Relative Contributions of Pseudohypoxia and Inflammation to Peritoneal Alterations with Long-Term Peritoneal Dialysis Patients

Raymond T. Krediet1 and Alena Parikova2

Abstract

Long-term peritoneal dialysis is associated with alterations in peritoneal function, like the development of high small solute transfer rates and impaired ultrafiltration. Also, morphologic changes can develop, the most prominent being loss of mesothelium, vasculopathy, and interstitial fibrosis. Current research suggests peritoneal inflammation as the driving force for these alterations. In this review, the available evidence for inflammation is examined and a new hypothesis is put forward consisting of high glucose-induced pseudohypoxia. Hypoxia of cells is characterized by a high (oxidized-reduced nicotinamide dinucleotide ratio) NADH-NAD⁺ ratio in their cytosol. Pseudohypoxia is similar but occurs when excessive amounts of glucose are metabolized, as is the case for peritoneal interstitial cells in peritoneal dialysis. The glucose-induced high NADH-NAD⁺ ratio upregulates the hypoxia-inducible factor-1 gene, which stimulates not only the glucose transporter-1 gene but also many profibrotic genes like TGFβ, vascular endothelial growth factor, plasminogen activator inhibitor-1, and connective tissue growth factor, all known to be involved in the development of peritoneal fibrosis. This review discusses the causes and consequences of pseudohypoxia in peritoneal dialysis and the available options for treatment and prevention. Reducing peritoneal exposure to the excessively high dialysate glucose load is the cornerstone to avoid the pseudohypoxia-induced alterations. This can partly be done by the use of icodextrin or by combinations of low molecular mass osmotic agents, all in a low dose. The addition of alanyl-glutamine to the dialysis solution needs further clinical investigation.

Inflammation in Peritoneal Dialysis

An acute inflammatory reaction is characterized by dolor, rubor, calor, and tumor. On the basis of knowledge in patients with acute peritonitis, it is known that this event is characterized by—other than pain—high peritoneal small solute transfer rates and impaired ultrafiltration, probably reflecting peritoneal hyperemia (5,6). Also, a greater loss of proteins with the drained dialysate is present. These phenomena are accompanied by high cell counts in the effluent and high dialysate concentrations of vasodilating prostaglandins and cytokines, like IL-6 and TNFα (7). Also, serum levels of acute phase proteins, like C-reactive protein and IL-6, can be increased (6,7). In contrast to the signs and symptoms of an acute inflammatory
reaction, a number of these can be absent in chronic inflammation. In the absence of a generally accepted definition of chronic inflammation, the described hallmarks of an acute inflammatory reaction in patients on PD will be used as a framework for a discussion on the presence of chronic inflammation in patients on PD. These consist of general signs of inflammation, peritoneal transport, peritoneal morphology, cells in peritoneal effluent (including their transcriptome), and locally produced proteins in effluent.

**General Signs of Inflammation**

Many patients with chronic kidney failure exhibit signs of chronic inflammation as assessed by the presence of high serum concentrations of inflammatory markers, like C-reactive protein, but no differences have been described between patients treated with hemodialysis or PD (8). The results of the Global Fluid Study, an international, multicenter, prospective, observational cohort study, confirmed the association between systemic inflammation and mortality, but it found no relation between mortality and peritoneal inflammation assessed by peritoneal effluent concentrations of locally produced inflammatory markers, like IL-6 (9). These were associated with a high peritoneal solute transfer rate.

**Peritoneal Transport**

An inflammatory reaction is characterized by hyperemia. An increase in peritoneal blood volume will, therefore, cause higher peritoneal small solute transfer rates with decreased ultrafiltration (10). The vascular filling is, however, not the only determinant of the small solute transfer rate. Also, the number of perfused peritoneal microvessels, especially the immature ones, is an important factor not directly related to inflammation (11).

**Morphologic Signs of Inflammation**

No study on peritoneal tissue of patients on PD without peritonitis has been supportive of microinflammation. The peritoneal biopsy study showed signs of chronic inflammation in 9% of patients (12), whereas a perivascular infiltrate was only found in a minority of biopsies during the first few years on PD and was absent in patients on long-term PD (13). Also, in children treated with low glucose degradation product/normal pH solutions, low scores were found for the T cell marker CD45 and the monocyte/macrophage marker CD68, irrespective of PD duration (14) and the presence of a previous peritonitis episode (15). High expression of these markers is found in inflammatory lesions like atherosclerotic plaques (16). These results give no support to the presence of an inflammatory process.

**Cells in Peritoneal Effluent, Immune-Effecter Characteristics, and Their Transcriptome**

Inflammatory processes often cause a cell reaction, leading to an increase in their number. High effluent cell counts are present in patients on PD after catheter implantation and also after temporary discontinuation of PD (17). This inflammatory reaction lasts for 1 week, after which the cell count decreases to $5 \times 10^6$/L. Cell counts exceeding $10 \times 10^6$/L are very rare. The differentiation shows on average 75% macrophages, 17% lymphocytes, 5% neutrophilic granulocytes, and 3% mesothelial cells, which are very similar to those of cells obtained with laparoscopy in patients with normal kidney function, except for the presence of mesothelial cells (18). The immunoeffecter characteristics of these cells, like their chemotaxis and phagocytosis capacity, also showed no signs of activation, giving no support to chronic inflammation. The transcriptome of effluent cells in stable patients on PD showed an upregulation of various genes involved in adaptive immunity, and therefore triggered by a specific antigen (19). The IL-6 gene was not upregulated, and nor was any gene of the IL-6 superfAMILY. Also, no relationship was present between IL-6 expression and the effluent concentration of the IL-6 protein. It can be concluded that effluent cell counts and their transcriptome are not in support of microinflammation mediated by IL-6. The upregulation of adaptive immunity genes may represent peritoneal defense against invading microorganisms.

**Proteins in Peritoneal Effluent**

The drained dialysate of patients on PD contains many proteins transported from the circulation, locally produced, or both. The magnitude of peritoneal transport of serum proteins from plasma to the dialysate-filled peritoneal cavity is dependent on their molecular mass (20). The relationship between the transport rate of individual serum proteins and their molecular masses is linear when plotted on a double-logarithmic scale (21). This finding can be used to distinguish between transport and local intraperitoneal production of a protein in peritoneal effluent; a clearance exceeding the expected one indicates local production on top of transport. Effluent vascular endothelial growth factor (VEGF) (22), plasminogen activator inhibitor-1 (PAI-1) (23), and the proinflammatory factors TNFα and IL-6 have gained much attention. The latter two will be discussed here in more detail. Both markers are markedly increased during acute peritonitis (7). Although TNFα was only locally produced in the acute phase, no relationship was found between effluent TNFα and the peritoneal solute transport rate in stable patients, as reported in the Global Fluid Study (9). The explanation for this finding is not clear. The inflammatory marker IL-6 has a molecular mass of 26 kD, which implies transport from the circulation with a peritoneal clearance in between that of albumin and β2-microglobulin. On top of the effluent concentrations of IL-6 by peritoneal transport, IL-6 effluent levels are also determined by local production because these are often higher than in serum (9,24) but with high inter- and intraindividual variabilities. Relationships between effluent IL-6 and small solute transfer rate have been reported in many cross-sectional and longitudinal studies (9,25–29). However, small solutes and IL-6 are transported through the same interendothelial pore system, which makes a pathophysio logic interpretation impossible due to mathematical coupling (30). Effluent IL-6 in the longitudinal studies showed an increase during the first 2 years of treatment, but this was not found thereafter (24).

It can be concluded that the evidence for peritoneal microinflammation during PD in the absence of peritonitis is weak and not supported by morphology, the cellular content of peritoneal effluent, and their transcriptome. Yet, peritoneal dialysate IL-6 is locally produced during PD. Production of
IL-6 by peritoneal tissue without a cellular representation in peritoneal effluent but with diffusion of their synthesized proteins is the only possible alternative to explain the high effluent IL-6 concentrations. Peritoneal interstitial tissue is a candidate, especially because adipocytes upregulate IL-6 expression under hypoxic conditions (31). This implies that hypoxia rather than inflammation may be the main cause of the high effluent IL-6 levels (Table 1).

**Hypoxia in Peritoneal Dialysis**

Other than mesothelial denudation, remodeling of peritoneal tissues in long-term PD consists of angiogenesis with immature vessels, vasculopathy, and interstitial fibrosis (3,11). Hypoxia causes angiogenesis and fibrosis in many organ systems, mediated by increased expression of the transcription factor hypoxia-inducible factor-1 (HIF-1) (32,33). Hypoxia also induces the epithelial-to-mesenchymal transition in various tumors (34). It is unknown if peritoneal hypoxia/ischemia is present in long-term PD, although peritoneal vasculopathy is characterized by multiple stenoses of the microvascular lumina and sometimes obstruction (12), potentially causing impaired tissue perfusion. However, the effects of hypoxia are also present in pseudohypoxia, a condition that has been described in patients with complications of diabetes mellitus (35) and in oncology, where it has been defined as an upregulated HIF-1 in the presence of a normal oxygen tension (36). The biochemical basis of pseudohypoxia due to a large influx of glucose will be described in the following paragraphs. The principle is on the basis of the notion that hypoxia reduces the oxidation of nicotinamide dinucleotide (NADH) to NAD\(^+\), leading to an increased intracellular NADH\(+/\)NAD\(^+\) ratio. The generated pyruvate is taken up in the mitochondria, where it is metabolized in the citric acid cycle in the presence of oxygen. This leads to normalization of the NADH\(+/\)NAD\(^+\) ratio. In the absence of a sufficient amount of oxygen, pyruvate is fermented to lactate by lactate dehydrogenase, in which reaction NADH is again converted to NAD\(^+\). Consequently, two compensatory mechanisms are present to prevent a too high NADH\(+/\)NAD\(^+\) ratio (i.e., the mitochondrial citric acid cycle and the lactate dehydrogenase reaction).

**Excessive Glucose Influx in Cells**

The presence of insulin-independent glucose transporters in the cell membrane means that high extracellular glucose concentrations can have effects on intracellular glucose metabolism, as has been shown in isolated rat glomeruli (39). In this study, exposure to a 30-mmol/L glucose solution had no effect on the pyruvate concentration but increased the lactate/pyruvate ratio, a reflection of the NADH\(+/\)NAD\(^+\) ratio. The sorbitol concentration also increased, indicating activation of the polyol or sorbitol pathway, in which glucose is first metabolized to sorbitol followed by conversion of sorbitol to fructose by aldose reductase. During this final step, NADH is generated, which contributes to the increase of the NADH\(+/\)NAD\(^+\) ratio. A scheme of the two pathways for glucose metabolism is given in Figure 1. The sorbitol pathway in the described experiments with isolated glomeruli could be inhibited by the addition of pyruvate to stimulate the mitochondrial citric acid cycle and by an aldose reductase inhibitor. These experiments formed the basis of the pseudohypoxia hypothesis formulated by the same group a few years later, in which a reduced cytosolic NADH\(+/\)NAD\(^+\) ratio caused by hyperglycemia was indicated as the culprit in the genesis of vascular and neuronal diabetic changes and also as a mediator of lipid metabolism imbalance, superoxide anion production, and increased nitric oxide formation (35).

---

**Table 1. Evidence for peritoneal microinflammation**

<table>
<thead>
<tr>
<th>Parameters of Peritoneal Inflammation</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal morphology</td>
<td>• Some perivascular infiltrate during the first years</td>
</tr>
<tr>
<td>Peritoneal effluent cells</td>
<td>• Low scores for T cell and macrophage markers</td>
</tr>
<tr>
<td>Transcriptome of effluent cells</td>
<td>• Increased after catheter implantation</td>
</tr>
<tr>
<td>Intraperitoneally produced proteins in effluent</td>
<td>• Stable at a low level in long-term PD</td>
</tr>
<tr>
<td></td>
<td>• Upregulation of adaptive immunity genes</td>
</tr>
<tr>
<td></td>
<td>• Upregulation of fibrogenesis genes</td>
</tr>
<tr>
<td></td>
<td>• No upregulation of IL-6 gene</td>
</tr>
<tr>
<td></td>
<td>• Are also transported from the circulation, making correlations between effluent concentrations and solute transfer subject to mathematical coupling and not allowing a pathophysiologic interpretation</td>
</tr>
<tr>
<td></td>
<td>• TNFα is only locally produced during the first days of peritonitis</td>
</tr>
<tr>
<td></td>
<td>• IL-6 only increases during the first 2 yr of PD</td>
</tr>
<tr>
<td></td>
<td>• CRP is not locally produced</td>
</tr>
</tbody>
</table>

PD, peritoneal dialysis; CRP, C-reactive protein.
the glucose concentrations in PD solutions are about 10 times higher than those in the circulation of patients with diabetes mellitus during severe hyperglycemia. About 60% of the instilled glucose amount disappears during a 4-hour dwell (41). This will initially be in the peritoneal interstitium. From there, the majority will diffuse to the circulation, but an unknown amount is likely to be taken up in interstitial adipocytes and fibroblasts. In 2002, our group postulated the presence of pseudohypoxia as a possible cause of peritoneal membrane alterations induced by long-term exposure to the high glucose concentrations of PD solutions (41). More recently, we developed the glucose/hypoxia/GLUT-1 hypothesis on the basis of increased peritoneal glucose consumption by fibroblasts caused by pseudohypoxia-induced increased GLUT-1 expression, leading to a decreased crystallloid osmotic pressure gradient for the endothelial water channel aquaporin-1 (2). In addition to the mechanisms for pseudohypoxia development in patients with diabetes (35), the usual compensatory mechanisms to increase the NADH/NAD⁺ may be impaired in patients on PD. First, mitochondrial dysfunction can be present in CKD (42), influencing the citric acid cycle. Second, because lactate is usually used as a buffer substance in PD solutions, extracellular lactate passes cell membranes by monocarboxylate transporters (43), resulting in high cytosol lactate concentrations. The lactate generated in the glycolysis is converted to pyruvate by lactate dehydrogenase. NADH is reduced to NAD⁺ during this reaction, thereby compensating for pseudohypoxia. High lactate concentrations inhibit the function of lactate dehydrogenase and therefore impair the normal compensation to hypoxia. The excessive glucose exposure in combination with impaired compensatory mechanisms indicate the importance of pseudohypoxia in long-term peritoneal alterations. This is supported by studies in a 20-week model of daily peritoneal exposure to dialysis solutions in rats with normal kidney function. Inhibition of the sorbitol pathway by the aldose reductase inhibitor zopolrestat decreased peritoneal vascular density and reduced submesothelial and perivascular fibrosis (44); replacement of lactate by pyruvate had similar effects and was associated with lower small solute transfer rates (45). The postulated effect of pseudohypoxia on nitric oxide formation in patients with diabetes (35) has been shown in patients on PD (46). In that study, long-term PD was associated with enhanced expression of nitric oxide and VEGF in peritoneal tissue.

### Pseudohypoxia in Peritoneal Dialysis

The glucose concentrations in PD solutions are about 10 times higher than those in the circulation of patients with diabetes mellitus during severe hyperglycemia. About 60% of the instilled glucose amount disappears during a 4-hour dwell (41). This will initially be in the peritoneal interstitium. From there, the majority will diffuse to the circulation, but an unknown amount is likely to be taken up in interstitial adipocytes and fibroblasts. In 2002, our group postulated the presence of pseudohypoxia as a possible cause of peritoneal membrane alterations induced by long-term exposure to the high glucose concentrations of PD solutions (41). More recently, we developed the glucose/hypoxia/GLUT-1 hypothesis on the basis of increased peritoneal glucose consumption by fibroblasts caused by pseudohypoxia-induced increased GLUT-1 expression, leading to a decreased crystallloid osmotic pressure gradient for the endothelial water channel aquaporin-1 (2). In addition to the mechanisms for pseudohypoxia development in patients with diabetes (35), the usual compensatory mechanisms to increase the NADH/NAD⁺ may be impaired in patients on PD. First, mitochondrial dysfunction can be present in CKD (42), influencing the citric acid cycle. Second, because lactate is usually used as a buffer substance in PD solutions, extracellular lactate passes cell membranes by monocarboxylate transporters (43), resulting in high cytosol lactate concentrations. The lactate generated in the glycolysis is converted to pyruvate by lactate dehydrogenase. NADH is reduced to NAD⁺ during this reaction, thereby compensating for pseudohypoxia. High lactate concentrations inhibit the function of lactate dehydrogenase and therefore impair the normal compensation to hypoxia. The excessive glucose exposure in combination with impaired compensatory mechanisms indicate the importance of pseudohypoxia in long-term peritoneal alterations. This is supported by studies in a 20-week model of daily peritoneal exposure to dialysis solutions in rats with normal kidney function. Inhibition of the sorbitol pathway by the aldose reductase inhibitor zopolrestat decreased peritoneal vascular density and reduced submesothelial and perivascular fibrosis (44); replacement of lactate by pyruvate had similar effects and was associated with lower small solute transfer rates (45). The postulated effect of pseudohypoxia on nitric oxide formation in patients with diabetes (35) has been shown in patients on PD (46). In that study, long-term PD was associated with enhanced expression of nitric oxide and VEGF in peritoneal tissue.

### Hypoxia-Inducible Factor-1 and Various Peritoneal Effluent Markers in Patients on PD

Upregulation of the transcriptional factor HIF-1 stimulates the transcription and expression of genes that are likely involved in long-term peritoneal alterations. These include

---

**Table 2. Causes and consequences of pseudohypoxia in peritoneal dialysis**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Upregulation of hypoxia-inducible factor-1 in the presence of a normal oxygen tension</td>
</tr>
<tr>
<td>Biochemical basis</td>
<td>Increased cytosolic NADH-NAD⁺ ratio</td>
</tr>
<tr>
<td>Cause</td>
<td>Excessive intracellular glucose influx, leading to increased glycolysis and stimulation of the sorbitol pathway</td>
</tr>
<tr>
<td>Pseudohypoxia in diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>• Vasculopathy</td>
<td></td>
</tr>
<tr>
<td>• Neuropathy</td>
<td></td>
</tr>
<tr>
<td>• Increased superoxide anion production</td>
<td></td>
</tr>
<tr>
<td>• Increased nitric oxide production</td>
<td></td>
</tr>
<tr>
<td>Impaired compensation in PD</td>
<td></td>
</tr>
<tr>
<td>• Mitochondrial dysfunction</td>
<td></td>
</tr>
<tr>
<td>• Lactate as buffer substance</td>
<td></td>
</tr>
<tr>
<td>Manifestations in PD</td>
<td></td>
</tr>
<tr>
<td>• Upregulation of genes of TGFβ, VEGF, PAI-1, and CTGF</td>
<td></td>
</tr>
<tr>
<td>• Upregulation of the IL-6 gene in adipocytes</td>
<td></td>
</tr>
<tr>
<td>• Increased effluent concentrations of VEGF, PAI-1, CTGF, and IL-6</td>
<td></td>
</tr>
<tr>
<td>Clinical manifestations in long-term PD</td>
<td></td>
</tr>
<tr>
<td>• Impaired free water transport</td>
<td></td>
</tr>
<tr>
<td>• Peritoneal fibrosis</td>
<td></td>
</tr>
<tr>
<td>• Contributes to EPS</td>
<td></td>
</tr>
</tbody>
</table>

NADH, nicotinamide dinucleotide; PD, peritoneal dialysis; VEGF, vascular endothelial growth factor; PAI-1, plasminogen activator inhibitor-1; CTGF, connective tissue growth factor; EPS, encapsulating peritoneal sclerosis.

---

**Figure 1. A scheme of intracellular glucose metabolism.** The sorbitol pathway is shown horizontally, and the glycolysis pathway is shown vertically. Note that nicotinamide dinucleotide (NADH) is shown vertically.
not only GLUT-1 but also erythropoietin, VEGF, TGFβ, PAI-1, and connective tissue growth factor (CTGF) (33).

Upregulation of the HIF-1 gene has been described in human and rat peritoneal mesothelial cells when cultured under hypoxic conditions (47). Effluent concentrations of the HIF-1 protein were assessed in 31 patients on prevalent PD, of whom ten with a mean PD duration of 7 years had impaired ultrafiltration compared with the other 21 with a mean PD duration of 4.5 years (48). Daily intraperitoneal injections with a 4% glucose dialysis fluid in a 28-day murine model induced interstitial fibrosis accompanied by upregulation of HIF-1 (49).

TGFβ is a key mediator in many fibrotic conditions (50). For instance, kidney fibrosis induced by hypoxia is regulated by a number of growth factors that are part of the TGFβ signaling pathway (51). Also, the hyperglycemia-induced fibrotic lesions in diabetic nephropathy are mediated by factors of the TGFβ pathway, suggesting pseudohypoxia (52). In addition, overexpression of the TGFβ gene transferred to the peritoneal cavity of rats induced morphologic and functional alterations similar to those present in patients on PD after a follow-up of 2-4 years (53). Serum and effluent TGFβ are biologically inactive. Therefore, peritoneal effluent concentrations are impossible to interpret (22). Therefore, other HIF-1 upregulated and TGFβ-related regulators, like VEGF, PAI-1, and CTGF, are probably more clinically relevant.

The original description of VEGF dates from the 1970s, when it was discovered as a glycoprotein secreted by tumors that induce neoangiogenesis and increased venular permeability to macromolecules (54). In contrast to other growth factors, like TGFβ, it is mainly secreted in a soluble form. VEGF expression is induced by hypoxia and by hyperglycemia (55). It induces peritoneal alterations in patients on long-term PD (56). Effluent VEGF can be explained by transfer from the circulation for about 30%, but 70% is locally produced in peritoneal tissues/cells (22). This locally produced VEGF was related to small solute transfer rates, suggesting a relationship with the number of perfused peritoneal microvessels. Longitudinal follow-up of locally produced VEGF showed an increasing trend, whereas non-glucose-based dialysis fluids were associated with a decrease of effluent VEGF (57). These results support the contention that pseudohypoxia drives peritoneal membrane alterations.

PAI-1 is encoded by the SERPINE 1 gene. Although this gene is not upregulated in peritoneal effluent cells (19), a relationship is present between gene expression and the effluent concentration of the PAI-1 protein, which increases with PD duration (58). About 75% of effluent PAI-1 is produced in peritoneal tissues (23), possibly by fibroblasts and adipocytes (59,60). This production is stimulated by hypoxia (61) and by high glucose concentrations (51,62). PAI-1 is a downstream regulator in the TGFβ pathway (63). Peritoneal effluent PAI-1 concentrations increase with PD duration (23) and have a sensitivity of 100% and a specificity of 56% for the clinical diagnosis of encapsulating peritoneal sclerosis within 1 year (64).

CTGF is another downstream regulator of TGFβ upregulated by hypoxia (65) and by hyperglycemia as shown in diabetic nephropathy (66) and other fibrotic processes (67), including PD (68). Mesothelial cells from drained peritoneal effluent of patients on PD expressed CTGF, which was upregulated by TGFβ. In addition, the CTGF protein was present in the effluent. These results were confirmed some years later (69). In that study, CTGF was shown in mesothelial cells and interstitial fibroblasts. The mRNA expression was correlated with submesothelial thickness; the effluent protein concentration increased with PD duration.

In summary, continuous exposure of peritoneal tissues to dialysis solutions with an excessive amount of glucose causes pseudohypoxia, similar to diabetes mellitus. This condition increases the expression of HIF-1 by interstitial cells, which leads to enhanced expression of GLUT-1 and of the profibrotic factors TGFβ, VEGF, PAI-1, and CTGF. Compensatory mechanisms may be impaired in PD due to the use of lactate as a buffer in PD solutions and mitochondrial dysfunction.

Conclusions and Therapeutic Options

It can be concluded from the data reviewed that glucose-induced pseudohypoxia is the driving force for the peritoneal alterations that can develop in patients on PD during long-term treatment. This does not exclude a role for inflammation because HIF-1 is also involved in the maturation of dendritic cells, the activation of T cells, and the induction of proinflammatory genes (70). However, the discussed literature and the universal use of dialysis solutions with glucose in high concentrations make it likely that microinflammation can only be secondary to glucose-induced pseudohypoxia.

The clinical consequence of pseudohypoxia is the insight that we now have on why peritoneal alterations occur in long-term PD. The continuous exposure to extremely high dialysate glucose concentration causes pseudohypoxia similar to diabetes mellitus, which induces fibrotic and vascular alterations, and it also enhances the production of nitric oxide. The obvious prophylactic and therapeutic paradigm consists of reducing peritoneal glucose exposure. This can be achieved by incorporation of nonglucose osmotic agents, like icodextrin or amino acids, as a routine, but these osmotic agents cannot be used for all exchanges. Dialysis solutions with a low content of glucose degradation products (“biocompatible solutions”) still contain the usual content of glucose but retard the formation of advanced glycosylation end products, which may contribute to peritoneal vasculopathy. Solutions with a mixture of several osmotic agents, all in a low concentration, are an attractive option, but these are currently not commercially available. Feasible but commercially unavailable options include a combination of low-dose glycerol, amino acids, glucose, or a combination of carnitine and xylitol. Replacing lactate in the dialysis solution with bicarbonate is another therapeutic alternative, but no clinical data are currently available. The addition of 8 mM alanyl-glutamine to glucose-based dialysis solutions is an attractive option because this dipeptide ameliorates peritoneal fibrosis both in peritoneal fibroblast cultured during hypoxia (71) and in a murine PD model (72). Furthermore, 8 weeks of exposure in prevalent patients on PD treated with “biocompatible” solutions led to increased effluent cancer antigen 125 (CA125).
concentrations, indicating an effect on mesothelial cell mass or turnover (73). This may indicate less pseudohypoxia. Prophylaxis by medication like drugs with anti-TGFβ properties, such as losartan, rosiglitazone, statins, or sodium-glucose transporter 2 (SGLT2) inhibitors, may be beneficial but have not been studied prospectively in a large number of patients on long-term PD. However, these distract from the basic problem of pseudohypoxia. The producers of commercially available dialysis solutions should feel the urgency for solutions that cause no glucose-induced pseudohypoxia when they really care for long-term PD.

Disclosures
R.T. Krediet reports serving on the editorial board of Peritoneal Dialysis International. The remaining author has nothing to disclose.

Funding
None.

Author Contributions
R.T. Krediet conceptualized the study; R.T. Krediet was responsible for data curation; R.T. Krediet and A. Parikova were responsible for investigation; R.T. Krediet was responsible for methodology; R.T. Krediet and A. Parikova were responsible for validation; R.T. Krediet was responsible for visualization; R.T. Krediet wrote the original draft; and R.T. Krediet and A. Parikova reviewed and edited the manuscript.

References
26. Oh KH, Jung YJ, Yoon MO, Song A, Lee H, Ro H, Hwang YH, Kim DK, Margetts P, Ahn C: Intra-peritoneal interleukin-6 system is a potent determinant of the baseline peritoneal solute


49. Lijnen HR: Pleiotropic functions of plasminogen activator inhibitor-1. *J Thromb Haemost* 3: 35–45, 2005


61. Robertson LM, Fletcher NM, Diamond MP, Saed GM: Evitar (L-Alanyl-L-Glutamine) regulates key signaling molecules in the
pathogenesis of postoperative tissue fibrosis. Reprod Sci 26: 724–733, 2019


Published online ahead of print. Publication date available at www.cjasn.org.