon covers the intestines and causes gastrointestinal dysfunction and intestinal obstruction. This leads to malnutrition, weight loss, infections and death. The last decade more attention has been focused on this complication and several registries and study groups have been started [1-5]. The recent attention concerns the increased incidence of EPS in recent years and identification of new risk factors. Although this search has given us more insight into the pathophysiology and possible risk factors of the development of EPS, we still do not know how to prevent or recognize the development of EPS in the early stages. As a consequence, there is much debate on whether there should be an arbitrary expiry date for PD because of the risk of EPS.

In this review we will give an overview of the current status of EPS. Regarding the pathophysiology of peritoneal fibrosis and EPS much progress has been made. Especially the role of different growth factors is emerging. Finally, an update for clinicians on the diagnostic and therapeutical options will be given.

EPIDEMIOLOGY

The reported prevalence of EPS varies between 0.5 and 2.5% [2,6-10]. The occurrence of EPS increases with the duration of PD therapy. An Australian registry study described an incidence of 19.4% after 8 years of PD treatment [9]. This was confirmed in a prospective Japanese study. The incidence of EPS increased with the duration of PD from 0.7% after 5 years, 2.1% after 8 years, 5.9% after 10 years and 17.2% after 15 years of PD therapy [10].

The last years an overall increase of EPS incidence has been reported of 0.9% in 1996 to 3.5% in 2005 despite the overall decrease in PD population [2,7-12]. It seems unlikely that the increase in incidence is caused by over diagnosis or more attention for this complication. The clinical presentation of EPS is very severe and thus a missed diagnosis is implausible. Reported mortality rates of EPS are high, especially in the year of the diagnosis. They vary between 25% and 55% and increase with the time on PD [2,7,9-12].

PATHOPHYSIOLOGY

Alterations of the peritoneum

The peritoneum is build upon a monolayer of mesothelial cells and its basement membrane. Between the mesothelial layer and the vascular plexus lays the submesothelial compact zone with fibroblasts , macrophages and blood vessels [13].

Several alterations of the peritoneum occur during the course of PD treatment [14-17]. The mesothelial layer disappears (denudation). The peritoneal vasculature shows progressive signs of fibrosis and hyalinization of the media, due to the deposition of collagen IV (vasculopathy) [17]. New vessels develop (neoangiogenesis) and the more vessels develop, the more severe the interstitial fibrosis appears to be [15,18]. The submesothelial compact zone thickening is caused by interstitial fibrosis and sclerosis that is composed of various types of collagen including collagen IV and myofibroblasts [15]. Also advanced glycation end products (AGE) accumulate in the mesothelial layer, submesothelial layer and vascular wall with time on PD [19-20]. The deposition of AGE is associated with the presence of peritoneal fibrosis and functional problems [19,21]. In vitro AGE's induce collagen and TGF-β expression in human peritoneal mesangial cells [22]. Experimental studies showed that ligand binding of AGE to its receptor (RAGE) led to submesothelial fibrosis and interstitial collagen accumulation [23-24]. It is unknown whether AGE's cause peritoneal damage or are innocent bystanders. But it is hypothesized that AGE accumulation influences the vessel wall, which would explain the association between AGE accumulation and fast solute transport [25].

Simple sclerosis is a mild sclerosis that may develop during PD. It is described as thickening of the parietal peritoneum and vascular alterations in absence of encapsulation [26]. When bowel encapsulation is present, clinical signs of EPS become manifest. In EPS the parietal peritoneal specimens show fibrin deposition, fibroblast swelling, capillary angiogenesis, and mononuclear cell infiltration [27]. Visceral peritoneal specimens show an excess of interstitial type IV collagen and a large number peritoneal vessels [15]. Whether EPS is the natural consequence of simple sclerosis, or whether they are two different disease entities remains a topic of debate. To study this, Garosi *et al*. compared the peritoneal thickness of peritoneal specimens of 224 patients with long term PD with peritoneal specimens of patients that developed EPS. Simple sclerosis was present in 180 of the 224 patients. In the EPS group the visceral and parietal specimens were 10 to 50 times thicker compared to the control group. They concluded that there was no intermediate stage between simple sclerosis and EPS and therefore they are two different diseases [28]. In contrast, a Japanese study compared peritoneal specimens of EPS patients and compared them to long-term PD patients. Angiogenesis, vasculopathy, new membrane formation, fibrosis and degenerative changes of the compact zone layers were present in both groups. Only the thickness of the compact zone and positive fibrin stains were unique for the EPS group [29]. The peritoneal changes may gradually develop from peritoneal remodelling associated with long-term PD to simple sclerosis, and eventually EPS. However, no uniformity exists on this sequence, and not every patient progress from simple sclerosis to EPS.

PATHOGENETIC FACTORS AT THE CELLULAR LEVEL

Growth factors, cytokines and enzymes

Several growth factors, cytokines and enzymes may be important for the development of fibrosis, neoangiogenesis and eventually EPS. Vascular endothelial growth factor (VEGF) plays an important role through proliferation and migration of endothelial cells [30]. Several in vitro experiments have shown that human peritoneal mesothelial cells (HPMC) have the capacity to produce VEGF in response to diverse stimuli present in PD fluids [31-32]. An experimental model of EPS demonstrated the crucial role of VEGF in the development of EPS-like changes in rats. The EPS group treated with anti-VEGF showed a thinner compact zone and less vasculopathy compared to the EPS group not treated with anti-VEGF [33]. This angiogenic inhibitory effect was confirmed in other studies [34-35]. VEGF has been demonstrated in peritoneal effluent, where it was locally produced or released by peritoneal tissues or cells. VEGF showed a linear relationship with the duration of PD treatment [36-37].

TGF-β appears essential in the formation of peritoneal fibrosis. TGF-β is important in different wound healing processes [38-40]. Overexpression of TGF-β is associated with several fibrosing syndromes. In vitro stimulation of HPMC with TGF-β leads to more collagen mRNA expression [41-42]. The experimental model by Liu *et al.* demonstrated the role of TGF-β in the development of EPS in mice. This EPS model was developed by using a helper-dependent adenovirus that actively transformed TGF-β. The short term exposure to the adenovirus expressing TGF-β led to simple sclerosis while longer exposure led to neoangiogenesis, extensive adhesions and cocooning or encapsulation of the intestines, also present in EPS [43-45]. When tissue TGF-β binds to the TGF receptor different intracellular pathway signals are triggered. TGF-β signalling through SMAD seems to be a crucial element in the signal transduction pathways involved in wound healing and fibrosis [46-48]. This was confirmed in an experimental study with SMAD3 knockout mice. These mice were resistant to peritoneal injury induced by TGF-β [46].

Other growth factors may also play a role in the development of peritoneal fibrosis. A positive correlation has been reported between the thickness of the peritoneal membrane and the expression of mRNA connective tissue growth factor (CTGF). Effluent CTGF levels correlated with dialysate-over-plasma ratios of creatinine and the estimated local peritoneal production of CTGF [49]. An association between CTGF and fibrosis has not been demonstrated and needs to be studied. Fibroblast growth factor (FGF) participates in several fibrotic diseases and induces the proliferation of various cultured cells such as fibroblasts and endothelial cells [50]. An in vitro study of mesothelial cells exposed to a high glucose concentration showed more mRNA expression of FGF [51]. FGF has not been demonstrated in clinical PD studies. Therefore it is unknown whether FGF is involved in EPS. Platelet derived growth factor (PDGF) is involved in many wound healing processes. Daily addition of PDGF to cultured cells stimulated collagen production [52]. The effect of PDGF expression on angiogenic and fibrotic effects in the mice peritoneum has also been studied. An adenovirus mediated gene transfer was used. The over

expression of PDGF led to a normal wound healing response with angiogenesis and fibroblast proliferation. However it did not lead to collagen protein expression. It can be concluded that PDGF is not responsible for the peritoneal membrane injury [53].

AGE accumulates in the peritoneal structures with time on PD. In vitro AGEs induce collagen and TGF-β expression in human peritoneal mesangial cells [22]. Experimental studies showed that ligand binding of AGE to its receptor (RAGE) led to submesothelial fibrosis, interstitial collagen and fibronectine accumulation [23-24]. The peritoneal expression of RAGE is increased in settings of diabetes and uremia [54].

Plasminogen activator inhibitor 1 (PAI1) and tissue-type plasminogen activator (tPA) are involved in fibrogenesis of various organs and can be produced by mesothelial cells. An in vitro study showed that HPMC produce PAI1 and t-PA in response to glucose based PD solutions [55]. A mouse model of peritoneal fibrosis showed that tPA aggravates peritoneal fibrosis, neoangiogenesis and peritoneal inflammation [56]. It remains unclear whether plasminogen is involved in the development of EPS.

In addition to increased formation of fibrosis a decreased degradation of fibrous tissue also contributes to the accumulation of fibrosis in the peritoneum. Metalloproteases (MMP's) are enzymes important in tissue destruction and excessive remodelling. Experimental EPS studies showed increased MMP2 levels in effluent, and inhibition of MMP2 led to less peritoneal injury [56-58]. A multicenter study investigated the MMP2 and MMP9 levels in effluent of EPS patients and PD patients with peritoneal injury. Patients with infectious peritonitis had high MMP9 levels. PD patients with mild peritoneal injury (ascites<100mL) had the highest MMP2 levels. EPS patients had moderate high levels of MMP2. However, half of the patients with MMP2>600ng/mL ended up with EPS (7 out of 15) [59]. An in vitro study of HPMC exposed to glucose demonstrated that a decreased expression of MMP1, 8, 13 and an increased expression of tissue inhibitor metalloproteinase (TIMP) leads to ECM accumulation [60]. Whether MMP's play a role in the development of EPS is uncertain. Mast cells produce tryptase, which has a fibrinolytic function. In an inflammatory state an increased number of mast cells is present in the peritoneum. Also in PD patients without any complications an increase of mast cells is found. However a recent histochemical study demonstrated that the number of mast cells in the peritoneum of EPS patients is extremely low, comparable to patients without inflammation [61].

Tumor necrosis factor-alpha (TNF-alpha) stimulates in vitro macrophages to induce neoangiogenesis and fibroblast proliferation [62]. Zemel *et al*. measured TNF-alpha in effluent and demonstrated that it was only produced by peritoneal tissues or cells in case of peritonitis [63]. A role of TNF-alpha in the development and early diagnosis of EPS is unclear.

A scheme of these potentially relevant factors in EPS development is given in Table 1.

Epithelial to mesenchymal transition

Epithelial to mesenchymal transition (EMT) is a physiological process which occurs throughout the body and in the peritoneum to repair damaged tissue. During EMT, mesothelial cells

Table 1 | Potentially relevant factors for the development of EPS and their evidence in literature.

Relevant factors for the development of EPS at cellular level		References
VEGF		
	In vitro	30-31
	In animals	33-35
	In humans	36-37
TGF-β		
	In vitro	41-42
	In animals	43-45
SMAD		
	In animals	46-48,53
CTGF		
	In humans	49
FGF		
	In vitro	51
PDGF		
	In animals	52-53
AGE		
	In vitro	22,52
	In animals	23,44
	In humans	19,21
PAI1		
	In vitro	55
	In animals	56
MMP		
	In vitro	60,64
	In animals	56-58
	In humans	59
Mast cells		
	In humans	61
TNF		
	In vitro	62
	In humans	63
EMT – in vitro		
	TGF-beta	44,65
	SMAD	66-67
	VEGF	68
	MMP2	59
	AGE	69
	HGF	70-72

VEGF: vascular endothelial growth factor; TGF-β: transforming growth factor beta; CTGF: connective tissue growth factor; FGF: fibroblast growth factor; PDGF: platelet derived growth factor; AGE: advanced glycation end products; PAI1:plasminogen activator inhibitor 1; MMP: metalloprotease; TNF: tumor necrosis factor.

that have been exposed to dialysate undergo a morphological and functional alteration that changes their epithelial phenotype to become fibroblastic. These fibroblasts then migrate to

the submesothelial compact zone and may overproduce TGF-β. This process starts at the initiation of PD treatment and continues with the duration of PD [73]. EMT is necessary for tissue repair under normal conditions, but uncontrolled it may lead to fibrotic processes [70]. Characteristics of EMT were present in fibrotic peritoneal tissue, predominantly in the submesothelial layer [74]. TGF-β plays a central role in EMT. The addition of TGF-β to HPMC leads to a myofibroblastic conversion of these cells [65]. An experimental model demonstrated that TGF-β is a promoter of EMT [44]. Although TGF-β signalling through the SMAD pathway seems crucial in the processes of wound healing and fibrosis, the role of SMAD in EMT remains controversial [66-67,75]. Several growth factors and cytokines important for the development of fibrosis, are produced by mesothelial cells that have undergone EMT. An ex vivo experiment showed higher VEGF production in mesothelial cells with fibroblastic features compared to mesothelial cells with an epithelial phenotype [68]. A Japanese study showed that MMP2 was produced by myofibroblast-like mesenchymal cells [59]. Other important promoters of EMT and the subsequent peritoneal fibrosis are MMP2, Il-1, AGE and transcription factor SNAIL [69,73,76].

In a recent study EMT was detected in parietal peritoneum of early PD patients (up to 2 years). In this study an association was suggested between fibrosis through EMT and a fast transport status without an increased vascular surface area [77]. Fibrosis and fast transport status are both associated with EPS. Although EMT is generally being accepted, the full contribution of EMT to the processes of EPS remains unclear [14,66].

THEORIES ON THE PATHOGENESIS OF EPS

Two hit theory

The "two-hit theory" of EPS hypothesizes that 2 factors are required for the onset of EPS. The first hit causes disruption of normal peritoneal and mesothelial physiology. This disruption generally occurs over a period of years and is a consequence of PD treatment. EMT takes care of the physiological repair process. During this time the patient may be predisposed to a second hit that triggers the development of EPS [78]. The second hit may be a peritonitis, the discontinuation of PD or perhaps a genetic predisposition [79-80]. The second hit theory was first described by Kawanishi *et al.* and is now generally accepted [80].

Genetic predisposition

Most patients that start PD treatment will never develop EPS. A genetic predisposition may influence the development of EPS [81]. Several polymorphisms of important factors in the development of EPS are known such as TGF-β and VEGF [82]. To study the genetic association with EPS a large DNA database has been started in Great Britain [5]. The joint occurrence of EPS and Alport syndrome has also been described, suggesting that Alport syndrome may predispose to EPS [83].

EPS AND CLINICAL PRACTICE

Clinical presentation

Gandhi *et al.* was one of the first to describe EPS associated with intermittent PD, and the international society for peritoneal dialysis (ISPD) was the first to make a definition of this complication [84-85]. The ISPD stated that EPS is a clinical syndrome with signs of intermittent and persistent or recurrent complaints of gastro-intestinal obstruction, with macroscopic and/or radiological confirmation of sclerosis, calcification, peritoneal thickening or encapsulation of the intestines.

Even though this definition of EPS is not specific, the presence of a disturbed intestinal function such as the clinical symptoms of partial or total obstruction, is essential for the diagnosis. The first signs may be accompanied by increased parameters of inflammation. At the time of EPS diagnosis, the obstruction often appears acute and non-infectious. However in hindsight, abdominal complaints like nausea, complaints of changing defecation, and passage problems are often present in earlier stages. The complaints may progress to severe abdominal pain, vomiting, anorexia, malnutrition, weight loss, and the development of an abdominal mass. The chronic and insidious nature of this developing clinical syndrome is specific for EPS [10]. As a consequence, EPS is often recognized in a late stage.

Blood-stained ascites may be present in the early stages of EPS; reports vary between 7 and 50% [9]. Peritoneal function often shows decreased net ultrafiltration (UF) and increased small solute transport [86]. A laparotomy reveals several peritoneal alterations, such as a thickened, brownish peritoneum with several adhesions, and intestines that are partially or totally encapsulated in a thick fibrous tissue. In the last phase a complete or total sclerotic layer may cover the intestines, which gives it the appearance of a cocoon.

Radiological diagnosis

The diagnosis of EPS is often confirmed by different radiological measures. Abdominal ultrasound may demonstrate a thick walled mass containing bowel loops, loculated ascites and, fibrous adhesions at the time of EPS [87]. Plain abdominal film may show gas fluid levels and dilation of the bowel lumen, indicating obstruction. In some patients, calcifications of the bowel wall are visible [88-89].

The CT scan is the most useful in confirming the clinical diagnosis of EPS. Peritoneal enhancement, peritoneal thickening, peritoneal calcifications, adhesions of bowel loops, signs of obstruction and fluid loculation/septation are visible at a CT scan at the time of EPS [90-93]. The scan should be evaluated by a radiologist experienced in assessing scans of PD patients. Unfortunately the CT scan is not reliable for making an early diagnosis of EPS. Tarzi *et al*. studied 13 CT scans taken at least 4 months before the diagnosis of EPS. Only 3 out of 13 scans showed abnormalities, indicating that the CT scan cannot be used as a screening tool [93].

Two case reports on magnetic resonance imaging for the diagnosis EPS have been described. Dilatation of the intestines and circumscribed focal wall thickening, massive ascites with wall

enhancement of the loculated ascites and compression of the bowel were found [94-95]. In conclusion, all the above described radiological measures show signs of obstruction. The CT scan has been tested most frequently for the diagnosis EPS and appears to be the most reliable choice for the definite diagnosis, but is not useful as screening tool.

RISK FACTORS

EPS is probably a multifactorial disease in which several risk factors must be considered. Many risk factors cause peritoneal changes and may play a role in the development of EPS. Recent studies have shown that besides PD duration there are novel risk factors associated with EPS development, such as age, dialysis solutions, ultrafiltration failure and kidney transplantation [3,86,96-97].

Even before the initiation of PD chronic renal failure induces some signs of vasculopathy and thickening of the submesothelial compact zone [98].

The duration of PD is the most important risk factor for peritoneal alterations and EPS [3,10]. This is probably because it represents the exposure to damaging influences, especially the exposure to dialysis fluids. PD fluids contain glucose which is a major cause of peritoneal membrane injury. Peritoneal specimens of PD patients showed that a high glucose load is associated with more submesothelial fibrous tissue [18]. Patients with EPS had been exposed to more glucose compared to controls with similar PD duration [86,99]. Furthermore, glucose forms glucose degradation products (GDP's) during the heat sterilization process of PD fluids. GDP's accelerate the formation of advanced glycation end products (AGE's), which leads to the described peritoneal changes [100].

New PD fluids contain less GDP's. Also, different dialysis solutions without glucose have been introduced such as icodextrin and amino acids [101-102]. Icodextrin has been studied most, especially since it caused episodes of culture negative peritonitis. This was due to contamination with proteoglycans [103]. Recently, some studies have described an association between icodextrin use and increased markers of local inflammation such as, interleukin-6 (IL-6), hyaluronan, tumor necrosis factor (TNF), and fibrin degradation products (FDP), but this was not persistently found [104-108]. Others argued that icodextrin preserves the peritoneal membrane function and mesothelial cell mass [108-109]. Although different studies showed that the majority of EPS patients used icodextrin, it is difficult to determine whether this is due to the abundant ultrafiltration failure in early EPS or this actually has a causative relation with EPS [2,86,96]. A recent case controlled study showed no difference in prescription of icodextrin between EPS and non-EPS patients [97]. At present there is no convincing evidence that icodextrin causes structural alterations in peritoneal tissues or promote EPS.

Since the first reports on EPS, peritonitis episodes are considered risk factors for its development [9,110-111]. In particular episodes caused by the Pseudomonas spp, Staphylococcus Aureus,

Haemophilus Influenza or fungal peritonitis have been incriminated [9,112-113]. The reports on the importance of peritonitis in the development of EPS remain, however, equivocal. The Japanese prospective study showed that 25% of the EPS cases were associated with bacterial peritonitis while a single center controlled study showed no relationship [10]. Recent studies could not confirm the association between peritonitis incidence and EPS [2,86,96]. Nonetheless, the number of peritonitis episodes caused by Pseudomonas spp, Staphylococcus Aureus and fungal peritonitis was higher in the EPS group compared to controls. This indicates that not the incidence, but the cause of the peritonitis may be relevant for the development of EPS [96].

Chlorhexidine was used in the past to sterilize tubing connections. A strong association was found between the use of chlorhexidine and the development of EPS [114]. In the early seventies an association between practolol and 3 cases of EPS have been described [115]. Other beta blockers have not been associated with EPS. Nowadays both are not used anymore.

Observational studies consistently showed that EPS patients are often young [3,12,99]. This finding is difficult to interpret. It could represent a bias by indication since older patients are less likely to remain on PD for a long time and thereby have less exposure risk than young patients. But it may also be considered a risk factor because younger people tend to have a more vivid repair process of damaged tissue. In case of peritoneal damage this may eventually lead to fibrosis.

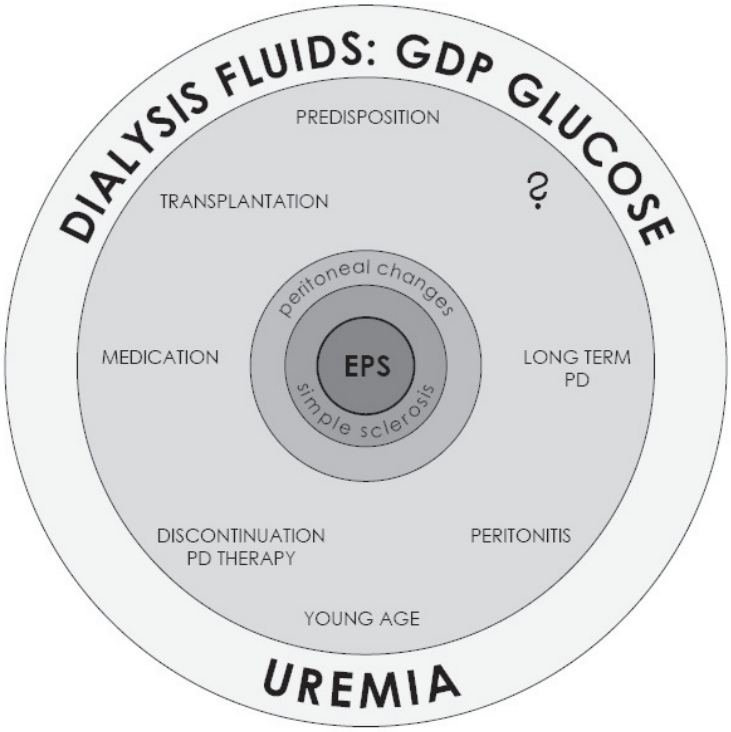
Another common finding in patients with EPS is dysfunction of the peritoneal membrane. EPS patients almost always have a fast transport status and ultrafiltration failure (UFF) [1,86,111,116-117]. The fast transport status reflects the effective peritoneal surface area, which is increased due to neoangiogenesis. This may cause a quick disappearance of the osmotic gradient and as a consequence ultrafiltration problems may develop [118]. In half of the patients with at least 2 years of PD treatment who developed UFF and continued PD therapy for three years or more, EPS developed. Therefore late UFF is sometimes considered a risk factor [119]. However, because the alterations are the result of the development of the disease, it is probably more appropriate to consider UFF as an associated factor.

It is striking that most cases of EPS are diagnosed after the discontinuation of PD. In a prospective study 69% of the Japanese EPS cases occurred after the termination of PD therapy [10]. The most common reasons to switch to hemodialysis therapy were recurrent peritonitis and UFF. Perhaps the cause of EPS after PD discontinuation is the lack of washing out and removal of fibrin, growth factors and cytokines. Subsequent studies with peritoneal lavage after the discontinuation of PD showed no effect in preventing EPS, except for one [10,120-121].

Recent studies have described a high incidence of post-transplantation EPS [1,8,122]. This form develops shortly after kidney transplantation and may be a frequent form of EPS in countries with a high transplantation rate. In the Pan-Thames study the median time after transplantation until EPS was 5.4 months [1]. A Dutch EPS study confirmed that EPS usually develops in the first year after kidney transplantation [96]. Different causes for this phenomenon have been proposed. The profibrotic properties of calcineurin inhibitors (CNI's) may be of influence on

the development of EPS. Both cyclosporin and tacrolimus cause an upregulation of TGF-β and other fibrogenic genes in animal models [123-124]. An experimental study showed that the administration of cyclosporin in rats chronically exposed to a 3.86% glucose based dialysis fluid led to peritoneal angiogenesis and fibrosis [125]. Case-reports of EPS have been described in patients treated with tacrolimus after liver transplantation without chronic renal failure and without PD treatment [126]. Furthermore, the introduction of CNI's has also led to lower and shorter corticosteroid prescriptions after kidney transplantation. Corticosteroids may have a protective effect on the development of EPS, and have been prescribed for treatment of EPS [127]. It remains unclear whether post-transplantation EPS is due to the discontinuation of PD or due to the transplantation itself. Figure 1 summarizes all these risk factors discussed above.

Figure 1 | A schematic representation of all the risk factors important for the development of EPS. All risk factors may lead to peritoneal changes and simple sclerosis and eventually EPS. However a minority of the PD patients undergo all stages.



EARLY DIAGNOSIS

Making an early diagnosis of EPS could prevent the severe onset of this condition by starting therapy in an earlier stage. Between the stage of normal PD and EPS there must be a stage

of pre-EPS. As mentioned previously, no radiological screening tools are available for early diagnosing EPS [93]. Up to now pre-EPS is ill defined, the number of patients that progress to the pre-EPS stage and who do not develop EPS is unknown [128]. Several attempts have been made to stage EPS, for instance Nakamoto [129], who divided the development of EPS in 4 clinical stages: a pre-EPS period, an inflammatory period, encapsulating or progressive period and, complete bowel obstruction/ cocoon (table 2). Functional characteristic features of a pre-EPS stage are UFF and fast solute transport [85-86]. Several diagnostic investigations for an early diagnosis have been studied; they will be discussed in the following paragraphs.

Table 2 | Proposed stages in the development of EPS and their clinical manifestation adapted from Nakamoto et al. [129]

Stage	Pathological findings	Clinical symptoms and investigation
Pre-EPS/	Mesothelial denudation	Ultrafiltration failure
Asymptomatical period	Vasculopathy	Fast transport status
	Peritoneal thickening due to fibrosis	Ascites
	Peritoneal calcifications	
Inflammation period	Inflammation	Loss of appetite, weight loss, diarrhea
	Mononuclear cells	Changes in defecation
	Fibrin degradation products	Fever
		Blood-stained ascites
		Increase in CRP levels, leukocytosis
Progressive or encapsulating period	Inflammation decreases	
	Adhesions and progressive encapsulating	Disappearance of the signs of inflammation
		Gastro-intestinal obstruction :
		Nausea, vomiting
		Abdominal complaints, obstipation
		Ascites, abdominal mass
		Blood stained effluent
Complete bowel obstruction/cocoon	No inflammation	Anorexia and complete ileus
		Abdominal mass

Functional parameters of the peritoneum

The morphological changes of the peritoneum may influence peritoneal function. Verger *et al*. was one of the first to describe the decrease in ultrafiltration and hyperpermeability in a patient with EPS [130]. Since then other studies have found similar results [1,116,131]. However, these features are not specific for the development of EPS. In two recent case controlled studies a number of peritoneal function parameters were longitudinal followed in the years prior to the diagnosis EPS. Ultrafiltration failure (UFF) appeared the predominant early change. This was associated with early loss of residual renal function and accumulative glucose exposure [86,119]. This decrease of ultrafiltration capacity was uncoupled of the also increasing small solute transport. It was

lower in EPS patients than in long term PD patients without EPS with comparable small solute transport status.

In long term PD treatment the small solute transport increases. In EPS patients this may change in the final years prior to EPS when it decreases again. Free water transport decreased in the four years prior to EPS [132]. The combination of an initial increase followed by a decrease in small solute transport, a declining free water transport, and the prominent UFF indicates a possible decreased osmotic conductance. This may reflect a limited intrinsic transport through the interstitium in EPS and is possibly due to interstitial fibrosis [86]. It is probably best to consider these alterations as parameters of the disease and thus as associated factors, rather than considering them as risk factors. In order to determine a fast transport state and UFF the peritoneal function could be assessed annually with a 3.86% glucose peritoneal function test. In combination with a reduced residual renal function and higher glucose exposure, this could identify patients prone to EPS and could suggest a modality switch to HD.

Effluent Markers

Several substances in PD effluent may serve as a surrogate marker for structural and functional alterations of the peritoneum. Some of these substances have been studied specifically for the diagnosis of EPS. Although there is no clear consensus, cancer antigen 125 (CA125) appears to be a marker for mesothelial cell mass [133-135]. In the years prior to the EPS diagnosis CA125 values were extremely low, which could represent the denudation of mesothelial mass. IL-6 is a marker for inflammation and 2 years prior to the diagnosis EPS values were very high. The combined appearance rates of CA125 and IL-6 had a sensitivity of 70% and a specificity of 100% for the diagnosis of EPS in patients with UFF. This makes them potentially useful for an early diagnosis of EPS [136].

All growth factors and cytokines involved in the process of peritoneal fibrosis and neoangiogenesis are potential (early) diagnostic markers for EPS. However, few studies investigated effluent markers. TGF-β appears important in the development of EPS. An inactive form of TGF-β has been demonstrated in peritoneal effluent, but the active form is not soluble [137]. Besides, soluble TGF-β is difficult to analyze in plasma or effluent and is therefore not useful in the diagnosis of EPS [36]. Hyaluronan is an important substance in the extracellular matrix. Hyaluronan measured in effluent increases with the duration of PD and in patients with UFF. However, it was not increased in patients with peritoneal adhesions [138]. Whether hyaluronan is an early diagnostic marker of EPS still needs to be studied. Hydroxyproline in tissue is a gold standard for the assessment of fibrosis. However, in an experimental study it appeared not useful as a marker for peritoneal fibrosis [139]. Effluent MMP2 has been studied as a diagnostic marker and seemed to correlate with profibrotic events, but has to be tested for EPS [59].

THERAPY

Supportive care with either enteral or parenteral nutrition has been shown to be beneficial and should be the mainstay of the treatment [140]. Surgical treatment of EPS is mostly performed in Japan. Kawanishi *et al*. showed that enterolysis is a successful alternative to the treatment of the abdominal cocoon. 96% of the patients reached restoration of abdominal transition [141-142]. During this time consuming operation (on average 6.9h) the fibrotic tissue is carefully peeled off the visceral and parietal peritoneum. Nowadays this operation is also conducted in Manchester [79]. Because of the risk of reoccurrence, patients are treated with high dose of immunosuppressives immediately after operation.

The rationale behind immunosuppressive therapy in treatment of EPS is to treat the preceding inflammatory state. Successful treatment of EPS with immunosuppressive therapy has been described with corticosteroids [85,127,143], azathioprine, mycophenolate mofetil (MMF) and sirolimus [144-148]. These reports are mostly anecdotal and probably this is a biased view, because negative results are not likely to be reported.

Tamoxifen is a nonsteroidal anti-estrogenic drug that showed to be successful in several fibrosing diseases such as retroperitoneal fibrosis [149]. Several small case-series have described positive effects of this drug on the treatment of EPS with improvement of the intestinal function and a decrease of the inflammatory features [150-151]. A large English trial could not confirm this effect, perhaps due to the patient selection, as only 33% had the clinical symptoms of severe EPS [1]. Recently, an retrospective analysis of the Dutch EPS study showed a decreased mortality in EPS patients treated with tamoxifen [152]. Adverse effects of tamoxifen in EPS patients, like tromboembolic events have been described by Eltoum *et al.* [151]. The risks of these events are probably outweighed by the devastating consequences of EPS. Therefore a trial of corticosteroids and/or tamoxifen is recommended when EPS is diagnosed.

Angiotensin II (ATII) inhibitors may be important in the prevention and treatment of EPS. ATII has proinflammatory and profibrotic effects which act through transforming growth factor-beta (TGF-β) [153-154]. The antifibrotic features of ATII inhibitors have been shown in renal fibrosis [155]. In vitro studies revealed that the production of TGF- β induced by high glucose concentrations in HPMC is inhibited by angiotensin converting enzymes inhibitors (ACEi) and angiotensin receptor blockers [153,156]. Also in EPS models less fibrosis was found after ACE inhibition [157]. In PD patients, ACE inhibitors appear to have a positive effect on the peritoneal function [158], but a protective effect for EPS has not been found [159].

CONCLUSIONS

What a nephrologist should know about EPS

The increased attention for EPS has led to more insight in the pathophysiology of this complication. It has an impressive time course. Although the prevalence of EPS may have increased, it remains a rare disease and contributes marginally to over-all mortality of PD patients.

A scheme linking the various proposed stages of EPS to pathological and clinical findings is given in Table 2. The diagnosis of EPS is made on the presence of bowel obstruction and a CT scan. Identifying EPS in an early stage remains difficult. Ultrafiltration failure and the appearance rates in effluent of CA-125 below 33mL/min and IL-6 above 350mL/min may be specific for the development of EPS. Patients with a prolonged PD therapy and high intraperitoneal glucose exposure, who develop ultrafiltration failure are prone to EPS and should probably discontinue PD therapy.

There may be an association with transplantation, a phenomenon known as post-transplantation EPS.

Patients have an increased risk of developing EPS when PD is discontinued, especially when UFF is present. The decision of switching patients to hemodialysis should take into account the high possibility of infection, the hemodynamic instability and different quality of life. Although there are no data on the prospective change of PD to HD, it was concluded by an ISPD study group that changing PD to HD in order to prevent the development of EPS is unnecessary [160].

Once EPS is suspected the outcome is poor. To date, there is no consensus on therapy, but besides supportive care a trial of corticosteroids and/or tamoxifen should be given. Adhesiolysis may be effective but only if performed by a surgeon familiar with EPS.

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Chapter 3.1

Increasing incidence of severe Encapsulating Peritoneal Sclerosis after kidney transplantation.

Mario R. Korte, Marieke Yo, Michiel G.H. Betjes, Marien W. Fieren,
Jan C.L.M. van Saase, Walther H. Boer, Willem Weimar, Robert Zietse.

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ABSTRACT

Background

Encapsulating peritoneal sclerosis (EPS) is a rare complication of peritoneal dialysis (PD), with a high mortality. The reported overall prevalence of EPS varies between 0.7 % and 3.3 %. It is our impression that in recent years an increase in incidence of EPS has occurred.

Methods

A retrospective analysis of the cases with severe EPS at two university hospitals in The Netherlands. EPS was defined according the criteria of the ISPD. PD, transplantation and patient related variables were investigated.

Results

Eighteen cases (13 male / 5 female, age 39.8 ± 10.2 years) of severe EPS were identified in the period 1998-2005 (mean time on PD of 71.2 ± 45.6 months). The majority of patients were on PD for a shorter period than five years. Thirteen patients developed EPS in 2004 and 2005, compared to one or two patients in the previous years. The total number of patients on PD did not change in time. Fifteen patients had a kidney transplantation and eight patients developed EPS shortly after this (mean time from kidney transplantation to EPS diagnosis was 39.3 ± 71.1 months). Seventeen patients used icodextrin and the mean time on icodextrin was 34.2 ± 22.2 months.

Conclusions

This study confirms our impression that the incidence of EPS has increased in the recent years. The design of this study precludes conclusions on the cause of the increased incidence, but the remarkable preponderance of EPS patients with a functioning renal allograft suggests a pathogenetic role of kidney transplantation.

INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) is a life threatening complication of peritoneal dialysis (PD). Since the first report in 1980 [1], the reported overall prevalence of EPS has varied between 0.7 % in Australia [2], 2.5 % in Japan [3] and 3.3 % in a single center study in Great Britain [4]. Because of the slow progression of intestinal cocooning, it is frequently not recognized until it has developed into a severe stage. Often the diagnosis is made after an infective peritonitis, which recovers slowly, despite adequate antibiotic treatment. Thereafter, the condition usually persists as a non-infectious inflammatory abdominal condition [5]. Because of progressive ultrafiltration failure, patients are often switched to hemodialysis (HD). Remarkably, the majority of patients that develop progressive EPS do so after the cessation of peritoneal dialysis. It has been suggested that this is due to the absence of continued lavage of fibrin [3].

The diagnosis of EPS is difficult, mainly because a uniformly used definition is lacking. Most clinicians use the criteria defined by the Ad Hoc Committee of the International Society of Peritoneal Dialysis (ISPD) [6]. This committee defined EPS as: "A clinical syndrome with persistent, intermittent or recurrent presence of intestinal obstruction with or without the existence of inflammation parameters and the existence of peritoneal thickening, sclerosis, calcifications and encapsulation confirmed by macroscopic inspection or radiological findings". It is our distinct impression that in recent years we are witnessing a marked increase in the incidence of EPS. In order to investigate whether this suspicion is justified, we initiated an analysis of the occurrence of EPS in two university hospitals in The Netherlands.

METHODS AND DESIGN

Design

This is a retrospective study at the dialysis and transplantation departments in two university hospitals in the Netherlands (Erasmus Medical University Center in Rotterdam and the Utrecht Medical Center in Utrecht). Both centers serve as regional transplantation centers. Cases were identified by retrospective investigation of the medical records of both PD populations in the period 1998-2005. All medical records of patients with EPS were reviewed in detail.

Classification of EPS

Encapsulating peritoneal sclerosis was defined according the criteria developed by the Ad Hoc Committee of the International Society of Peritoneal Dialysis [6]. Using this definition of EPS limits the study population to severe forms of EPS presenting with intestinal obstruction, but minimises the possibility of missing patients in the retrospective analysis. The date of diagnosis of EPS was defined as the date at which the patient fulfilled the diagnostic criteria of EPS. All patients underwent at least one abdominal CT scan.

Variables

Several PD-related and patient-related variables were investigated. The total duration on PD was calculated by adding all separate episodes on PD. Whenever a patient was on some other form of renal replacement therapy for longer than a week, this time was not included in the time on PD. Ultrafiltration failure (UFF) was defined by an ultrafiltration volume of less than 400 ml on a 4-hour dwell with a glucose concentration of 3.86 %. As an outbreak of icodextrin associated peritonitis occurred between November 2001 and July 2002 [7], we also determined which patients had been treated with icodextrin during that period.

When patients underwent a kidney transplantation, the time after the first transplantation until EPS diagnosis was also calculated.

Statistics

Data were entered in SPSS 12.0.1 datamanager (Chicago, USA). Statistical analysis was performed using a Pearson's chi-square test for trend analysis. A p-value below 0.05 was considered to indicate statistical significance. All data are presented as mean ± SD.

RESULTS

Patients

Eighteen cases (13 male / 5 female, mean age 39.8 ± 10.2 years) of severe EPS were identified. All patients underwent abdominal CT scanning and had moderate to severe abdominal complaints of obstruction. All patients fulfilled the ISPD criteria. Twelve of these patients were treated at the Erasmus Medical Center and six patients at the Utrecht Medical Center. Thirteen patients were not on PD at the time of diagnosis and were either on hemodialysis (4) or had received a functioning kidney graft (9). Patient's characteristics are described in table 1.

Patients had a mean time on PD of 71.8 ± 44.9 months at the time of EPS diagnosis. Seventeen patients used icodextrin and the mean time on icodextrin was 34.2 ± 22.2 months. Seven patients were treated with icodextrin within the period between November 2001 and July 2002, when an outbreak of icodextrin associated peritonitis occurred. In these patients there was no history of aseptic peritonitis.

Sixteen patients (89 %) developed at least one episode of peritonitis during the treatment with PD (Table 1). The mean number of peritonitis episodes was 0.54 ± 0.73 for every 12 months of PD. There was no specific micro-organism responsible for the majority of the peritonitis episodes.

Table 1 | Patient and PD characteristics

Case	Gender	Renal disease	PD time	UFF	Peritonitis episodes	CT scan	Outcome	Therapy	EPS related death
1	M	Nephrolithiasis	120	Yes	3	Dilatation, peritoneal thickening	Deceased	TPN	Yes
2	M	Alport's Syndrome	48	Yes	1	Dilatation, peritoneal thickening, fluid pocket, septation	Deceased	TPN	Yes
3	M	MPGN II	71	NA	2	Fluid pocket, dilatation, peritoneal thickening	Deceased	TPN	Yes
4	F	Chronic pyelonephritis	50	No	13	Narrowing, calcification, mesenterial thickening	Deceased	TPN	Yes
5	M	FSGS	83	Yes	3	Air-fluid levels, mesenterial thickening	Deceased	NA	Yes
6	M	FSGS	222	Yes	3	Dilatation, peritoneal and mesenterial thickening	Deceased	NA	Yes
7	M	Primary hyperoxalosis	18	No	1	Fluid pockets	Deceased	Prednisone, TPN	Yes
8	M	Diabetic nephropathy	43	NA	0	Fluid pocket, Dilatation, peritoneal thickening	Alive	TPN	
9	M	Alport's syndrome	104	Yes	4	Dilatation, peritoneal thickening	Alive	TPN	
10	F	Atherosclerotic	73	Yes	1	Fluid pocket, septation, peritoneal thickening	Alive	TPN	
11	M	Glomerulopathy	54	NA	1	Dilatation	Deceased	TPN	No
12	F	MPGN	50	Yes	3	Fluid pocket, peritoneal thickening	Alive	TPN	
13	F	Preeclampsia	90	No	1	Peritoneal thickening, fluid pockets	Alive	none	
14	M	Refluxnephropathy	79	NA	2	Dilatation, peritoneal thickening, fluid pockets	Deceased	Prednisone, TPN	Yes

Table 1 | Patient and PD characteristics (continued)

Case	Gender	Renal disease	PD time	UFF	Peritonitis episodes	CT scan	Outcome	Therapy	EPS related death
15	F	Hypertensive nephropathy	56	No	2	Dilatation, fluid pockets	Alive	Solumedrol, Prednisone	
16	M	HUS	46	Yes	5	Calcification	Alive	Prednisone, tamoxifen	
17	M	Calcineurin toxicity	27	Yes	1	Peritoneal thickening, fluid pockets	Alive	Prednisone, tamoxifen, colchicin	
18	M	Glomerulonephritis undetermined	47	No	0	Ascites, dilatation, peritoneal thickening	Alive	Prednisone, tamoxifen	

Time on PD in months, peritonitis expressed as total number of per patient, UFF means ultrafiltration failure, TPN total parenteral nutrition.

Fifteen patients (83 %) had a history of kidney transplantation, with eight patients having multiple transplantations. The mean time from the last kidney transplantation to the diagnosis of EPS was 39.3 ± 71.1 months.

Incidence

The PD population, treated in the period 1998 to 2005, comprised of 418 patients (206 patients in Rotterdam and 212 in Utrecht). In both 1998 and 1999 there was one EPS case each year, in 2000 and in 2001 no cases, in 2002 one case and in 2003 two cases. However, in 2004 and 2005 we observed three and ten cases, respectively. The number of patients on PD did not change significantly in time throughout the whole period in both centers. Given the great number of transplanted EPS patients, PD patients at risk for developing EPS were defined as either having previous PD treatment or patients with a history of PD having undergone renal transplantation no more than three years ago. Although there was a steady increase in patients alive with functioning kidney graft and a history of PD (in Rotterdam), the increasing incidence of EPS exceeded the increase in patients at risk (Figure 1, $p = 0.038$, using a Pearson's chi-square test for trend analysis).

Outcome

Nine patients died, resulting in an overall mortality of 50 %. The cause of death was attributable to EPS in eight patients. These patients had progressive abdominal complaints with malabsorption, bowel obstruction, developing peritonitis or bowel perforation with subsequent sepsis. One patient died because of lung cancer. Therapy consisted of total parental nutrition (TPN), surgical therapy (minimal adhesiolysis and catheter extirpation in 7 patients) and medication. Six patients were treated with corticosteroids. Three patients received tamoxifen and one received colchicin. One patient received azathioprine.

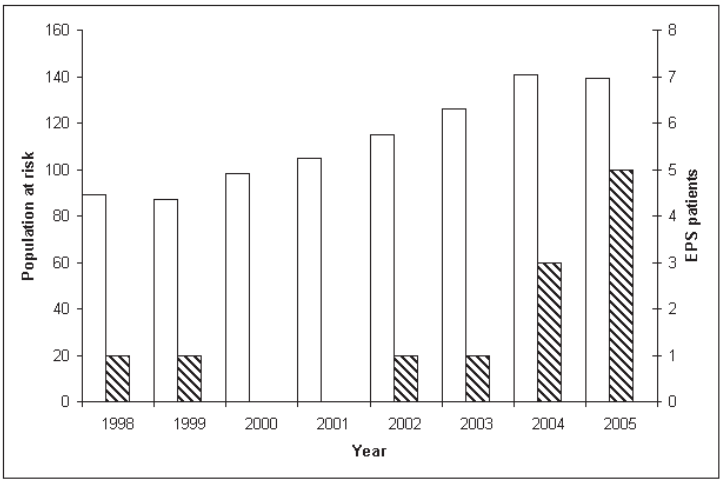

Figure 1 | EPS cases and the population at risk for EPS in Rotterdam center in 1998-2005.
Population at risk is defined by patients with a kidney transplant and a history of PD (open boxes). EPS cases are shown (lined boxes) in Rotterdam. Significant trend of increase of EPS independent of the increase in the defined population at risk (p = 0.038, chi square trend analysis).

DISCUSSION

This study shows that in two Dutch university hospitals the incidence of severe EPS has increased significantly in the period from 1998 to 2005 in stabile PD populations. Earlier reports also appeared to indicate an increased incidence of EPS [2,8]. In these retrospective surveys the apparent increase was related to the duration of PD treatment, with a substantial increased prevalence after 5 years of PD [2]. However, in our study the majority of patients were on PD for a considerably shorter period than five years when they developed EPS.

The pathophysiology of EPS is unknown, but it appears EPS is not solely the result of progression of peritoneal remodelling that happens with PD. Remodelling may form a background on which intestinal encapsulation with the extensive fibrin depositions can develop. A *second hit,* has therefore been postulated to aggravate the damage to the peritoneum and to induce the further development of EPS [9]. Although limited by the retrospective nature of this study, we investigated whether infection [2] or type of dialysis solution could be such a second hit [10-12]. However, the mean number of peritonitis episodes was only 0.54 ± 0.73 for every year of PD and we found no increase of specific microorganisms in the EPS population. Almost all of the patients developing EPS used icodextrin. Since half of our patients were treated with icodextrin during the period, in which the outbreak with icodextrin related aseptic peritonitis occurred [7,13], a possible contribution of icodextrin to the development of EPS cannot be entirely excluded and has to be evaluated.

As the majority of EPS patients underwent a kidney transplantation at some point in time. Transplantation, with subsequent immunosuppressive treatment, could also be considered as

the *second hit* in the development of EPS. This suggestion is strengthened by the fact that, in some patients, EPS developed shortly after kidney transplantation. It remains unclear whether the transplantation procedure itself or the concomitant medication is responsible. Cessation of peritoneal lavage after transplantation could lead to diminished clearance of fibrin and may thus contribute to peritoneal fibrosing. Also, the known profibrotic effects of calcineurin inhibitors (CNI's) may have had an effect on the development of EPS [14-15].

In conclusion, this study confirms our impression that the incidence of EPS has increased in recent years. The design of this study precludes conclusions on the cause of the increased incidence, but the remarkable preponderance of EPS patients with a functioning renal allograft may point towards a pathogenetic role of kidney transplantation. A multicenter study is urgently needed to address this increasing threat to the patients on PD.

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Chapter 3.2

Risk factors associated with increased incidence of Encapsulating Peritoneal Sclerosis in Dutch EPS study

Mario R. Korte , Denise E. Sampimon, Hester F. Lingsma, Marien W. Fieren, Caspar W.N. Looman, Robert Zietse, Willem Weimar, Michiel G.H. Betjes on behalf of the investigators of the Dutch Multicenter EPS Study.

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ABSTRACT

Objectives

Encapsulating peritoneal sclerosis (EPS) is a serious complication of peritoneal dialysis (PD) with a multifactorial pathophysiology and possible increasing incidence. The aims of the study were to investigate the incidence of EPS in recent years and to evaluate the independent associations of PD duration, age, dialysis fluids and kidney transplantation with EPS.

Methods

A multicenter case controlled study was performed in the Netherlands from January 1st 1996 until July 1st 2007. The population comprised of 63 cases of EPS and 126 control cases. Control cases were selected from the national registry and matched for the date of start PD. Associations were analysed using a log linear regression model. Primary outcome was appearance of EPS.

Results

EPS incidence increased until 2005, despite a stable PD population. The increase in incidence appears to be followed by a small decrease in 2006. EPS patients were younger at start of PD, compared with controls (34.7 ± 15.4 vs. 51.5 ± 14.7 years, $p<0.0001$). The cumulative period on PD was longer in the EPS than in the control group (78.7 ± 37.8 vs. 32.8 ± 24 months, $p<0.0001$). The cumulative period on icodextrin was longer in EPS patients (32.7 ± 23.3 vs. 18.1 ± 15.7 months, $p=0.006$). More EPS patients had kidney transplantations compared with the controls (47 vs. 59, $p<0.0001$). With regard to time after transplantation, the yearly probability of EPS increased in the year after transplantation from 1.75% to 7.5%. In multivariate regression analysis cumulative PD time, age at start PD, transplantation, time since last transplantation until EPS, calendar time, time on icodextrin and ultrafiltration failure (UFF) were independently associated with EPS. Transfer from PD to hemodialysis, for other reasons then suspected EPS, could not be identified as a risk factor for EPS.

Conclusions

The incidence of EPS has increased until 2005. PD duration, age at start PD, kidney transplantation, time since last transplantation, UFF, and time on icodextrin were associated with a higher risk of EPS.

INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) is a rare but serious complication of peritoneal dialysis (PD) with a considerable morbidity and mortality. In EPS patients extensive fibrosing of the peritoneum leads to symptoms of malnutrition and intermittent bowel obstruction. Finally, encapsulation may result in a complete cocooning of the bowel with clinical symptoms of ileus.

The pathophysiology of EPS is probably influenced by multiple factors. The widely accepted second hit theory assumes a progressively damaged peritoneum by prolonged use of dialysis fluids, whwich may be complicated by factors that aggravate the peritoneal sclerosis [1]. The bioincompatibility of dialysis fluids, in particular the unphysiologically high glucose concentrations and the presence of glucose degradation products are thought to be key elements in this process [2]. Some agents have been identified as possible second hit, such as chloorhexidine [3] and practolol [4], and are subsequently not used anymore. The data on the role of the presence of microbial peritonitis on the development of EPS remain equivocal [5-7]. The incidence of EPS appears to increase with prolonged PD duration [8-9]. This was also shown in recent cohort studies [10-11]. However until recently the association of PD duration was previously not multivariate analysed using larger controlled studies. In recent years other candidate factors besides PD duration came forth from a number of observational single and multicenter studies. These included cessation of peritoneal lavage [12-13] and possibly factors associated with kidney transplantation [14].

The reported prevalence of EPS ranges from 0.7 % to 3.3 % [5,10,12,15]. The majority of the experience comes from Japan, where patients tend to be on PD for a longer period because the availability of kidney transplantation is limited [12].

Recently, we reported an increased incidence of EPS over the last 10 years [16]. Particularly striking was the occurrence of EPS shortly after kidney transplantation. More definite conclusions could not be made due to the limited number of patients and the absence of a control group.

Therefore, we designed this case controlled study in which eight large centers participated, giving 26% coverage of the total Dutch PD population in the period 1996-2007. This design enabled us to investigate the incidence of EPS and investigate the separate influences of PD duration, age, peritonitis episodes, dialysis fluids and kidney transplantation on the development of EPS.

SUBJECTS AND METHODS

Design

The design of the study was a retrospective nested case controlled multicenter study. This is closest to a cohort study in which a defined cohort of PD patients is followed until some develop EPS. For each case two control patients were selected. We matched cases and controls for the start date of PD (calendar time) since the general changes in time (such as changes in surgical and nursing staff or procedures could be confounders. This matching on calendar time brings the design close to a cohort study: each set of a case and its controls start PD at a certain time point on which they theoretically have the same probability to develop EPS. Patients and controls were deliberately not matched for PD duration to allow for an evaluation of this potential EPS risk factor, throughout the study period and in relation to other potential risk factors. To assure comparability of cases and controls in this case control design the cases and controls without EPS in our study were taken from the same source population, a clearly defined cohort of all PD patients in the Netherlands (RENINE, Registratie Nierfunctievervanging Nederland). In this registry all Dutch end stage renal disease (ESRD) patients with renal replacement therapy are registered [17]. This makes the study a nested case-control study. The matching of the cases was done by using an Access generated query in the RENINE database. The controls are matched on date start PD closest to the EPS case (one control before and one after start date PD). The participating centers were five university hospitals and three large teaching hospitals. Cases in the period 1996 - 2007 were identified. The study protocol was approved by the medical ethics committee of the Erasmus University Medical Center, Rotterdam.

Classification and diagnosis of EPS

EPS was defined according the criteria developed by the International Society of Peritoneal Dialysis [18]. It is defined as a clinical syndrome with persistent or recurrent presence of intestinal obstruction with or without the existence of inflammation parameters and the existence of peritoneal thickening, sclerosis, calcifications and encapsulation confirmed by macroscopic inspection or radiological findings.

Using this definition the studied population was limited to severe forms of intestinal obstruction. This minimised the possibility of missing patients in the retrospective analysis. Medical records of patients with EPS were reviewed in detail. EPS diagnosis was retrospectively set at the date at which the diagnosis fulfilled the definition of EPS and was confirmed by two separate nephrologists. All patients underwent abdominal CT scanning.

Investigated variables

Demographics, PD and patient related variables were investigated. The duration on PD was calculated by adding all separate episodes on PD. Whenever a patient was on other renal replacement therapy, for longer than a week, this time was not included. Follow-up time was

defined as the period from start PD until EPS diagnosis in the cases and death or end of study in the controls. Calendar time was defined as the years since the chosen reference date, close to which the first patient in the study started PD (01-01-1983).

Small solute transport was analysed using the last available peritoneal equilibrium test. Ultrafiltration failure was defined by ultrafiltration volume of less than 400 ml on 4-hour 2000 ml dwell with 3.86 % glucose concentration [19] or symptoms of overhydration and necessity of increasing glucose concentrations (one or more daily use of 3.86%). All ever used dialysis fluids were reported. Since the introduction of icodextrin, the use of it was documented very accurate. Therefore the time on icodextrin could be assessed.

To assess the effect of transfer from PD to HD on EPS development, patients transferring with a suspected EPS were excluded. This was because of possible confounding by indication. Suspected EPS was defined as having intermittent intestinal obstruction with ultrafiltration failure and/or inconclusive evidence for EPS by radiological CT scanning (defined by Tarzi et al.[20]), without any other explanation for the symptoms. These criteria are also used in the current Dutch EPS registry [21].

Variables related to kidney transplantation were also investigated. Time since transplantation until EPS was defined as the time from the last transplantation until EPS or end of study (in control patients).

Statistical analysis

Primary outcome was appearance of EPS. Means were compared using unpaired t-tests. Proportions were compared with chi-square tests.

We analyzed the data by using a piecewise exponential model [22-23]. This model allows different time-dependent covariates, such as PD duration and time since transplantation to be taken into account. The theoretical model was implemented by fitting a Poisson log-linear regression model in a dataset in which the follow up history of each patient was divided in steps of maximally one year. If during a year, for example, transplantation was performed, the year was divided in two pieces. For every piece the outcome was established (EPS or not at the end of the period) and values for all relevant predictors. So we constructed a new database with more than one line - at least one for each year of follow up - per patient. The fitted Poisson model had EPS as outcome, the log of the length of follow up as offset variable and PD duration, age, transplantation, time since last transplantation, calendar time, follow up time, peritonitis episodes, transfer from PD to HD for other reasons than suspected EPS, time on icodextrin and presence of ultrafiltration as pre-specified predictors for the midpoint of the time step. All predictors were tested both univariate and multivariate.

The model estimates odds ratio's (OR) given the other variables, so these estimates are valid and by definition cannot be caused by differences in other possible risk factors included in the model.

There is an adjustment for the differences in other risk factors than the one of interest. All multivariate ORs are conditional on the difference in the other risk factors. For example, the OR for age at start PD is given considering the differences in cumulative PD time. That means that two patients with the same PD time, the one who started PD younger has a higher risk on EPS.

Statistical tests were done in SPSS 15.0.1 datamanager (Chicago, USA) and R statistical software. If data were not available, these were reported as missing.

RESULTS

Incidence of EPS

In the period January 1st 1996 until July 1st 2007, 63 cases of EPS occurred in the participating centers. Within the study prevalence was calculated using only the number of patients in the period January 1st 1996 until January 1st 2007. In this period there were 61 patients diagnosed with EPS and 2022 patients were on PD in the participating centers. Six EPS patients were excluded from these 61 patients, because they had originally started PD in other PD centers than those participating, resulting in a prevalence of 2.7%.

The annual occurrence of EPS increased until 2005 (Figure 1). Thereafter a small decrease in 2006 was present. The annual incidence in the PD population could not be calculated since the diagnosis of EPS was often made when PD was already discontinued. The overall PD population slightly decreased in the study period.

Patient demographics

The 63 EPS patients with 126 controls resulted in a study population of 189 patients. Cases and controls were equally distributed among the centers. EPS patients were significantly younger

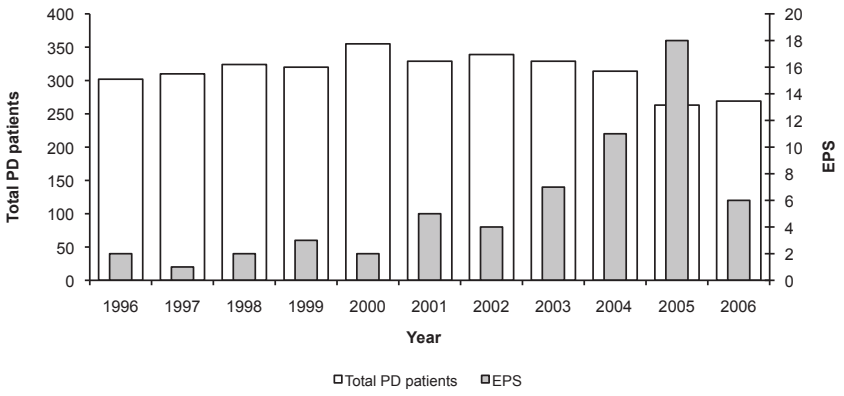

Figure 1 | Annual occurrence of EPS and overall PD population in period 1996-2006.

Table 1 | Patient characteristics

	EPS		
	Yes (63)	**No (126)**	***P*-value**
Gender (f/m)	21/42	43/83	NS
Age			
Age at diagnosis EPS	43.4 ± 14.4		
Age at start PD	34.7 ± 15.4	51.5 ± 14.7	0.0001
Age at death or end of study	45.1 ± 14.1	57.9 ± 13.4	0.0001
Periods			
Time until death after EPS diagnosis	20.5 ± 18.3		
Follow-up	124.8 ± 60.6	74.5 ± 62.3	0.0001
End of study (%)			
Deceased	34 (54.0)	83 (65.9)	NS
Alive, functioning graft	12 (19.0)	32 (25.4)	NS
Alive HD	17 (27.0)	8 (6.3)	0.0001
Alive, PD	0	3 (2.4)	NS

Age and periods are reported in respectively mean years and months ± SD. F means female, m male, PD peritoneal dialysis, HD hemodialysis. Follow-up is defined as time since start PD until EPS, death or end of study. Means were tested using t-test, proportions were compared with chi-square tests. NS means not significant.

Table 2 | Causes of end-stage-renal-disease

	EPS	**Control**
	63 (%)	**126 (%)**
Renal vascular disease due to hypertension	10 (15.8)	19 (15.0)
Chronic renal failure, aetiology uncertain	5 (7.9)	15 (11.9)
Glomerulonephritis, histologically examined	6 (9.5)	20 (15.8)
Pyelonephritis/Interstitial nephritis-cause not specified	12 (19.1)	17 (13.5)
Focal segmental glomerulosclerosis	6 (9.5)	0
Polycystic kidneys	1 (1.6)	9 (7.1)
Diabetes Type II (non-insulin dependent)	1 (1.6)	10 (7.9)
Diabetes Type I (insulin dependent)	0	7 (5.5)
IgA nephropathy	3 (4.8)	3 (2.4)
Hereditary nephritis with nerve deafness	3 (4.8)	1 (0.8)
Lupus erythematosus	0	4 (3.2)
Haemolytic Uraemic Syndrome	3 (4.8)	0
Other identified renal disorders	13 (20.7)	21 (16.9)

Causes were defined according the EDTA diagnosis definitions. Glomerulonephritis, pyelonephritis and renal vascular disease are composed of the related specified renal disease diagnoses. Other identified renal disorders are composed of various renal disease diagnoses.

than controls when they started with PD (Table 1). Twenty-nine patients were diagnosed with EPS when they were on hemodialysis (HD) and eighteen patients had a functioning kidney transplant. Follow-up from start PD until EPS (or end of study) was longer in EPS patients compared with controls (Table 1). Mortality was not significantly different between the groups. From a total of 34 EPS patients who died, 30 deaths were attributable to EPS related factors. The ESRD causes are shown in Table 2.

PD related variables

The cumulative period on PD was significantly greater in the EPS group in comparison to the controls (Table 3). EPS patients experienced more peritonitis episodes than controls (Table 3). Less peritonitis episodes occurred per patient year in the EPS group compared to the controls. From the various micro-organisms cultured during peritonitis only fungi were more often present in EPS patients (8 vs. 3 episodes in total, p=0.02). *Staphylococcus Epiderdimis* was less often

Table 3 | PD related variables

		EPS		
		Yes	**No**	***P*-value**
Time on PD		78.7 ± 37.8	32.8 ± 24	0.0001
Peritonitis				
	Peritonitis episodes	4.1 ± 3.8	2.4 ± 2.8	0.0020
	Peritonitis per patient-year	0.7 ± 0.8	1.1 ± 1.4	0.0090
Transport status (%)				
	Slow	2 (3.2)	2 (1.6)	NS
	Slow Average	5 (7.9)	29 (23)	0.0010
	Fast Average	17 (27)	33 (26.2)	NS
	Fast	25 (39.7)	12 (9.5)	0.0001
	Unknown	14 (22.2)	49 (38.9)	
Ultrafiltration failure (%)				
	Yes	38 (60.3)	19 (15.1)	0.0001
	No	14 (22.2)	85 (67.5)	0.0001
	Unknown	11 (17.5)	22 (17.5)	
Dialysis fluids				
	Dianeal	58	107	NS
	Physioneal	31	20	0.0001
	Icodextrin	49	28	0.0001
	Time on icodextrin	32.7 ± 23.3	18.1 ± 15.7	0.0060
	Icodextrin per patient-year	0.47 ± 0.3	0.53 ± 0.5	0.6

Periods and episodes of peritonitis are reported as mean ± SD. Time is reported as months. Other parameters are reported as number of patients (%). Ultrafiltration failure is defined as < 400 ml ultrafiltrate assessed with standard 3.86% PET or the presence of clinical symptoms. Dialysis fluids were scored if ever used in the period 1996-2007. Time on icodextrin is calculated as time (months) per patient using icodextrin. Icodextrin per patient-year is time on icodextrin calculated per year treated with PD. Means were tested using t-test, proportions were compared with chi-square tests. NS means not significant.

found in EPS patients (35 vs. 42 episodes, p=0.01). There was no difference in episodes with *Pseudomonas, Staphylococcus Aureus* or culture negative peritonitis.

EPS patients were more often fast transporters, but a relatively large number of missing tests was present in the controls (Table 3). The majority of EPS patients had ultrafiltration failure (60.3%). New dialysis solutions as a lactate/bicarbonate solution (Physioneal ®) and icodextrin (Extraneal ®) were more often used in EPS patients (Table 3). The cumulative period with use of icodextrin was significantly longer in EPS patients (Table 3). For other solutions the time periods could not be assessed accurately and are therefore not shown. The accumulative glucose load could not be retrieved accurately.

Transfer from PD to HD

In total 34 patients with a final diagnosis of EPS were transferred from PD to HD (54.0%). Of these, 22 were transferred to HD because of suspected EPS. Twelve patients transferred to HD for other reasons than suspected EPS (19.1%). Seven patients were transferred because of peritonitis, three patients because of ultrafiltration failure, one because of exit site infections and in one patient the reason was not clearly documented. In the control group 37 patients (29.4%) transferred from PD to HD.

Table 4 | Kidney transplantation and immunosuppressive medication

	EPS		
	Yes (63)	**No (126)**	***P*-value**
Patients transplantated	47	59	0.0001
Number of transplantations	1.6 ± 0.9	1.3 ± 0.7	0.05
Age at last transplantation	36.4 ± 13.4	44.3 ± 13	0.0030
Time start PD - last transplantation	68.9 ± 60.5	25.6 ± 61	0.0001
Immunosuppressive medication			
CNI	40	53	0.0080
tacrolimus	19	17	NS
CsA	27	37	NS
Prednisone	43	55	0.0001
MMF	27	27	NS

Age and time are reported respectively in mean years and months ± SD. Number of transplantations is reported in means ± SD per transplanted patient. Immunosuppressive medication is scored per patient, if ever used in the period 1996-2007 for kidney transplantation. CNI means calcineurin inhibitors, CsA cyclosporin and MMF mycophenolate mofetil. Means were tested using t-test, proportions were compared with chi-square tests. All patients were used for calculation of p-values. NS means not significant.

Variables related to kidney transplantation

Relative more EPS patients had kidney transplantations in comparison to controls (47/63 vs. 59/126, p<0.0001), with more transplantations per patient (Table 4). Twenty-one patients with a kidney transplant (44.7% of total transplanted EPS patients) developed EPS within 2 years after the last kidney transplantation. The median time from last transplantation to EPS was 12.4 months (IQR 39.4). Figure 2 shows the univariate relationship between time since the last transplantation and the yearly probability on the EPS development. Prior to the last transplantation the risk for developing EPS was 1.75% in the overall cohort. The year following the transplantation the risk increased to 7.5%. After the first twelve months this decreased again with 7.0% per year.

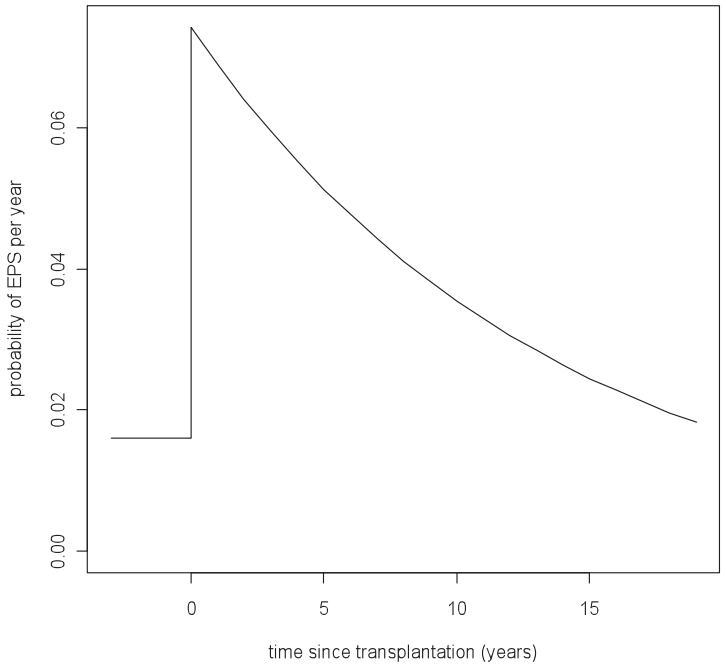

Figure 2 | Effect of time after last transplantation on EPS.
Effect of time after last transplantation on development of EPS calculated with univariate analysis. After the last transplantation the yearly probability on EPS increased in this cohort from 1.75 % to 7.50 % in first year after transplantation. Thereafter this risk decreased each year with 7%.

Regression analysis

Univariate analysis showed that time on PD, age at start PD, transplantation, time since last transplantation until EPS diagnosis (or end of study in control patients), calendar time (years since the reference date close to which the first patient started PD), period of using icodextrin, ultrafiltration failure and follow up time were associated with EPS. Multivariate regression analysis showed that time on PD, age at start PD, transplantation, time since last transplantation

Table 5 | Univariate and multivariate regression

	Univariate		Multivariate	
	OR	***P*-value**	**OR**	***P*-value**
PD duration	1.49	<0.001	1.40	<0.001
Age at start PD	0.97	<0.001	0.96	<0.001
Transplantation	4.63	<0.001	2.47	0.010
Time since last transplantation until EPS	0.93	<0.001	0.85	<0.001
Time (calendar)	1.28	<0.001	1.37	<0.001
Icodextrin duration	1.92	<0.001	1.35	<0.001
Ultrafiltration failure	4.55	<0.001	2.29	0.026
Follow up time	1.07	0.001		
Transfer PD to HD other than suspected EPS	0.98	0.1		
Peritonitis episodes	1.05	0.110		

Data were analysed by a piecewise log linear model (Poisson regression) with EPS as outcome. Time since last transplantation until EPS is defined as the time from the last transplantation until EPS or end of study (in control patients). Calendar time was defined as the years since the chosen reference date, close to which the first patient in the study started PD (01-01-1983). Follow up time was defined as the period from start PD until EPS, death or end of study. Odds ratios (OR) for time on PD, age at start PD, time since last transplant until EPS diagnosis, calendar time, time on icodextrin and follow up time are expressed per year. OR for transplantation and ultrafiltration failure is given for these conditions. Follow up time, transfer PD to HD for other reasons than suspected EPS and episodes of peritonitis were not significant in multivariate analysis and were therefore excluded from final model. There is an adjustment for the differences in other risk factors than the one of interest. For example, the OR for age at start PD is given the differences in cumulative PD time. That means that two patients with the same PD time, the one who started PD younger has a higher risk on EPS. All multivariate ORs are conditional on the difference in the other risk factors.

until EPS diagnosis, calendar time, period of using icodextrin and ultrafiltration failure were strongly associated with the presence of EPS (Table 5). In the multivariate analysis, using the log linear regression, follow up time, transfer from PD to HD for other reasons than suspected EPS and peritonitis episodes were not significant because of strong associations with PD duration and age. Therefore these were excluded from the final multivariate model. Since ultrafiltration failure was missing in 17.5% of the patients, and is a possible confounder, we performed a sensitivity analysis and analyzed ultrafiltration failure in two ways. First we coded it as yes, no or missing and estimated a separate odds ratio (OR) for the missing category. Subsequently we excluded patients with a missing value. Both approaches resulted in a similar significance level of ultrafiltration failure and similar OR's for the other variables.

DISCUSSION

The first aim of the present study was to investigate the incidence of EPS in recent years. The study shows an increasing incidence in a large representative Dutch PD population between January 1996 until January 2006, confirming our previous findings [16]. This occurred despite a slight decrease in the PD population and a stable mean duration on PD. The increase in

incidence appears to be followed by a small decrease in 2006. The reason for this is unclear. The most straightforward explanation for the increased incidence of EPS could be that increased awareness of the diagnosis led to subsequent inclusion of milder cases. However, this is unlikely, given the strict definition for inclusion. For instance, all patients had symptoms of intestinal obstruction.

The second goal of the study was to investigate the separate associations of risk factors with EPS development. From the candidate risk factors we confirmed the independent associations of PD duration and age with EPS development. In addition we were able to show novel independent associations as prolonged use of icodextrin, kidney transplantation and the time after kidney transplantation with the presence of EPS. We were not able to show an association with transfer from PD to HD. In contrast to others we found no significant relationship with peritonitis [15,24]. Despite these associations, there remains an unknown factor related to the recent increased incidence of EPS, as shown by the remaining independent association with calendar time. Currently we have no plausible alternative explanation for this.

The development of EPS is influenced by multiple factors and time is an important factor in the process of ongoing peritoneal remodelling and fibrosing. The second hit theory integrates individual predisposition with the time in which the peritoneal membrane is continuously exposed to conditioning agents and multiple hits, which result in the ultimate manifestation of EPS [1-2]. With respect to predisposition, our data showed no difference in gender. As in other reports diabetic patients hardly develop EPS [8,25].

The age at which PD was started, is associated with the presence of EPS. The younger a patient starts with PD the greater the chance to develop EPS. Given the independent significance this is not simply due to longer time on PD or to longer follow-up time from the moment of initiating PD. Peritoneal remodelling is a process in which injury of the mesothelial cell plays a key role. In reaction to multiple insults, with for example glucose, mesothelial cells secrete cytokines subsequently leading to recruitment of macrophages and fibroblasts [26]. Peritoneal fibrosing is then the result of disrupted repair with fibrin deposition on denudated mesothelial cell layer [2]. Possibly this repair process is more vivid in younger patients, leading to earlier development of fibrosis.

From the studied candidate risk factors, duration of PD treatment is probably the strongest predictor of EPS. Although Japanese studies have shown that continuing PD for a longer period is associated with EPS development, this was until recently not previously analysed in a matched case controlled design [12]. The Scottish Renal Registry showed that the incidence of EPS increased with PD duration [10]. The current study confirms these findings. Each year of prolonged PD had an increased relative risk for EPS of 40%.

The associations of young age and PD duration are in accordance with a recent report of the ANZDATA registry [9]. As in our study, this study has a controlled design with a multivariate

analysis. Although the designs differed, both studies used incident patients. The ANZDATA study used the whole cohort as reference group. This resulted in a significant difference in the era in which dialysis was commenced. Because we controlled at start date of PD we excluded this possibility. It appears that the EPS patients of both studies were not entirely comparable. For instance, there were no post-transplantation EPS patients in the ANZDATA report and their EPS related mortality was much less.

Novel findings of the current study are the associations of EPS with icodextrin and kidney transplantation. Solutions containing icodextrin permit good ultrafiltration during long time dwells and their use avoids the potential harmful effects of glucose [27-28]. As a result, the use of icodextrin has increased [29]. In Dutch practice icodextrin is not only used for patients with apparent ultrafiltration failure. Our study showed that, independent of ultrafiltration failure, prolonged use of icodextrin was associated with the presence of EPS. Recently, concerns have been raised about the increased levels of markers of peritoneal inflammation in icodextrin treated patients. The effluent showed a higher cell count and higher concentration of IL-6, TNF, hyaluronan, and fibrin degradation products [30-33]. This led the authors to suggest that these patients were possibly at risk for EPS [34]. Others argued that icodextrin preserves the peritoneal membrane function and mesothelial cell mass [28,33]. A recent case controlled study showed no difference in prescription of icodextrin between EPS and non-EPS patients [13]. A possible confounder, for which we were unable to correct, is cumulative intra-peritoneal glucose load, which might be higher in EPS patients [35]. Although our data show an association with icodextrin, it is premature to identify it as a risk factor for EPS. Further studies are certainly warranted to address this important issue.

Previously, we described a case series of patients who developed EPS shortly after kidney transplantation. We hypothesized that kidney transplantation could also be considered as a candidate factor for enhancing the EPS development [14,16]. Others also described post-transplant EPS cases [10,36-37]. We established kidney transplantation as a variable independently associated with EPS. The yearly probability on EPS after the last kidney transplantation increased from 1.75% to 7.5%. Each subsequent year after transplantation this risk decreased again. A possible explanation is the profibrotic property of calcineurin inhibitors (CNI's). Cyclosporin and especially tacrolimus have been shown to upregulate TGF-β in transplanted patients [38]. TGF-β is thought to be of major importance in the development of peritoneal fibrosis [39]. Recently, it was also shown that administration of cyclosporin to an experimental animal model with peritoneal exposure to a 3.86% glucose dialysis solution augmented peritoneal fibrosis and angiogenesis [40]. We were not able to identify the introduction of CNI's as a risk factor for EPS, because the large majority of patients was treated with either cyclosporin or tacrolimus. Finally, not the kidney transplantation itself, but rather the cessation of the PD, might be the risk factor for developing EPS [12,41]. This is underlined by results from other studies, which showed a number of patients diagnosed with EPS after switching to HD [13]. We were not able to show an association with

transfer from PD to HD. Instead, we found that the majority of patients switching from PD to HD already were suspected of having EPS. These patients had symptoms of (intermittent) bowel obstruction but did not fulfil the CT-scan criteria for EPS prior to transfer. Our data suggest that clinical symptoms and ultrafiltration failure dominate in the early phase of EPS development, and diagnostic CT-scan abnormalities are mainly found at the later stages of disease. This is in accordance with the findings of Tarzi et al. who showed that CT-scanning has no additional value for identification of EPS early in the course of the disease [20]. However, it remains an open question whether transferring PD patients with suspected EPS to HD accelerates the process of encapsulation.

The strength of the study is the large size of the EPS group and the controlled design, without premature controlling for PD duration. The multivariate analysis enabled us to investigate and quantify novel additional factors besides the PD duration. However, due to the design of the study and the RENINE registry, the study has some limitations. Recently, two studies described the increasing small solute transport status and decreased osmotic conductance in patients with developing EPS [42-43]. The current study also shows increased small solute transport in EPS patients, but has considerable missing results concerning the transport status. This is due to the fact that in the past annual evaluation was not common.

The risk ratio's are given in yearly risks and this might suggest a contradiction with the known exponential increase of EPS incidence within every year of PD treatment [12]. However, in any given PD population, a yearly calculated increase of a given risk factor for EPS will mathematically lead to an exponential increase in EPS incidence per year of PD treatment. The exponential nature of the model is demonstrated by the figure on the risk for EPS in univariate relation to time after transplantation.

It is interesting to speculate on the clinical consequences of these findings. Our data support the assumption that PD induced peritoneal damage underlies the post-transplantation EPS. A typical patient with EPS after kidney transplantation has started with PD at relatively young age (< 50 years), has been on PD for a prolonged time, with development of ultrafiltration failure and has been exposed to icodextrin. Instead of an arbitrary overall expiry date of PD, a timely switch of young PD patients to HD at the appearance of ultrafiltration failure, while waiting on renal transplantation, can be considered. Such a prudent policy might reduce EPS incidence.

In conclusion, we confirmed that the incidence of EPS has increased in recent years, followed by a decrease in 2006. We identified significant independent associations of PD duration, age, kidney transplantation, ultrafiltration failure and the use of icodextrin with EPS development. In particular the possible role of icodextrin needs to be further evaluated.

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Chapter 4

Early diagnostic markers for Encapsulating Peritoneal Sclerosis: a case - control study

Denise E. Sampimon, Mario R. Korte, Deirisa Lopes Barreto, Anniek Vlijm,
Rudy de Waart, Dirk G. Struijk, Raymond T Krediet

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ABSTRACT

Background

Encapsulating peritoneal sclerosis (EPS) is a life threatening complication of long-term peritoneal dialysis (PD). No tests are available to make an early diagnosis of EPS. Effluent cancer antigen 125 (CA125) is a marker of mesothelial cell mass, interleuking-6 (IL-6) is a marker of inflammation, potassium (K^+) is released during hypertonic cell shrinkage and vascular endothelial growth factor (VEGF) is a growth factor for the formation of new vessels. The aim of the present case-control study was to analyze the time course of the above described peritoneal membrane markers in patients who developed EPS and in those matched for the duration of dialysis that did not progress to this complication.

Methods

Dialysate and serum samples of 11 EPS patients and 31 control patients all treated with PD for at least 57 months were longitudinally collected during a standard peritoneal permeability analysis (SPA) performed once a year. The 4 most recent samples were analyzed. CA-125 and IL-6 were measured in dialysate alone, K^+ and VEGF were measured in both dialysate and serum. To correct for the effect of the drained volume, values of CA-125 and IL-6 are expressed as appearance rates (AR). Dialysate over serum (D/S) K^+ was divided by the D/S creatinine in order to correct for diffusion. The local production of VEGF was calculated by taking the difference between the measured and expected D/S VEGF, based on diffusion. The linear mixed model was used to analyze the time courses of the various markers. The sensitivity and specificity of the different markers were calculated based on the results of the last two time points.

Results

EPS patients were younger than controls (35 versus 53 years, $p=0.05$) and had a longer PD duration (104 months versus 72 months, $p=0.01$). No significant differences in time courses of the different markers were present between groups. However AR CA-125 was significantly lower in the last three years prior to EPS ($p<0.05$) and AR IL-6 was higher two years prior to EPS ($p=0.09$). Locally produced VEGF showed no differences among the groups. The combination of AR CA-125<33 U/min and AR IL-6>350 pg/min had a sensitivity of 70% and a specificity of 89%.

Conclusions

AR of CA-125 showed lower values and AR of IL-6 showed higher values during the last years prior to the diagnosis of EPS compared to controls. The sensitivity and specificity of the combination of CA-125 and IL-6 indicate the potential use for an early diagnosis of EPS.

INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) is a life threatening complication of long-term peritoneal dialysis (PD). No tests are available to make an early diagnosis of EPS. Typically, patients present with bowel obstruction, after which the diagnosis is made, either by laparotomy or CT scanning [1-2]. Ultrafiltration failure (UFF) is always present, but this is not diagnostic. Peritoneal solute transport is often fast, but may decrease before the diagnosis is made [3-4].

Peritoneal effluent contains a number of substances that are locally produced or released, additionally to their transport from the circulation [5]. These include potassium [6], cytokines [7-8], growth factors [9] and the mesothelial cell marker cancer antigen 125 (CA-125) [10].

The aim of the present case-control study was to analyze the time course of the above described peritoneal membrane markers in patients who developed EPS and in those matched for the duration of dialysis that did not progress to this complication. Our research question was whether any of the above mentioned effluent markers could be used as early diagnostic marker for EPS.

PATIENTS AND METHODS

Patients

All EPS patients who were diagnosed in our department between 1995 and October 2008 were selected for this study. The diagnosis of EPS was based on predefined criteria [2]. These included clinical features like bowel obstruction, ascites and blood stained effluent in combination with UFF, confirmed either by findings at radiology, laparotomy or autopsy, and reviewed by two experienced nephrologists.

All PD patients with at least 57 months of PD in the same period were included in this study as controls.

Samples

The effluent and serum samples of EPS patients and controls were obtained during a Standard peritoneal Permeability Analysis (SPA) [11]. None of the patients had peritonitis at time of the SPA or the four preceding weeks. The presence of ultrafiltration failure (UFF) was made based on the recommendation of the International Society for Peritoneal Dialysis [12]. PD patients undergo a SPA to assess the functional condition of the peritoneum once a year. Remaining effluent and serum samples are frozen and stored after centrifugation. Therefore several effluent and serum samples of different time points were available for all patients with an average interval of one year. The average interval between the diagnosis EPS and the time of the last available sample was 10 months. This allowed us to express the time points as years prior the diagnosis of EPS, whereas time point zero was the time of the diagnosis of EPS.

Markers

K^+ was measured in effluent and serum directly after the SPA with an ion selective electrode (Roche Diagnostics, Almere, The Netherlands). CA-125 levels in effluent were analyzed by using an enzyme labeled sandwich immunoassay (Roche Diagnostics, Almere, the Netherlands). Interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) were measured in effluent with commercially available enzyme-linked immunosorbent assays (human IL-6 and human VEGF, RandDsystems, Minneapolis, USA). Prior to the measurement of VEGF the effluent samples were concentrated 10 times through ultrafiltration by using an ultra-15 centrifugal filter with a molecular cut off point of 10,000 Da (Millipore, Molsheim, France). The concentration factor was defined as the albumin concentration in the concentrate divided by the albumin concentration in the original effluent sample.

Creatinine was measured with an enzymatic method on an automated analyzer (Hitachi H911, Boehringer, Mannheim, Germany). Albumin (Alb), immunoglobulin G (IgG) and alpha-2-macroglobulin (A2M) were all measured by nephelomethry (BN100, Behring, Marburg, Germany) with commercial antisera (Dakopatts, Glostrupp, Denmark). Beta-2-microglobulin (B2m) was determined with a microparticle enzym immunoassay with an IMX system (Abbott Diagnostics, North Chicago, IL, USA).

Calculations and Statistics

Data are presented as medians and ranges unless stated otherwise. In order to correct for peritoneal transport, dialysate over plasma ratio (D/P) of K^+ was divided by the D/P creatinine. Due to their size, diffusion of CA-125 and IL-6 is negligible and only effluent appearance rates (AR) were calculated to correct for the effect of the drained volume on their concentration.

Peritoneal handling of the macromolecules beta-2-microglobulin, VEGF, albumin, IgG and alpha-2-macroglobulin was expressed as the dialysate over serum ratio (D/S). A peritoneal transport line was computed for each patient based on the least squares regression analysis of the D/S ratio of B2m (MW=11,800 Da), Alb (MW=69,000 Da), IgG (MW=150,000 Da) and A2m (MW=820,000 Da) and their molecular weights when both were plotted on a double logarithmic scale [13]. By interpolation of the MW of VEGF (MW= 34,000 Da) in the regression equation the expected D/S ratio was calculated assuming that the effluent concentration would only be determined by transport from the circulation. The concentration of VEGF attributed to local production was defined as the difference between measured and expected effluent concentration.

The linear mixed model was used to analyze the time courses of the various effluent markers. A Mann-Whitney-U test was used to analyze the differences between groups on different time points. Sensitivity and specificity of all markers were calculated at one and two years prior to the diagnosis of EPS or prior to the discontinuation of PD in the control group. Cutoff values for these calculations were based on literature for K^+ [6], CA-125 [14], IL-6 [15], and VEGF [9].

RESULTS

Patients

Patient characteristics are listed in Table 1. We included 11 EPS patients and 31 controls. Patients who developed EPS were younger and the duration of PD treatment was longer. Reasons for discontinuation of PD treatment in EPS patients were: ultrafiltration failure (6), infection (2), transplantation (1) and EPS (2). Reasons for stopping PD treatment in controls were death (12), infection (2), transplantation (7), UFF (4) and other (1). Five patients were censored at October 2008. None of the control patients developed EPS in the three years of follow-up.

Table 1 | Patients characteristics of EPS patients and their time matched controls.

	EPS (n=11)	Controls (n=31)
Age *(years)*	35 (21-73)	53* (32-87)
Gender *(Male/female)*	7/4	19/12
PD duration *(months)*	104 (57-149)	72* (57-112)
Net UF at last SPA *(mL/4h)*	121 (-113-308)	494**(73-920)
Number of peritonitis episodes *(total episodes since start of PD)*	4 (0-15)	3 (0-11)
Peritonitis incidence *(episodes / year)*	0.47 (0-2.61)	0.41 (0-1.66)

Data are presented as medians and ranges. *p<0.05, **p<0.01

Markers

The time course of the various effluent markers is shown in Figure 1 for D/P K^+/ D/P creatinine, in Figure 2 for the CA-125 appearance rate, in Figure 3 for the IL-6 appearance rate and in Figure 4 for the effluent concentration of locally produced VEGF. For none of the markers a significant difference was found in the time courses, but lower values for CA-125 were found in the EPS patients compared to controls. This group also showed a tendency for a higher IL-6 appearance rate.

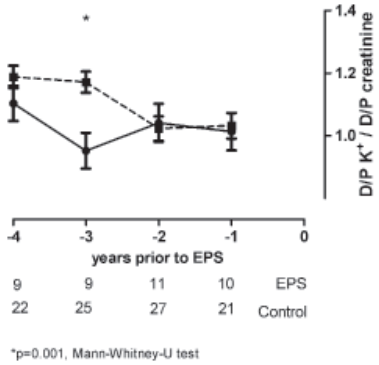

Figure 1 | Linear mixed model estimations (mean and SEM) of the time course of D/P K^+/ D/P creatinine in the EPS group (—♦—) and in the control group (- -■- -). The number of patients at each time point is given on the horizontal axis. The time course was not different between the groups (p=0.085), but lower values were found for EPS patients (p=0.029). This was mainly based on the difference at -3 years.

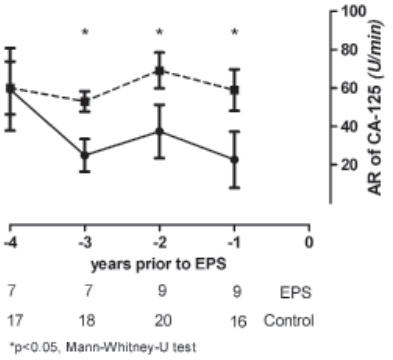

Figure 2 | Linear mixed model estimations (mean and SEM) of the time course of the CA-125 appearance rate in the EPS group (—♦—) and in the control group (- -■- -). The number of patients at each time point is given on the horizontal axis. The time course was not different between the groups (p=0.68), but lower values were found for EPS patients (p=0.045). Significant differences were found at the timepoints -3, -2 and -1 years.

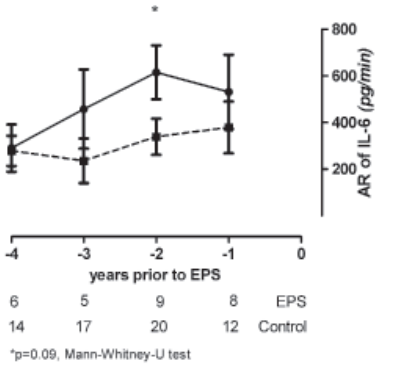

Figure 3 | Linear mixed model estimations (mean and SEM) of the time course of the IL-6 appearance rate in the EPS group (—♦—) and in the control group (- -■- -). The number of patients at each time point is given on the horizontal axis. The time course was not different between the groups (p=0.414), but higher values were found for EPS patients (p=0.06). This was mainly based on the difference at -2 years.

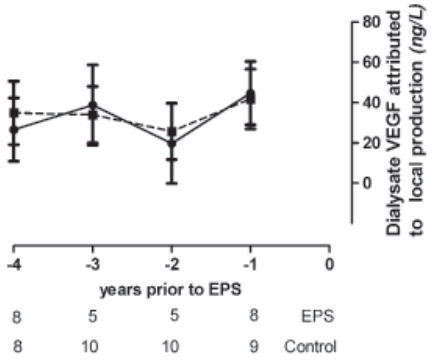

Figure 4 | Linear mixed model estimations (mean and SEM) of the time course of the local production of VEGF in dialysate in the EPS group (—♦—) and in the control group (- -■- -). The number of patients at each time point is given on the horizontal axis. The time course was not different between the groups (p=0.97), and similar values were found for EPS patients and controls (p=0.89).

Sensitivity and Specificity

Results are presented in Table 2. Sensitivity and specificity of the separate effluent markers were calculated at timepoint -1 plus -2. The combined sensitivity and specificity of AR IL-6 and AR CA125 was also calculated at these time points. This parameter had a sensitivity of 70% and a specificity of 89%. In patients with UFF, the combination of AR CA-125 <33 U/min and AR IL-6 > 350 pg/min had a sensitivity of 70% and a specificity of 100% for the development of EPS.

Table 2 | Sensitivity and specificity of different markers for the development of EPS

	Measurepoint -1 and -2 year	
	Sensitivity (%)	**Specificity (%)**
D/P K / D/P creatinine >1	10/11 (91%)	8/29 (28%)
AR CA-125 <33 *(U/min)*	7/10 (70%)	14/21 (66%)
AR IL-6 >350 *(pg/min)*	8/10 (80%)	10/20 (50%)
VEGF >15 *(ng/L)*	6/9 (33%)	3/12 (25%)
AR CA-125<33 *(U/min)* and AR IL-6>350 *(pg/min)*	7/10 (70%)	17/19 (89%)
AR CA-125<33 *(U/min)* and AR IL-6>350 *(pg/min)* in UFF patients	7/10 (70%)	8/8 (100%)

Sensitivity and specificity of different markers for the development of EPS at 1 year and 2 years prior to the diagnosis. The numbers before the slash refer to the number of positive findings; those behind the slash to the number of analyzed samples. The percentage refers to the sensitivity or specificity.

DISCUSSION

Encapsulating peritoneal sclerosis is a serious complication of long-term PD that should be tried to avoid. Therefore identification of patients at risk for its development is important. Almost all EPS patients have ultrafiltration failure [4,16], but its prevalence in long-term PD patients is much higher than the occurrence of EPS [17]. Therefore the current analysis of substances present in peritoneal effluent was performed. It appeared that until one year prior to the diagnosis of EPS, no differences were present between pre-EPS patients and time matched controls in the time courses of the various markers. However, effluent CA-125 was lower and effluent IL-6 tended to be higher in patients who developed EPS. The combination of an appearance rate of CA-125 <33 U/min and an IL-6 appearance rate >350 pg/min had a sensitivity of 70% and a specificity of 100% in patients with ultrafiltration failure.

The choice of the biomarkers was based on results from previous investigations and their interpretation. Effluent K^+ during a hypertonic 4 hour exchange is partly due to diffusion, but also to local release from cells [6]. Hypertonic cell shrinkage causing K^+ efflux is the most likely mechanism. This phenomenon is especially present in patients during the first few years of PD, while it is absent in long-term patients with UFF. The amount of local release was not related to effluent CA-125 [18]. Low values were found in both groups without an obvious trend, which may be caused by a lower number of cells or by impaired function of cellular K^+ channels.

Effluent CA-125 is a marker for mesothelial cell mass or turn-over [10,19]. It decreases with the duration of PD [19]. This is in accordance with the loss of mesothelium in PD as found in the peritoneal biopsy registry [20]. Complete loss of mesothelium has been described in EPS [21]. Our analysis showed lower values for effluent CA-125 in the pre-EPS patients at various time points when compared to the control group. This is in line with the alterations in peritoneal morphology.

Effluent IL-6 is considered a marker for local inflammation [15,22]. Also in the present analysis an increase with the duration of PD was found. This is in accordance with the inflammatory changes described in some EPS patients [23].

Soluble VEGF in effluent is partly derived from diffusion and partly by local production [9]. Locally produced VEGF is related to the mass transfer area coefficient of creatinine [9], which reflects the surface area of peritoneal microvessels [24-25]. Patients with EPS have high solute transport rates and an increased number of vessels. Yet, no high effluent concentration of locally produced VEGF was found in the present analysis. We speculate that neoangiogenesis occurs in an earlier stage than fibrosis during the development of EPS.

Some biomarkers were not analyzed, because of various reasons. Effluent transforming growth factor beta was not analyzed because we previously found that it was present in a non-active form and the results were not related to the duration of PD or any other parameter [9]. Similarly, effluent hydroxyproline was not informative [26]. Tumor necrosis factor alpha was not analyzed because it is only locally produced during acute peritonitis [13]. Fibrinolytic proteins were not measured, because no citrate or EDRA plasma was collected. Yet, these are potentially interesting because local peritoneal production has been shown for tissue plasminogen activator inhibitor type 1 antigen [27]. Methods for the measurement of collagen IV and alpha smooth muscle actin are not commercially available.

The sensitivity and specificity of the combination of effluent CA-125 and IL-6 in patients with UFF suggest that it is possible to identify those at risk for clinically established EPS. This is important, because preventive interventions to reduce morbidity and mortality might be more effective at this stage than after the establishment of the diagnosis. Besides discontinuation of PD, such interventions could include peritoneal resting [28], steroids and immunosuppressives [29-30] and also tamoxifen [31]. These interventions could potentially be monitored by effluent CA-125 and IL-6, but these would require further studying.

A potential weakness of the study is the difference in PD duration between both groups. Intentionally the shortest duration of PD in the control group was 57 months, similar to the observed shortest duration in the EPS group. It illustrates the importance of the duration of PD therapy in the development of EPS. Nevertheless six out of eleven EPS patients had an overlapping PD duration with the control group. The EPS patients were also younger. This may be relevant for the development of EPS, because it was also present in a different EPS cohort [2]. Another shortcoming is that not all analyses could be done in all patients, because of the limited number of available serum and effluent samples. However, the number of samples in the EPS group averaged 8 and was never smaller than 5.

It can be concluded that the dialysate appearance rate of the combination CA-125 and IL-6 is potentially useful for an early diagnosis of EPS, especially in patients with UFF. Both can be measured easily without specific preparation of the effluent sample. Further studies are required to confirm our findings and to investigate whether the effluent CA-125/IL-6 combination can be used for monitoring of interventions.

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Chapter 5

Tamoxifen is associated with lower mortality of Encapsulating Peritoneal Sclerosis; results of the Dutch multicenter EPS study.

Mario R. Korte, Marien W. Fieren, Denise E. Sampimon, Hester F. Lingsma, Willem Weimar, Michiel G.H. Betjes on behalf of the investigators of the Dutch Multicenter EPS Study.

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ABSTRACT

Background

Encapsulating peritoneal sclerosis (EPS) is a serious complication of peritoneal dialysis (PD) with an increasing incidence. There is no clear consensus on the treatment of EPS, but anecdotal reports indicate improvement in EPS patients treated with tamoxifen. At present there is no evidence for the effect of tamoxifen treatment in EPS patients. This study investigates the effect of treatment with tamoxifen on survival in EPS patients.

Methods

Retrospective analysis of survival in EPS patients as part of Dutch multicentre EPS study in the period January 1996 – July 2007. Sixty-three patients with severe EPS were followed up until August 2008. Demographic, patient and PD related variables of EPS patients were investigated. Patients treated with tamoxifen were compared to patients not treated with tamoxifen. Survival was analyzed with multivariate Cox regression analysis.

Results

Twenty-four patients were treated with tamoxifen and 39 were not treated with tamoxifen. The clinical and demographic characteristics were similar for the tamoxifen treated and non-treated group. The mortality rate was significantly lower in tamoxifen treated patients compared to EPS patients not treated with tamoxifen (45.8% vs. 74.4%, p=0.03). Survival in tamoxifen treated patients, adjusted for calendar time, age, use of corticosteroids, presence of functioning transplantation, use of parental nutrition and centre influences was longer in comparison to not treated patients (HR 0.39, p=0.056).

Conclusions

Tamoxifen treatment in EPS patients is associated with lower mortality and shows a trend to an increased multivariate-adjusted survival. This supports additional use of tamoxifen to treat patients with severe EPS.

INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) is a clinical syndrome characterized by intestinal encapsulating and subsequent obstruction of the intestinal tract by formation of excessive peritoneal fibrosis tissue [1]. Although EPS can be found in different clinical settings, the condition is most frequently seen in patients treated with peritoneal dialysis (PD).

Although rare, EPS has come to be recognized as a serious complication of PD with a high morbidity and a mortality of approximately 50% [2]. The development of EPS is insidious and probably starts with sterile visceral peritoneal inflammation with neovascularisation, followed by massive deposition of fibrous scar tissue that encases part or all of the bowels. As such, EPS is different from the sclerotic thickening of the peritoneum that appears after many years of peritoneal dialysis, a condition often referred to as simple sclerosis [3]. The inflammatory stage of EPS may be recognized clinically by the appearance of bloody ascites, ultrafiltration failure and signs and symptoms of chronic inflammation. When fibrous tissue progressively encapsulates the bowels, intermittent or definite intestinal obstruction will ensue, leading to severe malnutrition [4-5]. The symptoms of intermittent intestinal obstruction are mild in the beginning of encapsulation and often not appreciated as early signs of EPS.

Due to the slow nature of progression and the aspecific criteria for the EPS diagnosis there is often a delay in diagnosing the disease. Eventually, the diagnosis is primarily confirmed by radiological findings or by the macroscopical image of peritoneal encasement. Recently, criteria for abdominal CT scanning have been established, which can be of help in diagnosing EPS [6]. Supportive care with either enteral or parenteral nutrition has been shown to be beneficial and should be the mainstay of the treatment when intestinal obstruction with malnutrition is present [7]. Encouraging results from Japan have been reported with surgical enterolysis, releasing the complete small intestine [8]. However, there is little experience with this procedure outside Japan and it is rarely performed in Western-Europe. There is no uniform medical management strategy for EPS, as the efficacy of the intervention is not proven. Usually patients are treated with intestinal rest and additional treatment, such as immunosuppressive medication [9-11] or tamoxifen [12].

Tamoxifen is a selective estrogen receptor modulator (SERM) [13], predominantly used for the treatment of breast cancer [14-16]. Tamoxifen also influences the activity of the profibrotic cytokine TGF-β and has shown to be effective in fibrotic diseases as retroperitoneal fibrosis [17] and Riedels' thyroiditis [18]. The reported effects of tamoxifen in EPS are equivocal and result from a limited number of case reports and small series of patients [12,19-20]. A controlled study investigating the effect of tamoxifen on survival in a larger population is lacking.

Recently we performed a large Dutch multicentre study to investigate the incidence of EPS in the past years [21], preceded by an initial report indicating a possible increase of EPS [22]. As part of this study we investigated the survival of EPS patients treated with tamoxifen in comparison with not treated patients in the period of 1997-2007.

METHODS

Design and setting

The design of the study was a retrospective multicentre study. The participating centres were five university hospitals in the Netherlands and three large teaching hospitals. All cases in the participating centres in the study period 1996-2007 were identified by investigating the medical records. The university centres are the primary transplantation centres for their region.

The study protocol was approved by the medical ethics committee of the Erasmus University Medical Centre, Rotterdam.

Classification and diagnosis of EPS

Encapsulating peritoneal sclerosis was defined according the criteria developed by the Ad Hoc Committee of the International Society of Peritoneal Dialysis (ISPD) [23]. It is defined as a clinical syndrome with persistent or recurrent presence of intestinal obstruction with or without the existence of inflammation parameters and the existence of peritoneal thickening, sclerosis, calcifications and encapsulation confirmed by macroscopic inspection or radiological findings.

Using this definition of EPS the studied population was limited to severe forms of intestinal obstruction that lead to persistent clinical problems, the necessity of surgical intervention, immunosuppressive therapy and/or the necessary use of total parental nutrition (TPN).

Participants

Patients with EPS diagnosed in the period January 1st 1996 - July 1st 2007 were included. Medical records of patients with EPS were reviewed in detail by the investigating nephrologist, who was not the primary treating physician. Data were entered into the case report form and database. The date of diagnosis of EPS was retrospectively set at the date at which the diagnosis fulfilled the definition of EPS and confirmed by two separate nephrologists. All patients underwent abdominal CT scanning.

Outcomes and Follow-up

Demographics, patient and PD related variables were investigated. The duration on PD was calculated by accumulating all separate episodes on PD. Whenever a patient was on other renal replacement therapy, for longer than a week, this time was not included in the calculated time on PD. The follow-up of the included patients was extended to August 2008.

Renal replacement therapy was scored at the time of diagnosis of EPS. All episodes of peritonitis were scored. Variables related to kidney transplantation were also investigated. All dates of kidney transplantations were noted. The time after last transplantation until EPS diagnosis was calculated. All immunosuppressive medication was scored as ever used.

To ensure a complete record of medication, all medical records, including electronic prescription software (when used in the hospital) were investigated. Tamoxifen used for the

treatment of EPS was scored if the use was longer than two weeks. The use of prednisone both intended for treatment of EPS or as part of post-transplant regimen was scored if it was used at the moment of EPS diagnosis or after the diagnosis of EPS was made. The use of parenteral nutrition and azathioprine because of EPS was also scored as ever used.

Statistical Methods

Data were entered and statistical tests were done in SPSS 15.0.1 datamanager (Chicago, USA). Means were compared using unpaired t-tests. Proportions were compared with chi-square tests. A two sided p-value of less than 0.05 was considered to be statistical significant.

Survival was further analyzed with Kaplan Meier and Cox regression analysis. In a multivariate Cox model we adjusted for the possible confounders age, year of diagnosis, presence of a functioning kidney transplant at time of diagnosis, PD centre, use of concomitant prednisone and the use of total parenteral nutrition.

RESULTS

Patient characteristics

In the period January 1st 1996 until July 1st 2007, 63 cases of EPS occurred in the participating centres. Within the EPS multicentre study prevalence was calculated using only the number of patients in the period January 1st 1996 until January 1st 2007. In this period there were 61 patients diagnosed with EPS and 2022 patients were on PD in the participating centres. Six EPS patients were excluded from these 61 patients, because they had originally started PD in other PD centres than those participating, resulting in a prevalence of 2.7% [21].

For the remaining tests all 63 EPS patients were used. All 63 patients had objective symptoms of bowel obstruction, underwent abdominal CT scanning and were diagnosed with EPS according the ISPD criteria. Twenty-four patients were treated with tamoxifen and thirty-nine patients were not treated with tamoxifen.

There were no significant differences between the two groups in ages at start of PD, at EPS diagnosis, at last kidney transplantation or at death. The groups were also comparable concerning follow up time and the type of renal replacement at the time of the diagnosis (Table 1).

PD and kidney transplantation related variables

There were no significant differences between the treated and not treated groups of EPS patients with regards to the cumulative period on PD, the episodes of peritonitis, the number of transplanted patients and the number of transplantations per transplanted patient. Overall, 47 transplanted patients developed EPS after the last kidney transplantation with a mean of 50.8 ± 69.8 months after the last kidney transplantation. Mean age at the last transplantation was 36.4

Table 1 | Patient characteristics.

			Tamoxifen		*P*-value
		Total (n=63)	Yes (n=24)	No (n=39)	
Gender (f/m)		21/42	6/18	15/24	NS
Age					
	Age at diagnosis EPS	43.4 ± 14.4	44.7 ± 13.6	42.7 ± 15.1	NS
	Age at start PD	34.7 ± 15.4	36.0 ± 14.6	34.3 ± 16.4	NS
	Age at death or end of study	45.1 ± 14.1	46.4 ± 13.2	44.3 ± 14.8	NS
	Age at last transplantation	36.4 ± 13.4	39.9 ± 15.1	34.0 ± 12.0	NS
Periods					
	Time until death after EPS	27.3 ± 20.6	30.8 ± 18.6	25.2 ± 21.7	NS
	Follow-up	129.4 ± 60.5	134.8 ± 65.6	126.0 ± 57.7	NS
Renal replacement when EPS					
	PD	16	7	9	NS
	HD	29	8	21	NS
	Functioning graft	18	9	9	NS
End of study					
	Deceased	40	11	29	0.03
	EPS related death	35	11	24	NS
	Alive, functioning graft	9	6	3	0.07
	Alive HD	14	7	7	NS
	Alive, PD	0	0	0	NS

Data shown as means ± SD. F female, m male. Age expressed in years. Time periods expressed in months. Renal replacement therapy expressed in number of patients. Means were compared using unpaired t-tests. Proportions were compared with chi-square tests. A two sided P-value of less than 0.05 was considered to be statistical significant. NS means not significant.

± 13.4 years. Twenty-one patients with a kidney transplant (44.7% of the total 47 transplanted patients) developed EPS within 2 years after the last kidney transplantation (Table 2).

From the 47 patients with EPS after transplantation 18 patients had a functioning kidney transplant at the time of EPS diagnosis (Table 1). None of the patients was transplanted because of EPS symptoms.

Table 2 | PD and transplantation related variables in EPS patients.

			Tamoxifen		*P*-value
		Total (n=63)	Yes (n=24)	No (n=39)	
PD					
	Time on PD	77.4 ± 38.1	69.9 ± 35.1	82.0 ± 39.5	NS
	Episodes of peritonitis	4.1 ± 3.8	3.9 ± 3.6	4.2 ± 3.9	NS
Transplantation					
	Number of patients	47	19	28	NS
	Number of transplantations	1.6 ± 0.9	1.4 ± 0.9	1.7 ± 0.9	NS

Time periods and episodes of peritonitis shown as means ± SD. PD peritoneal dialysis. Time periods expressed in months. Number of transplantations expressed in means ± SD per transplanted patient. Means were compared using unpaired t-tests. Proportions were compared with chi-square tests. A two sided P-value of less than 0.05 was considered to be statistical significant. NS means not significant.

Table 3 | Treatment of EPS.

	Tamoxifen		*P*-value
	Yes (n=24)	No (n=39)	
Treatment for EPS			
Parenteral nutrition	14	21	NS
Prednisone	11	9	NS
Azathioprine	1	1	NS
Prednisone total use	12	14	NS

Data shown as number of patients. Prednisone total use means patients treated with prednisone because of EPS and because of renal transplant after the moment of EPS diagnosis. Proportions were compared with chi-square tests. A two sided P-value of less than 0.05 was considered to be statistical significant. NS means not significant.

EPS treatment

There were no differences between the groups of EPS patients with respect to the treatment with TPN or prednisone. The total number of patients using prednisone (patients using prednisone for the treatment of EPS or as part of post-transplant regimen combined) was also not different between the groups. In each group one patient was also treated with azathioprine (Table 3). Treatment with tamoxifen was started by the treating physician. Dosages of tamoxifen varied in time from 10 mg once a day to 20 mg twice a day. All patients in the treatment group were treated with tamoxifen for at least 4 weeks. There was no extensive enterolysis performed in any of the patients.

Outcome

The overall mortality rate was lower in tamoxifen treated patients compared to patients not treated with tamoxifen, respectively 11 out of 24 and 29 out of 39 patients (45.8% vs. 74.4%), p=0.03. Estimated survival analyzed with Kaplan Meier showed better survival in the group treated with tamoxifen (p=0.07, Figure 1). Univariate Cox regression analysis confirmed this trend with a hazard risk (HR) of 0.54 (p= 0.08). Multivariate Cox regression analysis with adjustment for age, year of diagnosis, presence of a functioning kidney transplant at time of diagnosis, PD centre, use of concomitant prednisone and the use of total parenteral nutrition also showed a trend to an improved survival in the tamoxifen treated group, although the level of statistical significance did not reach the predefined limit of less than 0.05 (HR 0.39, p=0.056).

DISCUSSION

The present study shows that mortality rate is lower in tamoxifen treated EPS patients compared to EPS patients not treated with tamoxifen with both groups having comparable demographic and clinical characteristics. More importantly, treatment of EPS patients with tamoxifen was associated with a trend to an improved survival, independent of other possible beneficial treat-

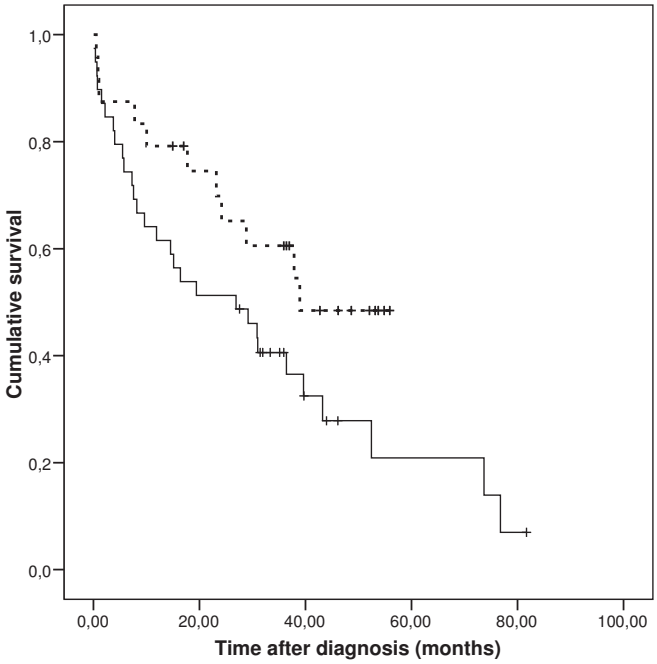

Figure 1 | Survival of EPS patients with and without treatment tamoxifen.
Kaplan Meier analysis showing survival of 24 patients treated with tamoxifen (- - -) and 39 patients without tamoxifen (—). Time after diagnosis means time in months after EPS diagnosis. + Means censored in analysis. P-value was 0.077.

ment options. In accordance with previous studies, the results identify EPS as a life-threatening condition with a very high mortality.

At present there are no randomized controlled trials that have shown the efficacy of any given drug for EPS. Because there is a presumed inflammatory response in the early development of EPS, corticosteroids are often given. Other immune suppressive agents like azathioprine, MMF or sirolimus have been given on a smaller scale. The beneficial effects of this immune suppressive therapy are predominantly anecdotal [10,24-29] and undoubtedly this is a biased view, because negative results are not likely to be reported.

In addition, a beneficial effect of immune suppressive medication appears to be in contrast with our finding that EPS is more likely to develop in the first year after renal transplantation, when patients are already immunosuppressed [22,30]. In this study we could not identify a beneficial effect of prednisone on survival of EPS patients. Therefore, the effect of immunosuppressive medication for the treatment of EPS remains to be proven.

Similar to immune suppressive medication, various anecdotal experiences and small case series have been reported on the effects of tamoxifen in EPS patients [12,19,31-40] and are summarized in Table 4. All reports show improvement of the intestinal function and a decrease of inflammatory markers, except for a recently published large case series from England [19]. In this latter study

Table 4 | Reports on tamoxifen in EPS.

Study	Report	N	Dose of tamoxifen	Steroids	Outcome
Turner et al.[40]	case	1	10 mg b.i.d.	No	Improvement
Allaria et al.[31]	case	1	10 mg q.d.	No	Improvement (3 months FU)
Pollock et al.[32]	case	1	10 mg q.d.	Yes	Improvement
Del Peso et al.[39]	series	9	20 mg b.i.d.	NR	Survival benefit
Evrenkaya et al.[33]	case	1	10 mg q.d.	Yes	Improvement (2 months FU)
Korzets et al.[38]	series	2	20 q.d.- 40 mg b.i.d.	Yes	Deceased
Moustafellas et al.[34]	series	2	20 mg b.i.d.	Yes	Improvement (3-4 months FU)
Dogan et al.[36]	case	1	10 mg q.d.	Yes	Resolved
Mesquita et al.[37]	case	1	20 mg b.i.d.	Yes	Improvement
Eltoum et al.[12]	series	4	20 mg b.i.d.	No	Resolved
Thirunavukasara et al.[35]	series	2	20 mg q.d.	No	Improvement (6 months FU)
Gupta et al.[20]	case	1	20 mg b.i.d.	No	Improvement
Balasubramaniam et al.[19]	series	31	NR	Yes (12)	No survival benefit
Korte et al. (present study)	Series controlled	24	10 mg q.d. - 20 mg b.i.d.	Yes (12)	Survival benefit (p = 0.056)

N means number of EPS patients treated with tamoxifen, b.i.d. means twice daily, q.d. means once daily, NR means not reported and FU means follow-up. The additional use of steroids is mentioned with number of patients when available. In the report of Eltoum et al. all 4 patients had restored intestinal function.

survival time in various treatment groups, including in 31 patients treated with tamoxifen was not different compared to patients not given any drug treatment. This apparent discrepancy to our results may result from inclusion of less severe cases of EPS in the English study. For instance, only 33% of the English patients had a clinical diagnosis of bowel obstruction, while all patients in the present study had objective signs of severe bowel obstruction, necessitating parenteral nutrition in 35 of the 63 EPS patients.

In addition, the comparison appears inappropriate due to a possible difference in aetiology of EPS. In the UK study only 14 out of 111 patients developed EPS with a functioning renal transplant compared to 18 out of 63 in our study (out of the total of 47 transplanted patients). The latter reflects our previous reported high incidence of EPS shortly after renal transplantation [22]. From the other reports on the effect of tamoxifen only Moustafellas et al. reports patients with post-transplant EPS [34]. A different response of post-transplant EPS to tamoxifen is not implausible, considering that in this condition the peritoneal inflammatory-fibrotic processes may be accelerated [30].

Our study was not randomized. Although we did take into account all available possible confounders by including them into a multivariate analysis, it is possible that the results are influenced by 'confounding by indication'.

Recently, EPS received more attention than before and subsequently there might be an improved strategy or increased use of tamoxifen in time. It is unlikely that this acts as a confounder, because the year of diagnosis was included in the analyses. A limitation of the study is

the fact that treated patients were retrospectively compared to patients who were not treated. Perhaps physicians are more likely to prescribe or retain certain drugs in more severe cases. Another possible confounder is the fact that non-tamoxifen treated patients tend to have more HD at the time of EPS diagnosis. This could imply that patients on HD are sicker and are less likely to receive tamoxifen. We minimized these possibilities by using strict definitions of EPS, with including only severe cases with intestinal obstruction.

Due to the nature of the study we were not able to report the median dosage or cumulative exposure to tamoxifen. In the present study we could not include the influence of enterolysis, since such a procedure was not applied in our study population.

During the development of peritoneal sclerosis, in which an inflammatory state develops into a fibrotic stage, neoangiogenesis and the transition of mesothelial cells with epithelial phenotype to mesenchymal type (EMT) with fibroblast like characteristics are essential [41]. In this process TGF-β and vascular growth factors have a pivotal role. TGF-ß is regarded to be a central mediator of EMT [42]. Overexpression of TGF-β in an animal model with chronic high glucose PD fluid exposure resulted in peritoneal fibrosis and neoangiogenesis [43]. Myofibroblasts originating from the epithelial phenotype mesothelial cell produce vascular growth factors leading to neoangiogenesis and vasculopathy. In long-term PD these vascular changes with upregulation of vascular growth factors were shown [44]. Blockade of these factors and inhibition of angiogenesis showed reduced angiogenesis and slowed the peritoneal fibrosis, confirming the important role of vascular growth factors in peritoneal fibrosis and possibly EPS [45-47].

The antifibrotic effects of tamoxifen seem to be related to the influence of TGF-β and inhibition of angiogenesis. In other diseases with excessive collagen deposition and involvement of TGF-β, like Dupuytren's, tamoxifen was able to down regulate the TGF-β production [48]. In oncology, levels of VEGF are associated with the extent of angiogenesis and have prognostic value. Tamoxifen decreased extracellular VEGF level in solid tumours [49] and attenuated VEGF mediated angiogenesis [50]. Extrapolating these findings, tamoxifen might ameliorate the process of peritoneal fibrosis by downregulating TGF-β and decreasing VEGF levels thereby inhibiting angiogenesis.

Patients with EPS development are historically treated with transfer to HD, nutritional support or more recently with enterolysis. Given the clear pathophysiological rationale for using tamoxifen in EPS patients combined with the encouraging results from this study, this may be a promising additional treatment option for a condition with a high mortality. To further establish our findings a randomized controlled trial has to be performed. Given the low frequency of EPS such a study should be performed in a large research collaboration [51].

When tamoxifen is considered as part of the treatment of EPS potential adverse effects of the drug must be taken into account. Most reported adverse effects are thromboembolism, endometrial carcinoma or strokes [15]. Only Eltoum et al. reported on the adverse events [12]. They

observed three episodes of thromboembolic disease in four EPS patients. Our retrospective design of the study did not allow for an adequate evaluation of possible tamoxifen-related adverse events. Due to the morbidity and the limited life expectancy of EPS patients, the benefits of tamoxifen probably outweigh the potential risks.

In conclusion, this study shows that tamoxifen treatment is associated with a lower mortality and shows a trend to a higher multivariate-adjusted survival of EPS patients. In addition to supportive therapy tamoxifen may therefore improve the prospect of this severe condition.

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Chapter 6

Post-transplantation Encapsulating Peritoneal Sclerosis contributes significantly to mortality after kidney transplantation.

M.R.Korte, S.M.Habib, H. Lingsma, W.Weimar, M.G.H.Betjes .

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ABSTRACT

Background

Encapsulating peritoneal sclerosis (EPS) is a severe complication of peritoneal dialysis (PD) and may present after kidney transplantation, a condition known as post-transplantation EPS. The prevalence and impact of post-transplantation EPS on survival after kidney transplantation is unknown.

Methods

From January[1st] 1996 until July[1st] 2007 1241 PD patients were transplanted in participating centers. Thirty-eight cases of post-transplantation EPS (3%) were identified from the Dutch multicenter EPS study. In EPS patients the mean pre-transplant dialysis duration was longer than in the controls (71.4 ± 37.5 months vs. 34.7 ± 25.5, $p<0.0001$). The majority of EPS cases were observed within the first two years after transplantation, but some cases appeared many years after transplantation.

Results

Two-hundred-and-one (16.2%) patients died after transplantation, of which seventeen EPS patients. After infection (23.9%), cardiovascular disease (21.9%) and malignancy (10.9%), EPS (8.5%) was the fourth known cause of death after transplantation. Kaplan-Meier analysis showed a significant decreased survival for transplanted patients with post-transplantation EPS compared to transplanted patients without EPS.

Conclusions

Post-transplantation EPS is rare but carries a high mortality. A prolonged clinical vigilance and a high index of suspicion for the diagnosis are warranted, specifically in PD patients with a relatively long cumulative pre-transplant duration of PD.

INTRODUCTION

Peritoneal dialysis (PD) is a well-established renal replacement therapy, preferred by many young patients with end-stage renal disease in good clinical condition. Most PD patients are eligible for kidney transplantation and there is no apparent difference in rate of infections or patient survival between transplanted PD and hemodialysis (HD) patients [1-2]. Early transplant function may even be improved in former PD patients receiving deceased donor kidney transplantation [3-4].

Common identified causes for death after kidney transplantation are primarily cardiovascular events followed by infections and malignancy [5-6].

Encapsulating peritoneal sclerosis (EPS) is a clinical syndrome characterized by intestinal encapsulating and subsequent obstruction of the intestinal tract by formation of excessive peritoneal fibrosis tissue [7]. EPS is most frequently seen in patients treated with or having a history of peritoneal dialysis (PD). EPS has come to be recognized as a serious complication of PD with a high morbidity and a mortality of approximately 50% [8].

A substantial proportion of EPS cases present after renal transplantation, an entity known as post-transplantation EPS. The pathophysiology of EPS is probably influenced by multiple factors. The widely accepted second hit theory assumes a progressively damaged peritoneum by prolonged use of dialysis fluids, which may be complicated by factors that aggravate the peritoneal sclerosis [9]. In support of this theory is the finding that EPS is related with longer PD duration [10-11]. The use of calcineurin-inhibitors after transplantation may promote EPS, as these drugs are considered profibrotic.

Recently, we showed an increasing incidence of EPS in the last decade with a surprisingly high frequency of EPS in the first years after renal transplantation [12-13]. The prevalence and impact of post-transplantation EPS on survival after kidney transplantation is unknown. We hypothesized that post-transplantation EPS may have a significantly contribution to the mortality after kidney transplantation, which has previously gone unrecognized.

To test this hypothesis we analyzed the mortality due to EPS of transplanted PD patients in the Netherlands in the period 1996 to 2007.

MATERIALS AND METHODS

Design and setting

The design of the study was a retrospective multicenter study in the period January 1st 1996 until July 1st 2007. All data analyzed are from patients transplanted in the four participating university hospitals in the Netherlands; Erasmus Medical Center Rotterdam, University Medical Center Utrecht, University Medical Center Nijmegen and the Academic Medical Center, Amsterdam.

The study protocol was approved by the medical ethics committee of the Erasmus University Medical Center, Rotterdam.

Participants

All post-transplantation EPS cases in the study period January1st 1996 until July1st 2007 were previously identified by investigating the medical records and were described in the Dutch multicenter EPS study [13]. Medical records of patients with EPS were reviewed in detail by the investigating nephrologist, who was not the primary treating physician. The date of diagnosis of EPS was retrospectively set at the date at which the diagnosis fulfilled the definition of EPS and confirmed by two separate nephrologists. All EPS patients underwent abdominal CT scanning.

Variables

Two compatible national registries were used for collecting the additional data. Information regarding renal replacement therapy in the Netherlands was retrieved from RENINE. This is a clearly defined cohort of all patients with renal replacement in the Netherlands (RENINE, Registratie Nierfunctievervanging Nederland) [14]. Information regarding the kidney transplantation was retrieved from the Dutch Transplantation Foundation, a registry for all transplanted patients in the Netherlands.

From these two databases all transplanted PD patients were identified. All demographic, dialysis and transplantation related variables were investigated using these databases and the medical records of patients. Pre-transplant peritoneal dialysis period is calculated by adding all separate peritoneal dialysis periods prior to the last transplantation for each patient.

Death due to EPS is defined as any cause related to the underlying EPS, for instance: ileus, abdominal infection and catheter (in case of parenteral nutrition) related sepsis.

Immunosuppressive medication is reported in the transplantation database as induction therapy, at three months, 1 year and 2 years after kidney transplantation. For the statistical analysis the use of immunosuppressive medication at three months after the last kidney transplantation was used when part of the maintenance therapy. Tacrolimus and cyclosporin were grouped as calcineurin inhibitors (CNI's).

Classification and diagnosis of EPS

Encapsulating peritoneal sclerosis was defined according the criteria developed by the Ad Hoc Committee of the International Society of Peritoneal Dialysis (ISPD) [15]. It is defined as a clinical syndrome with persistent or recurrent presence of intestinal obstruction with or without the existence of inflammation parameters and the existence of peritoneal thickening, sclerosis, calcifications and encapsulation confirmed by macroscopic inspection or radiological findings.

Using this definition of EPS the studied population was limited to severe forms of intestinal obstruction that lead to persistent clinical problems, the necessity of surgical intervention, immunosuppressive therapy and/or the necessary use of total parental nutrition (TPN).

Statistical Methods

Data were entered and statistical tests were done in SPSS 17.0.1 datamanager (Chicago, USA). Means were compared using unpaired t-tests. Medians were compared with non-parametric tests (Mann Whitney). Proportions were compared with chi-square tests. A two sided p-value of less than 0.05 was considered to be statistical significant. Survival was further analyzed with Kaplan-Meier statistics.

RESULTS

Demographics

In the period January 1st 1996 - July 1st 2007 1241 PD patients were transplanted. Thirty-eight (3%) patients developed a severe EPS after kidney transplantation. All EPS patients had abdominal complaints of intestinal obstruction and were diagnosed with EPS according the ISPD guidelines. EPS patients were previously described in the Dutch multicenter EPS study [13].

Table 1 | Patient characteristics.

Variable	Controls	EPS patients	*P*-value
Number of patients	1203	38	
Gender			
Female (%)	474 (39.4)	15 (39.5)	NS
Male (%)	729 (60.6)	23 (60.5)	NS
Cause of renal disease: (%)			
Glomerulonephritis	299 (24.9)	9 (23.7)	
Interstitial nephritis and pyelonephritis	125 (10.4)	5 (13.2)	
Cystic kidney diseases	129 (10.7)	2 (5.3)	
Congenital and hereditary kidney diseases	48 (4.0)	5 (13.2)	
Renal vascular disease, excluding vasculitis	165 (13.7)	5 (13.2)	
Diabetes mellitus	70 (5.8)	1 (2.6)	
Other multisystem disease	109 (9.1)	5 (13.2)	
Others	31 (2.6)	1 (2.6)	
Unknown	161 (13.4)	4 (10.5)	
Missing	66 (5.5)	1 (2.6)	
Time on pre-transplant peritoneal dialysis (months)	31.1 ± 22.6	65.8 ± 30.7	0.0001
Deceased patients (%)	184 (15.3)	17 (44.7)	< 0.0001

Months on pre-transplant dialysis as mean ± SD. Proportions were compared with chi-square tests. Means were tested with t-tests.

Patient's characteristics and the transplantation related variables are shown in table 1 and table 2, respectively. In EPS patients, pre-transplant PD duration was significantly longer than in the controls and they tended to be younger at last kidney transplantation. Ten EPS patients (26.3%) had a total PD duration shorter than 48 months.

EPS patients had more kidney transplantations and more overall transplant failures compared to non-EPS patients. There was no significant difference in cause of transplant failure of the last kidney transplantation between the EPS and non-EPS group.

Table 2 | Transplantation characteristics.

Variables	Control patients (1203)	EPS patients (38)	*P*-value
Number of transplantations	1.20 ± 0.5	1.50 ± 0.8	< 0.0001
Donor last transplantation	Deceased: 767 (63.8%) Living: 436 (36.2%)	Deceased:32 (84.2%) Living: 6 (15.8%)	< 0.0001
Mean age at last transplantation (years)	46.1 ± 14.7	42.0 ± 14.2	0.09
Overall transplant failure	0.32 ± 0.6	1.05 ± 1.1	< 0.0001
Transplant failure last transplantation	yes 139 (11.6%)	yes 21 (53.7%)	< 0.0001

Data as means ± SD, except for transplant failures of last transplant which are reported as number of patients. Means were tested using t-test, proportions were compared with chi-square tests. Medians were tested with non-parametric tests (Mann-Whitney).

Figure 1 shows the prevalence of EPS patients in time after the last kidney transplantation. EPS patients were diagnosed with EPS with a median time of 12.4 months (IQR 6.2 – 45.6) after transplantation. Sixty percent of the patients were diagnosed with EPS in the first 2 years after the last kidney transplantation. Three patients developed EPS more than 6 years after the last transplantation. The mean PD duration of these three patients was not significantly different (mean 56.2 ± 18.2 (SD) months) from patients with post-transplantation EPS within 6 years after transplantation (67.6 ± 32.6 months, p-value 0.6). There was no difference in number of transplants and graft failures between these groups.

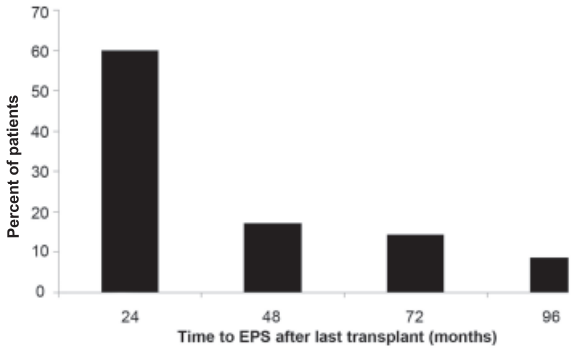


Figure 1 | EPS after kidney transplantation.

CNI's were the mainstay of immune suppressive therapy in both EPS and non-EPS patients (respectively 85% and 95% of patients at 3 months after transplantation, p-value>0.1). There was no significant difference in use of corticosteroids, azathioprine, mycophenolate mofetil or sirolimus as maintenance therapy between EPS patients and the non-EPS group (data not shown).

Mortality

During the ten-years follow-up 201 patients died after transplantation. Infections and cardiovascular events are the most important causes of death after kidney transplantation. Seventeen EPS patients died due to EPS related causes, 184 non-EPS patients died due to other reasons. EPS patients died with a median time of 15.2 months, (IQR 7.6 – 35.0), after the EPS diagnosis. Specific details about causes of death in the first two years after kidney transplantations are shown in table 3.

Overall EPS related mortality after kidney transplantation is 8.5%, which results in the fourth known cause of mortality after kidney transplantation (figure 2). There remains a large group of death due to unknown cause.

Kaplan-Meier analysis showed that patients with post-transplantation EPS had a significantly decreased survival after transplantation compared to patients without EPS (figure 3).

Table 3 | Diagnosis of death after kidney transplantation.

Cause of death	Overall	Percentage occurring within one year of transplantation	Percentage occurring within two years of transplantation
Infections	48 (23.9%)	15 (31.3%)	19 (39.6%)
Cardiovascular disease	44 (21.9%)	24 (54.5%)	26 (59.1%)
Malignancy	22 (10.9%)	4 (18.2%)	5 (22.7%)
Encapsulating Peritoneal Sclerosis	17 (8.5%)	6 (35.3%)	8 (47.1%)
Gastrointestinal	11 (5.5%)	7 (63.6%)	7 (63.6%)
Cerebrovascular accident	6 (3.0%)	-	2 (33.3%)
Social	6 (3.0%)	2 (33.3%)	2 (33.3%)
Pulmonary embolus	5 (2.5%)	3 (60.0%)	3 (60.0%)
Hemorrhage	3(1.5%)	1 (33.3%)	1 (33.3%)
Other	8 (4.0%)	1 (12.5%)	3 (37.5%)
Unknown	31 (15.4%)	4 (12.9.0%)	7 (22.6%)
Total number	201 (16.2%)	67 (33.3%)	83 (41.3%)

Data in numbers of patients (%). One and two-years post-transplantation represents deaths at one and two years after kidney transplantation (% of total of each cause of death).

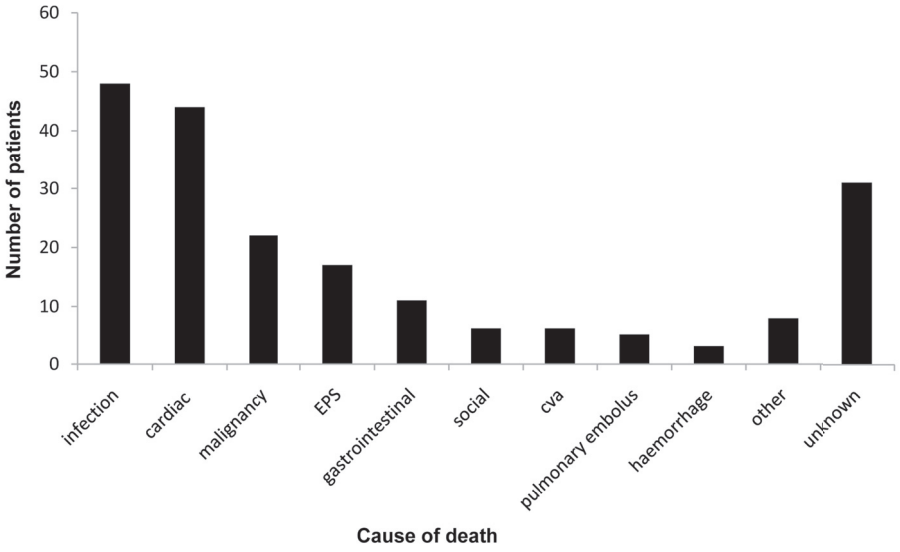


Figure 2 | Overall causes of death after kidney transplantation.

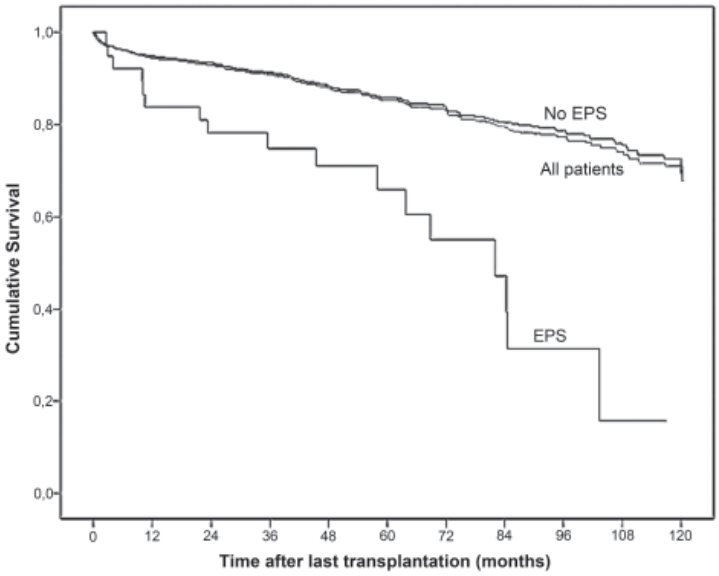
DISCUSSION

Post-transplantation EPS is a rare but severe complication in transplanted PD patients. Next to already known causes of death, like infections and cardiovascular events, EPS was identified as the fourth known cause of death after kidney transplantation and was associated with a decreased survival in these patients.

The contribution of EPS to mortality after kidney transplantation was previously not investigated and our findings can therefore not be compared to other studies. However, our general results, showing the various proportions of different causes of death after kidney transplantation, are comparable to other reports [16].

In accordance with other studies, there remains a large group of unknown causes of death [5]. In the past the EPS related mortality was possibly included in this group or in a group with gastro-intestinal causes.

Post-transplantation EPS appears to be a new phenomenon in transplantation practice. A recent Scottish study showed that the contribution of post-transplantation EPS might be even as much as 50% of the total EPS patients [17]. It differs from the classic form of EPS, which is predominantly associated with long term PD (longer than 5 years) and changed peritoneal membrane function, resulting in ultrafiltration failure. This latter form is extensively described in Japan, where patients tend to stay on PD longer, because kidney transplantation is limited [10]. In contrast, post-transplantation EPS patients tend to be younger when initiating PD and do



Number at risk

No EPS	1203	1019	898	766	644	510	413	323	236	153	87
EPS	38	30	27	22	17	13	8	6	3	1	0

Cumulative number of events

No EPS	0	61	75	95	118	134	145	161	167	175	184
EPS	0	6	8	9	10	11	13	14	16	17	17

Figure 3 | Influence of EPS on ten-year survival of PD transplanted patients.
Cox regression analysis with time after last transplantation, with analysis censored for ´time until end of study or death´.
Data presented as univariate analysis, P-value < 0.001.

not necessarily have a prolonged PD duration [13,18]. In this study, patients with post-transplantation EPS had a significantly longer PD duration compared to transplanted patients without EPS. The longer cumulative duration of PD may be partly explained by a higher frequency of transplant failure in this group. As pre-transplant PD duration is implicated as a risk factor for post-transplantation EPS, this information should be part of the informed consent procedure before transplantation. However, one must realize that there is a large variation in PD duration. This is shown in the current study, where a considerable number of EPS patients (26%) had a PD duration shorter than 48 months. The study design did not allow for a reliable multivariate analysis of this large variation and/or the impact on the incidence of post-transplantation EPS.

The post-transplantation EPS patients usually become symptomatic shortly after kidney transplantation, as was also shown in a recent study from the UK [19]. In this study, 21 post-transplantation EPS patients (identified from a total of 111 EPS patients) were diagnosed with a mean time from transplantation of only 5.4 months (1-19 months). In the current study the majority of EPS cases were also observed within the first two years after transplantation. However, in some

patients the diagnosis was even made after a number of years after transplantation. The clinical implication is that a prolonged clinical vigilance and a high index of suspicion for the diagnosis are warranted. Furthermore, our findings contribute to the ongoing discussion whether young PD patients should prematurely be transferred to hemodialysis after a few years of PD while awaiting transplantation or after transplant failure [20-21].

The etiology of post-transplantation EPS is yet unknown. But there are several hypotheses. The current accepted pathophysiological theory on EPS in general, is that the peritoneal membrane is preconditioned by damaging PD solutions. In reaction to this a repair process develops with an increased inflammation. After a second hit, such as a fungal peritonitis, this might result in an uncontrolled fibrosing process with an encapsulating of the intestines.

In post-transplantation EPS the relationship with the moment of transplantation is striking, suggesting that transplantation might impose the second hit. A possible explanation of the association with transplantation might be the discontinuation of peritoneal lavage of profibrotic factors after successful kidney transplantation. Another hypothesis is that post-transplantation EPS might be related to the concomitant use of profibrotic CNI's. In the damaged peritoneum there is already an upregulation of TGF-β which leads to fibrosis and neoangiogenesis [22]. Both tacrolimus and cyclosporin also lead to enhanced TGF-β expression and subsequent fibrosis [23]. The additional administration of cyclosporin to an experimental rat model of chronic peritoneal exposure to dialysis solutions indeed leads to EPS like abnormalities [24].

Furthermore, the introduction of CNI's has led to a trend to lower corticosteroids after kidney transplantation. Corticosteroids may, however, have a beneficial effect on the inflammatory state during the development of EPS. The role of CNI's in post-transplantation EPS remains unclear and given the evidence it is premature to conclude that the use or absence of CNI's are associated with EPS development.

The current study has a retrospective design, with its obvious limitations. One might argue that this design could lead to an underestimation of diagnoses, other than EPS. This is partially diminished because the used registries collect their data at the actual time of treatment with only a slight delay. There were some missing values in the use of maintenance immunosuppressive medication. These were equally distributed among both groups and it mainly concerned patients with kidney transplantation in the early nineties.

Once EPS has been diagnosed the therapeutical options are limited. Surgical treatment with extensive enterolysis might be successful, but it requires an experienced surgeon and has a high risk of recurrence and complications [25]. Successful treatment of EPS with immunosuppressive medication such as high dose steroids, azathioprine and MMF has been described [10,26-27], but these reports are anecdotal. Finally, we recently showed that tamoxifen treatment of EPS is associated with an increased patient survival [28].

In conclusion, post-transplantation EPS occurs infrequently but contributes significantly to a decreased survival in transplanted PD patients. A prolonged clinical vigilance and a high index of suspicion for the diagnosis is warranted, specifically in PD patients with a relatively long cumulative pre-transplant duration of PD.

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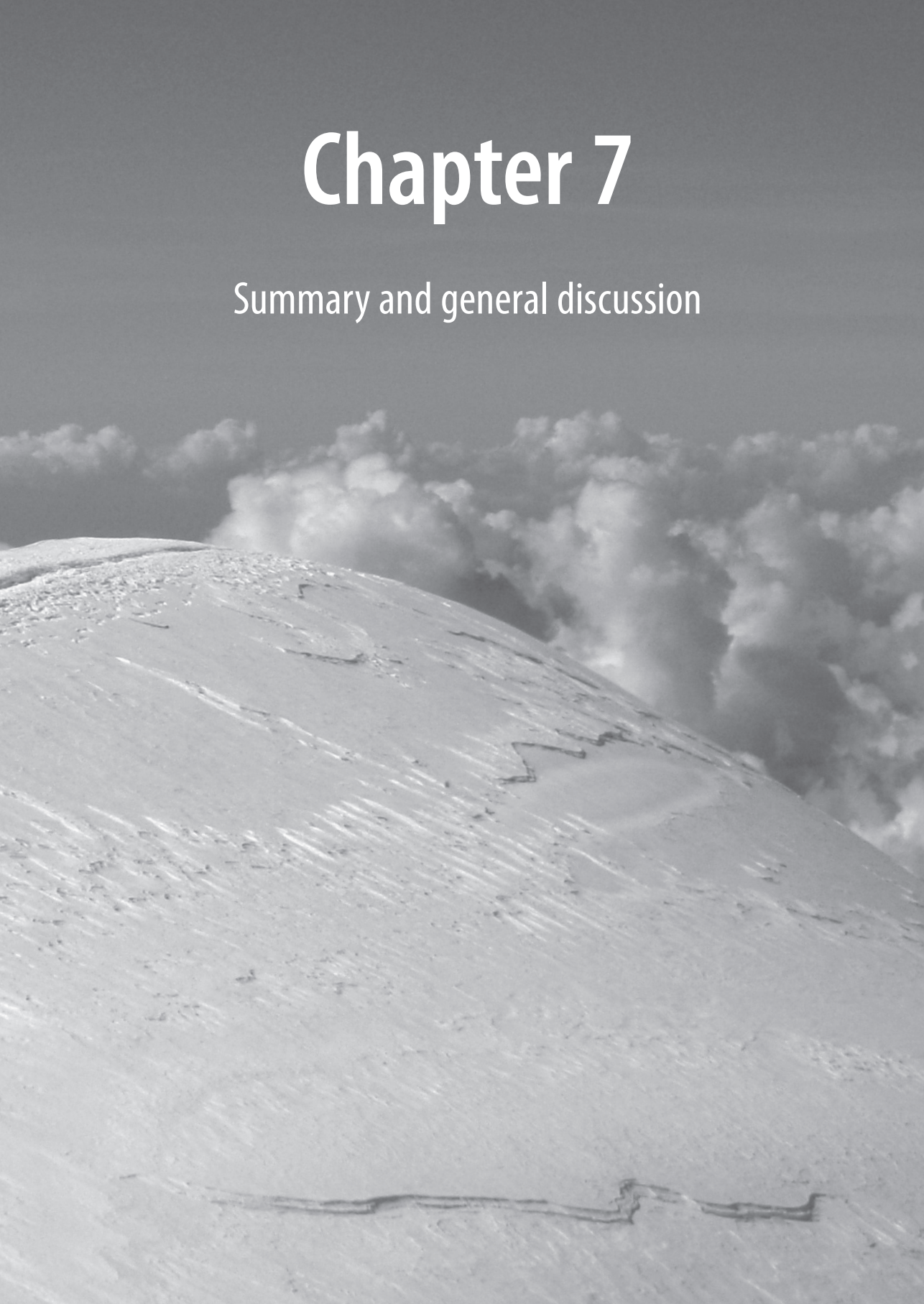
Chapter 7

Summary and general discussion



INTRODUCTION

This thesis describes the incidence of encapsulating peritoneal sclerosis (EPS) in the Netherlands, its risk factors and clinical consequences. It is primarily intended to provide the clinician with novel findings and associations with EPS.

In ***chapter 2*** of the thesis a global overview of the current understanding of EPS is given. Encapsulating peritoneal sclerosis (EPS) is a severe complication of long-term peritoneal dialysis (PD) with a high mortality (50%). A fibrous cocoon covers the intestines and causes dysfunction leading to intestinal obstruction. The last decade more attention has been focused on this complication. Although it is still rare, the incidence of EPS has possibly increased in recent years despite a stable PD population. The reported prevalence of EPS varies between 0.5 and 2.5% [1-6]. The occurrence of EPS increases with the duration of PD therapy. A registry study from Australia described an incidence of 19.4% after 8 years of PD treatment [5].

Several alterations of the peritoneum occur during the course of PD treatment. The mesothelial layer disappears (denudation). The peritoneal vasculature shows progressive signs of fibrosis and hyalinization of the media, neoangiogenesis with vasculopathy. The more vessels develop, the more severe the interstitial fibrosis appears to be. The submesothelial compact zone thickening is caused by interstitial fibrosis and sclerosis. In EPS this appears to be even more pronounced.

The pathophysiology is proposed as a "two-hit theory", which hypothesizes that 2 factors are required for the onset of EPS. The first hit causes disruption of normal peritoneal and mesothelial physiology and is mainly due to the incompatible features of the dialysis fluids. The second hit may be a peritonitis episode, the discontinuation of PD treatment or perhaps a genetical predisposition. In the primary process of repair of damaged peritoneum TGF-β plays a central role. It is associated with more fibrosis and angiogenesis. Epithelial to mesenchymal transition (EMT) may also be important [7]. EMT is a physiological process which occurs throughout the body and in the peritoneum to repair damaged tissue. During EMT, mesothelial cells that have been exposed to dialysate undergo a morphological and functional alteration that changes their epithelial phenotype to become fibroblastic. These fibroblasts then migrate to the submesothelial compact zone and may overproduce TGF-β. This process starts at the initiation of PD treatment and continues with the duration of PD. EMT is necessary for tissue repair under normal conditions, but uncontrolled it may lead to fibrotic processes. Other important players are vascular growth factors (e.g. VEGF), AGE's, cytokines (IL-6), metalloproteases, transcription factor snail and mast cells.

Besides prolonged PD duration novel independent associations with EPS as age, increased small solute transport, ultrafiltration failure, kidney transplantation and dialysis solutions might be present.

Recently radiological criteria for diagnosing EPS were developed [8]. It is however still difficult to prevent or recognize EPS in the early stages. Abdominal CT scans are not useful at this stage. Peritoneal functional parameters are probably useful. Ultrafiltration failure (UFF) appeared the predominant early change [9]. This was associated with early loss of residual renal function and accumulative glucose exposure. There usually is an increased small solute transport, which reflects the effective peritoneal surface area.

To date, there is no consensus on treatment. This should consist of supportive care and, when it is available, surgery. Corticosteroids and tamoxifen may be beneficial. Recent developments resulted in concerns among nephrologists and subsequently led to a debate on an arbitrary expiry date for PD because of the risk of EPS.

INCIDENCE AND RISK FACTORS OF EPS

Chapter 3 describes the two studies investigating the possible increasing incidence of EPS and the risk factors associated with EPS. The initial report is described in chapter 3.1.

It was our distinct impression that in recent years we were witnessing a marked increase in the incidence of EPS. In order to investigate whether this suspicion was justified, we initiated an analysis of the occurrence of EPS in two university hospitals in The Netherlands (Erasmus Medical University Centre in Rotterdam and the Utrecht Medical Centre in Utrecht). Cases were identified by retrospective investigation of the medical records in the period 1998-2005. This study shows that the incidence of severe EPS had increased significantly in the last few years in stabile PD populations. There was a remarkable preponderance of EPS patients with a functioning renal allograft which may point towards a pathogenetic role of kidney transplantation.

Due to the limited numbers it was impossible to draw firm conclusions on risk factors associated with EPS and its increased incidence. Therefore we performed an additional study.

This study is described in chapter 3.2. This is a multicenter study in which eight large hospitals in the Netherlands participated, which resulted in a representative study, as it covered 26% of all PD patients in the Netherlands in this period. The design is a retrospective nested case controlled study. It comprises of 63 EPS and 126 control patients. Control patients were selected from the national registry (RENINE) and controlled for start date PD with the controls closest to the start date of the EPS patients. In order to be able to investigate the association of PD duration in a controlled manner there was deliberately no matching for PD duration. Associations were analysed using a log linear regression model. PD duration, age, transplantation, time since last transplantation, calendar time, follow up time, peritonitis episodes, transfer from PD to HD for other reasons than suspected EPS, time on icodextrin and presence of ultrafiltration were pre-specified predictors.

The study showed that the incidence increased in the years 2003-2005, confirming our earlier results. This is probably not due to an increased awareness or a change in diagnostic criteria which could lead to inclusion of milder EPS stages. The presence of the severe EPS symptoms makes it unlikely that the diagnosis was missed in the past.

There also appeared to be a decrease of the incidence in 2006. This might suggest that the increase was just a temporary issue. We did not analyse the incidence in the years after 2006. However when the recent reports are interpreted, it can be concluded that the incidence is still increasing. For example, a recent observational study from London showed at most 1 patient a year until 2003 and in the years 2004-2008 respectively 5,6,4,6 and 11 EPS patients [10]. Although there is no information on the general PD population in this cohort, it appears unlikely this has increased with the same proportion.

In the multivariate regression analysis we confirmed the independent associations of PD duration, ultrafiltration failure (UFF) and age with EPS development. Each year of prolonged PD had an increased relative risk for EPS of 40%. The associations of young age and PD duration are in accordance with another recent report of the ANZDATA registry [11]. In addition we were able to show novel independent associations as prolonged use of icodextrin, kidney transplantation and the time after kidney transplantation with the presence with EPS.

Icodextrin permits good ultrafiltration during long time dwells and avoids the potential harmful effects of glucose. The association with EPS is somewhat surprising and deserves more attention in the future. The association with EPS appeared not be caused by the abundant presence of ultrafiltration failure in EPS.

Consistent with the first report there was an independent association with kidney transplantation. A possible explanation is the profibrotic feature of calcineurin inhibitors (CNI's). However, we were not able to identify the introduction of CNI's as a risk factor for EPS. With regard to time after transplantation, the yearly probability of EPS increased in the year after transplantation from 1.75% to 7.5% in the univariate analysis. Finally, not the kidney transplantation itself, but rather the cessation of the PD, might be the risk factor for developing EPS [6,12]. We were not able to show such an association with transfer from PD to HD. Instead, we found that the majority of patients switching from PD to HD already were suspected of having EPS.

EARLY DIAGNOSTIC MARKERS

Chapter 4 described the use of effluent substances as possible diagnostic markers of early EPS. Effluent cancer antigen 125 (CA125) is a marker of mesothelial cell mass, interleuking-6 (IL-6) is a marker of inflammation, and vascular endothelial growth factor (VEGF) is a growth factor for the formation of new vessels. In this case-controlled study the time course of these peritoneal

membrane markers in patients who developed EPS and in those matched for the duration of dialysis who did not develop EPS, was analyzed.

Dialysate and serum samples of 11 EPS patients and 31 control patients all treated with PD for at least 57 months were longitudinally collected during a standard peritoneal permeability analysis (SPA) performed once a year. Again, EPS patients were younger than controls and had a longer PD duration (104 months versus 72 months, p=0.01). No significant differences in time courses of the different markers were present between groups. However appearance rate (AR) of CA-125 was significantly lower in the last three years prior to EPS ($p<0.05$) and AR of IL-6 was higher two years prior to EPS (p=0.09). Locally produced VEGF showed no differences among the groups.

The combination of AR CA-125<33 U/min and AR IL-6>350 pg/min had a sensitivity of 70% and a specificity of 89% for predicting EPS diagnosis. Recent reports showed that ultrafiltration failure is a predominant sign in developing EPS [9,13]. When the presence of ultrafiltration failure was added to the predictive model it gained more strength. The specificity increased to 100%, indicating the potential use for an early diagnosis of EPS. In daily practice this might be useful to identify those at risk for clinically established EPS. This is important, because preventive interventions to reduce morbidity and mortality might be more effective at this stage than after the establishment of the diagnosis. It is therefore recommended to longitudinally monitor the peritoneal function with 3.86% glucose peritoneal equilibration tests.

There are some limitations of the study which concern the fact that not all the analyses could be done in all patients. Despite intended matching for PD duration there also appeared a slight difference in overall mean PD duration.

TAMOXIFEN AND SURVIVAL BENEFIT

Chapter 5 describes the possible use of tamoxifen in EPS therapy. Currently there is no consensus on therapeutical management of EPS. Nutritional status is important [14] and surgery with extensive adhesiolysis is recommended. The latter is rarely performed in Western Europe, probably because of fear of complications [15-16]. At present there are no randomized controlled trials that have shown the efficacy of any given drug for EPS, including tamoxifen. Tamoxifen influences the activity of the profibrotic cytokine TGF-β and has shown to be effective in fibrotic diseases as retroperitoneal fibrosis [17]. It was hypothesized that tamoxifen may result in lower mortality in treated patients. We performed a retrospective study in the multicenter EPS study to investigate whether tamoxifen was associated with an improved survival in these patients. EPS patients treated with tamoxifen and not treated with tamoxifen were compared. The study shows that mortality rate was lower in tamoxifen treated EPS patients compared to EPS patients not treated with tamoxifen (45.8% vs. 74.4%, p=0.03) with both groups having comparable demographic and clinical characteristics. More importantly, treatment of EPS patients with

tamoxifen was associated with a trend to an improved survival, independent of other possible beneficial treatment options (HR 0.39, p=0.056). Although all available possible confounders were taken into account by including them into a multivariate analysis, it is possible that the results are influenced by 'confounding by indication'. When considering tamoxifen for the treatment of EPS the possible adverse events like thromboembolism or endometrial carcinoma have to be considered. Due to the morbidity and the limited life expectancy of EPS patients, the benefits of tamoxifen probably outweigh the potential risks. The clear pathophysiological rationale for using tamoxifen in EPS patients combined with the encouraging results from this study supports the recommendation to use tamoxifen as an additional treatment option for EPS.

MORTALITY AFTER KIDNEY TRANSPLANTATION DUE TO EPS

Chapter 6 describes the impact of post-transplantation EPS on mortality after kidney transplantation. EPS frequently presents after kidney transplantation, a condition known as post-transplantation EPS. The prevalence and impact of post-transplantation EPS on survival after kidney transplantation is unknown. It was hypothesized that post-transplantation EPS may have a significantly contribution to the mortality after kidney transplantation, which has previously gone unrecognized.

From January[1st] 1996 until July[1st] 2007 1241 PD patients were transplanted in four participating university hospitals in the Netherlands. Thirty-eight cases of post-transplantation EPS (3%) were identified from the Dutch multicenter EPS study. Two-hundred-and-one (16.2%) patients died after transplantation, of which seventeen EPS patients. After infection (23.9%), cardiovascular disease (21.9%) and malignancy (10.9%), EPS (8.5%) was the fourth known cause of death after transplantation. Kaplan-Meier analysis showed a significant decreased survival for transplanted patients with post-transplantation EPS compared to transplanted patients without EPS. The majority of EPS cases were observed within the first two years after transplantation, but some cases appeared many years after transplantation. In conclusion, post-transplantation EPS is rare, but carries a high mortality. Therefore, a prolonged clinical vigilance and a high index of suspicion for the diagnosis are warranted, specifically in PD patients with a relatively long cumulative pre-transplant duration of PD. Furthermore, our findings contribute to the ongoing discussion whether young PD patients should prematurely be transferred to hemodialysis after a few years of PD while awaiting transplantation or after transplant failure [18-19].

CONCLUSIONS

1. The incidence of severe EPS has increased significantly in the period 1996-2006 in the Dutch PD population.
2. PD duration, age, kidney transplantation, time after kidney transplantation, prolonged use of icodextrin and ultrafiltration failure (UFF) are independently associated with EPS development. Each year of prolonged PD had an increased relative risk for EPS of 40%.
3. The combination of AR CA-125<33 U/min and AR IL-6>350 pg/min had a sensitivity of 70% and a specificity of 89% for predicting EPS diagnosis.
4. Tamoxifen reduces mortality in tamoxifen treated EPS patients compared to EPS patients not treated with tamoxifen. Treatment of EPS patients with tamoxifen was associated with a trend to an improved survival, independent of other possible beneficial treatment options.
5. After infection (23.9%), cardiovascular disease (21.9%) and malignancy (10.9%), EPS (8.5%) was the fourth known cause of death after transplantation. Survival for transplanted patients with post-transplantation EPS is significantly decreased compared to transplanted patients without EPS.

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Chapter 8.1

The Dutch EPS registry: increasing the knowledge of Encapsulating Peritoneal Sclerosis.

M.R. Korte, E.W. Boeschoten, M.G.H. Betjes on behalf of the EPS registry.

Netherlands Journal of Medicine 2009 Sep;67(8):359-62

ABSTRACT

Encapsulating peritoneal sclerosis (EPS) is a rare condition characterized by fibrotic thickening of the visceral peritoneum, leading to encapsulating of the intestines with partial or total intestinal obstruction. EPS is a serious complication of peritoneal dialysis (PD) with high morbidity and a mortality exceeding 50%. At present, there is uncertainty concerning the incidence and the risk factors involved in the development of EPS. To address these questions a nationwide registry has been initiated.

Primary goals of the registry are to record the incidence of EPS and investigate the association of different variables, such as PD duration, medication, dialysis solutions and kidney transplantation with EPS.

The registry will improve the knowledge of EPS and will serve to develop guidelines and necessary management strategies. From the registry different research activities can be initiated. A major challenge lies in the establishment of criteria that allow for a timely diagnosis of EPS. At present, there are no diagnostic tools that can accurately detect EPS at an early stage. For this reason, besides patients with proven EPS, the clinical suspicion of EPS will be a sufficient criterium for inclusion in the registry.

This nationwide EPS registry is currently enrolling patients.

INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) is a clinical syndrome characterized by intestinal encapsulating and subsequent obstruction of the intestinal tract [1]. EPS can be found in many different clinical settings, but the condition is most frequently encountered in patients treated with peritoneal dialysis.

Although rare, encapsulating peritoneal sclerosis (EPS) has come to be recognized as a serious complication of peritoneal dialysis (PD) with a high morbidity and a mortality of approximately 50% [2].

Reported prevalences for EPS range from 0.7 to 3.3 % [2-4]. Recently, more attention has been given to this complication, as several reports have suggested an increased incidence of EPS during the last years [5-6].

Peritoneal dialysis (PD) is an excellent modality of renal replacement therapy (RRT) and may have a superior patient survival compared to hemodialysis [7], due to a better preservation of the renal residual function [8]. In the period 1996-2006 approximately 7800 patients with end stage renal disease were treated with PD in the Netherlands (Renine database). However, in recent years a worldwide trend of treating fewer patients with PD has been noted. Among other reasons, an increased fear of EPS may be an incentive for the nephrologist to favor hemodialysis over PD when starting renal replacement therapy [9].

There is much uncertainty concerning the true incidence of EPS in the Netherlands. In addition, the clinical factors associated with the development of EPS seem to differ from previous reports, as we found a substantial number of severe cases of EPS after renal transplantation [6].

Given the severity of the condition and the current lack of data collaboration was started among Dutch nephrologists, which has resulted in the initiation of a nationwide registry for EPS.

DISCUSSION

Clinical spectrum of EPS

EPS, formerly known as sclerosing peritonitis, is characterized by progressive fibrosis of the visceral peritoneum resulting in a partially or total encasement of the bowel by a thickened and fibrotic membrane (Figure 1).

The development of EPS is insidious and initially there are only vague abdominal complaints. With progressive fibrosis, symptoms as nausea, vomiting, appetite loss, weight loss and constipation appear. Usually, ultrafiltration failure has developed and signs of a systemic inflammatory syndrome may be present. Eventually, in the last stage of abdominal cocooning there is partial or complete intestinal obstruction. At this stage there is a high morbidity and mortality.

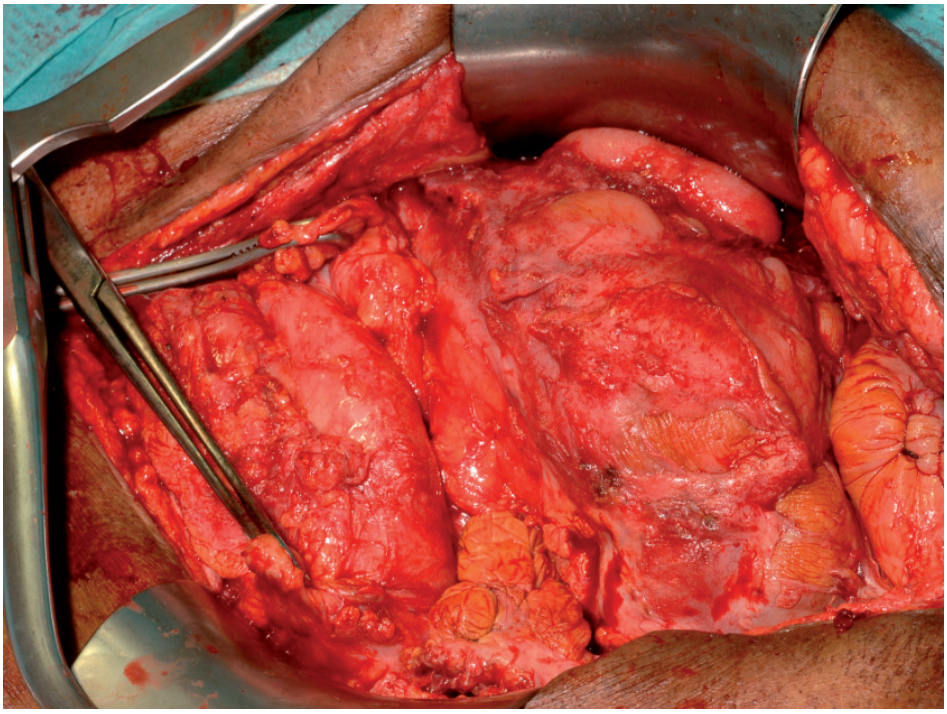

Figure 1 | Macroscopical EPS.
This patient with a history of PD has developed complaints of intestinal obstruction. At laparotomy there is a clear fibrotic and thickened membrane covering the bowel. There are also extensive adhesions.

Recently, we performed a multicenter study in which we analyzed the data of 2022 PD patients in the period 1996-2006. The results showed a high mortality-rate of EPS, in accordance with studies from other countries (Figure 2) [10].

The diagnosis of EPS is difficult because the criteria defined by the ISPD (Table 1) are rather aspecific [11]. The key feature of EPS is the presence of a clinical syndrome of intermittent or recurrent presence of intestinal obstruction, with or without inflammation parameters. The existence of peritoneal thickening, sclerosis, calcifications and encapsulation is confirmed by macroscopic inspection or radiological findings.

There is however a large overlap with simple sclerosis when patients are on PD for a longer time and CT scanning is not useful as a screening tool for early stages of EPS [12]. The use of macroscopic evidence of EPS is the only appropriate tool serving as golden standard for the diagnosis EPS. However, this approach is not always feasible in a clinical setting and macroscopic evidence of EPS is only obtained in the minority of cases.

Pathophysiology

The peritoneum of patients treated with PD is daily exposed to various dialysis fluids. This leads to changes of the peritoneal membrane over time characterized by mesothelial cell loss,

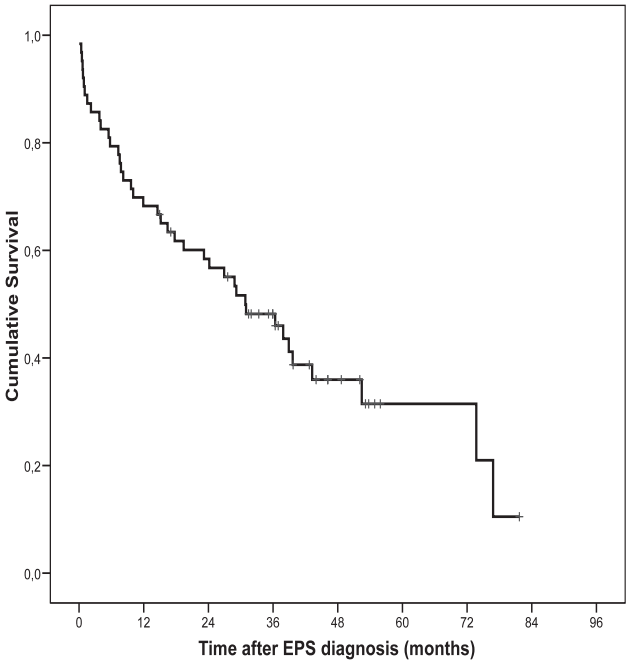

Figure 2 | Survival of EPS patients.
In a Dutch multicenter study in the period 1996-2007 there were 63 patients with severe EPS in a total of 2022 PD patients [10]. This figure shows the cumulative survival (Kaplan Meier analysis) of these patients after the diagnosis of EPS was made.

epithelial to mesenchymal transition of mesothelial cells, neovascularisation and vasculopathy [13-17]. These changes are probably induced by conventional dialysis fluids with bio-incompatible characteristics, high glucose concentrations, glucose degradation products, lactate buffers and acid pH. This process during long term PD with fibrosis of parietal peritoneum is sometimes referred to as simple sclerosis [18]. It is generally assumed that the abundant fibrosis of the visceral peritoneal as seen in EPS has a different etiology than simple sclerosis. The complete pathophysiology of EPS is yet unclear, but is probably multifactorial. The duration of PD is recognized as the single most important risk factor for EPS, as EPS within 3 years of treatment is rarely observed. Therefore, the most generally accepted theory assumes a progressively damaged peritoneum by prolonged use of incompatible dialysis fluids, which may be complicated by factors that aggravate the peritoneal sclerosis [4,19]. In recent years candidate factors came forth from a number of observational studies. These included cessation of peritoneal lavage [3], peritonitis [20-21] and factors associated with kidney transplantation [6].

Why a nationwide registry?

To date, there are still large gaps in our knowledge of EPS. This can be largely attributed to the lack of systemic prospective data collection, specifically necessary in the case of a condition

Table 1 | Criteria for the diagnosis of encapsulating peritoneal sclerosis (EPS).

ISPD[1]	Criteria
EPS	Intestinal obstruction[2] and Radiological or macroscopical evidence[3]
EPS registry	
Macroscopical EPS *(golden standard)*	Intestinal obstruction[2] and Macroscopically identified EPS
Clinical EPS	Intestinal obstruction and Radiological EPS[3]
Suspected early EPS	Intestinal obstruction *or* Two or more findings of: – weight or appetite loss – bloody ascites – radiological suggestion of EPS – fast transport status or ultrafiltration failure
No EPS	Intestinal obstruction but Other cause than EPS identified with certainty

[1]Criteria as used in the definitions by the ISPD (International Society of Peritoneal Dialysis) and the EPS registry of EPS in a patient that is currently being treated or has been treated with PD [11]. [2]Intestinal obstruction means any sign and symptom of persistent, intermittent or recurrent intestinal obstruction. [3]Radiological evidence for EPS means fulfilment of the criteria for EPS with CT scanning with findings such as peritoneal calcification, bowel thickening, bowel tethering, bowel dilatation, ascites or peritoneal thickening [12].

encountered less than once a year in an average dialysis center. Such a data collection is even more important as we reported a possible increased incidence of EPS [5]. Therefore, the first goal of this registry should be to record the current incidence of EPS and investigate whether it is still increasing.

Secondly, the registry needs to investigate the association of different variables, such as PD duration, medication, dialysis solutions and kidney transplantation. For instance, our case-controlled analysis of EPS cases in the Netherlands over the last 10 years showed a strikingly high percentage of EPS (50%) shortly after renal transplantation and suggested that the use of icodextrin was independently associated with EPS [10]. In addition, the statistical modeling indicated that large part of the variation was not accounted for by the clinical and demographical variables used for analysis. These observations, that may have major consequences for the management of the PD patients, need to be verified in a prospective database. Furthermore, in an effort to document early stages of EPS we will also include cases of suspected EPS. This also allows for identification of risk factors for progression and discovery of biomarkers for establishing EPS at an early stage.

In a recent survey among Dutch nephrologists it appeared that 16% of the responders feared EPS and subsequently considered to withhold PD as a first choice of RRT [9]. Given the rarity of the disease and good overall survival on PD this decision is unlogical, but illustrates the need for a registry recording data and yielding evidence-based guidelines to the treating physicians. As such, these data are currently not available and there is a lack of prospective studies on EPS. The majority of the experience comes from Japanese observational studies, where patients tend to be on PD for a longer period because the limited availability of kidney transplantation [8]. It is not clear whether the Japanese findings can be extrapolated to the PD population of Western Europe.

An important part of the guidelines is the development of an uniform management strategy for EPS. Given the presence of malnutrition in the presence of intestinal obstruction, supportive care with either enteral or parenteral nutrition is the mainstay of the treatment [22]. Immune suppressive medication and others agents, like tamoxifen have been suggested [23-26]. But the level of evidence is low as the data are from anecdotal reports or small case series. Encouraging results from Japan have been reported with surgical enterolysis, releasing the complete small intestine [27]. However, there is yet little experience with this procedure in Western-Europe. Finally, the registry will function as a central organization from which different research activities, for example genetic and marker studies can be initiated. To strengthen the importance of the registry there will be extensive collaboration within Europe, for instance with the UK EPS study group.

Design

Collaboration of all university centers and the Hans Mak institute resulted into a steering committee, which has initiated the nationwide EPS registry. Patients with a history of PD with a diagnosis of EPS or suspicion of EPS will be prospectively included. Ideally, the registry would include all patients treated with PD. This way, all data could be accurately registered. However, giving the low prevalence of EPS, inclusion of all PD patients would be time consuming and requires a very large, expensive database.

Every 6 months an e-mail will be sent to all Dutch nephrologists inquiring whether they can report a patient (suspected of) having EPS. In the registry patients are divided into four groups by the steering committee; macroscopically definite EPS, clinical EPS, possible EPS and no EPS, by the criteria shown in Table 1. As multiple factors may influence the development of EPS, there will be an extensively reviewing of all possible diagnostic, prognostic and therapeutically variables. Demographics, PD, HD, transplantation related factors of all included patients will be reviewed. In addition, a sample of peritoneal effluent and plasma will be taken and stored for later analysis.

An easy accessible website (www.epsregistry.com) is developed to give more detailed information on EPS and the EPS registry. The registry is made so that it can easily be extended to a European format.

For professionals it also has the opportunity to submit a patient with EPS There will be a yearly update on the progress of the registry. In the future research developments and guidelines will be published on the website.

CONCLUSION

EPS is a potential devastating disease with a high mortality. Recently, it was shown that the prevalence of EPS may increase in the Netherlands. The low prevalence of EPS has hampered the research in this area, which has resulted in a lack of knowledge about natural history, pathophysiology and risk factors, and treatment options. A nationwide registry is required to collect data prospectively. Such an EPS registry has recently been initiated. The database of this EPS registry will allow establishment and monitoring of the prevalence of EPS, identifying risk factors, basic research of the pathophysiology of EPS and development of management guidelines. The EPS registry is currently enrolling patients. We kindly call upon all nephrologists to cooperate with the registry in order to obtain a representative registry and thus contribute to a better understanding of EPS.

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Chapter 8.2

Future perspectives and recommendations

INTRODUCTION

In this thesis we described the results of studies on risk factors of EPS, showed new diagnostic markers and evaluated tamoxifen as a possible therapy. Furthermore, we evaluated the entity post-transplantation EPS and its clinical consequences. These observations have raised new questions and revealed potential areas of interest for future research. In this section some of these future questions and possible research initiatives on EPS and post-transplantation EPS, in particular, are explored. In addition, recommendations for diagnostics and therapeutical approach are given.

IN WHAT WAY IS POST-TRANSPLANTATION EPS DIFFERENT FROM "CLASSIC" EPS?

Post-transplantation EPS appears to be different in comparison with the "classic form of EPS". The latter is found in association with prolonged PD and mainly reported in Japanese literature. The post-transplantation EPS is characterized by the appearance of EPS shortly after kidney transplantation and seems to be triggered by either cessation of PD treatment and/or the transplantation procedure itself.

Classical EPS can be seen as a result of an exaggerated healing response of the peritoneum, which has been exposed for a prolonged time to "toxic" dialysis fluids. At the early stage of development of EPS this process is probably associated with local inflammation to a variable degree[1]. It is unknown to what extent inflammation is involved in post-transplantation EPS. It is possible that post-transplantation EPS is in fact occurring in patients that are already at the early stage of EPS. In post-transplant EPS patients there appear to be no abdominal complaints prior to the kidney transplantation, but this has not been thoroughly investigated. Possibly, there are also signs of enhanced peritoneal inflammation present, indicative of an early stage of EPS. On the other hand, post-transplantation EPS may have a very different etiology, e.g. CNI-induced fibrosis (see below), without the presence of inflammation. We will need to understand the natural clinical course of post-transplantation EPS better and investigate to what extent post-transplantation EPS differs from the classical form of EPS. The answers to these questions are relevant as they could be important to identify patients prone for EPS after transplantation.

In the study on post-transplantation EPS it became clear that there is also a small number of patients who develop EPS much longer after kidney transplantation. It needs to be investigated in what way these patients differ from patients with EPS presenting shortly after kidney transplantation. For example, did these patients have a more prolonged PD treatment compared to the patients with EPS shortly after kidney transplantation?

WHAT IS THE ETIOLOGY OF POST-TRANSPLANTATION EPS?

Post-transplantation EPS has only recently gained interest as an important clinical entity and the question concerning the etiology is still open for debate. Various possibilities are plausible.

As stated before, it is possible that post-transplantation EPS occurs in patients already having the early stage of EPS, which has gone unrecognized. Another possibility is the use of CNI's that are known to have profibrotic features. Although we were unable to show an association with CNI's in the described studies, this does not exclude an influence of this class of immunosuppressive drugs on the development of EPS. There are two main reasons for this statement. First, the increase in the number of EPS patients seems to coincide with the increasing number of transplantations and the subsequent use of CNI's. Second, the pro-fibrotic quality of CNI's has been documented in an animal model of EPS [2].

However, at present the evidence for the involvement of CNI's in post-transplantation EPS is not firm enough to propose a change of CNI's into e.g. sirolimus as part of immunosuppressive regimen after kidney transplantation. In addition, post-transplantation EPS has been reported in patients that were given a CNI-free drug regimen [3]. To answer this question a large randomized prospective trial comparing a CNI-free drug regimen with a standard CNI-containing regimen after transplantation needs to be performed. Given the low incidence of post-transplantation EPS this would require a multicenter, international study design.

Hypothetically the development of post-transplantation EPS might be influenced by certain viruses. It is well known that fibrosing polyoma viruses are more present shortly after kidney transplantation and cause chronic allograft failure due to fibrosis [4-5]. A comparable reaction could also happen in the peritoneum. The course of post-transplantation EPS with the absent symptoms prior to the transplantation and the relation with the transplantation could suggest such an association.

Finally, it has to be established what the contribution is of discontinuation of PD treatment on EPS development. With the cessation of peritoneal dialysis the peritoneal lavage of fibrin, possible profibrotic and pro-inflammatory mediators is decreased, which results in an increased peritoneal concentration of these mediators. Furthermore the abdominal structures are more closely aligned because of the absence of the fluid, which possibly facilitates the formation of adhesions. Perhaps the impact of kidney transplantation on EPS development is overestimated because it coincides with the termination of PD? We tried to answer this question in the study described in chapter 3.2, analyzing the role of termination of PD treatment in all our cases of EPS. However, the majority of EPS cases without prior kidney transplantation discontinued PD treatment because of signs of developing EPS. The number of PD patients developing EPS after terminating PD treatment, without previous symptoms of EPS, is therefore quite small. Therefore, this important question appears difficult to answer and requires a prospective study in a very large cohort of PD patients.

IS THERE A GENETIC SUSCEPTIBILITY FOR EPS?

There are patients who are on PD for many years and never develop EPS. This is an intriguing observation and suggest the possibility of interindividual differences for the risk of developing EPS. Are these patients in some way protected for EPS development or do EPS patients have certain susceptibility for EPS? In the near future this will probably gain more attention. Registries are already collecting effluent and serum samples of EPS patients [6-7]. Gene polymorphisms of all important players in peritoneal remodeling and in the EPS development will be investigated. For instance, an association between EPS and a polymorphism of the RAGE receptor, one of the main players, has already been described [8]. Other candidate polymorphisms include vascular growth factors, TGF-β and its downstream mediators, metalloproteases and PAI-1.

HOW CAN THE DIAGNOSTICAL APPROACH BE IMPROVED?

Laparoscopy?

There is a lack of diagnostic criteria for the early stages of EPS, which may present with rather a-specific abdominal complaints or in patients with inconclusive radiological evidence. This often leads to a substantial delay in the diagnosis of EPS. Subsequently a possible beneficial therapy is withheld at the early stage of the disease. Given the high morbidity of EPS it is justified to be more aggressive in the diagnostic approach. In the view of the author there should be more focus on laparoscopy with performing biopsies. There is some reluctance to perform such a procedure. This is because of the possibility of complications such as perforation of the bowel. This is however likely to be overestimated. In general the risk of perforation on laparoscopy is low [9]. In the specific case of emerging EPS an abdominal CT scan is performed. When this shows a retracted bowel at the dorsal side of the abdomen there is usually an overlying fluid collection which minimizes the risk of perforation even more. A diagnostic laparoscopy can provide the diagnosis when there is a clinical suspicion of EPS, but the CT scan is not yet conclusive. A laparoscopy also facilitates peritoneal biopsies for the differential diagnosis of malignancies, tuberculosis or fungal peritonitis. Furthermore it provides biopsy material for future research.

MRI and ultrasound

Although abdominal CT scanning is useful for diagnosing EPS, it has some limitations. Two of the most important ones are that it is useless as screening tool and it has to be interpreted by an experienced radiologist. The radiological reports on EPS are scarce [10], but there is ongoing research to the contribution of MR imaging in case of EPS. There may be an enhanced contrast between overlying structures [11]. One limitation is the motility of the bowel which interferes with the imaging. Ultrasound might be more promising. With the improving quality of the ultrasound early changes might be detected. Perhaps this should be monitored on a regular

basis to be able to compare the abdominal images and learn on the natural course of peritoneal remodeling. Additionally, ultrasound is easily accessible and can be learned by an enthusiastic nephrologist.

SHOULD THERE BE PRE-EMPTIVE TRANSFERRING FROM PD TO HD?

There is much debate on the subject of a fixed expiry date of PD. As the development of EPS is associated with long term PD, it is sometimes suggested to discontinue PD after 3 to 4 years and switch to HD. In two recent commentaries on this subject it was postulated that there is currently little evidence to transfer patients from PD to HD, because of a chance of EPS [12]. One of these commentaries concerned a statement from an ISPD working group [13].

However, the arguments given in these commentaries can be criticized.

First, one of the main reasons used by the authors to not transfer patients is the fact that EPS is not common. It is indeed true that, although the incidence of EPS is possibly increasing, it still has a low overall incidence. However, summarizing the different studies/registries of EPS, one notices that although EPS has a low incidence in the general PD population, this increases to 19.4% after 8 years of PD treatment [14]. In order to make a correct judgment towards the individual risk of EPS the survival on PD has to be taken into account. From the RENINE database (registry of all Dutch ESRD patients with renal replacement therapy) it can be shown that in the period 1996-2006, 5604 patients started on PD (www.renine.nl). After 4 years only slightly less than 20% of these patients was still on PD. The incidence of EPS after 4 years of PD is approximately 5%. In the period 1996-2006 this would have resulted in approximately 1120.8 patients still on PD for 4 years of which 56 patients would have developed EPS. Thus, although the absolute numbers of PD patients developing EPS are small, this is largely because relatively few patients are on PD for more than 5 years.

Second, the complications of HD such as infections and cardiovascular risks are frequently mentioned as reasons to not transfer patients to HD. Additionally, the switch to HD could have important implications on the quality of life. Although these arguments are true, they primarily focus on the downside of HD. There are also other modalities of HD, which are reported to have good results concerning quality of life and outcome, such as home dialysis or nocturnal dialysis [15-16].

The third argument concerns the limited knowledge on the EPS pathophysiology. The majority of the data regarding EPS incidence and pathophysiology has originated from the era where conventional dialysis fluids were used. The newer more biocompatible are supposed to have less damaging effects and subsequently lead to less EPS. However the influence of these new dialysis solutions on EPS development has not been investigated.

It appears that EPS may develop after discontinuation of PD, therefore a switch could actually provoke an EPS exacerbation. This is possibly true for patients with long-term PD and

already having some early symptoms. It is unknown whether a pre-emptive switch to HD would prevent further peritoneal deterioration when it is done early enough. The exclusion of the damaging influence of dialysis fluids may in the end result in less peritoneal changes.

Finally, the majority of authors advocate a more individualized assessment of patients at risk for developing EPS. The primary focus should be on identifying patients using the current data on risk factors and markers in early stages of EPS. However, it is also recognized that there is a current lack of biomarkers or clinical features that are able to reliable identify the patients at risk for EPS. This is used as an argument against pre-emptive transfer from PD to HD. When using the most recent data two risk factors, ultrafiltration failure and kidney transplantation, can be useful for such an individualized approach. Although it is not discriminating between long-term PD and EPS, ultrafiltration failure is an universal finding in EPS patients. Recently the group of Davies et al. showed that EPS patients have on average a rapid decrease of ultrafiltration failure in the first years of PD treatment. This decrease of ultrafiltration capacity in EPS patients was uncoupled from the also increasing small solute transport, which distinguishes them from the other PD patients [17]. Our data show that on average 3% of all transplanted PD patients develop EPS and this percentage is probably significantly higher in the subgroup of patients that had ultrafiltration failure prior to transplantation. After kidney transplantation, the long-term survival and quality of life of these relatively young PD patients without EPS are very well, which can be dramatically changed by EPS.

Therefore, it seems that in the Dutch population it is justified to switch each PD patient eligible for kidney transplantation to HD, if he develops ultrafiltration failure within the first 2 to 3 years after starting PD. This decision would probably result in a relatively modest impact on the total number of patients on PD, as the number of PD patients fulfilling these criteria is rather small.

In conclusion, the life expectancy of older patients and patients with co-morbidities is limited. Few patients will therefore not survive long enough to develop EPS. With the decision to switch the modality to HD, the risk of EPS must also be weighed against the tolerance to HD and possible associated complications. But in the end, the decision to transfer to HD will be made by the nephrologist and the patient, provided he is well informed. The most important question to be answered is whether a patient is to be exposed to the risk of disease with a high morbidity when he has had a few years of PD, develops ultrafiltration failure and awaits a kidney transplantation within a few years.

THERAPEUTICAL MANAGEMENT

Once a patient is diagnosed with EPS the therapeutical options are limited. There are numerous case reports on different therapies in EPS patients, but these lack appropriate comparisons. At this stage we need to reach a clear consensus on management based on the current data and rationale. In the future uniform management algorithm the mainstay of the therapy should be adequate nutrition. In early stages corticosteroids may be applied, provided an infectious cause is excluded. In addition tamoxifen should be applied. In case of intestinal obstruction an adhesiolysis, performed by an experienced surgeon, can be considered. The latter is mainly performed in Japan and has shown promising results [18]. Nowadays these operations are also conducted in the UK, but they have not reported any findings yet [19].

In my view there needs to be more focus on an integrated approach with multiple disciplines, like dialysis nephrologists, transplantation nephrologists, dieticians, radiologists and surgeons. At this moment there is not a single specialized center in the Netherlands, which also has the surgical experience in these cases. The achievement of guidelines on therapy and at least one specialized center with surgical expertise should be one of the main priorities of the Dutch working group on EPS [20].

IS A PREDICTIVE MODEL FOR EPS POSSIBLE?

PD is a well tolerated choice of renal replacement therapy with a fair prognosis [21]. Although EPS is increasing in incidence, it is still rare. This calls for a well-balanced decision when to initiate treatment and when to stop treating patients with PD with respect to the risk of EPS. The clinician is best helped with an algorithm. In this algorithm the choice of possible kidney transplantation should also be included. When one summarizes the findings of the recent studies, one may conclude that we are probably close to such a predictive model.

Therefore, an important goal for the near future is to design a predictive model for EPS development. In the specific case of predicting the risk of post-transplantation EPS this should ideally include; the time on PD, the age at which the patient started with PD, the presence of ultrafiltration failure, the longitudinal results of small solute transport tests, the expected date of transplantation, the possible availability of effluent markers and the use of icodextrin.

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Chapter 9

Nederlandse samenvatting en discussie

INTRODUCTIE

Dit proefschrift beschrijft de incidentie van encapsulating peritoneal sclerosis (EPS) in Nederland, de risico factoren en de klinische consequenties. Het is in eerste instantie bedoeld om de nieuwe resultaten en associaties met EPS te presenteren aan de klinisch praktiserende dokter.

In ***hoofdstuk 2*** van dit proefschrift wordt een algemeen overzicht gegeven van de huidige kennis omtrent EPS. Encapsulating peritoneal sclerosis (EPS) is een ernstige complicatie van langdurige peritoneaal dialyse (PD) met een hoge mortaliteit (50%). Een fibreuze membraan bedekt de darmen en veroorzaakt een intestinale obstructie. In de laatste tien jaar is er meer aandacht geweest voor deze complicatie. Hoewel het nog zeldzaam is, lijkt de incidentie van EPS toegenomen te zijn, ondanks dat er een stabiele PD populatie is. De gerapporteerde prevalentie van EPS varieert tussen 0.5 tot 2.5%. Het voorkomen van EPS neemt toe met het langer continueren van de PD. Een registratie studie vanuit Australië liet een incidentie zien van 19.4% na 8 jaar PD.

Er treden verschillende peritoneale veranderingen op tijdens de PD behandeling. De mesotheliale laag verdwijnt (denudation). De peritoneale vasculatuur vertoont tekenen van progressieve fibrose en hyalinisatie van de media, neoangiogenese met vasculopathie. Hoe meer vaten worden ontwikkeld, des te meer interstitiële fibrose er is. De verdikking van de submesotheliale compact zone wordt veroorzaakt door interstitiële fibrose en sclerose. In EPS is dit nog nadrukkelijker aanwezig. De pathophysiology wordt voorgesteld als een "two-hit theory", welke veronderstelt dat er minimaal twee factoren noodzakelijk zijn voor de ontwikkeling van EPS. Het eerste insult veroorzaakt een verstoring van de normale peritoneale en mesotheliale fysiologie en wordt voornamelijk veroorzaakt door de incompatibele eigenschappen van de dialysevloeistoffen. Het tweede insult kan dan een peritonitis, het stoppen van de PD behandeling of een genetisch predispositie zijn. In the primaire herstel proces van het beschadigde peritoneum speelt TGF-β een centrale rol. Het is geassocieerd met meer fibrose en angiogenese. Epitheliale tot mesenchymale transitie van de mesotheel cel (EMT) kan een belangrijke rol spelen. EMT is een fysiologisch proces wat plaats vindt in het gehele lichaam, zo ook in het peritoneum om beschadigd peritoneum te herstellen. Tijdens EMT, ondergaan mesotheel cellen, welke bloot gesteld zijn aan dialysaat, morfologische en functionele veranderingen. Het epitheliale fenotype wordt meer fibroblastisch. Vervolgens migreren deze fibroblasten naar de compacte submesotheliale zone en hebben mogelijk een overmatige productie van TGF-β. Dit proces start bij het begin van de PD behandeling en gaat door gedurende de behandeling. EMT is noodzakelijk voor herstel van beschadigd weefsel, maar ongecontroleerd kan het leiden tot fibrotische processen. Andere belangrijke spelers zijn de vasculaire groeifactoren (bv. VEGF), AGE's, cytokines (IL-6), metalloproteases, transcriptie factor snail and mestcellen.

Naast verlengde PD duur zijn er nieuwe onafhankelijke risico factoren geassocieerd met EPS, zoals leeftijd, toegenomen transport van "small solutes", ultrafiltratiefalen, niertransplantatie en dialyse vloeistoffen.

Recent zijn er radiologische criteria ontwikkeld voor de diagnostiek van EPS. Het is echter nog steeds moeilijk om EPS te voorkomen of in een vroeg stadium te herkennen. Abdominale CT scans zijn nog niet bruikbaar in dit stadium. Functionele peritoneale parameters kunnen wellicht bruikbaar zijn. Ultrafiltratie falen (UFF) is een overheersende vroege verandering. Dit was geassocieerd met een vroeg verlies van residuale nierfunctie en de cumulatieve peritoneale glucose blootstelling. Gewoonlijk is er een toegenomen "small solute transport" wat representatief is voor de effectieve peritoneal oppervlakte.

Tot op heden is er geen consensus over de behandeling van EPS. De therapie moet in ieder geval bestaan uit ondersteunende therapie en wanneer beschikbaar chirurgie. Corticosteroïden en tamoxifen kunnen eveneens effectief zijn.

Recente ontwikkelingen hebben een onrust teweeg gebracht onder de nefologen en hebben geleid tot een discussie omtrent een mogelijke arbitraire grens van staken PD vanwege het risico op EPS bij langdurige PD.

INCIDENTIE EN RISICO FACTOREN VAN EPS

Hoofdstuk 3 beschrijft de twee studies die de incidentie en risicofactoren van EPS onderzochten. Het eerste onderzoek is beschreven in hoofdstuk 3.1.

In de afgelopen jaren hadden we sterk de indruk dat er een toename was in incidentie van EPS. Om deze verdenking nader te onderzoeken initieerden we een analyse naar het voorkomen van EPS in twee Nederlandse academische ziekenhuizen (Erasmus MC in Rotterdam en Universitair Medisch Centrum Utrecht). De patiënten werden geïdentificeerd met behulp van een retrospectieve analyse van de medische dossiers in de periode 1998-2005. Deze studie toonde dat de incidentie van ernstige EPS significant was toegenomen. Daarnaast was er een opmerkelijke voorkomen van EPS patiënten met een functionerend niertransplantaat. Wellicht kan er een pathogenetische rol worden verondersteld van een nier transplantatie in de ontwikkeling van EPS.

Wegens de beperkte aantallen was het niet mogelijk om duidelijke conclusies te maken aangaande risicofactoren en de toegenomen incidentie van EPS. Daarom werd een aanvullende studie verricht.

Deze studie wordt beschreven in hoofdstuk 3.2. Dit is een multicenter studie waarin acht grote ziekenhuizen in Nederland participeerden. Dit resulteerde in een representatieve studie, aangezien het in totaal 26% van alle PD patiënten in Nederland betrof. Het design is een retrospectieve "nested" case gecontroleerde studie. Het bestond uit 63 EPS en 126 controle patiënten. Controle patiënten werden geselecteerd uit de nationale registratie (RENINE) en

gecontroleerd voor de start datum van PD, controles voor en na de start datum van de EPS patiënten. Om de associatie van PD duur in een gecontroleerde opzet te onderzoeken was er opzettelijk geen controle voor PD duur. Associaties werden onderzocht met een log lineair regressie model. PD duur, leeftijd, transplantatie, tijd sinds transplantatie, kalender tijd, follow-up tijd, peritonitis, overgaan van PD naar HD om ander redenen dan EPS, tijd op icodextrin en de aanwezigheid van ultrafiltratie falen waren van te voren gedefinieerde voorspellers.

De studie laat zien dat de incidentie toenam in de jaren 2003-2005, en bevestigde hiermee de vorige studie. Dit is waarschijnlijk niet het gevolg van een toegenomen aandacht voor het ziektebeeld of een verandering van de inclusie criteria welke zouden leiden tot inclusie van mildere vormen van EPS. De aanwezigheid van symptomen van ernstige EPS maakt het onwaarschijnlijk dat de diagnose gemist werd in het verleden.

Daarnaast leek er een afname van de incidentie in 2006. Dit kan suggereren dat de toename slechts een tijdelijk fenomeen was. Wij onderzochten de incidentie niet in de jaren na 2006. Maar uit nadere bestudering van recente artikelen kan geconcludeerd worden dat de incidentie nog steeds toeneemt. Bijvoorbeeld, een recente observationele studie in London rapporteert tot 2003, maximaal 1 patiënt per jaar. In de daarop volgende jaren (2004-2008) worden er respectievelijk 5,6,4,6 en 11 EPS patiënten per jaar gerapporteerd. Hoewel er geen informatie is omtrent de hele PD populatie in deze studie, lijkt het onwaarschijnlijk dat deze in vergelijkbare mate is toegenomen.

In de multivariate regressie analyse hebben we de onafhankelijke associatie met PD duur, ultrafiltratiefalen en leeftijd met de ontwikkeling EPS bevestigd. Elk jaar van verlengde PD duur heeft een relatief risico van 40% op EPS. De associaties van leeftijd en PD duur worden ook gevonden in een recente beschrijving van de ANZDATA registratie. Hiernaast konden wij nieuwe onafhankelijke associaties met de ontwikkeling van EPS laten zien, namelijk verlengd gebruik van icodextrin, niertransplantatie en de tijd na niertransplantatie.

Icodextrin maakt een goede ultrafiltratie mogelijk en voorkomt het overmatig gebruik van glucose met potentieel schadelijke gevolgen. De associatie met EPS is dan ook verrassend en dient in de toekomst beter geanalyseerd te worden. De associatie lijkt niet veroorzaakt te worden door het veelal aanwezige ultrafiltratie falen in EPS.

Consistent met het eerste onderzoek was er ook nu een onafhankelijke associatie met niertransplantatie. De profibrotische eigenschappen van calcineurin inhibitoren (CNI's) vormen een mogelijke verklaring. In dit onderzoek bleek het echter niet mogelijk om de introductie van de CNI's te identificeren als mogelijk risicofactor voor EPS. Met betrekking tot de tijd na transplantatie nam de jaarlijkse kans op EPS in het jaar na de transplantatie toe van 1.75% tot 7.5%. Tenslotte zou niet de niertransplantatie de risicofactor kunnen zijn, maar wellicht het hiermee samenhangende staken van de PD. In deze studie waren we niet in staat om een dergelijke associatie aan te tonen. In tegendeel, we vonden dat de meerderheid van de patiënten, die overgingen op HD al verdenking hadden op EPS.

VROEGE DIAGNOSTISCHE MARKERS

Hoofdstuk 4 beschrijft hoe effluente markers gebruikt zouden kunnen worden als vroege markers van EPS. Effluent cancer antigen 125 (CA125) is een marker van mesotheel cel massa, interleuking-6 (IL-6) is een marker of inflammatie, en vascular endothelial growth factor (VEGF) is een groei factor voor vaatnieuwvorming. In deze case gecontroleerde studie werd het tijdsbeloop van deze peritoneale markers onderzocht in EPS patiënten en in patiënten gecontroleerd voor PD duur, die geen EPS ontwikkelden.

Dialysaat and serum afnames van 11 EPS patiënten en 31 controle patiënten, allen behandeld met PD voor tenminste 57 maanden werden longitudinaal verzameld gedurende een jaarlijkse standaard peritoneale permeabiliteits analyse (SPA). Zoals eerder waren EPS patiënten jonger en hadden ze een langere PD duur (104 maanden versus 72 maanden, p=0.01). Tussen de groepen was er geen significant verschil in het tijdsverloop van de verschillende markers. De appearance rate (AR) van CA-125 was echter significant lager in de laatste drie jaren voor het ontwikkelen van EPS ($p<0.05$) en de AR of IL-6 was in de laatste twee jaar voor EPS hoger (p=0.09). Lokaal geproduceerde VEGF toonde geen verschil tussen de groepen.

De combinatie van de AR CA-125<33 U/min en de AR IL-6>350 pg/min had een sensitiviteit 70% en een specificiteit van 89% voor het voorspellen van de EPS diagnose. Recente artikelen toonden dat ultrafiltratie falen een vroeg dominante aanwijzing is voor ontwikkelende EPS. De voorspellende waarde van het predictieve model nam toe als dit ultrafiltratie falen werd meegenomen. De specificiteit werd 100%, waarmee het potentieel bruikbaar werd voor het voorspellen van EPS. In de dagelijkse praktijk zou het nuttig kunnen zijn om patiënten te identificeren die meer kans hebben op EPS. Dit is belangrijk, aangezien preventieve interventies om de morbiditeit en mortaliteit te reduceren mogelijk effectiever zijn in deze fase dan na het vaststellen van de ziekte. Daarom wordt het aangeraden om de peritoneale functies longitudinaal te vervolgen met jaarlijkse peritoneale equilibratie testen met 3.86% glucose.

Er zijn enkele beperkingen aan de studie. Niet alle analyses werden gedaan in alle patiënten en ondanks dat er gestreefd was naar een controle voor PD duur, bleek er toch een klein verschil in de gemiddelde PD duur aanwezig te zijn.

TAMOXIFEN EN OVERLEVING

Hoofdstuk 5 beschrijft het mogelijke gebruik van tamoxifen in de behandeling van EPS. Tot op heden is er geen consensus over de behandeling van het ziektebeeld. Aandacht voor de voedingstoestand is belangrijk en chirurgie met een uitgebreide adhesiolyse wordt aangeraden. Dit laatste wordt zelden uitgevoerd in West Europa, waarschijnlijk komt dit door de kans op complicaties. Er zijn nog geen gerandomiseerde studies die een effect laten zien van een medicamenteuze therapie, inclusief tamoxifen. Tamoxifen beïnvloedt de activiteit van het

profibrotische cytokine TGF-β en heeft al aangetoond effectief te zijn in fibrotische aandoeningen als retroperitoneale fibrose. De hypothese was dat tamoxifen zou resulteren in een lagere mortaliteit in behandelde patiënten. We verrichtten een retrospectieve analyse in de multicenter EPS studie om te onderzoeken of tamoxifen was geassocieerd met een toegenomen overleving in deze patiënten. EPS patiënten die behandeld waren met tamoxifen werden vergeleken met patiënten die niet behandeld waren. De studie laat zien dat de mortaliteit lager was in tamoxifen behandelde EPS patiënten vergeleken met EPS patiënten die niet behandeld waren met tamoxifen (45.8% vs. 74.4%, p=0.03). Beide groepen hadden vergelijkbare demografische en klinische karakteristieken. Nog belangrijker, de behandeling van EPS patiënten met tamoxifen was geassocieerd met een trend naar betere overleving, onafhankelijk van andere mogelijke goede behandelingsopties (HR 0.39, p=0.056). Ondanks dat verschillende mogelijke confounders werden meegenomen in de multivariate analyse, is het mogelijk dat er een 'confounding by indication' is.

Indien overwogen wordt om tamoxifen te gebruiken in de behandeling van EPS, zullen ook de mogelijke nadelige effecten, als tromboembolische complicaties en endometrium carcinoom, meegenomen moeten worden. Gezien de mortaliteit en de beperkte levensverwachting van EPS patiënten, lijken de voordelen van tamoxifen op te wegen tegen de mogelijke nadelen. De combinatie van de pathofysiologische rationale achter tamoxifen gebruik en de bemoedigende resultaten van deze studie ondersteunt de aanbeveling tamoxifen te gebruiken als additionele behandelingsoptie.

MORTALITEIT NA EEN NIERTRANSPLANTATIE TEN GEVOLGE VAN EPS

Hoofdstuk 6 beschrijft de invloed van post-transplantatie EPS op de mortaliteit na niertransplantatie. EPS presenteert zich veelal na een niertransplantatie, een fenomeen tegenwoordig bekend als post-transplantatie EPS. De prevalentie en invloed van post-transplantatie EPS op de overleving na niertransplantatie zijn onbekend. De hypothese was dat post-transplantatie EPS mogelijk een significante bijdrage levert aan de mortaliteit na niertransplantatie, welke voorheen niet als zodanig herkend werd.

Van 1 januari 1996 tot 1 juli 2007 werden 1241 PD patiënten getransplanteerd in de vier deelnemende universiteit ziekenhuizen in Nederland. Er werden 38 patiënten met post-transplantatie EPS (3%) geïdentificeerd in de Nederlandse multicenter EPS studie. Tweehonderd-en-een (16.2%) patiënten overleden na transplantatie, van welke 17 EPS patiënten. Na infecties (23.9%), cardiovasculaire ziekte (21.9%) en maligniteit (10.9%), was EPS (8.5%) de vierde bekende oorzaak van dood na transplantatie. Kaplan-Meier analyse toonden een significante afgenomen overleving van getransplanteerde patiënten met EPS. De meerderheid van de EPS patiënten werd waargenomen in de eerste twee jaar na niertransplantatie, echter sommige patiënten ontwikkelden EPS pas vele jaren na transplantatie. Concluderend, post-transplantatie EPS is

zeldzaam, maar heeft een hoge mortaliteit. Derhalve is een verlengde klinische waakzaamheid en verhoogde verdenking op de diagnose noodzakelijk, voornamelijk in PD patiënten met een relatieve lange PD duur. Tenslotte dragen de bevindingen bij aan de discussie of jonge PD patiënten vroegtijdig over moeten gaan op HD na enkele jaren van PD, terwijl ze wachten op een niertransplantatie of na een falend niertransplantaat.

CONCLUSIES

1. De incidentie van ernstige EPS is significant toegenomen in de periode 1996-2006 in de Nederlandse populatie.
2. PD duur, leeftijd, niertransplantatie, tijd na niertransplantatie, verlengd gebruik van icodextrin en ultrafiltratie falen (UFF) zijn onafhankelijk geassocieerd met EPS ontwikkeling. Elk jaar van PD heeft een toegenomen relatief risico op EPS van 40%.
3. De combinatie van de AR CA-125<33 U/min en de AR IL-6>350 pg/min heeft een sensitiviteit van 70% en een specificiteit van 89% voor het voorspellen van EPS.
4. Tamoxifen reduceert de mortaliteit van EPS patiënten behandeld met tamoxifen in vergelijking met patiënten die niet behandeld werden met tamoxifen. Behandeling van EPS patiënten met tamoxifen was geassocieerd met een trend naar toegenomen overleving, onafhankelijk van andere goede behandelingsopties.
5. Na infecties (23.9%), cardiovasculaire ziekten (21.9%) en maligniteiten (10.9%), was EPS (8.5%) de vierde bekende oorzaak van dood na niertransplantatie. De overleving van getransplanteerde patiënten met EPS is significant afgenomen in vergelijking met getransplanteerde patiënten zonder EPS.

List of abbreviations

AGE	Advanced Glycation Endproducts
AR	Appearance Rate
AT II	Angiotensin II Inhibitors
CA 125	Cancer Antigen 125
CAPD	Continuous Ambulatory Peritoneal Dialysis
CNI	Calcineurin Inhibitor
CsA	Cyclosporin
CTGF	Connective Tissue Growth Factor
D/S	Dialysate over Serum ratio
EMT	Epithelial Mesenchymal Transition
EPS	Encapsulating Peritoneal Sclerosis
ESRD	End Stage Renal Disease
FGF	Fibroblast Growth Factor
FSGS	Focal Segmental Glomerulosclerosis
GDP	Glucose Degradation Product
HD	Hemodialysis
HPMC	Human Peritoneal Mesothelial Cell
HR	Hazard Risk
HUS	Hemolytic Uremic Syndrome
Il-6	Interleukin-6
IQR	Interquartile Range
ISPD	International Society Of Peritoneal Dialysis
K	Potassium
MMF	Mofetil Mycophenolate
MMP	Metalloprotease
MPGN	Membranous Proliferative Glomerulonephritis
OR	Odds Ratio
PAI-1	Plasminogen Activator Inhibitor 1
PD	Peritoneal Dialysis
PDGF	Platelet Derived Growth Factor
PET	Peritoneal Equilibration Test
RAGE	Receptor of AGE
RENINE	Renal Replacement Registry in The Netherlands
RRT	Renal Replacement Therapy
SD	Standard Deviation
SERM	Selective Estrogen Receptor Modulator
SMAD	Proteins that transduce extracellular signals from TGF-β ligands to the nucleus

SPA	Standard Peritoneal Permeability Analysis
TGF-β	Tumor Growth Factor-β
TNF-A	Tumor Necrosis Factor-A
Tpa	Tissue-Type Plasminogen Activator
TPN	Total Parental Nutrition
UFF	Ultrafiltration Failure
VEGF	Vascular Endothelial Growth Factor

Dankwoord

Een ieder die mij kent, weet dat ik altijd geroepen heb, dat een proefschrift niets anders is dan een aantal artikelen met een kaft erom heen. Dat vind ik na deze jaren nog steeds. Het zou meer moeten gaan om de onderzoeksvraagstukken en niet zo zeer om het afronden van het boekje zelf. Nu de onderzoeken eenmaal gebundeld zijn in dit boekje, durf ik echter wel toe te geven dat dit toch een mooie voldoening geeft.

In de afgelopen jaren is het onderzoek verlopen, zoals ik me altijd had voorgesteld, hoe een ideaal onderzoek zou verlopen. Het begon met het constateren van een echt klinisch relevant probleem, in dit geval de indruk dat EPS toenam in ernst en voorkomen. Daarna hebben we hypothesen geformuleerd en een onderzoeksvoorstel geschreven. Van begin tot eind hebben we het daarna als ons eigen onderzoek beleefd. We hopen hiermee te hebben bijgedragen aan de zorg van patiënten met EPS, want uiteindelijk is dit toch het belangrijkste doel!

De uiteindelijke publicaties zijn met veel hulp tot stand gekomen. Er zijn dan ook veel mensen, die ik dankbaar ben voor hun bijdrage aan de onderzoeken.

Allereerst, mijn co-promotor, Michiel Betjes; veel goede ideeën ontstaan op merkwaardige momenten. Zo geldt dat ook voor dit onderzoek. De basis voor onze belangrijkste ideeën voor het gehele EPS onderzoek is ontstaan terwijl we stonden te brainstormen buiten de HRU naast de enorme (en stinkende) prullenbak. Ik was me op dat moment al bewust van de combinatie van een merkwaardige omgeving en de goede ideeën. Het mooie is dat al deze ideeën uiteindelijk uitgewerkt zijn. Ik vind onze samenwerking erg plezierig, buitengewoon stimulerend en effectief. Daarnaast ben je gewoon een hele prettige vent om mee te ouwehoeren of om bubbels mee te drinken. Dank je wel!

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In dit deel van het dankwoord, kom ik met de bekentenis dat (ook) ik dit niet zonder hulp van vrouwen had kunnen voltooien. Hiervoor wil ze danken.

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Zoals in elk onderzoek en eigenlijk ook in de dagelijkse praktijk zijn dialyse verpleegkundigen en secretaressen onmisbaar. Voor hen in alle deelnemende centra, veel dank. In het bijzonder, Saida en Natalie dank voor jullie hulp in de laatste fase van dit boekje.

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All the members of the EPS study group, both in The Netherlands and in the international working group; I am looking forward to our further collaboration and am convinced that the registry will be successful and lead to an improved management of the EPS patient. Els Boeschoten, jouw aandeel als de initiator van de EPS registratie is niet te onderschatten. Ik waardeer de fijne samenwerking.

Sinds 2008 mag ik deel uitmaken van de maatschap Interne Geneeskunde van het Albert Schweitzer ziekenhuis in Dordrecht. Ik wil mijn maten danken voor hun interesse. En in het bijzonder Eric, Gijs en Peter; jullie hebben mij de vrijheid gegeven om dit onderzoek verder te voltooien. Onze samenwerking ervaar ik als bijzonder plezierig, eerlijk en stimulerend. Peter, dank voor je kritische review op het transplantatie stuk (it payed off).

Iedereen weet dat mijn prioriteit altijd zal liggen bij mijn familie en vrienden. Daarom wil ik hen allen danken. Niet zozeer voor de bijdrage aan het proefschrift, maar simpelweg omdat dit altijd een goede manier is om hen te danken voor hun vriendschap! Ik hoop dat er nog vele mooie momenten van samenzijn en plezier zullen zijn. Van de beste vrienden die ik heb, zullen er twee mij bijstaan op deze dag als paranimf.

Tundi, we hebben al mooie dingen gedaan en beleefd (samen met de mannen en tegenwoordig ook vrouwen). Wij weten dat we niet veel nodig hebben om elkaar te begrijpen. Jij zult de voorkant van dit boekje hebben herkend. Want ook daar was de uitwisselingen van blikken onderaan de MB top voldoende om de gevoelens weer te geven. Dat gaf toen veel steun en goede moed, want ik had het moeilijk. Op dat soort momenten wordt alleen maar bevestigd wat voor vriend je bent. Daarom vind ik het ook super dat je vandaag naast mij wilt staan.

Bas, samen hebben we gestudeerd in de bieb, afgewisseld met wat basketballen op de Kade. Het is veelzeggend voor onze band, dat jij met mij in een te smalle roeiboot kan zitten, terwijl ik zit te tieren en te vloeken (en jij alleen maar lacht)! De afgelopen jaren hebben we fijne, bijzondere en moeilijke momenten gedeeld. Het is mooi dat we de lijn mogen doorzetten en jij mijn paranimf bent. Dank voor je vriendschap!

Dit proefschrift is voor mij niet los te zien van een aantal andere life events, waaronder het verbouwen van een huis. Dit bleek een lastige combinatie, maar werd behaald met veel hulp. Tineke, Paul, Ria, Karel, Mam en Pa, veel dank!

Pap en mam, dit proefschrift is ook voor jullie. Jullie hebben er uiteindelijk voor gezorgd dat Mariska en ik zijn, wie we nu zijn. In de laatste jaren van het onderzoek vond ik het grappig dat jullie na een tijdje ook door hadden hoe dat werkt met artikelen en reviseren van artikelen, vooral dat ene irritante stuk. Dank jullie wel voor jullie liefde.

Essie, voor ons geen promotie clichés! Dit soort boekjes betekende namelijk een goed excuus voor samen relaxen (in het bijzonder in de bergen). Jouw afronding in Chamonix betekende gelijktijdig mijn wetenschappelijk begin en wat volgde waren fijne "werkweken" in

onder andere Tubbergen en Odoorn. Heel graag wil ik samen met jou nog veel meer genieten van die letterlijke en figuurlijke toppen. Om in onze stijl af te sluiten: …"Somewhere over the Rainbow"…HvJ en DZ, Chico

Mario

Publications

PUBLICATIONS RELATED TO EPS

M.R.Korte, S.M.Habib, H. Lingsma, W.Weimar, M.G.H.Betjes. Post-transplantation Encapsulating Peritoneal Sclerosis contributes significantly to mortality after kidney transplantation. *Am J Transplant* 2011 (in press).

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M.R.Korte. Encapsulating peritoneal sclerosis: stand van zaken. *Capita Selecta Nefrologie*, nummer 1 2010.

ORAL PRESENTATIONS RELATED TO EPS

Nederlandse Nefrologie Dagen maart 2011: "Post-Transplantation Encapsulating Peritoneal Sclerosis Contributes Significantly to Mortality after Kidney Transplantation."

Nederlandse Nefrologie Dagen maart 2010: "Tamoxifen is associated with lower mortality of encapsulating peritoneal sclerosis: results of the Dutch Multicentre EPS Study. *Award best clinical scientific abstract.*

Nederlandse Transplantatie Congres februari 2010, Rotterdam. "Encapsulating Peritoneal Sclerosis contributes significantly to mortality after kidney transplantation."

Symposium " De toekomst van Peritoneale Dialyse", Rotterdam juli 2010: "Risicofactoren voor encapsulating peritoneal sclerosis."

Nederlandse Nefrologie Dagen april 2009: "Meer zicht op peritoneale sclerose".

Nederlandse Nefrologie Dagen april 2009: "Early Diagnostic Markers for encapsulating peritoneal sclerosis: a case - control study.

Workshop Nefrologie Papendal 9 december 2009 "De epidemiologie van Encapsulating Peritoneal Sclerosis in Nederland".

Annual dialysis conference 2009, Houston, USA. " Early Diagnostic Markers for encapsulating peritoneal sclerosis: a case - control study."

POSTERPRESENTATIONS RELATED TO EPS

World Congress Nephrology Milaan mei 2009 " Early Diagnostic Markers for encapsulating peritoneal sclerosis: a case - control study. "

Annual Dialysis Conference 2009, Houston, VS. "Dialysis markers prior to EPS".

American Society of Nephrology 2009, San Diego, VS "Tamoxifen reduces mortality of encapsulating peritoneal sclerosis; results of the Dutch Multicentre EPS Study."

American Society of Nephrology 2009, San Diego, VS "Risk factors associated with Increased Incidence of Encapsulating Peritoneal Sclerosis in a Controlled Multicenter Study."

European Renal Association Congress 2010, München. "The development of a European encapsulating sclerosis registry".

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PUBLICATIONS UNRELATED TO EPS

Korte MR, van Heerde MJ, de Man RA, Betjes MH. Rituximab for the treatment of glomerulonephritis in hepatitis C associated cryoglobulinaemia. *Neth J Med*. 2008 Jan;66(1):27-30.

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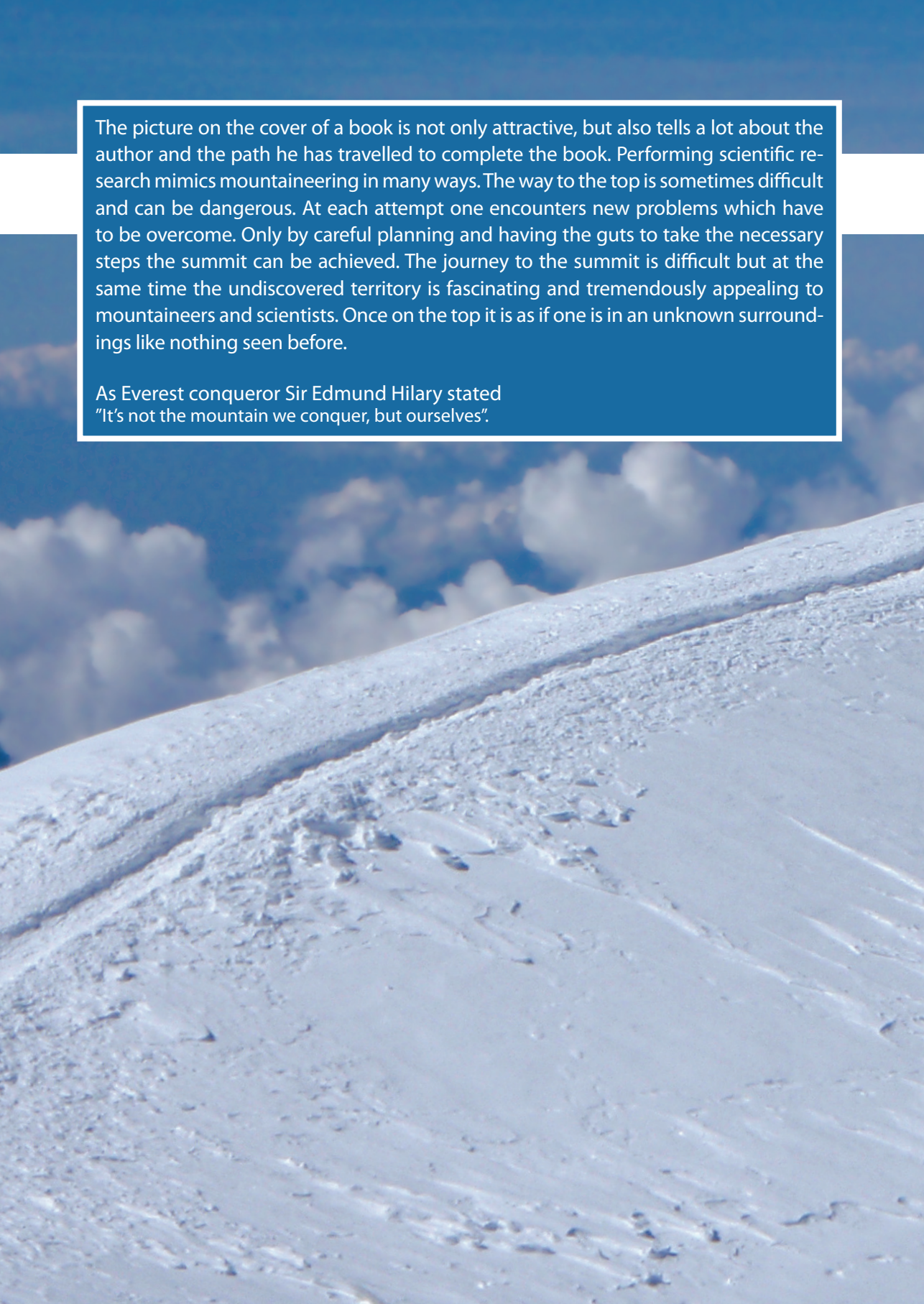
Brown DM, Van Dokkum RP, **Korte MR**, McLauglin MG, Shiozawa M, Jacob HJ, Provoost AP. Genetic control of susceptibility for renal damage in hypertensive fawn-hooded rats. *Ren Fail*. 1998 Mar;20(2):407-11.

Curriculum Vitae

Mario werd op 21 november 1972 geboren in 's Gravenhage. Vanaf zijn derde jaar woonde hij samen met ouders en zusje in Maassluis. Voor de middelbare school fietste hij elke dag naar Vlaardingen. Hij deed het VWO op de Prof. Casimir school, hoewel zijn grootste aandacht uitging naar het judo. In Rotterdam werd er vanaf 1991 onder andere ook geneeskunde gestudeerd, en op 16 april 1999 werd het artsexamen behaald.

Na twee jaar als AGNIO in "de Clara"op Rotterdam-Zuid gewerkt te hebben, begon aldaar op 1 januari 2002 ook de opleiding interne geneeskunde onder de leiding van dr. Albert Grootendorst. Na vijf jaar Clara werd de opleiding afgerond in het Erasmus MC. Aanvankelijk was dit onder leiding van prof.dr. Huib Pols als opleider, later werd hij opgevolgd door prof.dr. Jan van Saase. Vanaf 2005 kon hij onder leiding van prof. dr. Bob Zietse de nefrologie leren. Vanaf juni 2008 is hij werkzaam als internist-nefroloog in het Albert Schweitzer ziekenhuis, in Dordrecht.

Na vele jaren in de energieke stad, Rotterdam, woont hij nu aan de Waal in Her…wijnen. In 2007 mocht hij trouwen met Esther.



The picture on the cover of a book is not only attractive, but also tells a lot about the author and the path he has travelled to complete the book. Performing scientific research mimics mountaineering in many ways. The way to the top is sometimes difficult and can be dangerous. At each attempt one encounters new problems which have to be overcome. Only by careful planning and having the guts to take the necessary steps the summit can be achieved. The journey to the summit is difficult but at the same time the undiscovered territory is fascinating and tremendously appealing to mountaineers and scientists. Once on the top it is as if one is in an unknown surroundings like nothing seen before.

As Everest conqueror Sir Edmund Hilary stated
"It's not the mountain we conquer, but ourselves".