Peritoneal Dialysis Solutions

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Keywords
Peritoneal dialysis solution • Fluid composition • Biocompatible PD

Introduction

PD has traditionally been performed with acidic solutions containing glucose as osmotic and lactate as buffer agent. These solutions confer marked local and systemic toxicity (Fig. 12.1). Within few years, the peritoneal membrane undergoes profound morphological transformations including progressive mesothelial denudation, submesothelial fibrosis, hyaline vasculopathy, and neoangiogenesis [1]. Hypervascularization of the peritoneal membrane results in increased solute clearance, but also in rapid glucose uptake and thus ultrafiltration loss and eventually PD failure [2]. Peritonitis episodes, chronic inflammation, and a persistently elevated calcium* phosphate product further accelerate membrane transformation, which in severe cases results in life-threatening, encapsulating peritoneal sclerosis. Even though most patients will not develop these complications if early transplantation is available, they still represent a major clinical problem on a global scale as reflected by the limited long-term technique and patient survival [3]. In recent years, PD solutions with a markedly improved biocompatibility profile have been developed to remedy this problem. They which are gradually becoming available for routine patient care around the globe. These "biocompatible" solutions allow for a refined and individualized therapy with a significantly reduced toxin load. Knowledge of the specific features of each solution is necessary to provide a most efficient and biocompatible PD regimen.

*The askerik denotes the calcium -phosphate product, i.e. the multiplication of both serum concentrations. This product is highly relevant and often used in nephrology publications

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PD Fluid Composition

Peritoneal dialysis fluids are composed of an osmotic agent, a buffer substance, and electrolytes, which determine their purification and ultrafiltration capacity as well as clinical tolerability.

Osmotic Agents

The standard osmotic agent is glucose at supraphysiological concentrations (1,500–4,250 mg/dL). The high dialysate glucose concentration creates an osmotic gradient via the peritoneal mem-

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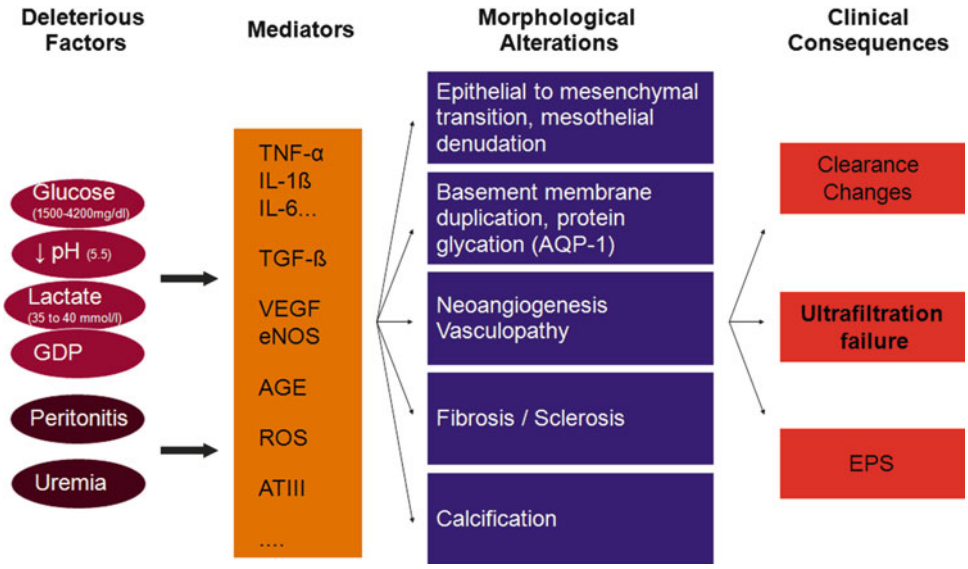

Fig. 12.1 PD fluid toxicity and associated morphological and functional alterations. *AGE* advanced glycated endproducts; *ROS* reactive oxygen species; *AQP-1* Aquaporin 1; *EPS* encapsulating peritoneal sclerosis; *GDP* glucose degardation product

brane to achieve ultrafiltration. On the other hand, the hyperosmolar and hyperglycemic milieu, is also a major driving force for the peritoneal membrane transformation and progressive increase in peritoneal solute transport rates [4]. Depending on the transporter status, from low to high, 45–88% of the intraperitoneal glucose is absorbed within 4 h. While providing some usually welcome additional calorie supply, glucose resorption is the rate-limiting factor for ultrafiltration capacity.

Moreover, sterilization of the glucose at high temperature and a relatively high pH (5.5) as well as prolonged storage promotes the generation of numerous glucose degradation products (GDP), such as formaldehyde, acetaldehyde, 3-deoxyglucosone (3-DG), 3,4-dideoxyglucosone (3,4-DGE), and 5-hydroxymethyl furaldehyde (5-HMF). GDP impair peritoneal mesothelial cell function [5], induce pro-angiogenetic factors such as VEGF [6] and impair local host defense mechanisms [7]. They are rapidly absorbed via the peritoneal membrane [8] and contribute to inflammation, fibrosis, and vasculopathy. GDP are potent precursors for advanced glycation endproduct (AGE) formation. AGE accumulate in the PD membrane but also in the entire body [9], and further accelerate the process of vascular and tissue aging (Fig. 12.2).

Based on these deleterious effects of glucose, three alternative technological measures have been realized to improve PD fluid biocompatibility: the separation of glucose at a very low pH from the buffer in double- and triple-chamber bag systems; the replacement of glucose by icodextrin, a glucose polymer derived from stark; and the replacement of glucose by amino acids. All these solutions contain significantly less GDP than conventional dextrose-based fluids (Tables 12.1 and 12.2) [10, 11].

Buffer Substances

Lactate has been the only buffer available for PD fluids until recently. It is added to PD solutions at concentrations far above the physiological range (Table 12.1), is rapidly absorbed via the peritoneal membrane and is metabolized to bicarbonate in the liver. The net buffer gain is counterbalanced by the simultaneous loss of blood bicarbonate into the dialysate [12]. In vitro and animal studies have provided ample evidence that the high amounts of lactate, present in conventional PD solutions at a low pH, have detrimental effects on peritoneal mesothelial cells. Lactate alters specific cytokine release [13], reduces the avail-

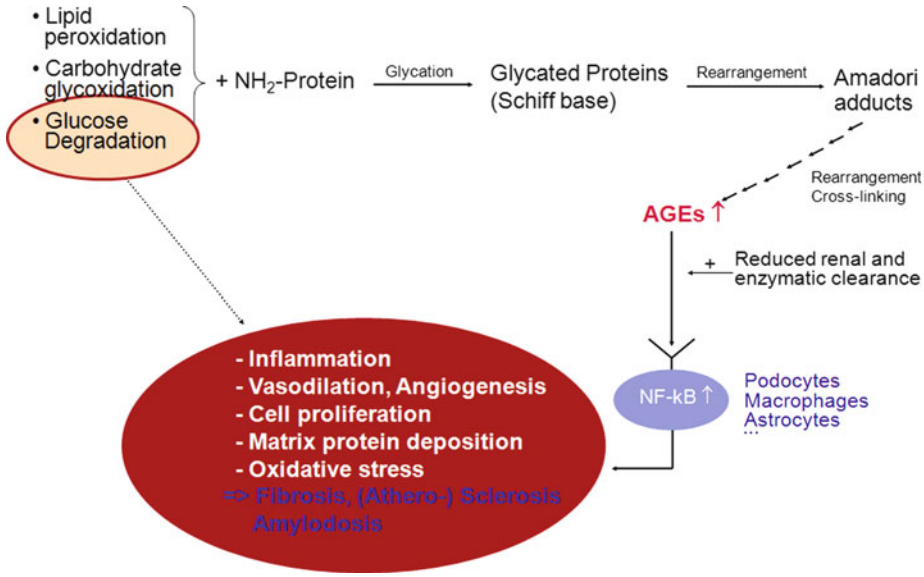

Fig. 12.2 Deleterious effects of glucose degradation products (GDP) and advanced glycation endproducts (AGE) in PD patients. PD fluids accelerate the aging process by delivery of glucose degradation products, which act directly and indirectly via enhanced generation of AGE on the peritoneum membrane but also systemically

Table 12.1 Composition of conventional, single-chamber PD solutions

	CAPD 2/3/4 17/18/19	Dianeal PD 1, PD2[a], PD4	Gambrosol 10/40
Sodium (mmol/L)	134	132	132
Chloride (mmol/L)	102.5	102/96/95	96/95
Calcium (mmol/L)	1.25/1.75	1.75/1.75/1.25	1.75/1.35
Magnesium (mmol/L)	0.5	0.75/0.75/0.25	0.25
Glucose (%)	1.5/2.3/4.25	1.36/2.27/3.86	1.5/2.5/4.0
Osmolarity (mosmol/L)	356–509	344–486	353–492
Lactate (mmol/L)	35	35/40/40	40
pH	5.5	5.5	5.5
Formaldehyde (μmol/L)[b]	5.4 ± 0.4	6.8 ± 0.2	6.4 ± 0.5
3,4 DGE (μmol/L)[b]	16.2 ± 0.8	11.3 ± 0.5	13.1 ± 1.1
Bag size (L)	1.5/2/2.5	1.5/2/2.5/3/5 (APD)	0.5/1/1.5/2/2.5/3 (G40)/4.5/5

GDP concentrations taken from Ref. [10], for Gambrosol 10/40 from Ref. [11]
[a]Not available in all countries
[b]At medium glucose concentration

ability of antioxidants such as gluthatione [14] and induces neoangiogenesis [15]. Adjustment to a physiological pH markedly improves but does not normalize the ex vivo viability and function of mesothelial cells [16, 17]. In patients with acute renal failure, especially when in poor tissue perfusion states such as shock, lactate acidosis and multiorgan dysfunction, lactate inadequately buffers metabolic acidosis. This is especially true in patients with impaired hepatic metabolism.

Dialysis fluids containing bicarbonate, the physiological buffer of the blood, have been demonstrated to improve the outcome of patients who require acute dialysis [18, 19]. Bicarbonate-based PD solutions used to require local manufacturing and rapid consumption due to the ready dissociation of HCO_3 to gaseous CO_2 [20]. In recent years, advances in foil technology have made it possible to produce industrially manufactured, stable PD fluid bags containing either pure bicarbonate or a mixture of bicarbonate and lactate buffer (Table 12.2). Superior control of metabolic acidosis has been demonstrated for the pure 34 mmolar bicarbonate solution and

Table 12.2 Composition of biocompatible PD solutions

	BicaVera	Balance	Gambrosol trio 10/40	Physioneal 35/40	Extraneal (7.5% Icodextrin)	Nutrineal (1.1%AS)
Sodium (mmol/L)	132	134	132[b]	132	132	132
Chloride (mmol/L)	104.5	100.5	96[b]	101/95	96	105
Calcium (mmol/L)	1.75	1.25/1.75	1.75/1.35[b]	1.75/1.25	1.75	1.25
Magnesium (mmol/L)	0.5	0.5	0.25[b]	0.25	0.25	0.25
Glucose (%)	1.5/2.3/4.25	1.5/2.3/4.25	1.5/2.5/3.9	1.36/2.27/3.86	0	0
Osmolarity (mosmol/L)[a]	358–511	358–511	356–483	344–484	284	365
Lactate (mmol/L)	0	35	40[b]	10/15	40	40
Bicarbonate (mmol/L)	34	0	0	25/25	0	0
pH	7.4	7.0	5.5–6.5[a]	7.4	5.5	6.7
Formaldehyde (μmol/L)[b]	<3.3	<3.3	<3.3	3.4±0	3.6±0.7	n.d.
3,4 DGE[b] (μmol/L)	<2.4	<2.4	<2.4	14.3±2.5	<2.4	n.d.
Bag size (L)	2/2.5/3 (APD)	2/2.5/3 and 5 (APD)	2/2.5/5 (APD)	1.5/2/2.5/5 (APD)	2.0 and 2.5	2.0

GDP concentrations taken from Ref. [10]
n.d. not done
[a]Low to high glucose concentration
[b]Medium glucose concentration

the 25/10 mmolar bicarbonate/lactate solution as compared to single-chamber, 35 mmolar lactate PD fluid [21, 22]. Overcorrection to metabolic acidosis may occur with very frequent cycles and with higher dialysate buffer content [23]. *Pyruvate*, a natural radical scavenger with buffer capacity, might be an attractive alternative buffer agent but thus far has only been investigated in experimental settings [24].

Electrolytes

Sodium, chloride, calcium, and magnesium are added to the PD solutions to maintain mineral homeostasis. *Sodium chloride* balance is closely related to the ultrafiltration rate. Depending on dwell time and the relative contribution of free water transport via aquaporin-1 in the early phase of a dwell, more than 100 mmol of sodium per liter ultrafiltrate can be lost. In infants, the relatively higher ultrafiltration rates may therefore result in reduced total body sodium chloride content, hypovolemia, and hypotension. Since the losses are isotonic, sodium depletion is commonly not associated with hyponatremia; rather, nocturnal hypotension and tachycardia may be the first symptoms of sodium chloride deficiency. Sodium chloride supplementation is mandatory in these patients. Only if dwell time is very short and dialysate glucose concentration is high, as for example required in severely volume overloaded patients, aquaporin-1 mediated free water transport predominates. Since the drained dialysate sodium mass is low in these cases ("sodium sieving"), relative body sodium concentrations increase and results in third. The third scenario usually affects older children and adults who are typically salt and thus water overloaded due to poor dietary adherence, especially if anuric. In these patients, the complementary use of icodextrin solution has proven beneficial (see below). Sodium balance, hydration status, and blood pressure might also be improved by low sodium dialysate solutions, which have shown promising results in clinical studies [25, 26] but have not yet been admitted to the market.

Optimal *calcium* control, i.e., serum levels in the lower normal range, is crucial for bone and vascular health. Dialysate calcium concentrations range from the physiological 1.25 mmol/L, which usually allows for a calcium neutral dialysis, unless ultrafiltration occurs, to 1.75 mmol/L, which results in a positive calcium balance. The net dialytic calcium balance can be estimated from the dialysate turnover and the difference between PD fluid and effluent calcium concentrations and the calcium losses via the ultrafiltrate. It adds to the total body calcium balance determined by urine losses and intestinal absorption from nutrients and phosphate binders and modified by vitamin D treatment. While calcium balance should be mildly positive to meet the mineral requirements of a growing child, routine administration of 1.75 millimolar PD fluid will result in calcium overload in most children. The use of solutions containing 1.0 mmol/L calcium leads to aggravated secondary hyperparathyroidism and have become dispensible with the advent of calcium-free phosphate binders [27]. Since *magnesium* accumulates in advanced CKD, dialysate magnesium concentrations are low to low normal relative to serum concentrations (Tables 12.1 and 12.2). Harmful effects of increased serum magnesium levels include altered nerve conduction velocity, pruritus, and altered bone and parathyroid gland function. On the other hand, hypermagnesemia may also slow vascular calcification rate. An inverse relationship between serum Mg, hyperparathyroidism, and vascular calcification has been demonstrated in adult dialysis patients [28, 29].

PD Fluid Types

Conventional PD Solutions

Single-chamber PD solutions allow for efficient ultrafiltration, transperitoneal solute transport, and, thus, blood purification. They, however, contain high amounts of toxic GDP and expose the patient to supraphysiological lactate concentrations at an unphysiologically low pH (Table 12.1). They impair peritoneal mesothelial cell function, local host defense [13, 14, 30, 31], and lead to largely irreversible alterations of PD membrane morphology and function within a few years of usage [1, 2, 15].

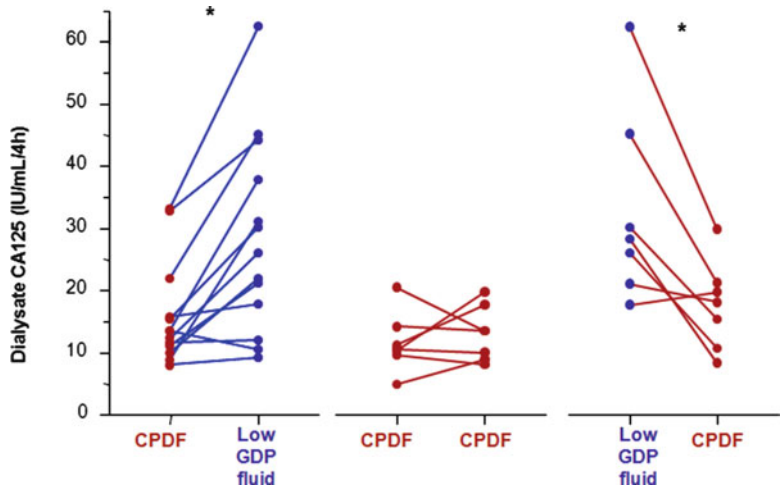

Fig. 12.3 CA125 effluent concentration in children treated with conventional (CPDF) and low GDP solution (BicaVera®). Twenty-eight children were randomly assigned to undergo 12 week treatment periods with low GDP solution followed by CPDF or vice versa. CA125 effluent concentrations, a marker of peritoneal mesothelial cell mass, increase with low GDP solution (*left*), remain low in patients who continue to receive CPDF, and decrease in children switched from low GDP fluid to CPDF (*right*) (With permission from Ref. [21])

Multi-Chamber PD Fluids

By separating the glucose at a very low pH in double- and triple-chamber bags, formation of GDP is markedly reduced. Most, albeit not all, of the solutions are buffered at neutral or even physiological pH with lactate, bicarbonate, or a mixture of both. Numerous experimental and clinical studies have demonstrated an improved biocompatibility profile of multi-chamber PD solutions.

In vitro, multi-chamber PD fluids improve mesothelial cell viability and function, preserve innate peritoneal immune defense mechanisms, and reduce the synthesis and secretion of cytokines related to inflammation, fibrosis, and angiogenesis [31–34].

Animal studies confirmed improved in vivo peritoneal host defense [35, 36], reduced peritoneal TGF-ß and VEGF expression, reduced deposition of AGE, preservation of the mesothelial cell layer, and markedly reduced fibrosis, vasculopathy and neoangiogenesis [37]. The acute peritoneal hyperperfusion observed with conventional solutions is largely prevented when perfusion is performed with multi-chamber PD fluid [38]. Finally, multi-chamber fluids have been associated with preserved ultrafiltration capacity in an experimental long-term dialysis model [39].

In humans, effluent CA125 concentration, a surrogate parameter of peritoneal mesothelial cell mass increases (Fig. 12.3), whereas the inflammation markers IL-6 and hyaluronic acid decrease [21, 40–43]. The effluent concentration of VEGF, a putative marker of peritoneal neoangiogenesis, decreased in some but not all studies [34, 42, 43]. Several prospective randomized trials demonstrate similar solute transport and ultrafiltration capacity in children and adults treated with multi-chamber as compared to conventional PD solutions [8, 21, 23, 44]. In case of reduced ultrafiltration rate, this was compensated by improved residual renal urine output [40, 45]. Indeed, residual renal function appears to be better preserved with multi-chamber PD fluids [46, 47], most likely due to reduced GDP resorption. GDP are toxic to podocytes and tubular cells [48]. Switch from conventional to low GDP solutions results in a peritoneal washout of AGE [49, 50] and a 15% decline in systemic AGE levels in children [8] and adults [41].

A relevant clinical benefit of multi-chamber PD fluids is likely but difficult to ascertain. An immediate advantage is the reduction of abdominal discomfort due to reduced inflow pain and intraperitoneal pressure [51, 52]. Some but not all groups observed a reduced overall peritonitis

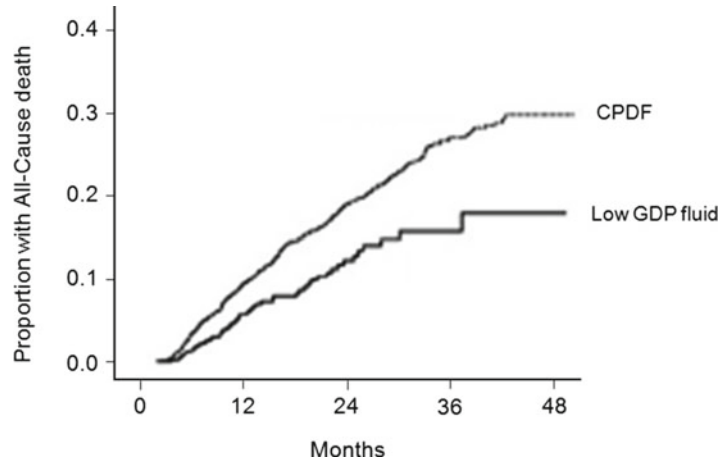

Fig. 12.4 Observational data on all-cause mortality in adult PD patients on low GDP solution (n = 1,621) and patients on conventional PD solution (CPDF, n = 542) suggesting improved patient survival with the low GDP solution ($p < 0.01$, With permission from Ref. [55]). This association is currently validated in prospective clinical trials

incidence in patients treated with PD solutions with reduced GDP content, new cyclers, and improved connection devices [53, 54]. Two large-scale registries demonstrate significant improvement of patient morbidity and mortality in adults using multi-chamber as compared to conventional fluids [55, 56] (Fig. 12.4). These promising findings have stimulated large-scale randomized comparative trials which are currently underway.

An interesting side note related to triple-chamber systems is the option to mix a hypoosmolar solution with 0.75% dextrose, which may be used for rehydration of dehydrated children.

Taken together, a plethora of beneficial effects has been demonstrated experimentally for low-GDP multi-chamber PD solutions, and evidence for relevant clinical benefits is beginning to emerge. It should be noted though that the different currently available solutions still differ considerably with respect to their GDP contents and final pH, obviously due to differences in the manufacturing process. Some manufactures reduced total GDP content by 50%, others by more than 90% compared to single-chamber PD fluid (Table 12.2) [10, 11]. The clinical impact of these differences has not yet been delineated.

Icodextrin Solution

Exposure to glucose at high concentrations confers some degree of toxicity to the peritoneum even in the absence of GDP. Therefore, a complementary research strategy besides minimization of GDP formation has been the search for alternative, less toxic osmotic agents. Icodextrin is derived from starch and consists of a mixture of glucose polymers with an 85% molecular weight range of 1.7–45 kD. The GDP content of the icodextrin solution is low, lactate concentration is 40 mmol/L at a pH of 5.5 (Table 12.2). Although the transperitoneal absorption rate is much lower than that of glucose, 40% of the icodextrin molecules are absorbed within 12 h [57]. Icodextrin is metabolized to maltose and its derivatives, which accumulate in the human body and increase serum osmolality by 5 mosmol/L [58]. A clinical impact of chronic maltose accumulation has not yet been discerned. After icodextrin discontinuation, the plasma levels of its metabolites return to baseline within 3–7 days [57].

Unlike the hyperosmolar, crystalloid osmotic gradient of glucose solutions, icodextrin solution is characterized by iso-osmotic, colloid osmotic ultrafiltration. This type of ultrafiltration is aquaporin-1 independent, i.e., sodium sieving does not occur. The ultrafiltration pattern is delayed as compared to glucose-containing PD fluids, with sustained net fluid withdrawal for more than 12 h (Fig. 12.5). Icodextrin should therefore be administered once daily during the long dwell.

Once daily administration of icodextrin increases sodium removal and improves the daily ultrafiltration rate and hydration status [58, 59],

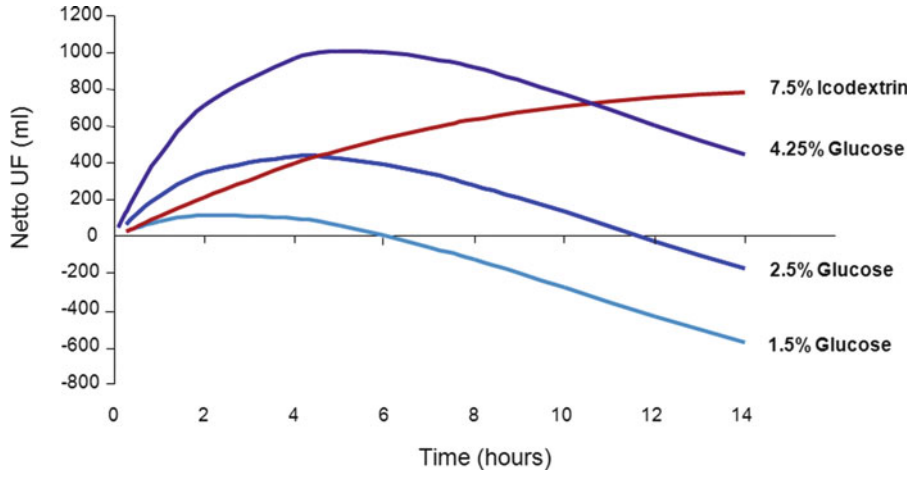

Fig. 12.5 Scheme of icodextrin and glucose-dependent ultrafiltration kinetics. Icodextrin induces relative slow, AQP-1 independent, but sustained ultrafiltration and should be used for a single long dwell

independent of the prevailing peritoneal transporter status [60]; blood pressure and left ventricular mass are improved within 3–6 months [61, 62].

The local and systemic glucose load is significantly reduced and the plasma lipid profile improves with icodextrin usage [63, 64]. In anuric APD patients, icodextrin administration during the daytime dwell preserves peritoneal membrane function as compared to patients receiving conventional, high GDP solution only [65].

In many centers, icodextrin is combined with conventional single-chamber PD solution. Whether long-term results are comparable to prescription of pH neutral, low GDP solutions only is yet unknown. Twice daily administration of icodextrin has been proposed in seriously hypervolemic patients [66]. Caution, however, is mandatory, since the metabolic impact of the additional icodextrin and oligosaccharide load is yet unknown.

Disadvantages of icodextrin solution concern the high lactate concentration and the low pH (Table 12.2). Allergic skin reactions to icodextrin and exfoliative dermatitis have been reported in up to 10% of the patients. Discontinuation of icodextrin usually is curative. In the past, aseptic peritonitis outbreaks were repeatedly noted with icodextrin fluid; these were mainly due to transient contamination with peptidoglycan, a bacterial membrane compound inducing local inflammation, which had escaped endotoxin testing [67]. The last published outbreak occurred in 2006 [68]. The reduced GDP content improves peritoneal host defense mechanisms in an ex vivo model, but not to a similar extent as double-chamber PD fluids [36].

Glucose-specific assays are required to measure serum glucose levels in patients treated with icodextrin since falsely increased plasma glucose determinations are obtained when glucose dehydrogenase-based (GDH PQQ) or glucose-dye-oxidoreductase-based methods are used. Total alpha-amylase activity is 75% lower in the serum of patients treated with icodextrin than in patients only treated with glucose solutions and 66% lower as compared to healthy subjects, for unknown reasons [69]. This needs to be considered if a pancreatic disease is suspected. Mild increases in serum GOT, GPT, and AP have been observed in 1–10% of the patients.

In summary, icodextrin solution has important advantages over conventional PD solutions with respect to sodium removal and ultrafiltration, which are particularly relevant in anuric subjects and those with a high peritoneal transporter status. In the future, the emergence of a high transporter status, and consequently the need for icodextrin treatment, is hoped to decline with the administration of biocompatible PD solutions from the very beginning.

Amino Acid Solutions

Amino acids are another alternative to glucose as osmotic agent. Amino acid–based PD solutions contain very low amounts of GDP [70] and allow for a phosphate-free amino acid supply. The solution is only slightly hyperosmolar, similar to 1.5% glucose solution, and contains 40 mmol/L of lactate at a slightly acidic pH of 6.7. Experimental studies, however, do not unequivocally support the notion of improved biocompatibility [37, 71]. Amino acids induce mesothelial NO production, a factor involved in neoangiogenesis [72], increase effluent IL-6 concentrations, a potential surrogate marker of inflammation [73], and suppress leukocyte recruitment in rats [36]. Long-term dialysis in rats, however, revealed only minor peritoneal changes and preserved ultrafiltration capacity, similar to double-chamber PD fluid [37]. In children and adults, solute and water transport is similar as compared to conventional, high GDP fluids [74, 75].

With respect to the nutritional effect of amino acid solutions, early studies yielded disappointing results with no improvement in anthropometric indices, increased serum nitrogen levels, and metabolic acidosis [76]. More recent stable isotope studies in adult CAPD patients using amino acid and glucose PD fluid exposure at a ratio of 1:4 yielded increased protein anabolism [77] and a 4% higher protein synthesis rate as compared to patients treated with a double-chamber PD solution only. Increases in serum nitrogen levels and metabolic acidosis were not observed, protein breakdown was not affected [78]. The anabolic effect was most pronounced in malnourished patients. This is in line with clinical observations in four malnourished patients followed over 3 years [75]. Outcome data from appropriately sized randomized controlled trials, however, are not yet available.

The limited anabolic effects of the relatively expensive solutions, concerns regarding their biocompatibility, and the usual achievement of adequate nutrition with enteral feeding thus far have prevented wider administration of amino acid–based PD fluids in children, although the concept is intriguing. The few pediatric reports available comprise ten patients or less and suggest good clinical tolerance and similar transport kinetics as compared to other solutions [74, 79–81].

Combination Therapies

Different combinations of biocompatible PD solutions are feasible, and the concept appears intriguing. Icodextrin can be administered together with multi-chamber PD fluids. Combination of icodextrin with multi-chamber PD and amino acid-based fluid has been advocated to substantially reduce glucose and GDP exposure, e.g., by 40–50% in patients on CAPD. While results from prospective, randomized controlled trials are not yet available, observational clinical reports suggest that the triple combination is safe and effective [82, 83] and may improve metabolic acidosis control [84]. The anecdotally reported overcorrection of metabolic acidosis [85] may be related to intensive PD protocols with frequent cycles and could probably be mitigated by choosing PD solutions with lower buffer content.

Perspectives

Biocompatible PD fluids and the new cycler systems are increasingly used in children with end-stage renal disease. According to the International Pediatric PD Network Registry, 60% of the PD children in Europe were treated with multi-chamber PD solutions with reduced GDP content in 2010, 15% with icodextrin solution (www.pedpd.org). Lower numbers have been reported for Asia (25% and 15%) and North America (10% and 17%). In face of the increasing scientific and clinical evidence of local and systemic benefits of these solutions, the associated increase in costs should be offset by reduced infectious complications [53, 54], improved long-term preservation of the PD membrane [37, 39, 65], improved cardiovascular health [61, 65, 66], and ultimately improved long-term patient survival (Fig. 12.6). Registry data support this assumption [55, 56] which is currently being tested in randomized clinical trials.

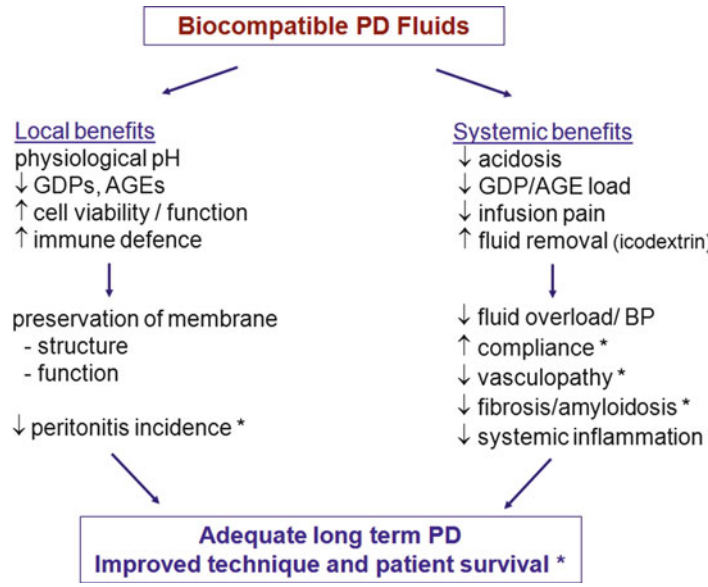

Fig. 12.6 Local and systemic benefits of biocompatible PD solutions. *Asterisks* indicate that only limited scientific evidence is available

Future prospects should include the complete replacement of glucose by a nontoxic (and thus GDP free), nonabsorbable osmotic agent. Several such agents are currently under investigation. To optimize mineral and acid base balance and thus to reduce CKD-MBD and cardiovascular sequelae, novel PD systems should furthermore allow for a more refined, continuous adaptation of electrolyte and buffer supply according to individual needs.

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