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New Fluids for Peritoneal Dialysis : why do we need them and what is it about?

(Nouvelles solutions pour la dialyse péritonéale : pourquoi en avons-nous besoin et de quoi s'agit-il ?)

Celeste Smeys[1,2], Freya Van Hulle[1,2], Florine Janssens[1,2], Karlien François[1,2]

[1]Département de néphrologie et d'hypertension artérielle, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Bruxelles, Belgique
[2]Unité de recherche sur les maladies rénales, la dialyse et la transplantation (NIER), Groupe de recherche Vitalité, Vrije Universiteit Brussel (VUB), Bruxelles, Belgique

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Summary

Peritoneal dialysis (PD) fluids generate concentration and osmotic gradients across the peritoneal membrane to remove uremic toxins and to achieve ultrafiltration. The use of current-era dialysis fluids also drives peritoneal and systemic pro-inflammatory, pro-fibrotic and pro-angiogenic processes that could be linked to patient outcomes. As the most frequent causes of PD technique failure are mortality, infections, insufficient solute clearance and ultrafiltration failure, it is important to reflect on the effects and modifiable power of the PD fluids' compositions.

This paper discusses the peritoneal and systemic effects of glucose-based PD fluids and the evidence on the use of icodextrin and amino-acid based alternatives. Recent innovations in PD fluids try to overcome the peritoneal and systemic toxicities of current formulations by using an alternative osmotic agent and/or by counteracting the metabolic effects of the carbohydrate load by the PD fluid.

Keywords: peritoneal dialysis, biocompatible solutions, glucose toxicity, xylitol, L-carnitine, alanine-glutamine

Résumé

Les solutions de dialyse péritonéale (DP) génèrent des gradients de concentration et d'osmose à travers la membrane péritonéale afin d'éliminer les toxines urémiques et de réaliser l'ultrafiltration. L'utilisation des solutions de dialyse actuelles entraînent également des processus péritonéaux et systémiques pro-inflammatoires, pro-fibrotiques et pro-angiogéniques qui pourraient être liés aux résultats des patients. Les causes les plus fréquentes d'échec de la technique de DP étant la mortalité, les infections, la clairance insuffisante des solutés et l'échec de l'ultrafiltration, il est important de réfléchir aux effets et au pouvoir modificateur des compositions des solution de DP.

Cet article traite des effets péritonéaux et systémiques des solutions de DP à base de glucose et des preuves de l'utilisation d'alternatives à base d'icodextrine et d'acides aminés. Les innovations récentes en matière de solutions de DP tentent de surmonter les toxicités péritonéale et systémique des formulations actuelles en utilisant un agent osmotique alternatif et/ou en contrecarrant les effets métaboliques de la charge en hydrates de carbone par la solution de DP.

Mots-clés : dialyse péritonéale, solutions biocompatibles, toxicité du glucose, xylitol, L-carnitine, alanine-glutamine

Correspondence : Pr Karlien Francois, courriel : Karlien.Francois@uzbrussel.be

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Introduction

Peritoneal dialysis (PD) fluids generate a concentration gradient across the peritoneal membrane allowing diffusion of uremic toxins from the patient's circulation towards the peritoneal cavity. Diffusion is a bi-directional process, hence, small molecules within the PD fluid will also be absorbed by the patient during a PD dwell. The osmotic gradient exerted by the PD fluid on the other hand allows water flux across the peritoneal membrane. The application of the physical principles of diffusion and osmosis by a PD fluid dwelling in the peritoneal cavity allows to manage clearance and volume status of the patient during PD.

PD offers similar overall survival compared to center-hemodialysis with a trend towards a survival advantage for patients treated with PD in the first years after dialysis start [1, 2]. Nevertheless, overall patient survival remains poor with survival probability of only 47% at 5 years after dialysis initiation [1]. Among patients surviving, PD technique failure is not uncommon with 1- and 2-year death-censored PD technique failure rates of 23% and 35% respectively in a contemporary European cohort [3]. Common causes of death-censored PD technique failure over time are infections, insufficient clearance and/or ultrafiltration problems [3].

This article describes the composition of PD fluids and their peritoneal and systemic effects. Although the primary goal of PD fluids is to serve solute removal and ultrafiltration, dialysis fluids also play a role in peritoneal membrane integrity, and systemic absorption of PD fluids influence systemic metabolic pathways. We discuss how novel developments in PD fluids overcome the downsides of current-era PD fluids and how PD fluids innovations aim to optimize the composite outcome of solute clearance, ultrafiltration, peritoneal membrane changes over time on PD and systemic effects by the PD fluid *(Figure 1)*.

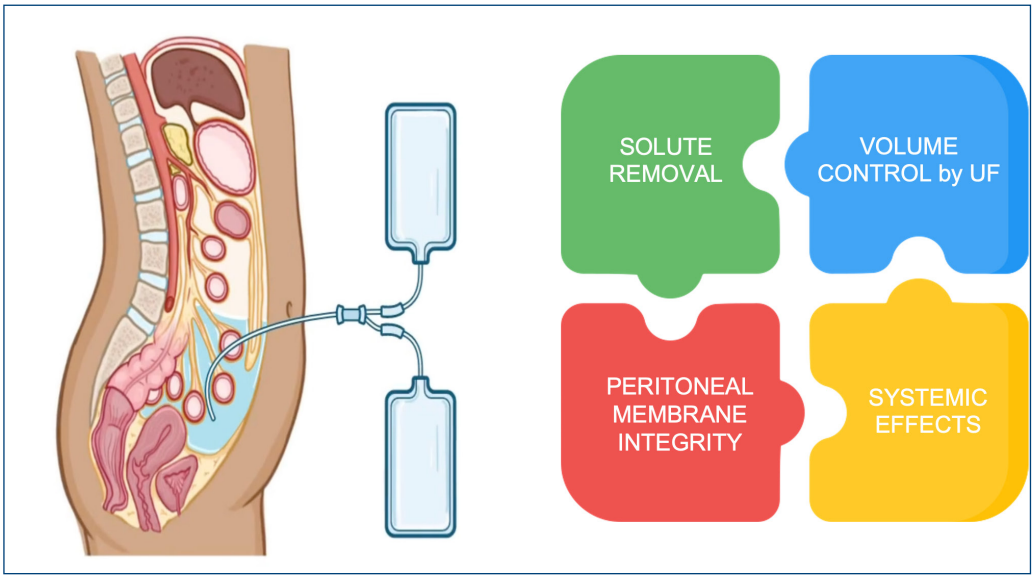

Figure 1. Peritoneal dialysis fluids serve solute removal and ultrafiltration. PD fluids also affect peritoneal membrane integrity and systemic absorption of PD fuids solutes influence systemic metabolic pathways. PD fluids innovations aim to optimize the composite outcome of solute clearance, ultrafiltration, peritoneal membrane changes over time on PD and systemic effects by the PD fluid.

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First-generation peritoneal dialysis fluids

First-generation PD fluids, also called conventional PD fluids, contain electrolytes, a buffer, and glucose as the primary osmotic agent *(Table 1)*. The glucose content of these solutions is 10-50 times higher than the plasma glucose concentration. The heat sterilization process of the PD fluids leads to the production of glucose degradation products (GDPs), despite being performed at low pH. Conventional PD fluids are thus characterized by low a pH, a high glucose and a high GDP content.

Table I. Composition of currently commercially available PD fluids.

	Plasma reference (adult)	**First-generation G%-based fluid** *(Low pH, high GDP solutions)*	**Second-generation G%-based fluid** *(Neutral pH, low GDP solutions)*	Amino-acid solution	Icodextrin
Electrolytes (mmol/L)					
Sodium	136-145	132	132-134	132	133
Calcium	1.12-1.32	1.25/1.75	1.25-1.75	1.25	1.75
Magnesium	0.65-1.05	0.25/0.75	0.25/0.5	0.25	0.25
Chloride	98-107	95/102	95-104	105	96
Potassium	3.5-5.1	0	0	0	0
Buffer (mmol/L)					
Acetate	0				
Lactate	0.5-2	40/35	10-15/35/0	40	40
Bicarbonate	22-28		25/0/34		
pH	7.4	5.5	7.0-7.4	6.7	5.5
Osmotic agent (g/dL) (osmolality)					
Glucose	0.05 - 0.1	1.36/2.27/3.86	1.36-1.5/2.27-2.5/3.86-4.25		
	280-300	347/398/486	350/397/490		
Amino acid	0.05 - 0.1			1.1	
	280-300			365	
Icodextrin					7.5
					284

A landmark study published in 2002 showed significant histopathologic damage of the peritoneal membrane over time with the use of these conventional PD fluids. After prolonged exposure to low pH, high glucose and high GDP fluids, follow-up histopathological assessments of the patients' peritoneal membrane demonstrated mesothelial cell loss, submesothelial thickening, angiogenesis, and peritoneal vasculopathy [4]. In the early 2000's, it was also recognized that peritoneal solute transport increases with time on treatment in a proportion of patients treated with PD and that this increase was associated to a higher peritoneal exposure to hypertonic glucose [5]. Although change in solute transport status over time is associated to glucose exposure, the functional and histopathological changes within the peritoneal membrane induced using low pH, high glucose and high GDP PD fluids guided the "biocompatibility hypothesis of PD fluids". The hypothesis of biocompatibility suggests that morphological and functional peritoneal damage might be caused by conventional PD fluids - low pH, high glucose and high GDPs content PD fluids - and that these changes might be attenuated by second generation, so called biocompatible fluids.

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Second-generation peritoneal dialysis fluids

To decrease the toxicity of low-pH, high glucose and high GDP PD fluids on the peritoneal membrane, multi-chambered bags were developed allowing glucose to be sterilized separately at very low pH, generating less GDPs. Before use, the glucose compartment is mixed with the other compartment(s) of the PD fluid containing electrolytes and a buffer. After mixing the different chambers of the PD fluid bag, a neutral pH PD fluid is obtained containing less GDPs compared to the first-generation PD fluids. Second-generation PD fluids are thus defined by their neutral pH and lower GDP content and are so-called biocompatible solutions *(Table 1)*.

Preclinical in vitro and in vivo studies using second-generation PD fluids showed promising histopathological effects with reduced mesothelial damage induced by the biocompatible fluid, less epithelial-to-mesenchymal transition (EMT), less deposition of GDPs, decreased sub-mesothelial fibrosis and angiogenesis and less progression of vasculopathy with better preservation of the endothelial glycocalyx [6-9]. Also, observational data from clinical practice in Japan suggest that biocompatible PD fluid use contributes to decreased encapsulated peritoneal sclerosis development, the ultimate stage of histopathological changes of the peritoneal membrane [10, 11]. However, evidence of clinical benefits is still debated. Results of randomized controlled clinical trials and meta-analyses comparing the effects of biocompatible versus conventional PD fluids are less clear. Overall, the use of second-generation biocompatible fluids is associated with a better preservation of residual kidney function and urine output although these changes might be secondary to a decrease in ultrafiltration capacity. Moreover, no improvements in peritoneal membrane function could be demonstrated using second-generation PD fluids [12-14].

In 24 children treated with second-generation PD fluids only, serial peritoneal biopsies showed early fibroblast activation, neoangiogenesis, and vasculopathy. In these children, microvascular density and peritoneal transport rates (D/P creatinine at 2 hours) correlated well [15]. These data demonstrate that biocompatible solutions too lead to early inflammation, epithelial-to-mesenchymal transition, submesothelial thickening, angiogenesis, and vasculopathy in pediatric patients.

The lack of clinical benefits with the use of neutral pH, low GDP solutions and the persistence of histopathological and functional changes of the peritoneal membrane induced using these so-called biocompatible solutions swept aside the biocompatibility hypothesis. An unphysiologically high glucose concentration, a feature common to both first- and second-generation PD fluids, led to the development of the "glucose hypothesis".

The glucose hypothesis: systemic and peritoneal effects of glucose exposure

During a PD dwell using either first- or second-generation PD fluids, bi-directional transport of solutes across the peritoneal membrane leads to systemic absorption of glucose. Daily systemic glucose absorption is estimated to vary between 90 - 300g [16, 17] accounting for a significant caloric load, subsequently increasing fat mass and dyslipidemia. The rise in plasma glucose and GDPs, secondary to the diffusion from the PD fluid to the patient's circulation, promote the formation of advanced glycosylation end products (AGEs) in plasma and lead to glucose-induced cytotoxic effects [18, 19]. Cytotoxicity of glucose is linked to several molecular disturbances. Firstly, AGEs bind to their receptors (RAGE) and induce inflammatory and pro-angiogenic effects

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through the generation of reactive oxygen species and by the release of cytokines and growth factors. Glucose also triggers intracellular signaling via protein kinase C and polyol pathways and intracellular hyperglycemia causes metabolic disturbances leading to an increase in the ratio of NADH/NAD+, a state known to be induced by insufficient oxygen supply. This glucose-induced pseudohypoxia causes hypoxia-inducible-factor gene expression, subsequently leading to an upregulation of genes encoding for profibrotic and angiogenic factors such as vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β), contributing to angiogenesis and extracellular matrix deposition [20-22]. The cytotoxic effects of glucose thus lead pro-inflammatory, pro-fibrotic and pro-angiogenic changes, which are evident in the peritoneal membrane exposed to the PD fluids [4, 15].

New therapeutic approaches

Recent advances in PD fluid developments focused on strategies to counteract the peritoneal and systemic toxicity of glucose-based PD fluids. Hereby, two main strategies have emerged:

(i) The osmotic approach whereby glucose is replaced by an alternative osmotic agent.
(ii) The metabolic approach whereby the PD fluid is supplemented with (an) agent(s) that mitigate the metabolic effects of the glucose exposure.

Before discussing new developments in PD fluids, we first discuss the already commercially available alternatives to glucose-based PD fluids.
In general, it should be acknowledged that residual cytotoxicity through mechanisms unrelated to glucose or glucose degradation products is possible. Buffer-related toxicity has been suggested in studies assessing cytotoxicity of different glucose-based fluids [23]. Also, tonicity or osmolality-related changes to the peritoneal membrane have been described in preclinical studies, unrelated to the high-glucose induced pseudohypoxia[24-26]. Identifying these pathways will help to complete the picture of what makes a fluid truly biocompatible.

Commercially available alternatives to glucose-based PD fluids

Icodextrin is a starch-derived high-molecular weight glucose polymer used in peritoneal dialysis as an alternative to glucose. Its larger molecular size causes it to be less readily absorbed than glucose. After entering the circulation, icodextrin is metabolized into smaller oligosaccharides such as maltose, maltotriose and maltotetraose. To date, no histopathological data on the effects of icodextrin use during PD have been published. Clinical studies including randomized controlled trials show improved ultrafiltration with better fluid status control when using icodextrin, especially in patients with fast peritoneal membrane transport status and in those not meeting ultrafiltration goals and at risk of fluid overload [27, 28]. Replacement of a glucose dwell by icodextrin showed better insulin sensitivity in non-diabetic patients treated with PD [29]. In patients with diabetes mellitus and treated with PD, a glucose-sparing PD prescription using icodextrin and amino-acid-based PD fluids improved HbA1c results [30]. These data support that lowering glucose exposure during PD lowers the systemic effects of PD-associated glucose absorption. It has to be acknowledged that, to date, the largest body of evidence on the use of non-glucose PD fluids is with icodextrin, with a clear signal of safety and efficacy. Future research into patient-centered outcomes and cost-effectiveness associated with icodextrin is needed.

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Amino-acid-based PD fluids are solutions composed of electrolytes, a buffer and a mixture of amino-acids as the osmotic agent. Amino-acid based PD fluids were developed to optimize nutritional status of malnourished patients on PD. Preclinical data on peritoneal membrane cytotoxicity are limited and conflicting, and no histopathological data describing the effects of amino-acid PD fluids on the peritoneal membrane are available to date [8, 31]. Clinical relevance in terms of improving nutritional status by the use of long-term amino-acid-based PD fluids is limited as only a short-term (7 days follow-up) small-sized (8 patients) trial was published showing small improvement in protein kinetics [32].

All together, the use of glucose-based PD solutions remains indispensable for a full-dose PD prescription. Despite maximizing icodextrin and amino-acid-based PD fluids use in the PD prescription, patients continue to be exposed to a significant carbohydrate absorption, glucose exposure and GDP absorption [33].

Promising new osmometabolic agents

L-carnitine is an osmotically and metabolically active compound essential for fatty acid metabolism and mitochondrial function with a molecular weight similar to glucose. It is highly water soluble and chemically stable in an aqueous solution and thus suitable for use in PD. Preclinical in vitro and in vivo studies demonstrated improved endothelial cell survival, increased aquaporin-1 expression on endothelial cells, and reduced glucose-induced cytotoxicity when PD-fluids were supplemented with L-carnitine [34, 35]. Reassuringly, equimolar solutions of glucose and L-carnitine result in comparable net ultrafiltration with L-carnitine supplemented fluids causing less mesothelial damage and fewer vascular alterations [34, 35]. A clinical study randomized 35 non-diabetic patients treated with PD to a PD prescription with glucose-based day dwells versus 0.1% L-carnitine supplemented glucose-based dwells for a treatment period of 4 months. Both groups received icodextrin overnight. Insulin sensitivity improved in the patients who received L-carnitine supplemented PD [36]. Importantly, supplementation with L-carnitine was well tolerated and peritoneal membrane function did not change differently between groups. Patients receiving L-carnitine supplemented PD showed no change in urine output while patients in the control group significantly lost diuresis over the study period. Osmotic diuresis induced by L-carnitine absorption is suggested as the cause of maintained urine output in the intervention group [36].

Xylitol is a 5-carbon sugar used as a sugar substitute in parental nutrition. It is an osmotically active compound with a low glycemic index causing a slower and lower increase in plasma glucose levels and less insulin stimulation compared to when glucose is absorbed. An old-dated clinical trial published in 1982 showed 50% reduction in insulin requirement and improved metabolic parameters when 6 insulin-dependent diabetics received 1.5% and 3.0% xylitol PD dwells compared to when receiving glucose-based PD [37].

Recently, the combined use of 0.7% or 1.5% xylitol with 0.02% L-carnitine and 0.5% glucose has been investigated *(Table 2)*.

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Table II. Composition of the novel Xylitol, L-carnitine, glucose based PD fluid

	Plasma reference (adult)	Xylitol – L-carnitine - Glucose
Electrolytes (mmol/L)		
Sodium	136-145	132
Calcium	1.12-1.32	1.3
Magnesium	0.65-1.05	0.5
Chloride	98-107	101
Potassium	3.5-5.1	0
Buffer (mmol/L)		
Lactate	0.5-2	35
pH	7.4	6.5-7.5
Osmotic agent (g/dL) (osmolality)		
Xylitol		0.7/1.5/2.0
L-Carnitine		0.02
Glucose	0.05 - 0.1	0.5/0.5/1.5
Osmolality	280-300	346.5/399.1/480.8

In vitro, a PD fluid containing a low-dose glucose, L-carnitine, and xylitol improved cell viability of human umbilical vein endothelial cells of mothers with or without gestational diabetes, improved human mesothelial cell viability and better preserved mesothelial cell layer integrity compared to glucose-based PD fluids [38, 39]. Importantly, the low dose glucose in this PD fluid did not have the deleterious histopathological effects of higher glucose concentrations in first- and second-generation PD fluids [39]. A recently published open-label phase 2 trial compared safety and tolerability of the xylitol – L-carnitine – glucose PD fluid to a conventional glucose and icodextrin PD prescription in 10 CAPD patients over a 4-week period. The use of xylitol - L-carnitine – glucose was well tolerated and patients did not experience infusion pain nor discomfort. Adequacy and peritoneal transport characteristics did not differ between groups [26]. Currently, a phase 3 randomized controlled study with blinded outcome assessment is recruiting in Italy, Denmark, Sweden, UK, Germany and Spain (ELIXIR trial, NCT03994471 [40]). This study aims to randomize 170 CAPD patients to either a standard PD regimen using 1 to 3 glucose-based day dwells and icodextrin overnight versus 1 to 3 day exchanges using 0.7-1.5% xylitol, 0.02% L-carnitine and 0.5% glucose and icodextrin overnight for 6 months. The primary endpoint is non-inferiority in weekly Kt/Vurea. Secondary endpoints include 24h peritoneal ultrafiltration, residual kidney function, urine output, metabolic parameters on lipid and glucose metabolism, patient reported outcome measures, and safety [40]. Data collection is expected to be completed by the end of 2025.

Low glutamine levels in the peritoneal cavity during PD are associated with cytotoxicity related to reduced glutamine-dependent post translational protein modification (so-called O-GlcNAcylation) [41]. Glutamine supplementation of glucose-based PD fluids enables heat-shock-protein mediated cytoprotection. Supplementation of glucose-based PD fluids with the alanine-glutamine dipeptide allows the release of glutamine within the peritoneal cavity. In vitro, in vivo and pilot studies have demonstrated better survival of mesothelial cells, lower endothelial cell damage and better preservation of the peritoneal barrier when glucose-based dialysis fluids were supplemented with the glutamine-releasing alanine-glutamine dipeptide compared to no supplementation [41-47]. These studies also showed an improved peritoneal membrane immune function, a reduction in oxidative stress and restored stress responses [41-

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47]. A phase 2 randomized controlled crossover study in 6 PD patients compared the effects of alanine-glutamine-supplemented PD fluids versus placebo-supplemented PD fluids over a period of 8 weeks. Results showed improved markers of peritoneal membrane integrity, reduced systemic inflammation, and enhanced peritoneal membrane immune competence [48].

Mesothelial cells express both sodium/glucose cotransporter (SGLT) 1 and SGLT2 and therefore it is relevant to assess the effects of SGLT1/2 inhibitors use in PD. Indeed, inhibiting glucose absorption across the peritoneal membrane through inhibiting SGLT1/2-mediated glucose transport might decrease local and systemic glucose-related toxicity while also maintaining osmotic gradient hence enhancing ultrafiltration capacity. In vitro studies showed that empagliflozin and dapagliflozin reduce peritoneal fibrosis and epithelial-to-mesenchymal transition [49-52]. Animal studies with intraperitoneal administration of dapagliflozin showed improvements in peritoneal membrane integrity and enteric empagliflozin administration reduced glucose uptake and protected against glucose-induced epithelial-to-mesenchymal transition [50, 51, 53, 54]. However, additional data suggest that SGLT1-mediated transport might be more important in facilitating peritoneal glucose transport compared to SGLT2 [55]. The EMPOWERED trial (jRCTs051230081) is a currently recruiting randomized double-blind placebo-controlled crossover trial randomizing 36 Japanese patients with heart failure and treated with PD to two 8-weeks treatment periods of peritoneal dialysis either complemented with oral empagliflozin or placebo. The primary endpoint of the study is the change in the daily ultrafiltration volume from baseline to week 8 [56]. Other randomized controlled trials assessing the effects of SGLT2-inhibitors in patients on peritoneal dialysis are assessing brain natriuretic peptide levels as primary endpoint (jRCT1011210022), glucose absorption from the PD fluid (NCT05671991) or reno- and cardioprotective efficacy and safety (NCT05374291).

2-Deoxyglucose is a synthetic glucose analog that inhibits glycolysis and so counters TGF-β1-mediated profibrotic signaling. In vitro studies showed that supplementation of PD fluid with 2-deoxyglucose improved mesothelial cell survival, reduced epithelial-to-mesenchymal transition, reduced fibrotic changes and improved peritoneal mesothelial and endothelial barrier integrity [57, 58]. Clinical validation is pending.

Taurine, hyperbranched polyglycerol, lithium, and steviol glycosides are other molecules under preclinical investigation. All demonstrated peritoneal membrane protection in vitro and in animal models but lack clinical trial data [59-62].

Of note, adapted PD fluids have been investigated in recent years such as glucose polymers with low polydispersity, bimodal PD combining crystalloid and colloid osmosis, low-sodium and sodium-free PD solutions. While these modifications may lower carbohydrate absorption and increase sodium removal, they do not eliminate glucose exposure, suggesting a potential role for adjunct metabolic protection[63-65].

Conclusion

The ideal PD solution should ensure effective solute clearance, ultrafiltration, preserve peritoneal membrane integrity, and limit systemic toxicity. Glucose-based PD fluids, while effective in providing solute and water removal, contribute to peritoneal membrane damage and systemic complications. Amino-acid and icodextrin-based PD fluids offer the potential to reduce glucose

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exposure and its related local and systemic toxicity; however, they do not eliminate the need for of glucose-based PD fluids. Emerging osmometabolic PD fluids combining xylitol, L-carnitine, and low-dose glucose or PD fluids supplemented with alanine-glutamine show the most promise in better preserving peritoneal membrane integrity and lowering systemic toxicity of the PD fluid based while maintaining adequate solute and water removal compared to glucose-based PD fluids.

Strategies to reduce PD-related glucose toxicity, including metabolic adjuncts and SGLT inhibitors represent an evolving research frontier. Clinicians, researchers and industry must engage in structural collaboration to increase knowledge around PD fluid toxicity, to research existing solutions and to support new developments. Without reliable involvement from any party, opportunities to improve the outcomes of patients treated with peritoneal dialysis will be delayed.

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Conflicts of Interest

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Numéro ORCID
Celeste Smeys : https://orcid.org/0000-0003-3924-6764
Freya Van Hulle : https://orcid.org/0000-0001-7079-4705
Florine Janssens : https://orcid.org/0009-0004-2863-6155
Karlien François : https://orcid.org/0000-0003-0071-8402

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