BIOCOMPATIBILITY OF NEW PERITONEAL DIALYSIS SOLUTIONS: WHAT CAN WE HOPE TO ACHIEVE?

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Despite the bioincompatibility of the “old”, standard, high glucose, lactate-buffered peritoneal dialysis (PD) solutions, PD is itself a highly successful dialysis modality with patient survival equivalent to that of hemodialysis (HD) during the initial 3 – 5 years of dialysis therapy. Nevertheless, PD technique survival is often limited by infectious complications and alterations in the structure and function of the peritoneal membrane. These local changes also have a negative impact on patient survival owing to systemic effects such as those often seen in patients with high peritoneal transport rate and loss of ultrafiltration (UF) capacity.

Patient mortality remains unacceptably high in both HD and PD patients, with most premature deaths being associated with signs of malnutrition, inflammation, and atherosclerotic cardiovascular disease (MIA syndrome). These systemic signs are likely to be influenced by PD solutions both directly and indirectly (via changes in the peritoneal membrane). New, biocompatible PD solutions may have favorable local effects (viability and function of the peritoneal membrane) and systemic effects (for example, on MIA syndrome). Amino acid–based solution [Nutrineal (N): Baxter Healthcare Corporation, Deerfield, IL, U.S.A.] may improve nutritional status as well as peritoneal membrane viability. Bicarbonate/lactate–buffered solution [Physioneal (P): Baxter Healthcare Corporation] may ameliorate local and systemic effects of low pH, high lactate, and high glucose degradation products. Icodextrin-based solution [Extraneal (E): Baxter Healthcare SA, Castlebar, Ireland] may improve hypertension and cardiovascular problems associated with fluid overload and may extend time on therapy in patients with loss of UF capacity.

The positive effects of each of these new, biocompatible solutions have been demonstrated in several studies. It is likely that the combined use of N, P, and E solutions will produce favorable synergies in regard to both local effects (peritoneal viability) and systemic effects (less malnutrition, inflammation, and fluid overload). Solution combination is an exciting area for clinical study in the coming years. Furthermore, dialysis fluid additives such as hyaluronan, which protects and improves the function of the peritoneal membrane, may further improve PD solutions. The new, biocompatible PD solutions represent an entirely new era in the evolution of the PD therapy; they are likely to have markedly positive effects on both PD technique and PD patient survival in coming years.

KEY WORDS: Biocompatibility; peritoneal dialysis solution; peritoneal membrane; malnutrition; inflammation; atherosclerosis.

The mortality rate in patients with end-stage renal disease (ESRD) is about 10 – 20 times higher than in the age-matched general population (1,2). Despite substantial improvements in the science and technology of peritoneal dialysis (PD), the mortality rate in PD patients remains at this high level.

Although several factors contribute to the high mortality in PD patients, cardiovascular disease (CVD) is by far the most common direct cause of death in these patients (3,4). The increased CVD mortality rate in PD patients may have many causes. Recently, it has been suggested that malnutrition and inflammation are strongly associated with CVD (5–7). We have proposed that malnutrition is, in part, the consequence of heart disease (cardiac failure), or is caused by infection/inflammation, which also triggers the development of atherosclerotic cardiovascular disease, contributing to high mortality (5). Stenvinkel et al (6,7) suggested that a syndrome consisting of malnutrition, inflammation, and atherosclerosis—“MIA”—may be responsible for most premature deaths in ESRD patients (8).

It is now clear that peritoneal permeability is another factor associated with CVD. Several studies have reported that increased peritoneal membrane transport is associated with high mortality in PD patients (3,9–12). These studies partly imply that fluid overload, resulting from insufficient fluid removal in high transporters, may magnify the cardiovascular problems that these patients already have (11,13–16). However, peritoneal transport rate often
changes after initiation of PD (10,17–19), indicating that chronic PD (using bioincompatible PD solutions) may induce peritoneal membrane alterations. Furthermore, malnutrition (20–23) and inflammation are present in a large proportion of dialysis patients (24–27), and both are powerful predictors of patient survival.

Peritoneal membrane transport appears to be an important determinant not only of nutritional status but also of clinical outcome (28). For PD to be successful as long-term therapy, strategies that preserve adequate peritoneal membrane function must be developed (28). Therefore, it is not surprising that the new PD solutions are eliciting considerable interest, considering that they may be more suitable for preserving peritoneal membrane function and perhaps preventing MIA syndrome in PD patients.

The purpose of this report is to review the pathophysiological mechanisms of peritoneal membrane alterations in long-term PD patients; to look at the possible relationship between these alterations and malnutrition, inflammation, and atherosclerosis; and to discuss what can be achieved with the new solutions in terms of preservation of peritoneal membrane structure and function, and prevention of MIA syndrome (Figure 1). The present review is therefore focused less on the local effects of bioincompatibility of PD solutions and more on the possible systemic effects of poor biocompatibility of "old" PD solutions. Finally, we underline that hope now exists that the improved biocompatibility of the new PD solutions can improve clinical outcome for PD patients. This improvement should be the focus of many studies during the coming years.

PATHOPHYSIOLOGICAL MECHANISMS OF PERITONEAL MEMBRANE ALTERATIONS IN LONG-TERM PD PATIENTS

Glucose Induces Peritoneal Membrane Alterations: Conventional PD solutions contain glucose as an osmotic agent at supraphysiologic concentrations (75 – 214 mmol/L), and the peritoneal membrane is continuously exposed to them. Moreover, approximately 75% of the initial intraperitoneal glucose load is absorbed during a 6-hour dwell (29). Thus, not surprisingly, pathophysiological alterations in the peritoneal membrane of long-term PD patients are similar to those seen in diabetic angiopathy. Several studies showed glucose-induced diabetic alterations in the peritoneal microvasculature, such as reduplications of the capillary basement membrane (30) and a marked increase in the number of microvessels (31) with deposition of collagen IV (31,32).

Glucose is associated with the stimulation of growth factors, such as vascular endothelial growth factor (VEGF) (33) and transforming growth factor β1 (TGFβ1) (34–37), leading to peritoneal neoangiogenesis with deposition of extracellular matrix (ECM) (37,38). Vascular endothelial growth factor is the most important growth factor involved in the neoangiogenesis of diabetic retinopathy (39), and TGFβ1 is a key factor in the development of diabetic complications.

Figure 1 – Possible local and systemic effects of peritoneal dialysis solutions, and relationships between peritoneal membrane alterations and pathophysiological changes in the patient.
mediator in the ECM proliferation in diabetic nephropathy (40).

Zweeken et al (33) reported local production of both VEGF and TGFβ1 in the peritoneal membrane of long-term PD patients, and significant correlations of VEGF levels with the mass transfer area coefficient for creatinine and with transcapillary ultrafiltration rate. Ha and Lee (37) found that high glucose upregulated monocyte chemotactic peptide 1, TGFβ1, fibronectin synthesis, and generation of reactive oxygen species.

On the other hand, leptin has been shown to play an important physiological role as an angiogenic factor (41,42). Bouloumié et al (42) reported that chronic oxidative stress in endothelial cells under hyperleptinemia may activate atherogenic processes and contribute to the development of vascular pathology. It is also possible that elevated serum leptin during PD (43,44) may contribute to both malnutrition and angiogenesis, as leptin may have an important physiological role as an angiogenic factor (41,42).

Peritoneal accumulation of advanced glycosylation end-products (AGEs) has been also found in continuous ambulatory peritoneal dialysis (CAPD) patients (45–47). Although little is known about a causal relationship between glucose-based PD solutions and AGE formation, glucose reacts non enzymatically with amino groups to produce cross-linking moieties and AGEs (48). The rate of protein cross-linkage is markedly dependent on glucose concentration (49). The AGEs act to produce complex vascular alterations closely resembling diabetic vasculopathy (50). It has been shown that AGEs are dominantly accumulated in the vascular wall (45) and that accumulation of AGEs is associated with the development of interstitial fibrosis and microvascular sclerosis (51).

Glucose degradation products (GDPs), generated during heat sterilization and storage of PD solutions, are considered to contribute to alterations in the peritoneal membrane by various mechanisms. Single GDPs or combinations of GDPs not only have significant cytotoxic effects on peritoneal cell function (52–54), they also accelerate AGE formation (53). It has been suggested that more than 70% of the measured formation of AGEs may be a consequence of GDPs present in PD solutions (53) and that the AGE formation triggered by glucose-based PD solutions may be related to the presence of GDPs rather than to glucose itself (55,56).

Inflammation Induces Peritoneal Membrane Alterations: It is well documented that peritoneal inflammation plays a major role in peritoneal membrane alterations. Peritonitis is one of the challenges to peritoneal membrane viability (17,57–59). However, study results regarding the relationship between peritonitis and peritoneal membrane alterations are controversial. Selgas et al (57) reported that the high rate of accumulated days of peritoneal inflammation is related to significant functional change in the peritoneum. Other investigators found that severe and multiple peritonitis episodes cause changes in peritoneal function (17), while a single peritonitis episode does not (17,58). Selgas et al (59) also demonstrated that late, mild peritonitis has distinct consequences for peritoneal function as compared with early peritonitis.

Although it is difficult to answer the question about the extent to which peritonitis is involved in peritoneal membrane alteration, local release of cytokines owing to various stimulations—such as infection or exposure to bioincompatible PD solutions—are known to be associated with peritoneal membrane alterations (60). Yang et al (61) reported that that interleukin-1β (IL-1β) stimulated the production of ECM in cultured human peritoneal mesothelial cells, and induced morphologic changes. Kang et al (36) demonstrated that the state of chronic induction of TGFβ1 is further exacerbated in the presence of peritonitis because of the stimulatory effect of pro-inflammatory cytokines.

It follows from the aforementioned facts that peritonal membrane alterations have been linked to the bioincompatible nature of PD solutions, with the resulting exposure to high concentrations of glucose, GDPs, and other factors (such as peritonitis) that stimulate release of cytokines (Figure 2). However, it should be noted that the important pathogenetic roles of glucose and inflammation do not exclude an important additive contribution of low pH, hyperosmolarity, and high lactate concentration in the “old” PD solutions as reviewed previously (62,63).

RELATIONSHIP BETWEEN MALNUTRITION, INFLAMMATION, AND ATHEROSCLEROSIS

Inflammation Causes Malnutrition: Although several factors contribute to the nutritional status of PD patients, inflammation, which is a consequence of several factors (as shown in Table 1), may be an important cause of malnutrition. Many studies report a negative correlation between serum albumin and inflammatory markers (64–66). Still, it should be noted that serum albumin is far from ideal as a nutritional marker (5). Qureshi et al (67) reported that elevated serum C-reactive protein (CRP) not only was associated with hypoalbuminemia, but that it also was more common in malnourished patients as assessed by subjective global assessment of nutritional status.

The reason for this association is that inflammation may have direct effects on nutritional status, nutritional intake, and utilization of various substrates—the result being decreased muscle and fat mass, and alterations in serum protein composition.
Pro-inflammatory cytokines have been proposed to inhibit feeding by causing a decrease in gastric motility and emptying, and a decrease in intestinal motility; by modifying gastric secretion; and by eliciting taste aversion (69). Indeed, several animal studies have demonstrated that cytokines raise leptin mRNA levels (70–72). This rise may contribute to anorexia, suggesting that inflammation may cause anorexia by a stimulatory effect on serum leptin.

Stenvinkel et al (73) found that increases in serum leptin levels are associated with elevated serum CRP levels, and decreased lean body mass. On the other hand, cardiac disease may also lead to malnutrition (81), as has been demonstrated in dialysis patients (67,82). Suliman et al (82) reported a higher prevalence of malnutrition and hypoalbuminemia in patients with CVD.

However, it is not clear how cardiac disease, hypoalbuminemia, and malnutrition in ESRD patients are interrelated (5). Although the relationship between CVD and malnutrition has not been clearly established, it has been demonstrated that patients with CVD have increased levels of pro-inflammatory cytokines (83–85), suggesting that the development of malnutrition in CVD patients may be associated with cytokine activation, resulting in suppression of appetite, muscle proteolysis, and hypoalbuminemia. Thus, malnutrition and hypoalbuminemia in ESRD patients may be a consequence of heart disease.

**Relationship Between Malnutrition, Inflammation, and Atherosclerosis:** Inflammation plays an important role in the evolution of atherosclerotic lesions (87). In a study of pre-dialysis patients, Stenvinkel et al (6) found strong associations between inflammation, elevated plasma levels of lipoprotein(a) and fibrinogen, increased carotid intima-media area, and presence of carotid plaques. In addition, Kim et al (88) stated that the association of high levels of fibrinogen and plasminogen activator inhibitor type 1 with lipid disorders may be of importance in the development of atherosclerosis in CAPD patients.

Inflammation is also associated with reduced energy expenditure. In general, increased resting energy expenditure was reported in patients with wasting disorders (75–78). Nguyen et al (77) found that, in chronic obstructive pulmonary disease patients, resting energy expenditure is related to plasma TNFα concentration, but is independent of parameters of respiratory function. Ikizler et al (79) observed increased energy expenditure in uremic patients. On the other hand, Schneeweiss et al (78) reported that renal failure has no influence on energy expenditure as long as septicemia is absent. Nevertheless, inflammation may be an important cause of wasting related to energy expenditure in ESRD patients.

**Chronic Heart Failure May Cause Malnutrition:** It is well appreciated that hypoalbuminemia and malnutrition per se may be risk factors for cardiac disease. Foley et al (80) reported that, among PD patients, a 10 g/L fall in mean serum albumin was independently associated with progression of left ventricular dilatation, the development of de novo cardiac failure, and high mortality. On the other hand, cardiac disease may also lead to malnutrition (81), as has been demonstrated in dialysis patients (67,82). Suliman et al (82) reported a higher prevalence of malnutrition and hypoalbuminemia in patients with CVD.

**TABLE 1 Potential Causes of Inflammation in Peritoneal Dialysis (PD) Patients**

<table>
<thead>
<tr>
<th>General causes</th>
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<tr>
<td>Reduced renal clearance of cytokines</td>
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<tr>
<td>Chronic heart failure</td>
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<tr>
<td>Atherosclerosis per se</td>
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<tr>
<td>Various inflammatory conditions</td>
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<tr>
<td>Unrecognized persistent infections</td>
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<tr>
<td>PD-related causes</td>
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<tr>
<td>Peritonitis</td>
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<tr>
<td>Bioincompatibility</td>
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<tr>
<td>Exposure to endotoxins and other cytokine-inducing substances from contaminated dialysate</td>
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Pro-inflammatory cytokines have been proposed to inhibit feeding by causing a decrease in gastric motility and emptying, and a decrease in intestinal motility; by modifying gastric secretion; and by eliciting taste aversion (69). Indeed, several animal studies have demonstrated that cytokines raise leptin mRNA levels (70–72). This rise may contribute to anorexia, suggesting that inflammation may cause anorexia by a stimulatory effect on serum leptin. Stenvinkel et al (73) found that increases in serum leptin levels are associated with elevated serum CRP levels and a decrease in lean body mass. Aguilera et al (74) reported that PD patients with anorexia, or anorexia with nausea or vomiting, had higher plasma levels of tumor necrosis factor α (TNFα) than did patients without these symptoms.

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observed that pro-inflammatory cytokines induce transient and reversible endothelial dysfunction. Sinisalo et al (89) reported that the concentration of serum CRP was an independent determinant of endothelium-dependent vascular function. Similarly, Cleland et al (90) found a relationship between elevated serum CRP and basal endothelial nitric oxide synthesis.

Recent data indicates that increased oxidative stress, an important co-factor for development of atherogenesis and endothelial dysfunction, occurs in malnourished (92) and inflamed patients (6). Stärwinkel et al reported that, in pre-dialysis patients, malnourished patients show reduced plasmalogen levels in erythrocyte membranes (92) and a positive correlation exists between CRP and oxidized low-density lipoprotein (6). Thus, it is likely that, during malnutrition, increased oxidative stress in combination with chronic inflammation may lead to an increased risk of atherosclerotic cardiovascular disease. On the other hand, it is also possible that increased production of cytokines during oxidative stress could result in an acute-phase response.

It could therefore be argued that increased levels of pro-inflammatory cytokines are closely linked to malnutrition, inflammation, and atherosclerotic cardiovascular disease in PD patients as well as in ESRD patients (Figure 2).

INFLUENCE OF NEW PD SOLUTIONS ON THE PERITONEAL MEMBRANE AND MIA SYNDROME

Amino Acid-Based PD Solution: It is well known that using amino acid-based PD solutions can correct protein malnutrition and replace amino acids lost during PD (93–96). Evidence exists for a significant increase in nitrogen balance (95,96) and biochemical markers of nutrition (93,96) after treatment of malnourished CAPD patients with one or two exchanges of 1.1% amino-acid PD solution. Furthermore, the amino-acid solution is efficaciously utilized for protein synthesis in CAPD patients, with no effect on protein breakdown (97).

In general, the use of amino acid-based PD solutions results in no or only slight peritoneal membrane alteration. Although a tendency toward an increased transport rate exists (93,96), the use of amino-acid solution is beneficial because it reduces exposure to glucose and improves the biocompatibility of the solution owing to a relatively high pH (98). A recent study revealed in vivo the benefit of amino-acid solutions, presenting practically no mesothelial damage, no submesothelial fibrosis, and no vascular alterations in a 60-day rabbit dialysis model (99).

However, minor dose-dependent episodes of nausea, vomiting, and unspecific gastrointestinal symptoms and an expected increase in serum urea and metabolic acidosis have been reported with the use of amino acid-based solution (93,96). To prevent these symptoms, patients receiving amino-acid solution should be monitored, and oral alkalizing agents, such as sodium bicarbonate, should be used as needed (94,96). The use of multiple exchanges should be avoided. Nevertheless, once-daily use of an amino-acid-based solution can be expected to contribute to the prevention of malnutrition and to the better preservation of the peritoneal membrane.

Bicarbonate-Buffered PD Solution: The recent advent of PD solutions containing bicarbonate at a physiologic pH has been made possible by the introduction of improved manufacturing and sterilization processes and the use of double-chambered bags. The neutral pH, bicarbonate/lactate-buffered or bicarbonate-buffered solutions have better biocompatibility than conventional, acidic, lactate-buffered solutions with regard to mononuclear cytokine release and viability (100) and improvement of bactericidal activities of neutrophils, macrophages, and mesothelial cells (101–104). Moreover, bicarbonate/lactate-buffered or bicarbonate-buffered solutions are effective in reducing infusion pain, which is the most direct and immediate clinical consequence of the biocompatibility of low pH, lactate-buffered solutions. The bicarbonate/lactate solution is the most effective, as assessed with a verbal rating scale and a validated McGill pain questionnaire (105). Reduced GDPs were also observed in double-chambered PD solutions with a high pH (106); the impact on biocompatibility was shown by increased cancer antigen 125 concentrations in overnight fluid and no change in hyaluronic concentrations (107). However, a reduction in the rate of peritonitis with such solutions remains to be demonstrated.

Metabolic acidosis is a common problem in ESRD patients. It is the only identified toxic factor that stimulates protein catabolism and increases protein degradation, producing muscle wasting and a negative nitrogen balance (108). After correction of metabolic acidosis, decreases in protein degradation (109–111) and amino acid oxidation (109) have been demonstrated in ESRD patients. The use of bicarbonate-buffered or bicarbonate/lactate-buffered solutions is also effective for correction of metabolic acidosis (112). Thus, the new bicarbonate/lactate-buffered solutions may have several positive local and systemic effects.

Icodextrin-Containing PD Solutions: The increasing interest in icodextrin-containing solutions is mainly due to the beneficial effect on sustained ultrafiltration for long dwells in PD. Congestion owing to chronic fluid overload is common in PD patients.
and chronic congestive heart failure is associated with elevated levels of pro-inflammatory cytokines (114). In fact, Niebauer et al recently showed that diuretic treatment controlling volume status in chronic heart failure patients was associated with a significant decrease in systemic endotoxin levels (114). Thus, it could be speculated that rigorous control of volume status is very important to optimize cardiac performance, which, in turn, may help to prevent MIA syndrome. The use of icodextrin for the long dwell can improve fluid balance (115–118) and blood pressure control (118). Moreover, during peritonitis, the use of icodextrin is also of benefit, as it may lead to an increase in ultrafiltration volume (119,120), possibly due to a larger vascular surface area and to increased degradation of icodextrin and a faster increase in dialysate osmolality (120).

The use of icodextrin solution may reduce peritoneal membrane alterations because of decreased AGE and GDP formation (121,122). A recent study showed an in vitro effect of icodextrin solution on phagocytic function; the effect was attributed to the low osmolality of the solution (123). Therefore, the use of icodextrin-containing PD solution may not only help to prevent chronic heart failure and hypertension, but it may also better preserve peritoneal membrane viability and function.

Association Between PD Solutions and Appetite: Although several factors may contribute to anorexia in PD patients, absorption of osmotic agents and other substances from the PD fluid may be involved. Recently, using animal appetite models, hypophagia induced by PD solutions (owing to utilization of absorbed nutrients from the solutions) has been emphasized by our group and other authors (124–127). The inhibition of appetite caused by PD solutions may be specific for each nutritional constituent and not simply an effect of hyperosmolality or a large dialysate fill volume (125). More recently, we found that Nutrineal and Dianeal (Baxter Healthcare Corporation) inhibited intra-oral intake and that the degree of appetite inhibition was higher with a higher concentration of glucose. Furthermore, Physioneal solution had less impact on appetite than Dianeal solution, while Extraneal solution had no impact on appetite (126). We also observed that GDPs in the PD solution are probably involved in the suppression of appetite and that the degree of inhibition is proportional to pH and glucose concentration during heat sterilization (127).

Therefore, one may speculate that the concentration of nutrients such as glucose, amino acids, and lactate in the solutions may play a key role in the regulation of appetite. In addition, factors such as pH and hypertonicity may possibly be of importance. Finally, dialysate GDPs, perhaps more than hypertonicity and glucose per se, seem to play a pivotal role in appetite inhibition (127). However, the clinical relevance of these experimental results is not yet clear; further studies are needed.

Hyaluronan as an Additive to Peritoneal Dialysis Solutions: Hyaluronan (HA) is a major component of the interstitial tissues. It plays an important role in tissue hydraulic conductivity. Recently, an acute animal model of PD described that the addition of HA could significantly reduce fluid absorption from the peritoneal cavity, thereby improving fluid removal by PD (128,129). Furthermore, the use of HA in PD solutions may have a protective effect against peritoneal injury (130). Addition of HA to PD solutions may soon become a reality, provided that clinical studies confirm the results from the animal studies. Fluid re-absorption from the dialysate is a slow but continuous process; if the rate of this flow could be reduced by just 0.5 mL/min, the additional fluid removal would be 720 mL in 24 hours. This additional fluid removal would have a marked effect on fluid balance and blood pressure control in PD patients. However, regulatory requirements mean that many years are likely to pass before this possible improvement will become routine clinical practice.

CONCLUSIONS

The recent introduction of new, more biocompatible PD solutions represents a significant improvement in PD. These solutions may first of all reduce the negative impact of high glucose, high lactate, high GDPs, and low pH on peritoneal membrane viability. If this local effect can prevent peritoneal membrane alterations leading to an increased peritoneal transport rate, then the impact on clinical outcome via improvements in fluid and solute removal would be significant, and the mortality caused by MIA syndrome might be reduced. In addition, the possible systemic effects of the new solutions—in the form of improved nutrition, decreased inflammatory stimuli, and improved fluid removal during the long dwell—could also have a significant impact on MIA syndrome, helping to reduce the mortality in cardiovascular disease. There is now time to study the combined effects of the new solutions on cardiovascular morbidity and mortality in PD patients. Furthermore, the possible future use of hyaluronan as an additive may produce improvement in fluid balance, peritoneal viability, and patient survival. With these changes, the future of PD looks very promising indeed. In the coming years, we will hopefully see many studies evaluating the possible positive effects of the new solutions on both PD patient retention and survival.
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