PERITONEAL DIALYSIS: MISPERCEPTIONS AND REALITY

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Dr. Saxena will not be discussing off-label uses in this presentation.

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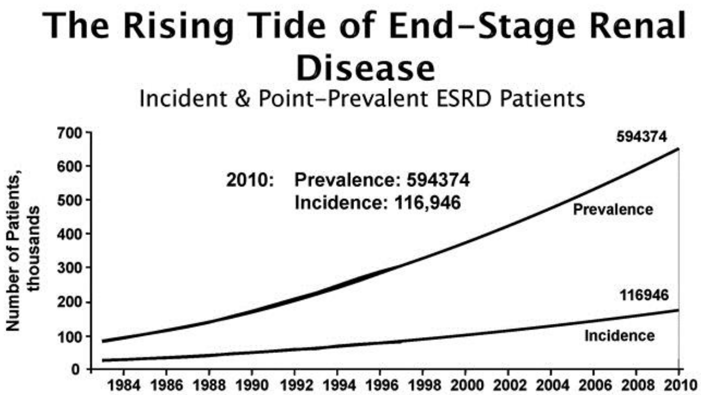
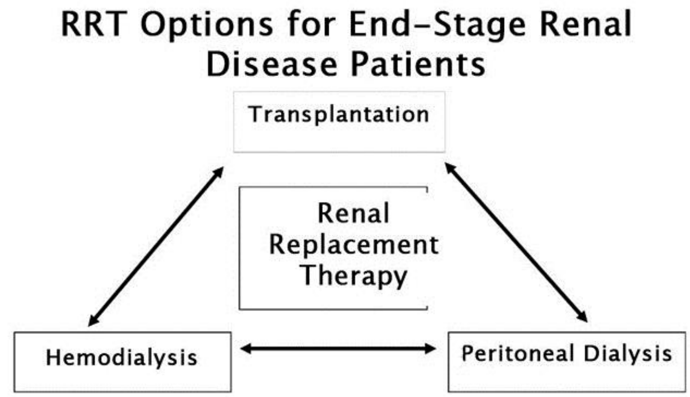
Purpose: To discuss the status of peritoneal dialysis in the management of end stage kidney disease

Objectives:

1. To discuss the current status of peritoneal dialysis
2. Understand misconceptions about peritoneal dialysis among physicians
3. Learn how increase in use of peritoneal dialysis can help improve outcomes of end stage kidney disease.

The past two decades have witnessed an immense growth of end stage renal disease (ESRD) population. The 2012 United States Renal Data System (USRDS) report showed more than 40% increase in the prevalent dialysis population between 2000 and 2010 [1]. There were 594,374 ESRD patients in 2010, and with an annual growth of 4%, the ESRD population is projected to grow to more than 775,000 dialysis patients by 2020 [1]. While ESRD comprises only1% of total Medicare population, it consumes 8.1 % of the Medicare budget and $47.5 billions in total costs [1]. With extensive efforts made to prevent or slow progression of renal disease, there has been a recent stabilization of the overall ESRD incidence [1]. Nevertheless, the incidence of ESRD continues to grow particularly among elderly patients. This increase in the numbers of ESRD patients has obvious social and economic dimensions that are even more pronounced in the case of older patients [1,2].





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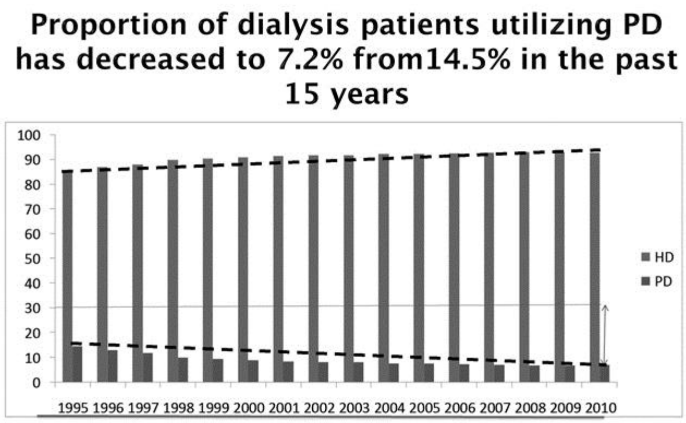

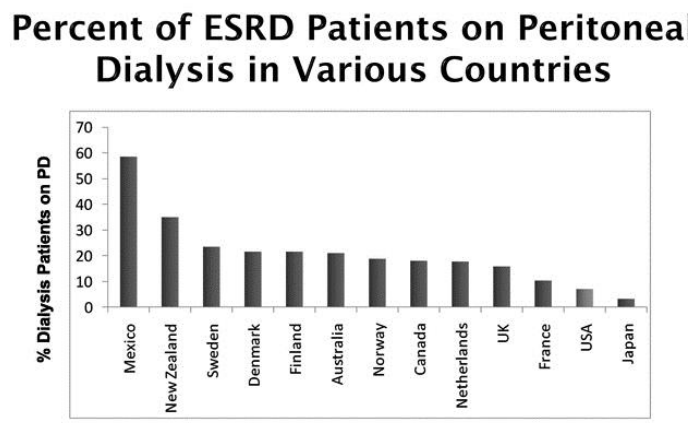

USRDS 2012

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Currently three renal replacement therapy (RRT) options are available for ESRD patients: renal transplantation, hemodialysis (HD) in various forms (in-center HD, home HD, nocturnal HD), and peritoneal dialysis (PD). Renal transplantation by far is the most cost efficient RRT modality and provides ESRD patients highest quality of life (QOL) and longest life expectancy. However, due to limited availability of organs, the proportion of ESRD patients receiving renal transplants has not changed in the past decade [1]. Thus, the majority of ESRD patients depend upon various dialysis modalities to survive. With increasing number of ESRD patients requiring dialysis, an equitable growth of all dialysis modalities would be expected. However, on the contrary, while utilization of HD has progressively increased, there has been a steady decline of PD usage over the last two decades, with paltry 7.2 % of the total US dialysis patients receiving PD in 2010 [1]. In contrast, PD is employed much more frequently elsewhere in the world, and is the primary mode of dialysis therapy in places such as Mexico and Hong Kong[1].

Many complex confounding factors influence the crucial selection of the best RRT modality for the individual patient. A thorough understanding of these factors and implementation of appropriate measures are explicitly essential to enhance the growth of a PD in the USA.

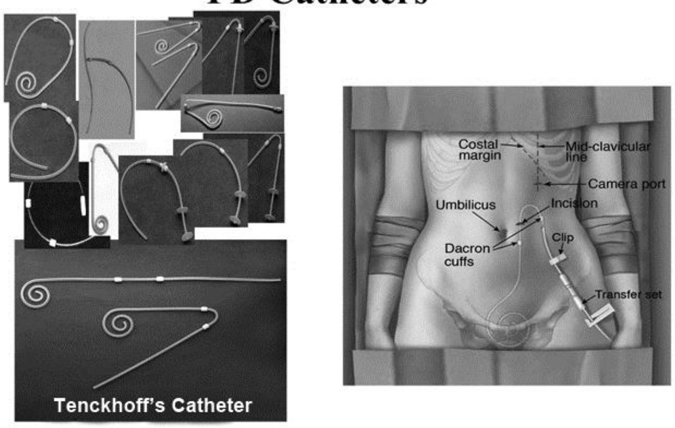
OVERVIEW OF PERITONEAL DIALYSIS

PD is achieved by instilling a dialysis solution into the peritoneal cavity using a percutaneous abdominal catheter. The efficacy of PD depends on the structural and functional integrity of the peritoneum, which is a thin layer (40μm) of membrane lining the peritoneal cavity. It consists of a mesothelial monolayer and an underlying connective tissue interstitium comprising collagen, mucopolysaccharides, blood vessels and lymphatics [3]. In normal circumstances, the closed peritoneal cavity contains 50-100 ml of surfactant like phospholipid-rich fluid secreted mainly by mesothelial cells. [4]. In PD, water and solutes are exchanged between the capillary blood and the intraperitoneal dialysate across the peritoneum [3].

PD can be done manually (Continuous ambulatory peritoneal dialysis or CAPD) or with automated devices (Cyclers) (automated peritoneal dialysis or APD), either continuously (fluid in the abdominal cavity 24 hours a day i.e. Continuous cycler assisted PD or CCPD) or intermittently only during the night-time with dry abdominal cavity during the day (nocturnal intermittent PD or NIPD). NIPD is reserved for patients who still have good residual renal function (RRF)

A variety of silastic and polyurethane catheters are available for PD access. The catheter can be placed laparoscopically, percutaneously or by open surgical technique [5]. A double-cuff catheter with an arcuate subcutaneous tunnel and a caudad-oriented exit is recommended. It is best to wait at least 2 weeks before commencing PD to assure good healing and to prevent dialysate leaks [5,6]. However, if needed, PD can be initiated almost immediately following placement of PD catheter.

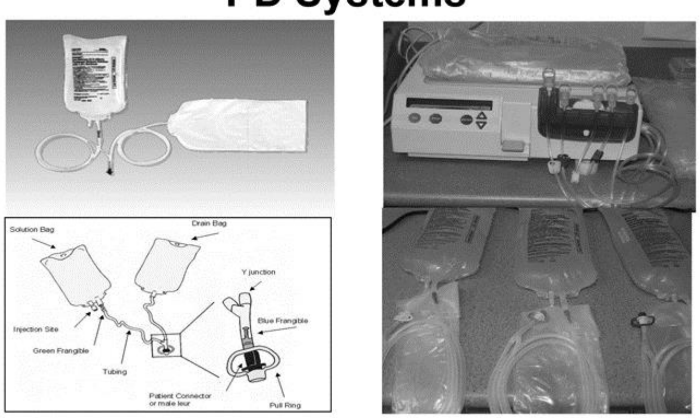
PD Catheters



PD Solutions

	Icodextrin	Conventional
Dextrose (g/dL)	—	**1.5, 2.5, 4.25**
Icodextrin (g/dL)	7.5	—
Sodium (mEq/L)	132	132
Chloride (mEq/L)	96	96
Calcium (mmol/L)	1.75	1.75
Magnesium (mEq/L)	0.5	0.5
Lactate (mEq/L)	40	40
Osmolality (mOsm/kg)	**282-286**	**346-485**
pH	5.2	5.2

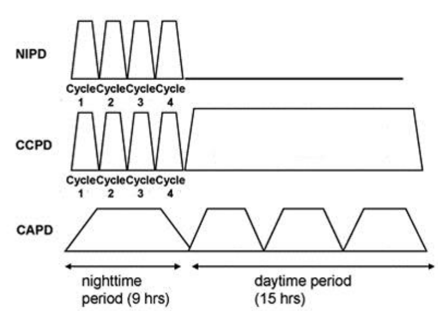
PD Systems



PD Schedules

Acute: Very rare

Chronic:
- Manual
  - CAPD
- Automated PD (APD)
  - CCPD
  - NIPD



Conventional PD fluids consist of aqueous solutions of electrolytes similar to the plasma, a bicarbonate precursor (usually lactate) as a buffer, and an osmotic agent, glucose for ultrafiltration (UF) [7]. Various concentrations of dextrose (1.5%, 2.5%, 4.25%) are used to produce fluids of different osmolality. Glucose is widely accepted as an osmotic agent for PD because it is inexpensive and is considered relatively safe (at least until recently). However, due to its small size, it is rapidly absorbed into the blood with progressive loss of the osmotic gradient and long-term metabolic consequences related to glucose load in some patients. Furthermore, chronic exposure of the peritoneum to contemporary PD fluids provokes activation of various inflammatory, fibrogenic and angiogenic cytokines, interplay of which may lead to progressive peritoneal fibrosis, vasculopathy and neoangiogenesis [8]. As a result, peritoneal membrane failure may ensue in some longstanding PD patients [8]. Three novel, more biocompatible PD solutions have been recently introduced for clinical use with a goal to minimize peritoneal toxicity and prevent treatment failure [8]. Of these, two solutions are non-glucose based. They include icodextrin-based solution (a large glucose polymer with a molecular weight of 16 KD) and amino-acid based solution that contains a mix of various essential and non-essential aminoacids instead of glucose as osmotic agent. The third solution is a glucose-based solution that contains bicarbonate (instead of lactate in conventional PD solution) as the buffer with physiologic pH. Several recent studies have shown that the use of these novel PD solutions is associated with improvement in peritoneal membrane integrity and prolongation of PD technique survival [8-12]. Of these solutions, only icodextrin is approved by the Food and Drug Administration (FDA) for clinical use in the USA

BASIC PHYSIOLOGY OF PERITONEAL DIALYSIS

In PD, two major mechanisms, diffusion and convection (ultrafiltration), are involved in fluid and solute transport across the peritoneum [13]. The three pore model of peritoneal transport assumes that capillary endothelium is the major barrier to solute and water transport, which ensues through a system of pores. These pores can be classified into three broad categories, ultrasmall, small and large pores [14–16]. The abundant small pores (40–60 A^o) are the tortuous intercellular clefts between the endothelial cells. The ultrasmall pores (radius 3–5 A^o), also present in a large number, are the transendothelial aquaporin-1 [17–19]. Additionally, a small number of large pores (200–300 A^o) are present. Their nature remains unclear.

Diffusion, the most important transport mechanism for low molecular weight solutes and occurs through the small pore system. It is investigated by performing a standardized peritoneal equilibration test (PET), using a 4-hour exchange with 2.0 liters of 2.5% dextrose dialysate [20]. The dialysate to plasma (D/P) ratio of creatinine at 4 hours is used to classify the peritoneum into four transport categories: Low, Low-average, High-average, and High. Patients who exhibit high transport character will rapidly equilibrate creatinine and urea and achieve excellent small solute clearance. However, they will also rapidly absorb glucose from the peritoneal cavity and therefore swiftly lose osmotic gradient leading to poor UF. In contrast, patients who are low transporters will have poor urea and creatinine clearance but excellent UF.

Ultrafiltration is achieved by using hypertonic glucose to create crystalloid osmotic pressure gradient between dialysate and blood [21]. The concentration of glucose is greatest at the beginning of dialysis but progressively diminishes during the dwell because of diffusion of glucose into blood across small pores. Consequently, the UF rate is utmost at the start but declines during the PD dwell. A variable amount of the instilled glucose is absorbed during a PD exchange, depending upon the dwell time, transport characteristic of the peritoneum and amount of glucose exposure during a dwell.

In addition to diffusion and convection, peritoneal fluid is being reabsorbed at a relatively constant rate of 1–1.5 ml/min, either directly into the sub-diaphragmatic lymphatics or into the interstitium and thereafter to lymphatics and post-capillary venules [21]

HOW TO PROMOTE GROWTH OF PD?

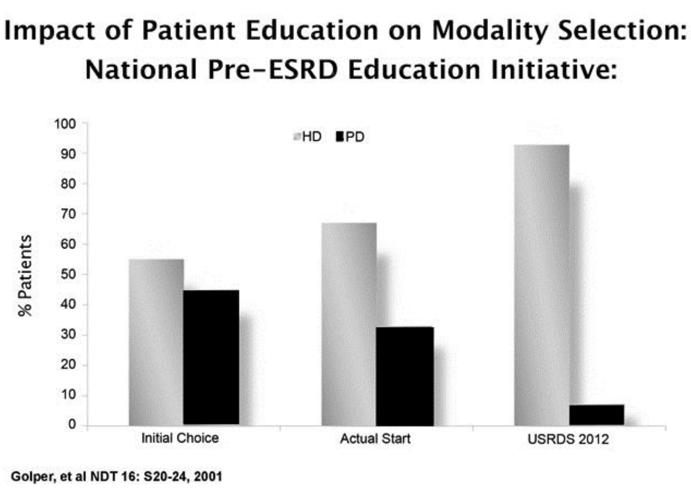
In order to augment PD utilization, first and foremost it is essential to comprehend underlying factors that have led to progressive diminution in PD use over the years. It is quite apparent that dwindling PD population would result from a combination of a slump in admission rateand excessive loss of patients from a PD program. Development of comprehensive infrastructure and support system for PD programs that will enhance enrollment of patients who otherwise would have been excluded as PD candidates and minimize loss of PD patients to HD should considerably help to promote growth of PD.

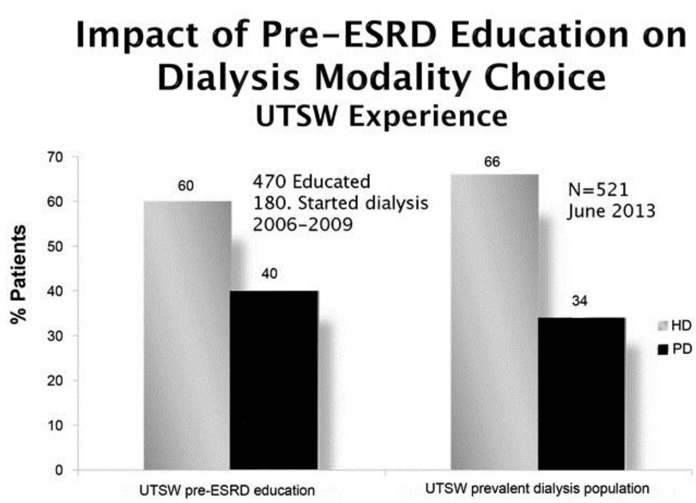
INCREASING ENROLLMENT OF PATIENTS TO PD PROGRAMS

A steady drop in the number of de novo ESRD patients starting PD is one of the major reasons for progressive decline of the US PD population, notwithstanding the perception of US nephrologists who believe that approximately 30% of dialysis population should utilize PD [22]. Factors influencing underutilization of PD include lack of access of patients and families to pre-dialysis education, exposure to PD among trainee physicians, bias among healthcare professionals, financial incentives, ownership of dialysis units (large and small dialysis organizations [LDOs and SDOs]), availability of health care resources, as well as demographic and psychosocial issues. Efforts should be made to understand these factors and implement appropriate measures to enhance the growth of a PD program.

Access to pre-dialysis education

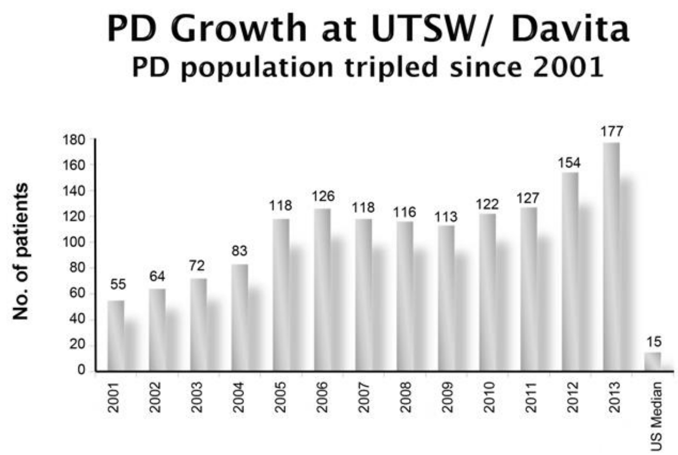
Lack of pre-ESRD education is a key factor that has contributed to waning of PD population in the USA. The USRDS Dialysis Morbidity and Mortality Wave 2 study drew attention to the lack of pre-ESRD education among chronic kidney disease (CKD) patients [23]. It noted that among new ESRD patients initiating HD between 1996-1997, only 25% of patients reported PD being discussed with them before they started treatment for kidney failure [23]. Since then, rates of discussion of PD among CKD patients have increased as suggested by the recent Comprehensive Dialysis Study (CDS), comprising a cohort of incident patients beginning dialysis in the 2005- 2007 period [24]. In this study, it was observed that 58.6% of patients who initiated HD, reported that PD had been discussed with them before the start of dialysis. However, of the 990 CDS participants who reported that PD had been discussed with them before dialysis, only 108 (10.9%) began treatment with PD. Moreover, mere 10 of the 631(1.6%) CDS participants who reported that PD had *not* been discussed with them began treatment with PD. This suggests that pre-dialysis information of RRT options was important in selecting PD. Conversely, the proportion of those who actually began PD treatment after receiving this information remained relatively small (10.9%) [24,25]. This parallels the decline in PD utilization countrywide in the corresponding period. In a study of patients in the Southern California ESRD Network, Mehrotra et al, suggested that the extent of time spent discussing RRT options,including PD, was the most important determinant of PD selection [26]. The CDS did not obtain information about the content, duration, or patient satisfaction with the PD discussions, all of which might influence patient decision making.Thus, it is quite likely that low rate PD acceptance among informed patients in the CDS is likely a result of lack of quality and quantity of information presented to them as a part of their pre-ESRD education. The importance of quality patient education is underscored by the results of the National Pre-ESRD Education Initiative, where 45% of the patients who received quality pre-ESRD education opted for PD and 33% actually started PD [27]. Similarly, in a report from Hong Kong, 50% patients who were offered PD were reluctant to start PD initially





but agreed after pre-dialysis counseling [28]. Another report from United Kingdom showed that close to 50% patients who receive explanations for PD and HD through pre-dialysis counseling would choose PD [29].

A multidisciplinary pre-ESRD education program that includes nephrologists, nurses, dieticians and social workers, can considerably enhance the growth of a PD program. We have developed a robust Pre-ESRD patient education program at UT Southwestern Medical center. Between 2006 and 2009, 470 patients with CKD were provided Pre-ESRD education at our program. Of these,180 patients initiated dialysis, 40% of them starting on PD. This is almost six times greater than the proportion of US dialysis patients commencing PD [1]. Utilizing our Pre-ESRD program at UT Southwestern Medical center the number of PD patients has more than tripled at UTSW/ Davita PD clinic over the past 10 years. Our experience suggests that high quality patient education must begin in CKD stage 4, using a multidisciplinary team approach. This will facilitate patients and families to understand various treatment options and make judicious decisions, thereby allowing orderly planned initiation of appropriate RRT modality.



Exposure to PD among trainee physicians

Two studies illuminated inadequate exposure to PD during nephrology fellowship training in the USA [30,31]. It was observed that 29% of US nephrology training programs had fewer than 5 PD patients per fellow, and that fellows spent less than 5% of their time receiving training in the care of PD patients in 14% of programs. When asked, only 32% of fellows stated that they had attended an outpatient PD clinic; 52% stated that their PD rotation was less than 4 weeks in duration; 24% of fellows had never initiated PD in a patient; 57% initiated PD on less than five patients; and 38% felt training was inadequate. A practicing nephrologist, who did not have an adequate PD training, will be reluctant to offer this therapy to the patients. In order to improve PD training, fellowship programs must provide fellows adequate exposure to PD. Programs with small or no PD clinics should offer fellows elective rotation in centers with larger PD populations. Residency Review Committee should consider requirement of 5-10 PD patients per fellow to accredit a fellowship program.

Mirroring nephrology fellowship programs, most US surgery residency programs provide insufficient training for PD catheter (PDC) placement. For success on PD, a well functioning PDC is absolutely necessary. PDC malfunction is a leading cause of technique failure in PD and problems with PDC placement and malfunction can disrupt efforts to grow and develop a PD program. Reluctance by surgeons to place PDCs and suboptimal PDC outcomes might stem from inadequate residency training. In a national survey of surgery training programs, it was observed that most surgeons placed less than 5 PDC during training. It has been recognized that surgical outcomes correlate strongly with training during residency [32]. Most program directors felt that PDC training wasimportant, affected outcomes and influenced the likelihood surgeons would place PDCs in practice. Lack of referrals from nephrology was the most frequently cited barrier to PDC training. However, 62% of programs expressed willingness to provide more PDC training. Therefore nephrologists and surgeons should develop coordinated initiatives to nurture PDC training. Moreover, nephrologist should include surgeons in quality improvement initiatives and provide appropriate feedback to surgeons on catheter outcomes.

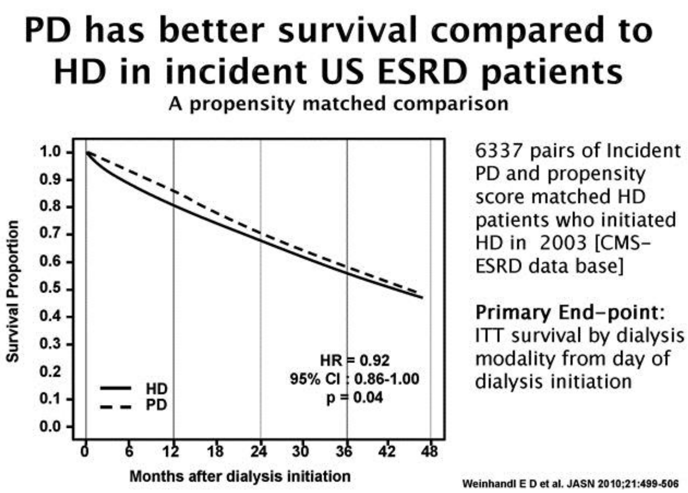
Bias against PD among healthcare providers

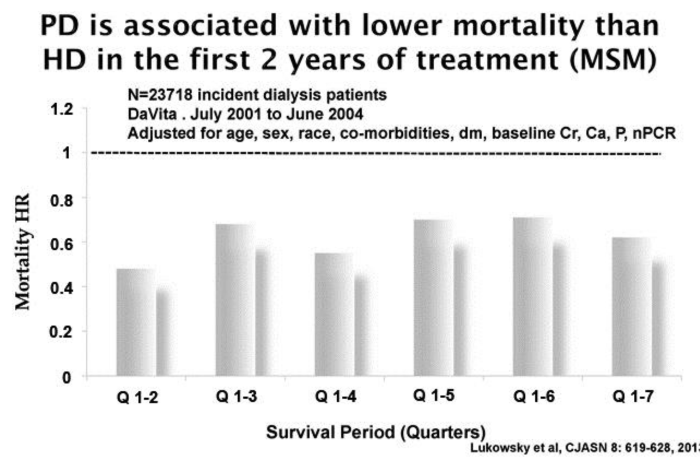
Inadequate exposure to PD during training can lead to bias and misperceptions against PD among nephrologists and internists. Even though, US nephrologists, in a survey, suggested that about 30% of dialysis population should utilize PD, the reality is plagued by the fact that only 7% of all dialysis patients initiate PD [1,22]. It is likely that significant misperceptions or prejudices against PD exist among practicing nephrologists and other medical professionals. Notably many believe that PD is a poor form of dialysis and is associated with abysmal outcomes, high rate of infections such as peritonitis, and is disruptive to quality of life of patients. Furthermore it is a common perception among many physicians that PD is not suitable for obese individuals or those with abdominal surgeries. Others consider PD to be associated with excessive weight gain due to large caloric load from glucose absorption and hence unsuitable for individuals with diabetes or those who want to lose weight. Such misgivings need amendment through appropriate training and education

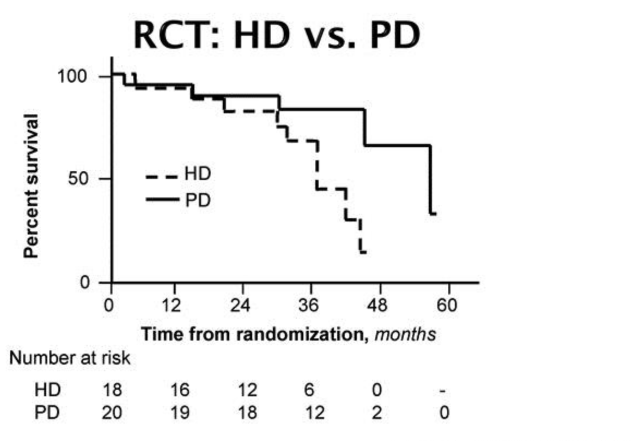
Peritoneal dialysis outcome studies

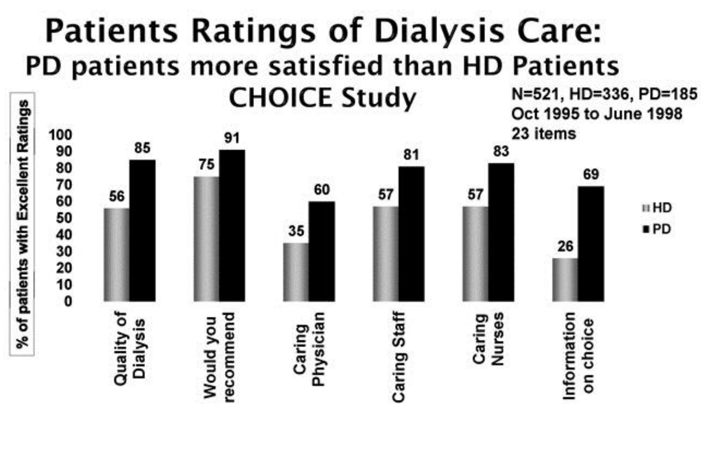
An earlier report based on the USRDS data of prevalent patients showed that PD patients had a 19% higher mortality risk compared to HD patients [33]. This study was partly instrumental in subsequent shrinkage of the PD population in the USA. However, when a case-mix of USRDS incident and prevalent patients was later analyzed, no difference in mortality between HD and PD was observed [34]. Subsequent analysis of incident dialysis patients from the Canadian, US and Danish registry data found a significantly lower relative risk of mortality in PD compared to HD in all groups of patients, except elderly diabetic women, particularly in the first 2-3 years of treatment [35-38]. More recent studies have shown better outcomes with PD compared to HD. In a propensity matched mortality comparison of incident HD and PD patients using center of Medicare and Medicaid services (CMS) database, it was observed that among patients who initiated dialysis in 2003, PD provided 8% survival advantage over HD during a mean follow up of 4 years. The survival benefit was higher when estimated from the day of dialysis initiation compared to that from day-90 [39]. A more recent study estimating survival of incident dialysis patients initiating dialysis between July 2001 and June 2004 at DaVita facilities in the USA observed that PD was associated with significantly greater survival (48% lower risk of death) compared to HD patient throughout the follow up period of 2 years, independent of known confounding factors including modality switch and transplant censorship [40].

So far, the studies comparing outcomes of PD with HD have been observational, based largely upon









registry data. The mortality results from these studies should be viewed with caution since other unmeasured co-morbid factors and severity of the reported co-morbidities may be unevenly distributed between the two groups and can lead to the difference observed in mortality risks between the two modalities, notwithstanding sophisticated statistical adjustments. There is a great need for a randomized controlled trial (RCT), but the challenge to conduct one is underscored by the only RCT yet done [41]. This multi-center Dutch trial was discontinued prematurely because of poor enrollment. Albeit the small sample size, the study showed a significant survival benefit for PD over HD in the first 4 years of the treatment. A large RCT comparing outcomes of HD and PD patients is currently underway in China.

Taken together, the results from the aforesaid studies suggest that overall mortality is at least similar in HD and PD. Peritoneal dialysis may offer survival benefit particularly in early years of treatment.

Peritoneal dialysis and quality of life

It is a common belief among many physicians and patients that PD foists an excessive burden to patients and their families, limits physical and social activities thereby significantly reducing quality of life (QOL).

There is no single, ideal or best dialysis modality. The decision of choosing a dialysis modality by a well-informed patient depends upon personal preferences and values, and belief that the dialysis modality should not only prolong life but also improve QOL. Least disruption or intrusion for the QOL is perhaps the strongest attribute that influences the choice of the dialysis modality. In a recent synthesis of qualitative studies of patients' experiences, beliefs, and attitudes about PD, it was observed that most patient chose PD to gain independence, freedom, and flexibility and retain the ability to travel, work, and care for children [42]. However, to some PD was made less preferable by concerns about body image, ability to maintain sterility in the home environment and store dialysis supplies [43]. Thus, PD can have a detrimental impact on the self-esteem and physical functioning of some patients particularly if they lack social support or are unable to develop resilience and confidence. In contrast, other patients can be resolute, confident, and overcome their initial uncertainty about managing PD with strong support from family and staff.

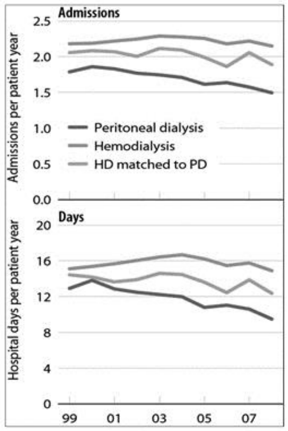
By and large, PD patients seem to be more satisfied with their treatment compared to their HD counterparts. A cross-sectional survey of 656 US incident dialysis patients at 37 centers observed that PD patients rate their care higher than HD patients do [44]. After adjusting for case mix, patients receiving peritoneal dialysis were 1.46 times more likely to rate their dialysis care as excellent and 1.2 times more likely to recommend their dialysis center to others as were patients receiving hemodialysis. Ratings were higher for all 23 items investigated, including dialysis dose, clinician caring and concern, availability, information, and technical aspects of care [44]. In another study of 62 PD and 84 HD patients from 3 dialysis centers in New Haven, CT, USA, the mean satisfaction score of PD patients was higher than that of HD patients [45]. Moreover, PD patients felt that there was less impact of dialysis therapy on their lives compared to HD patients. Furthermore, PD patients noted less impact of the dialysis therapy in 14 of the 15 domains examined. These studies suggest that PD is less intrusive on the lives of the patients and provides higher degree of patient satisfaction compared to HD.

Morbidity in PD

Infection remains a major cause of morbidity and mortality among dialysis population. There has been a common perception that PD is associated with very high infection related complications.

Impact of dialysis modality on infection was studied in a prospective observational cohort study comprising 181 dialysis patients (119 HD, 62 PD) who initiated dialysis between 1999 and 2005 at a single dialysis center in the USA [46]. It was observed that overall infection rates were similar between the two modalities. However, only HD patients had bacteremia and only PD patients had peritonitis. Rate of bacteremia was almost 3 times higher than the overall rate. HD catheter, used in 67% of patients who started HD, were associated with this strikingly higher rate of bacteremia in the early course of HD treatment. No such difference in peritonitis rate was observed among PD patients. Dialysis modality was not an independent predictor of overall infections [46]. Similarly, in another study, no difference in infection rates was observed between US-Medicare-adult HD and PD patients who initiated dialysis between 1996 and 2001 [47]. A retrospective study for Canada further attempted to compare the rates of infection related hospitalization (IRH) in incident HD and PD patients [48]. Among 71 PD and 97 matched HD patients, the unadjusted and adjusted

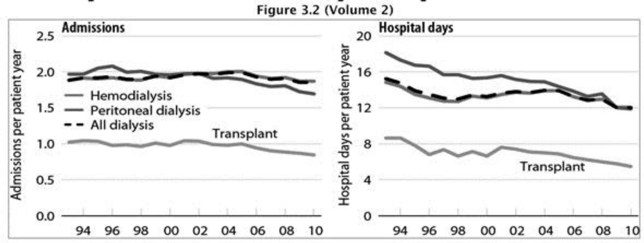
Adjusted first-year hospital admission rates & days (from day 90) in matched incident hemodialysis & peritoneal dialysis patients
Figure 3.7 (Volume 2)



Incident hemodialysis & peritoneal dialysis patients age 20 & older. Adj: age/gender/race/primary diagnosis; ref: 2005 incident hemodialysis & peritoneal dialysis patients.

USRDS 2011

Adjusted hospital admission rates & days, by modality in prevalent dialysis patients
Figure 3.2 (Volume 2)



Period prevalent ESRD patients. Adj: age/gender/race/primary diagnosis; ref: ESRD patients, 2005.

USRDS 2012

Access events & complications in prevalent dialysis patients (CPM data; rate per patient year)

	CVC			AVF			AVG			PD		
	1998	2003	2007	1998	2003	2007	1998	2003	2007	1998	2003	2007
Complications												
Infection of access	1.24	1.67	1.45	0.24	0.22	0.18	0.44	0.42	0.39	0.46	0.51	0.56
Sepsis	1.65	2.89	2.32	0.43	0.54	0.52	0.67	0.74	0.61	0.49	0.52	0.44
Angioplasty	-	-	-	0.16	0.28	0.47	0.49	0.77	1.10	-	-	-
Declot	-	-	-	0.06	0.08	0.12	0.15	0.38	0.48	-	-	-
Peritonitis	-	-	-	-	-	-	-	-	-	0.65	0.63	0.61

Catheter, fistula, graft: prevalent hemodialysis patients age 20 & older, ESRD CPM & claims data.
Peritoneal dialysis device: prevalent peritoneal dialysis patients age 20 & older.

USRDS 2012 Table 2.c (Volume 2)

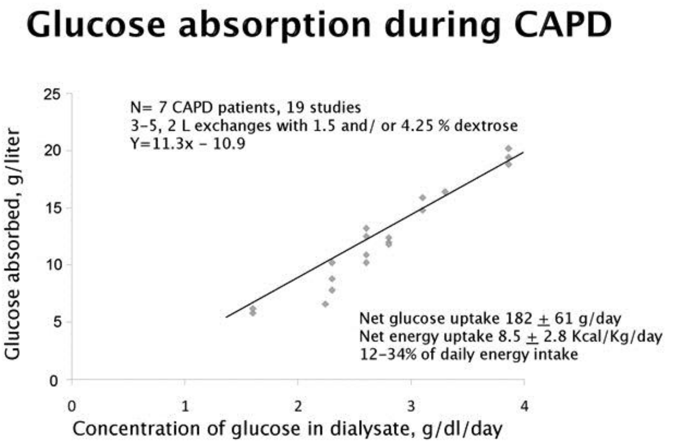
incidence rate ratios of IRH did not-differ significantly between the two groups. There was no significant difference between PD and HD in the risk of mortality, technique failure or access loss following IRH. Clearly, PD patients were more likely to be hospitalized for peritonitis and there was a trend towards higher hospitalization for bacteremia among HD patients [48].

The recent USRDS report expressed additional concern over high infection rate among the US-ESRD population [1]. It noted that compared to 1994, there was 31% greater rate of IRH among ESRD patients in 2010. When comparing different dialysis modalities, it observed a considerably higher overall unadjusted hospitalization rates in the first and second years for HD patients than for those treated with PD. When HD patients were matched to those on PD, however, these differences were attenuated, and the higher rates of IRH in the first year in HD patients were reversed by the second year. Overall, however, it still that appears that PD patients have fewer hospitalizations than their matched HD counterparts [1]. Moreover, while there has been steady decline in admissions per patient-year among PD population to 1.69, the admission rate for HD population has remained unchanged at 1.89 since 1993 [1]. Of particular concern are the rates of IRH in the hemodialysis population, which have increased 43 percent since 1994. Increasing use of central venous HD catheters continues to have the largest associated risk, a finding well known in the dialysis community and reflected in the USRDS report that shows that the admissions for bacteremia remained highest among HD patients in 2010 [1]. On the other hand, the admission rates for peritonitis and PD catheter infections have been falling since 1993, although the overall rate of hospitalization for infection has changed little over time among PD population [1].

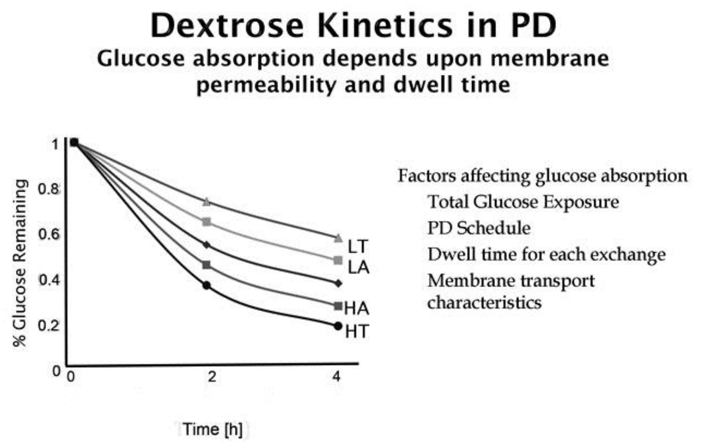
These data undoubtedly show that patients that initiate on PD do not have higher risk of infections and consequent morbidity or mortality as compared to those who initiate HD. Thus the common perception that PD is associated with high infection rate is unfounded. However, infections, in general remain a cause of concern in ESRD population as a whole, irrespective of dialysis modality. Collective team efforts are urgently needed to reduce infections among dialysis population.

Glucose absorption in PD

Conventional PD fluids use glucose as an osmotic agent, to facilitate UF. However, due to its small size, variable quantity of glucose instilled into the peritoneal cavity is absorbed into blood during PD dwell. It has been a commonly mentioned in the literature that about 100-300 g of glucose is absorbed day in CAPD patients. This amounts to about 400-1200 calories or up to 20% of daily energy intake. Most of these estimations are based upon a study performed by Grodstein et al in 1981 on 19 measurements in 7 CAPD patients using 1.5% and 4.25% dextrose solutions [49]. They observed that the amount of glucose absorbed per liter of dialysate (y) varied with the concentration of glucose in dialysate (x= g/dl) and could be predicted by the equation y=11.3x-10.9. A net average glucose absorption of 182 g/day was noted in the study. This equaled to



Grodstein, et al KI 19: 564-567, 1981



Mujais et al, Peritoneal Dialysis Int. 2001

an energy intake of about 8.5 kcal/kg of body wt per day, or 12 to 34% of daily total energy intake. However, this study was small and estimated glucose absorption in CAPD patients with long dwell time, without any knowledge of peritoneal transport characteristics of the individual patients. Another study on 12 CAPD patients, mainly estimating protein and nitrogen balance, also noted daily caloric intake of 4-13 kcal/kg [50].

Unlike CAPD patients examined in the aforementioned studies, the vast majority of contemporary PD patients in the USA, however, use APD with short dwell times [1]. With the advent of PET, which estimates the ratio of remaining dextrose (Dt) to the initial dextrose concentration in the dialysate at zero hour (Dt/D0), it has become obvious that glucose absorption depends upon the membrane characteristics, dwell time and PD modality [20]. Hence in patients performing APD, the estimation of glucose absorption cannot be performed using the method of Grodstein, et al [49]. A new method of estimating glucose absorption is needed that will take into account the PD modality, dwell time and membrane characteristics. Using such estimate in 40 CAPD and 17 APD patients, Bodnar, et al observed that there was much lower absorption of glucose in APD patients than in CAPD patients [51].

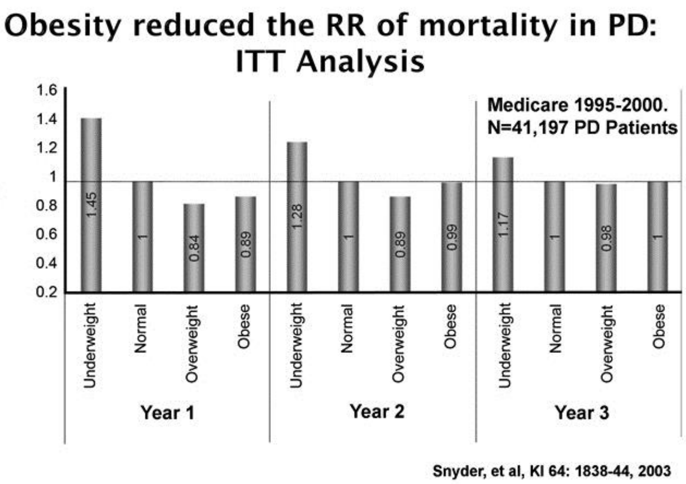
Since APD is the predominant form of PD modality, accurate estimation of glucose uptake is essential. It is also essential to amend the misconception that patients get large caloric and energy load from PD. With the use of APD, lower dextrose dialysates and novel dialysis solutions, the amount of glucose absorption has been considerably reduced in contemporary PD patients, compared to that in the earlier days of PD. Accurate estimation of caloric load and incorporating it in the daily caloric intake of the individual will help to reduce metabolic consequences of hyperglycemia and weight gain. In fact patient can be successful in losing weight while on PD following this approach. Hence, obesity or diabetic status should not be barriers to initiate PD in patients with ESRD.

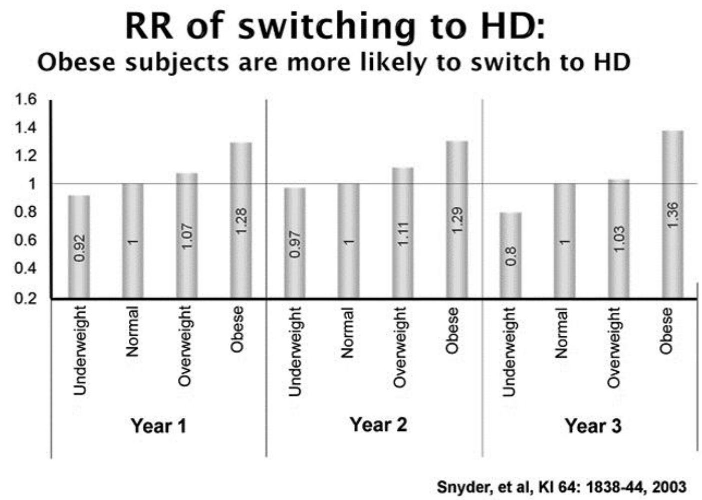
Obesity and Peritoneal Dialysis

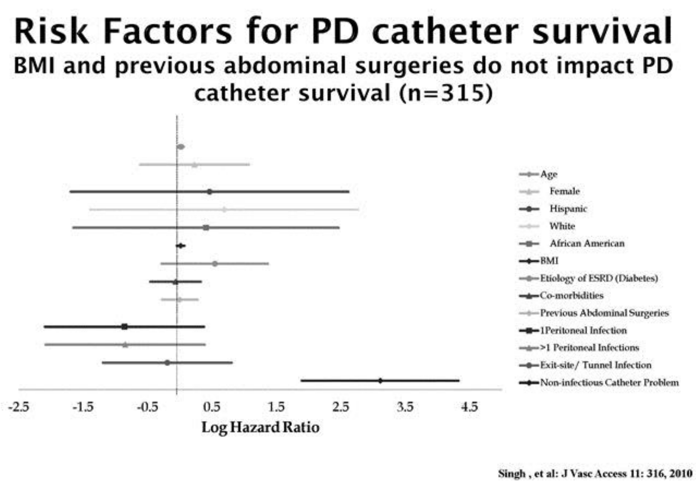
The prevalence of obesity in the United States has reached epidemic proportions. From 1980 to 2004, the percentage of obese US adults more than doubled from 15% to 33% and that of a morbidly obese quadrupled from 1 in 200 to 1 in 50 [52,53]. If recent trends continue, more than half of US adults (51.1%) are likely to be obese and 86.3% are likely to be categorized as overweight or obese by the year 2030 [54].

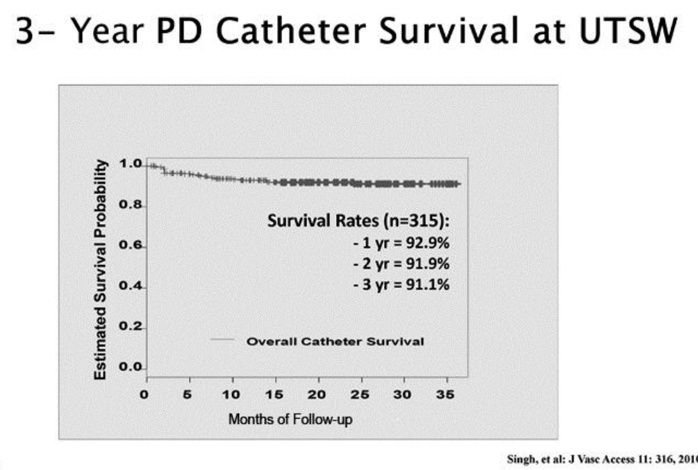
Obesity is not only associated with diabetes and hypertension, two primary causes of ESRD, but is also an independent risk factor for the development of ESRD [55]. Therefore, it should come as no surprise that the prevalence of obese dialysis patients in the US is increasing. It has been observed that rate of increase in mean BMI among incident dialysis population is twice than that seen in the US population as a whole [56]. It is expected that the prevalence of obesity within the US dialysis population will continue to grow for two reasons. First, although somewhat controversial, evidence suggests that obesity is protective and associated improved survival in dialysis patients [57-59]. Some believe that the higher level of adiposity found in obese patients provides a survival advantage because ESRD represents a catabolic disease state in which normal or underweight patients are disadvantaged by their inability to maintain an adequate daily nutrient intake [59]. If this scenario of "reversed epidemiology" is found to hold true, over time it will result in the further amplification of the prevalence of obesity among dialysis patients. Second, as opposed to ESRD patients of normal weight, obese ESRD patients experience barriers to renal transplantation. Consequently, obese patients are listed and transplanted at a much lower rate than their non-obese counterparts [60]. Thus further increase the obesity prevalence among US dialysis patients can be expected.

PD is perceived to be not an appropriate RRT for obese ESRD patients. However, the data on survival outcomes of obese patients on PD is controversial. A study using data from the Australia and New Zealand









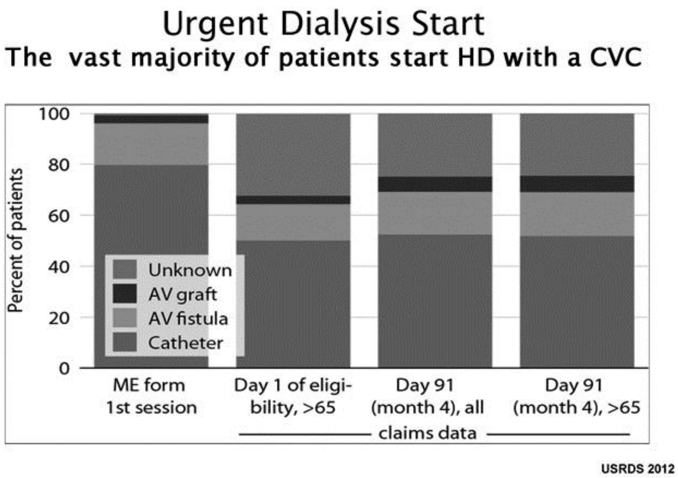
dialysis and transplant registry noted obesity to be associated with 36% higher risk of death and 17% higher risk of technique failure compared to non-obese PD patients [61]. On the other hand, the largest epidemiologic study of over 46000 US Medicare PD patients showed a longer survival of overweight and obese PD patients compared to those with lower body mass index (BMI) [62].

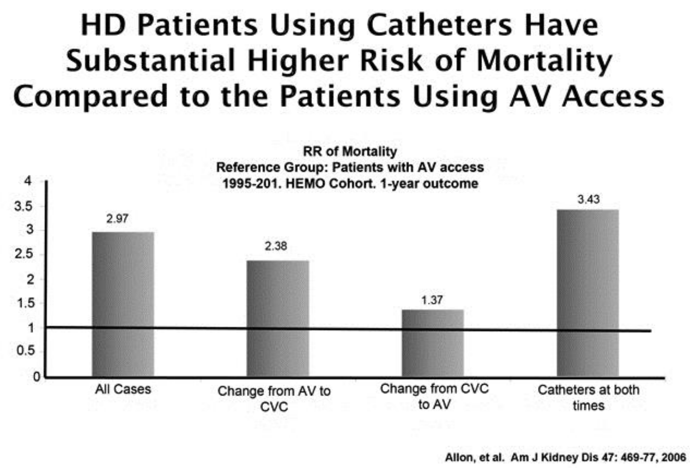
Whether or not obesity affects survival of PD patients, it is commonly considered an impediment for catheter surgery. However, there is limited data on the effect of obesity on PD catheter survival and technique failure. We recently carried out a retrospective study on 315 patients who had their first PD catheter placed between January 2001 and September 2009 at our center [63]. The primary endpoint of the study was PD catheter failure, defined as removal of a dysfunctional PD catheter. The mean BMI for the group was 28.6 ± 13.8 kg/m^2. Overall, PD catheter survival rates at 12, 24, and 36 months were 92.9%, 91.9%, and 91.1%, respectively. The study did not reveal any significant risk of higher BMI on PD catheter outcomes. Similar results were observed in a previous study on 351 PD catheters, which showed that body weight has no significant correlation with PD catheter removal due to non-infectious/mechanical causes [64].

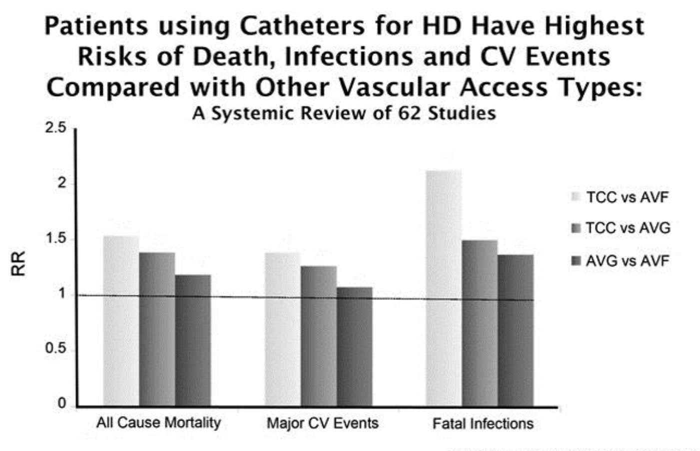
Based on the results of available data, obesity should not be considered a barrier influencing the eligibility of a patient to perform PD.

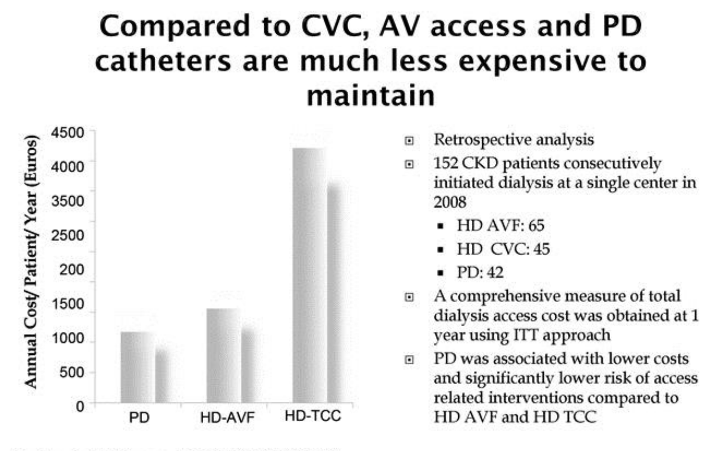
Urgent PD start

In the ideal world, the impending ESRD diagnosis is proactively managed with a pre-emptive kidney transplant. In sharp contrast, because of patient denial and variety of other reasons, a vast number of patients start dialysis acutely without any pre-ESRD education or planning. The majority of such acute-start ESRD patients begin with HD using central venous catheter (CVC). Based on USRDS report, more than 80% of all patients who initiated HD in 2010 had a dual-lumen catheter [1].

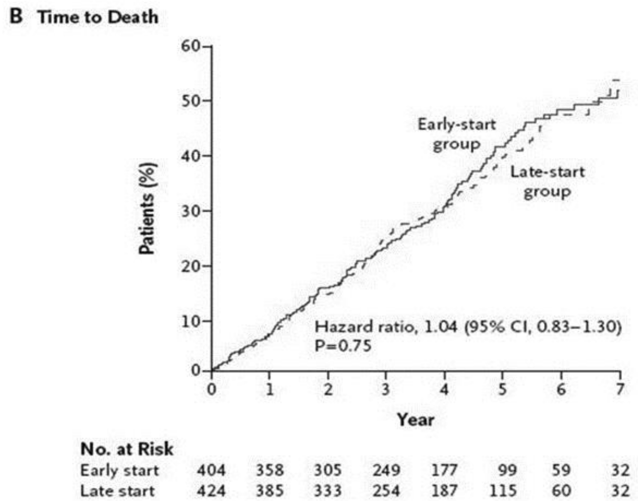


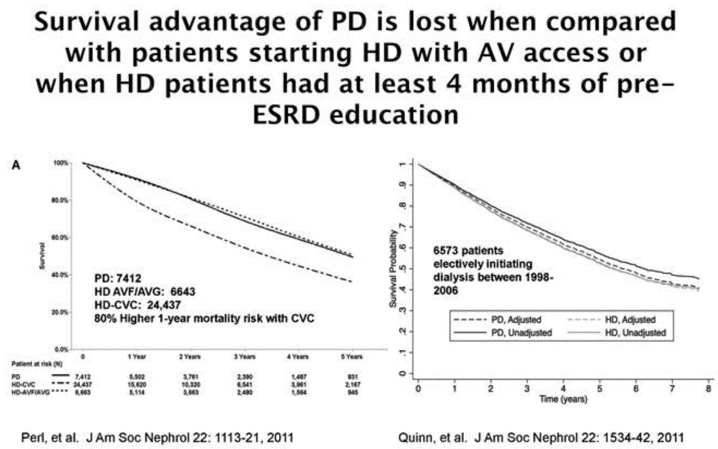






Vascular access is an important predictor of death in HD patients. Various studies have shown that incident HD patients using catheters have 2-3 folds higher relative risk for death compared with those using an arteriovenous (AV) access. Analysis of over 1800 patients enrolled in the HEMO Study demonstrated that compared with patients who used AV access, those dialyzing with a catheter had almost 3.5 fold higher risk of mortality over a year [65]. Similarly, a study from Netherlands showed over three folds higher risk of mortality, particularly in elderly patients dialyzing with catheters compared to those with AV access [66]. A recent meta-analysis confirmed these finding showing significantly higher risk of all-cause, cardiovascular and infection related mortalities in patients dialyzing with CVC compared to those with AV fistula (AVF) and AV grafts (AVG) [67]. Therefore, all efforts should be made to avoid initiation of HD with a CVC. Unless the situation is critical and HD initiation is absolutely indicated, CKD patients with acute presentation should be managed medically and promptly educated about RRT options. Delaying initiation of dialysis does not affect the outcomes, as shown in a RCT of early versus late initiation of dialysis [68]. In this study, 828 ESRD patients were randomized to early start (median time to dialysis initiation of 1.80 months) and late start (median time to initiation of dialysis 7.40 months). No significant difference in mortality, cardiovascular events,





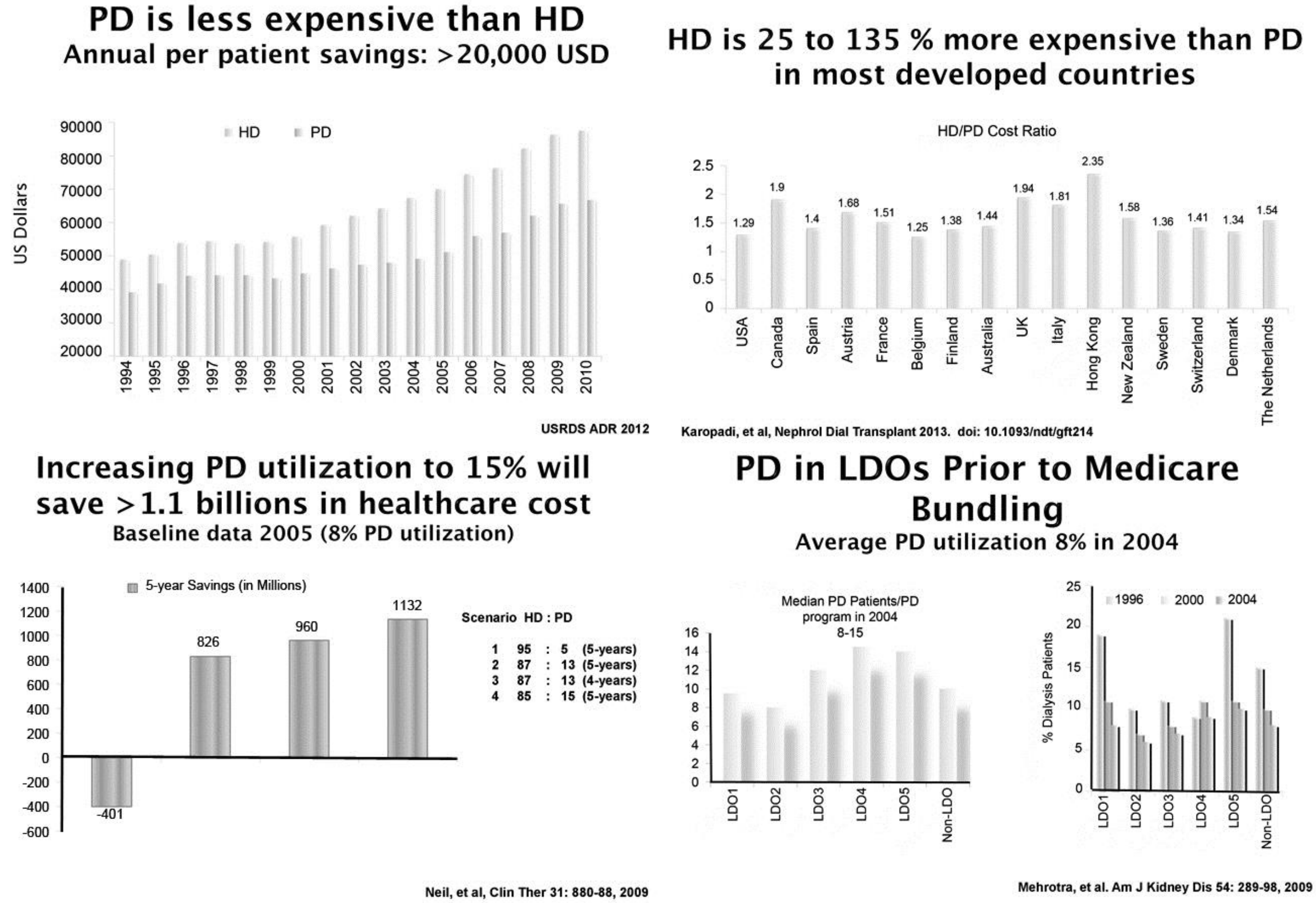
infections or dialysis complications was observed between the two groups during a mean follow up of 3.59 years [68]. There was a difference of 6 months between the two groups in the start time of dialysis. This would provide adequate time for the patient and families to receive pre-ESRD education and initiate appropriate RRT modality with proper access, thereby avoiding HD initiation with CVC.

The importance of initiating dialysis with appropriate access is underscored in a recent study from Canada. This study compared survival of incident PD patients with those who initiated HD with CVC or with functional AV access (AVG or AVF). Compared with the 7412 PD patients who initiated PD between 2001 and 2008, 1-year mortality was similar for the 6643 HD-AVF/AVG patients but was 80% higher for the 24,437 patients initiating HD with CVC [69]. This suggests that the use of CVC in incident HD patients may considerably account for the higher mortality among HD patients in early years of treatment, as observed in other studies. Furthermore, it highlights the importance of avoiding HD-initiation with CVC. Pre-dialysis care and patient education play an important role in this regard as suggested another study from Canada [70]. Since patients who start dialysis urgently have high risk of mortality and are almost exclusively treated with HD, this study examined the outcomes of incident HD and PD patients who had at least 4 months of pre-ESRD care. In contrast to most recent studies, which show early survival advantage with PD, it observed a similar survival rate between HD and PD in this cohort of 6573 patients electively initiating dialysis between 1998 and 2006 [70]. It is likely that better survival among elective start HD patients is due to planning and placement of appropriate AV access during pre-ESRD care.

To summarize, the above studies suggest that initiation of dialysis with appropriate access is of paramount importance to improve outcomes in ESRD population. However a large number of CKD patients start dialysis urgently without any prior education and care [1]. They are treated almost exclusively with HD using CVC, without benefit of an informed decision regarding other options. Most of these patients remain on in-center HD with CVC in place for a prolonged period of time. This exposes them to high risk of morbidity and mortality and poor outcomes associated with CVC. It is extremely important to give education about RRT modalities while these patients are in hospital, rather that continuing HD as a “default” modality. PD is an excellent option for these patients and should be offered to this group, notwithstanding initiation of acute HD. Expeditious placement of PD catheter while the patient is in hospital can avoid HD initiation with CVC or minimize time on CVC. Once PD catheter is in place, PD can start almost immediately, if needed. This approach of accelerated education in acute ESRD patients in hospital setting has led to avoidance of CVC in a large proportion of these individuals and resulted in a sizeable number of acute PD starts in a center in Canada [71,72]

Financial issues

Health spending in the United States is much higher than that in the other Organization for Economic Co-operation and Development (OECD) countries. The United States spends two-and-a-half times more than the OECD average health expenditure per person. At 17.4% of GDP in 2009, US health spending is more than 1.5 times than any other country, and nearly twice the OCED average [73]. Additionally, expenditure on ESRD patients is disproportionately higher than the general Medicare cost. While total Medicare spending in 2010 rose 6.5 percent, to$522.8 billion, expenditures for ESRD rose by 8.0 percent, to $32.9 billion [1]. In this landscape of rising healthcare expenditure, annual per patient cost of HD was more than $20,000 higher than that of PD [1]. Moreover, a recent study comparing cost of various dialysis modalities in 46 countries across the world, the cost of HD was found to be between 1.25 to 2.35 times higher than PD in most developed



countries [74]. This makes PD more economically attractive dialysis modality. It has been estimated that the USA could realize savings in excess of $1.1 billionover 5 years if PD utilization is increased from 8% to 15% [75].

Till recently, Medicare payments to dialysis centers included a composite rate, which incorporated the dialysis procedure, supplies, routine laboratory tests, and personnel, and additional payments for "injectable" drugs such as erythropoietin, vitamin D analogs and iron, on as used basis. The potential profit margin of dialysis provider was heavily depended on the amount of "injectable" drugs used. Since there is a lower requirement of "injectable" medications in PD as compared with HD, this made HD more profitable than PD for dialysis providers including LDOs that treat more than 60% of US dialysis patients [1,76]. While LDOs in the United States increased by 53% between 1996-2004 with a corresponding increase in the number of patients undergoing HD in these units from 39% to 63%, there was a steady decline in the number of PD patients [76]. This was supported by the analysis of data from USRDS 2007 Network's annual report, which found a negative association between PD utilization and affiliation of dialysis facilities with LDOs [77]

In an attempt to control costs, the US Centers for Medicare and Medicaid Services instituted the prospective payment system (PPS) for dialysis on January 1, 2011. The new payment system tightened payments to dialysis facilities by merging composite rate services as well as injectable and certain oral medications, laboratory tests currently not a part of composite services, and some other supplies such as blood products into a single bundled payment. Thus PD, which uses far fewer injectable medications and labor, financially became more attractive to the dialysis facilities.

The Study to Evaluate the Prospective Payment System Impact on Small Dialysis Organizations (STEPPS) is a prospective observational cohort study of 1,873 adult HD and PD patients from a sample of 51 small dialysis organizations (SDO), designed to evaluate trends in care and outcomes over the period of PPS implementation [78]. It noted a trend toward greater use of PD in SDOs (from 2.4% to 3.6%; $P = 0.09$) in the early period of PPS implementationfrom October 2010 to June 2011. Whether this early trend of greater PD utilization will persist and extend to LDO and other PD programs remains to be seen.

REDUCING LOSS OF PD PATIENTS TO HD

In order to expand PD population, apart from augmenting enrollment of new PD patients, it is exceedingly important to reduce the rates of PD technique failures that lead to transfer of patients to HD. It has been observed that a large proportion of dialysis patients transfer from PD to HD every year that could be a significant cause for the diminishing PD population [79,80]. Recurrent episodes of peritonitis, inadequate dialysis, or ultrafiltration failure as well as system issues and psychosocial reasons make up most reasons for the transfer to HD. PD-to-HD switch rates of more than 35% have been reported in the first 2 years in the United States [79]. Strategies to prevent or resolve the issues that lead to transfer to HD may help inenhancing PD population

Peritonitis and exit-site/ tunnel infections

Despite considerable improvement in PD techniques over the years, PD-related infections including peritonitis, and catheter infections (exit site and tunnel infections) remain the most frequent and important complication of PD, often resulting in catheter removal and discontinuation of PD. In a recent prospective study of 292 PD patients from 28 dialysis centers, it was found that the most common reason for the switch from PD to HD was infection related (peritonitis and catheter infections) at 36.9%, followed by volume overload at 18.5% [81]. Another recent study from 10 centers in Scotland noted 42 % of all PD technique failures from peritonitis [82]. It addition, they observed that about 15% of all episodes of peritonitis resulted in technique failure.

The incidence of peritonitis ranges from one episode per 24.8 months to one episode every 46.4 months in various studies [83]. No significant difference in risk of peritonitis has been observed with the design of catheters, surgical techniques used to place the catheters or location of catheter exit sites (pre-sternal or abdominal) [84,85]. Quality improvement initiatives in PD, using a comprehensive approach that includes use of prophylactic antibiotics for peritonitis, exit site and catheter care, as well as training and re-training of patients can go long way in having positive effect in reducing rates of peritonitis and exit-site infection. PD outcomes can further by improved by implementation of rigorous continuous quality improvement (CQI) programs to track the root cause of peritonitis, and monitor rates of exit-site infection, peritonitis and technique failure. By meticulous collecting and analyzing data, and providing feedback to the PD team to implement appropriate interventions, outcomes can be considerably improved. Higher infection rates should trigger a review of techniques and reeducation of both patients and staff to ensure break in technique is not contributing to high rates of peritonitis. By using these tools, it is vastly possible for a center to substantially lower PD related infection and technique failure rates and help PD program to grow and improve overall outcomes.

Peritoneal membrane and ultrafiltration failure

PD is a viable treatment option for ESRD patients worldwide. However, the benefits of PD are short-lived as peritoneal membrane failure ensues in many patients mainly owing to structural and functional changes in the peritoneal membrane from the use of conventional bio-incompatible PD solutions, which are hyperosmolar, acidic and have high concentration of glucose and glucose degradation products (GDPs). There is mounting evidence that with time, ultrafiltration (UF) capacity of peritoneal membrane is progressively lost with concomitant increase in the peritoneal small solute transport rate [86-88]. Current data suggests that chronic exposure of the peritoneum to contemporary PD fluids provokes activation of various inflammatory, fibrogenic and angiogenic cytokines, interplay of which leads to progressive fibrosis, vasculopathy and neoangiogenesis of the peritoneal membrane. However, the precise pathophysiologic mechanisms initiating and propagating peritoneal fibrosis and angiogenesis remain elusive. Altered peritoneal membrane function has a significant impact on both technique and patient survival [86-91]. As prevalence of UF failure increases, it becomes the predominant reason for drop out in long-term PD patients [92,93]. Reduced UF capacity leads to a chronic volume overload state with resultant congestive heart failure and cardiovascular mortality [93-95]. Poor UF can also lead to low drain volumes and consequently to poor solute clearance and thus lower dialysis adequacy. In addition, patients with UF failure experience rapid absorption of glucose from the dialysate (with inhibition of appetite) and a greater loss of proteins in the dialysate leading to poor nutritional status and adverse outcomes [93-95]. UF failure may be due to causes other than peritoneal membrane dysfunction. Dietary indiscretion, excessive sodium and fluid intake, inadequate dialysis prescription, loss of residual renal function (RRF) without adjustments in dialysis prescription, and catheter malfunction are often the causes of chronic volume expansion.

Protecting peritoneal membrane from long-term toxic and metabolic effects of the conventional glucose-based solutions is a key objective to improve PD outcomes [96]

Recent development of new, more biocompatible PD solutions may help to preserve peritoneal membrane function, promote ultrafiltration, improve nutritional status and hopefully improve overall PD outcomes [9-12, 96]. Unfortunately these novel solutions, with exception of icodextrin, are not FDA approved and are unavailable in the United States. Consequently, alternative approaches are required to maintain volume homeostasis in PD patients. Maintaining RRF is of paramount importance in PD patients, and rates of decline of RRF have been associated with all-cause mortality and technique failure [8,96]. Measures to maintain RRF such as avoiding nephrotoxic agents like non-steroidal anti-inflammatory agents, intravenous contrast and aminoglycosides should be implemented as much as possible. Furthermore, recent studies have demonstrated beneficial effect of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in preservation of RRF among PD patients and should therefore be prescribed unless contraindicated [97,98]. Additionally, close attention to the prescription as well as frequent dietary counseling of patient are essential to prevent fluid overload in PD patients, improve overall outcomes and reduce the incidence of technique failure.

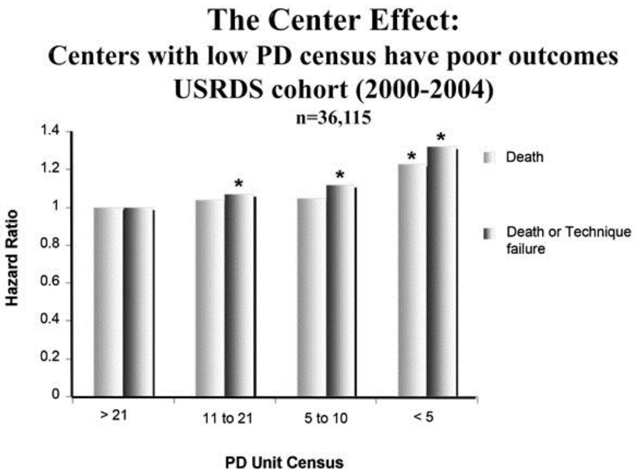
Catheter complications

We recently observed that catheter-related mechanical complications are significantly associated with PD catheter failure [63]. These complications include intra-luminal/ extra-luminal catheter obstruction, catheter malpositioning, catheter migration, omental wrap around the catheter, catheter leakage and catheter extrusion. Many causes of catheter malfunction such as extra-luminal occlusion by the bladder or bowels can be prevented or corrected with use of laxatives or emptying the bladder. Intra-luminal obstruction due to clots or fibrin plug can be treated by injecting heparinized saline, and if unsuccessful by instillation of tissue plasminogen activator in the catheter. Appropriate laparoscopic or open surgical techniques can correct several other common mechanical problems such as omental wrapping, adhesion formation, catheter migration and leaks.

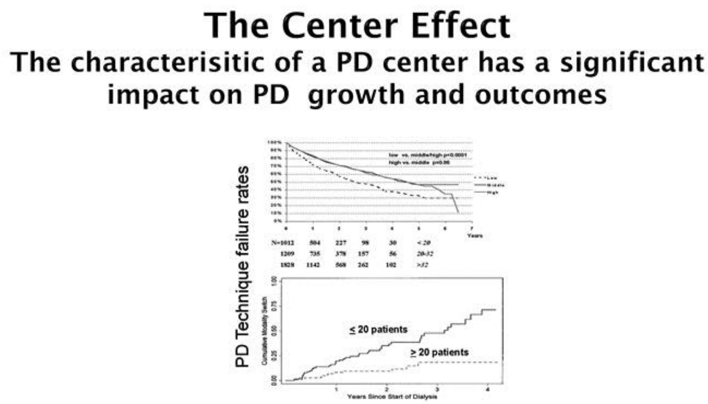
One year actuarial catheter survivals of 80% should be expected by International Society for Peritoneal Dialysis standards [6]. Superior catheter outcomes can be accomplished with proper patient management and availability of surgical expertise. We have demonstrated excellent catheter survival rates at our center [63]. In a retrospective study of 315 patients, examining various risk factors associated with the survival of first PD catheters placed at our center between January 2001 and September 2009 we observed 1-year, 2-year and 3-year PD catheter survival of 92.9%, 91.9% and 91.1%, respectively. On further investigation of different variables in our study, we observed that PD catheter-related non-infectious complication was the single covariate that significantly reduced the catheter survival time. Each PD catheter-related problem increased the risk of catheter failure more than 3 times. None of the other demographic (age, gender, race) or clinical characteristics (Body mass index, diabetic status, co-morbidities, previous abdominal surgeries or any infections (peritonitis, exit-site or tunnel infections) were found to be significantly associated with the PD catheter survival [63]. Our study suggests that, contrary to general perception, morbid obesity, multiple abdominal surgeries, presence of co-morbidities and advanced age should not be considered barriers to patient selection to PD. Inclusion of surgeon as a part of multidisciplinary team caring for CKD and ESRD patients can lead to long-term success and growth of PD program.

The center effect

Characteristics of PD centers may play significant role on PD outcomes [99-101]. Using data obtained from the Canadian Organ Replacement Registry, Schaubel, et al observed a significant association between cumulative number of PD patients treated in a facility and mortality and treatment failure rates. As the cumulative number and proportion of PD patients treated increased, covariate-adjusted mortality and treatment failure significantly decreased [99]. Similarly, Huisman et al, analyzed data from the comprehensive Dutch End-Stage Renal Disease Registry (RENINE) and showed 68% lower technique survival rates in centers with less than 20 patients on PD compared to the larger centers [100]. Likewise, in a prospective cohort study from 26 US-PD centers, it was observed that PD patients treated at clinics with more than 25 patients were at



Mehrotra, et al Am J Kidney Dis 54: 289-98, 2009



significantly lower risk of treatment failures and cardiovascular events than centers treating lower number of PD patients [101]. Similar results were reported by Mehrotra and coworkers in an analysis of ownership patterns of peritoneal dialysis units in the United States. They noted 7 to 32 % higher risks of death or PD technique failure in PD centers treating 21 or less patients compared to centers treating more than 21 PD patients. Highest risk (32%) was observed in centers caring for less than 5 PD patients [102].

These results suggest that the degree of experience and specialization in a PD center has a strong impact on PD outcomes. It is suggested that propensity to exploit technical and non-technical advances in PD increases directly with experience and the centers become more adept at selecting patients to receive PD and treating their complications [103]. Most of the PD programs in the USA are, however, small, typically comprising 10-15 PD patients [102] . On the other hand,most states and ESRD-networks require one full time nurse for 20 PD patients. Therefore, having full time nurse for smaller programs is not cost-effective and they usually utilize part-time staff caring for both PD and HD patients [104]. This leads to lack of expertise and comfort of the staff treating PD patients, which in turn affects the decision to offer PD and high patient drop out from the program. Patient outcomes and PD growth can be improved if smaller programs in a given geographical area can be consolidated into one large PD center that will allow staff to assume primary responsibility of patient care and develop expertise in treating patients with PD and thereby contribute to the growth of the program.

SUMMARY

PD continues to be underutilized in the United States,even though it is less expensive, provides better quality of life and has better outcomes compared to HD. The reasons for low utilization of PD are influenced by complex psychosocial and economic factors, lack of physician training, physician bias and inadequate pre-ESRD care and education to the patients. Providing quality pre-ESRD education to patients and families and improving education and training of physician in PD, so that they become comfortable with the therapy, are of paramount importance to increase PD growth. Minimizing episodes of PD related infections and non-infectious complications, preserving peritoneal membrane by using more biocompatible solutions and drugs such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers, and careful management of volume status can reduce loss of PD patients to HD. Timely surgical interventions can prevent the malfunction and loss of PD catheters. Consolidating smaller PD facilities in a given geographical area into a single large PD center can further improve PD outcomes and PD growth. Finally, with introduction of bundled payment for dialysis services, PD may emerge as a cost-effective therapy and rekindle interest in the dialysis community to consider PD as a better RRT option.

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