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Biocompatibility of the new peritoneal dialysis solutions. Basic features

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Abstract
Over time, peritoneal dialysis (PD) produces morphological and functional changes in the peritoneal membrane. This process is related to uremic status as well as to continuous exposure to PD solutions. Novel PD fluids (PDFs) have greater biocompatibility, as they are designed to minimize the formation of glucose degradation products (GDPs) and the ready-to-use solution has a neutral pH. These properties have been achieved in both the balance and the bicavera® solutions manufactured by Fresenius Medical Care (Bad Homburg, Germany).
GDPs are strong catalysts of the formation of advanced glycation end products (AGE). In turn, AGEs, mediated by interaction with their receptor RAGE, lead to various cellular responses, such as up-regulation of inflammatory markers and cellular transdifferentiation. Moreover, cell growth, viability and functionality are impaired in the presence of GDPs, but are less affected if low GDP solutions are applied. Structural changes in the peritoneal membrane, such as membrane thickening and neovascularization are less pronounced with low GDP solutions than with conventional solutions. A more intact structure of the peritoneal membrane is further suggested by the increased levels of CA125, a marker of mesothelial cell mass and function associated with the use of biocompatible PDFs.
As a consequence of these alterations, functional changes in the peritoneal membrane are also associated with AGE deposits, correlating with increased membrane permeability and decreased ultrafiltration capacity.
Evidence supports further a systemic effect of GDPs present in PDF on serum AGE. Low GDP solutions exert both fewer local effects on the peritoneal membrane and less pronounced systemic effects. Clinical studies show better preservation of residual renal function and improved survival with the use of low GDP solutions.

Key words: *Peritoneal dialysis. Peritoneal dialysis fluid. Biocompatibility. Glucose degradation products. Advanced glycation end products.*

BIOCOMPATIBILIDAD DE LAS NUEVAS SOLUCIONES DE DIÁLISIS PERITONEAL. ASPECTOS BÁSICOS

Resumen
Con el tiempo en diálisis peritoneal (DP), la membrana peritoneal sufre cambios morfológicos y funcionales. Esto está relacionado con el estado urémico, pero también con la exposición continua a las soluciones de DP. Los nuevos líquidos de DP (PDF) son más biocompatibles, pues han sido diseñados para minimizar la formación de los productos de degradación de glucosa (PDG) y para que la solución esté lista para su uso con un pH neutral. Esto se ha logrado en ambas soluciones balance y bicavera® de Fresenius Medical Care (Bad Homburg, Alemania).
Los PDG son fuertes catalizadores de la formación de productos finales de glucación avanzada (AGE). Los AGE a su vez conducen, mediados por la interacción de su receptor RAGE, a varias respuestas celulares como la expresión exagerada de marcadores de inflamación y la transdiferenciación celular. Además, el crecimiento celular, la

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viabilidad y la funcionalidad se ven debilitadas en presencia de PDG, y se afectan menos con la aplicación de soluciones cuyos PDG sean escasos. Cambios estructurales de la membrana peritoneal, como en su grosor, y la neovascularización son menos pronunciados utilizando soluciones con bajas concentraciones de PDG que con las soluciones convencionales. Además, el aumento del CA125, un marcador de masa y función celular mesotelial asociado con el uso de líquidos de DP biocompatibles, indica una estructura más intacta de la membrana peritoneal.
Como consecuencia de estas alteraciones, los cambios funcionales de la membrana peritoneal también se asocian a los depósitos de AGE y a la extensa correlación con el aumento de la permeabilidad de la membrana y la reducción de la ultrafiltración.
La evidencia muestra también efecto sistémico de los PDG presentes en los líquidos de DP en el AGE del suero. Soluciones con pocos PDG producen menos efectos locales en la membrana peritoneal y efectos sistémicos menos pronunciados. Varios estudios clínicos muestran una mejor preservación de la función renal residual y mejora de la supervivencia con el uso de soluciones con bajas concentraciones de PDG.

Palabras clave: *Diálisis peritoneal. Líquidos de diálisis peritoneal. Biocompatibilidad. Productos de degradación de glucosa. Productos finales de glucación avanzada.*

Introduction

The peritoneal membrane is subject to morphological and functional changes with time on peritoneal dialysis (PD) which are related to the uraemic state and to the dialysis treatment. Various changes of the peritoneal membrane, such as increased thickness of the submesothelial zone and higher prevalence of vasculopathy are described both in haemodialysis and PD patients. In the latter in particular, these alterations further increase with time on treatment[1]. Continuous exposure to peritoneal dialysis solutions, the cumulative time on dialysis and the occurrence of peritoneal infections accumulate their effect on the cellular systems in the peritoneal membrane, such as mesothelial cells and immuno defence cells, and on submesothelial, interstitial and vascular structures[1]. These morphological changes lead to functional changes of the peritoneal membrane. Long-term application of PD may be limited as peritoneal permeability increases and ultrafiltration reduces. Moreover, peritoneal immune defence may be affected, increasing the risk of infections inducing further inflammation associated changes in the peritoneal membrane – a vicious circle starts.
Therefore during the last decade major emphasis has been put on the development of more biocompatible PD fluids (PDF), and of safer PD systems to minimise the infection risk, such as to prolong both the integrity and functionality of the peritoneal membrane. The following review will focus on the role of PD solution characteristics and glucose degradation products (GDP) on their effect on morphological and functional alterations in the peritoneal membrane, and on how the reduction of GDPs potentially improve membrane longevity and provide a clinical benefit to the PD patient.

Low GDP peritoneal dialysis solutions

PDFs are composed of electrolytes, a buffering component and an osmotic agent. Conventional solutions contain glucose as the osmotic agent, and lactate as the buffering component. The pH is adjusted to approx. 5.5, which is necessary to avoid caramelisation of glucose during the sterilisation process. Nevertheless, GDPs are formed to an extent depending on the pH of the glucose containing solution, the glucose concentration in the PDF, duration and temperature of the sterilisation process. Furthermore, time and conditions of solution storage can contribute to GDP formation.
To reduce the GDP load to the patient, single exchanges can be replaced by solutions, which do not contain glucose as osmotic agent and are thus lower in their GDP content than conventional solutions. In

glucose containing solutions the GDP content can be minimised by the appropriate bag design and manufacturing process. At an acidic pH of approx. 3 the GDP formation is lowest[2]. However, use of such an acidic PDF is not feasible in clinical practice. Therefore, the PD solutions developed recently with the aim to minimise GDP formation are produced in two compartment bags. This allows preparation of one compartment containing glucose and electrolytes at a pH around 3 and the other compartment with lactate at pH 8.0-8.6. Both solutions are mixed before use which allows the patient an intraperitoneal application of a solution not only with a minimised GDP content but at a neutral pH of 7.0-7.4.

This solution design has been realised both with the balance and the bicavera® solution of Fresenius Medical Care (Bad Homburg, Germany), either being lactate buffered (balance) or bicarbonate buffered (bicavera®). In these solutions the GDP formation is markedly reduced compared to conventional PDF, some of the GDPs are even below the detection limit[3].

The role of GDPs in changes of the peritoneal membrane

Cellular and morphological changes

Recent work has tried to elucidate the processes occurring in the peritoneal membrane to understand the relationship between the presence of GDPs in the PDF and membrane changes together with the long-term impairment of peritoneal function, and how the reduction of the GDP content might delay such alterations.

The capacity of GDPs to catalyse the formation of AGEs was demonstrated in vitro by Tauer et al[3]. When human serum albumin was incubated with conventional PD solutions, carboxymethyl-lysine (CML) and imidazolone, both major AGE compounds, were formed. In contrast, AGE formation was minimal both with low GDP solutions as balance, bicavera® and a conventional PD solution which was not heat, but filter-sterilised. Analogously to the in vitro formation, local in vivo AGE formation in the peritoneal membrane has been observed. Nakayama et al could identify AGE deposits in the mesothelial layer, the vascular wall and connective tissue of the peritoneal membrane, which increased with duration of CAPD. These findings are related to the cumulative exposure to glucose containing PDF together with increasingly impaired residual renal function, the main route of AGE excretion[4]. GDPs not only catalyse AGE formation, but also seem to induce reactions of cellular stress, such as the formation of heat-shock proteins (HSP). Arbeiter et al measured, among others, the formation of HSP-72 in mesothelial cells. Upon incubation with conventional PDF, the HSP-72 expression was up-regulated to a level exceeding 4 to 8 times the control values, whereas with a balance solution the HSP-72 expression was not affected[5].

The identification of the AGE receptor RAGE shed light on how signal transduction from AGE to various cellular responses might occur. Boulanger et al. could show a RAGE mediated pathway by the finding that blocking the AGE-RAGE interaction with anti-RAGE antibodies inhibited the subsequent expression of VCAM-1, a marker of endothelial activation and of inflammatory processes[6].

The same authors found that the formation of vascular endothelial growth factor (VEGF) and TGF-β was lower with the low GDP solutions balance and bicavera®. VEGF seems to be involved in various processes in the peritoneal membrane contributing to morphological and functional changes such as enhancing vascular permeability and angiogenesis. TGF-β is involved in the process of epithelial-to-mesenchymal transition, in the peritoneal membrane the conversion of mesothelial cells to fibroblast-like cells. By adding recombinant RAGE to compete with the natural RAGE, the VEGF and TGF-β production was reduced underlining again the role of the AGE-RAGE

interaction in the transduction pathway from GDP to various biological reactions[7].

VEGF production increased upon exposure to methylglyoxal, further co-localised immunohistochemically in the mesothelial layer and vascular walls of the peritoneal membrane[8]. Data by Leung et al hints at a possible role of VEGF also on the integrity of the peritoneal membrane. Zona occludens protein (ZO-1) is a tight-junction-associated protein in human peritoneal mesothelial cells. The addition of GDPs to cultures of human peritoneal mesothelial cells (HPMC) induces the formation of VEGF and down-regulation of ZO-1 expression in a time-and-dose-dependent manner. The latter in turn could be partly restored by adding anti-VEGF antibodies, underlining the reaction cascade, in which GDPs via VEGF formation and finally disintegration of the mesothelial layer might contribute to the deterioration of the peritoneal membrane[9]. Not only can disintegration of the mesothelial layer be observed but also transdifferentiation of the mesothelial cell type into fibroblast-like cells[10]. In vitro, animal and clinical studies confirmed that the type of PDF influences the extent of transdifferentiation being significantly lower with pH neutral, low GDP solution than in conventional PDF[11-13]. As shown recently by De Vriese et al, also the mesothelial-fibroblast transdifferentiation process concomitant to a TGF-β up-regulation is AGE-RAGE mediated, which might link to the development of peritoneal fibrosis[14].

The histological disintegration of cellular structures in the peritoneal membrane is also demonstrated in vitro by experiments on peritoneal cell growth. Single GDPs were shown to inhibit cell proliferation in a dose-dependent manner[15]. Furthermore, mixtures of GDPs in concentrations equivalent to those found in conventional PDF impair cell viability and function[16]. Ex vivo experiments show that proliferation and viability of HPMCs were better preserved in the presence of effluent obtained from dialysis with balance than in effluent from dialysis with conventional PDF[17].

Before understanding the importance of GDPs in PDF, bioincompatibility of PD fluids has been attributed among other factors to high glucose concentrations. However, Witowski et al could show by exposing HPMCs to either heat- or filter-sterilised PDF that primarily GDPs, less the glucose impair viability and function of HPMCs[18]. This was confirmed in experiments testing glucose and GDP solutions both alone and in combination for their effect on cell viability and functionality. Being only minimally affected by the glucose solution, a marked effect was however exerted by GDPs which was not further enhanced by adding glucose[19].

The impairment of cell viability and functionality by the presence of GDPs translates also in a deterioration of wound repair. An artificially set scratch wounding of a mesothelial cell layer was healing within 15 hours when incubated with a low GDP solution, whereas in the cell layer incubated in a conventional PDF remesothelialisation was retarded considerably[20].

Data by Boulanger et al[7] suggest that GDPs play a role in the entire cell cycle. Not only cell proliferation was disturbed by the presence of GDPs but also apoptosis and oncosis of mesothelial cells were enhanced. Both processes were less pronounced, when the cells were incubated in the low GDP solutions such as balance and bicavera®.

The previously discussed results of in vitro studies and animal models have demonstrated a pivotal role of GDPs present in PD solutions on mesothelial cells in terms of their morphology, viability and functionality. This raises the question as to the relevance of these observations for morphological and functional changes in the peritoneal membrane over time on PD. Several clinical studies have been performed comparing low GDP and conventional solutions and addressing the effect of biocompatible PDF on indicators of peritoneal membrane integrity. CA125 has been established as a marker of mesothelial cell mass in peritoneal dialysis. Higher levels are associated to

a higher mesothelial cell mass[21] and cell function[22]. All clinical studies uniformly demonstrate higher CA125 levels in the peritoneal effluent when balance[23-27] or bicavera® [28] were applied, in comparison to patients or study phases with conventional PDF. Hyaluronan, a marker of intraperitoneal inflammation and wound healing was reduced when the balance solution was used[23,24,29], indicating a lower level of peritoneal injury.

Changes in the peritoneal membrane over time not only affect the mesothelial cell layer but the entire peritoneal membrane. Williams et al. demonstrated with data from the Peritoneal Biopsy Registry that with time on dialysis the thickness of the peritoneal membrane and the prevalence of vasculopathy increase[1]. An animal study by Wieczorowska-Tobis et al[29] demonstrates that the extent of membrane thickening and of vascular density was lower in animals treated with balance than in those treated with conventional PDF. This underlines that not only time but also the solution characteristics are of importance for changes occurring in the peritoneal membrane. This is also supported by studies applying intravital microscopy to investigate the effect of different PDF on vascularisation and arteriolar flow. Both are increased and remain elevated during the complete time of exposure to conventional PDF, whereas with balance only a short and transient and with bicavera® no effect was observed[30].

Functional changes of the peritoneal membrane

GDPs and AGEs have various effects on the peritoneal membrane. As early as 1997 Nakayama et al[4] could relate the AGE deposition in the peritoneal membrane to functional changes. The longer the patients were on PD the more pronounced were the AGE deposits shown by a score of AGE staining in the mesothelial layer, the vascular wall and the interstitial tissue. In parallel the peritoneal function changed as demonstrated by increased permeability for small molecules and proteins. The extent of AGE deposition in the interstitial layer and vasculature of the peritoneal membrane was associated with interstitial fibrosis and peritoneal vascular sclerosis which in turn inversely correlated to ultrafiltration capacity[31]. Similarly, Park et al[32] found a higher degree of AGE deposition in the peritoneal tissues in long-term than in new PD patients, further a correlation of peritoneal AGE content to peritoneal permeability and an inverse correlation to ultrafiltration volume.

Systemic effects and clinical importance of PD solution biocompatibility

In vivo GDPs act locally at the peritoneal membrane, but as they are also absorbed during the peritoneal dwell systemic action can also be assumed.

Serum levels of AGEs are elevated in patients with chronic kidney disease either on haemodialysis or peritoneal dialysis[33]. The significant reduction of serum imidazolone after three months application of the low GDP solution balance suggests that not only the uraemic state and decreased renal function plays a role, but supports also a link between GDP content in PDF and systemic AGE formation[24]. As systemic AGEs are renally eliminated, adverse effects on kidney function can also be assumed. Indeed, recent studies provide evidence on better preservation of residual renal function associated with the use of the low GDP solution balance[24]. Since the importance of residual renal function for survival of peritoneal dialysis patients was confirmed in several studies[34], the positive effect of low GDP solutions on renal function might give a link to improved survival observed in patients treated with the balance PD solution[35].

Conclusions

As the peritoneal membrane is the functional dialysis membrane in PD, its preservation is essential to provide adequate solute and fluid removal. Not only time on PD as such seems to be a factor changing morphological and functional parameters of the peritoneal membrane but also the quality of the therapy in terms of solution biocompatibility and frequency of peritoneal infections. PDFs low in GDP and at neutral pH catalyse AGE formation to a lesser extent, lead to less AGE formation in the peritoneal membrane and lower systemic AGE levels. Moreover, reactions associated to GDPs such as lower formation of mediators of inflammation, neovascularisation and other cellular responses are less pronounced with biocompatible PDF. In addition, cell viability and functionality are better maintained with more biocompatible solutions, and are also reflected in improved markers of peritoneal membrane integrity. Thus, treatment with more biocompatible PD fluids has the potential to longer preserve the peritoneal membrane not only morphologically but also functionally and to contribute to long-term clinical benefits to the PD patient.

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