Preserving Peritoneal Membrane- anything new?

Dr Marjorie Foo
Head, Department of Renal Medicine
Director of SGH PD program
Singapore General Hospital
The natural course of peritoneal membrane biology during peritoneal dialysis

**John D. Williams, Kathrine J. Craig, Chris von Ruhland, Nicholas Topley, and Geraint T Williams, for the Biopsy Registry Study Group**

*Institute of Nephrology; Medical Microscopy Sciences; and Department of Pathology, University of Wales College of Medicine, Heath Park, Cardiff, UK*
Fig. 1. (A) Normal parietal peritoneum. There is a surface layer of flattened, cohesive mesothelial cells bearing microvilli and with indistinct cytoplasm containing occasional small vesicles. Nuclei are relatively inconspicuous and nucleoli are not seen. There is a submesothelial compact zone of mature collagen fibers. Toluidine blue stain. (B) Parietal peritoneum from a patient treated only by hemodialysis. The mesothelial cells show "reactive" changes. While cohesive, they are enlarged and appear rounded or cuboidal. The cytoplasm is prominent and finely granular, and the nuclei are irregular with prominent nucleoli and margination of chromatin. There is thickening of the submesothelial compact zone. Toluidine blue stain. (C) Parietal peritoneum from a patient treated with peritoneal dialysis. The mesothelial cells show reactive changes similar to those in B, but they are beginning to separate, both from each other and from the underlying stroma. Toluidine blue stain. (D) Parietal peritoneum from a patient treated with peritoneal dialysis. There is thickening of the submesothelial compact zone by coarse collagen bundles and the overlying mesothelium shows degenerative changes superimposed on the reactive changes seen in B and C. The mesothelial cells are pale, rounded, and dissohesive and some are shedding from the surface. Toluidine blue stain.
Peritoneal dialysis: Changes to the structure of the peritoneal membrane and potential for biocompatible solutions

John D. Williams, Kathrine J. Craig, Nicholas Topley, and Geraint T. Williams

Institute of Nephrology and Department of Pathology, University of Wales College of Medicine, Heath Park Cardiff, Wales, United Kingdom
Fig. 2 Changes in the submesothelial compact (SMC) zone with biopsy origin and with PD duration.
The thickness of the SMC zone in (micrometers) was measured in biopsies from normal individuals, uremic patients and patients undergoing HD, and patient undergoing PD, grouped according to duration of dialysis. Data are represented in boxplots, with the boxes representing the interquartile range (IQR). Lines extend from the box to the highest and lowest values, excluding outliers. The circles represent outliers.
Figure 3. Changes in the grade of vasculopathy according to the origin of the peritoneal biopsy.
Grade 1, subendothelial hyaline zone <7um
Grade 2, subendothelial hyaline zone >7um
Grade 3, the lumen is distorted or narrowed
Grade 4, the vascular lumen is obliterated by connective tissue which sometimes contains calcific stippling
What causes this transition?
The morphological change of PD membrane over time

Early changes

• Loss of mesothelial layer and reduplication of peritoneal basement membrane
• Duplication of sub-mesothelial layer
The Peritoneal Membrane

What happens to the membrane?

**Morphologically:**
- Loss of mesothelium and reduplication of basement membrane
- Increased thickness in the submesothelial compact (SMC) collagenous zone of parietal peritoneum, due to increase in extracellular matrix.
- Epithelial to mesenchymal transition (EMT) of mesothelial cells: presence of fibroblast cell of mesothelial origin in SMC, starting process for fibrosis
- Interstitial fibrosis subendothelial hyalinosis of venules and arterioles
- Lamellation of capillary and mesothelial basement membrane
- Neoangiogenesis

Fibrosis can reduce permeability of membrane
Increased vasculature increases permeability of membrane
The morphological change PD membrane over time

- Medium to long term 4 years and beyond
- 20-30% acquired HT status
- Risk factors for acquired HT
  - Peritonitis episodes (severe or repeated)
  - Prolonged high glucose exposure
- Pathogenesis:
  - Angiogenesis and fibrosis by induction of VEGF and TGF-β
  - Sclerosis vs EPS
Peritoneal Membrane Preservation

M. Auxiliadora Bajo, MD, PhD,* Gloria del Peso, MD, PhD,† and Isaac Teitelbaum, MD‡

Figure 1. Pathogenesis proposal for ultrafiltration failure and acquired peritoneal hyperpermeability. RAGE, receptor for advanced glycation end products. Adapted with permission from López-Cabrera et al.39
Classification of Ultrafiltration Failure

1 yr <3%, 3 yr 9.5%, 6 yr 30%

- **Type I**
  - High transport status
  - Rapid loss of glucose gradient
  - Commonest; increases with time

- **Type II**
  - Low transport status
  - Loss of peritoneal surface area
  - Uncommon

- **Type III**
  - High lymphatic flow rate
  - By exclusion
  - ? Prevalence

- **TYPE IV**
  - Aquaporin dysfunction
  - Rare
WHAT ARE THE FUNCTIONAL CHANGES OVER TIME?
Longitudinal relationship between solute transport and ultrafiltration capacity in peritoneal dialysis patients

Simon J. Davies

Department of Nephrology, University Hospital of North Staffordshire, Stoke-on-Trent, Staffordshire, United Kingdom; and Institute of Science and Technology in Medicine, Keele University, Keele, Staffordshire, United Kingdom
Fig. 1. The upper panel shows the linear best-line fit for the relationship between solute transport and UF capacity at each time-point during the study. The gradients (±95% CI), shown in the lower panel are remarkably similar, but tend to become steeper at 6 and 7 years.

Fig. 2. Longitudinal changes in solute transport (A) and UF capacity (B) for the whole cohort. A significant increase in solute transport was seen by 6 months and for each subsequent time point, \( P = 0.008 < 0.001 \). A reduction in UF capacity occurred at 24 months and beyond, \( P = 0.047 < 0.001 \). For numbers of patients at each time point, see legend to Figure 1.
Longitudinal relationship between solute transport and ultrafiltration capacity in peritoneal dialysis patients

**PET and UF**

Fig. 4. Longitudinal changes in solute transport (A) and UF capacity (B) for the patients who subsequently developed UF failure (□) and the remainder of the cohort (●). Despite better membrane function at the start of treatment, the rate of increase in solute transport tends to be faster with significantly worse UF capacity at 24 and 48 months, $P < 0.05$.

Fig. 5. In this case two lines are plotted, that for patients with low (□) and high (●) intraperitoneal glucose exposure during the first 12 months of dialysis treatment. At each time point, the latter group has higher solute transport and less UF capacity, but in those exposed to low glucose concentrations, membrane function is stable for the first 4 years of therapy, and UF capacity never becomes disproportionately low. See Figure 3 for description of this graph format.
Glucose as a cause of UFF

Peritoneal Glucose Exposure

Glucose Exposure (g/year)

Transport Changes (D/P Creatinine)

Serial Monitoring PET and UFF to predict UFF
Biomarkers

Studies so far:

- CA 125: a glycoprotein, release proportional to MC mass
  - Decrease over time
  - Higher levels at baseline in biocompatible solution use
- IL-6, cytokine with proinflammatory and anti-inflammatory properties
  - Increase in peritonitis
  - Reduced in biocompatible solution use
- Chemokine ligand 18 produced by monocyte and macrophages, associated with peritoneal dysfunction and fibrosis
  - Increased in EPS, high transport state and UFF

New technologies

- Genomics, metabolomics and proteomics on PD effluent
# Biomarkers

**Table 1. Biomarkers of the Peritoneal Membrane That Have Been Explored for Use in PD Patients**

<table>
<thead>
<tr>
<th>Name</th>
<th>Marker of</th>
<th>Findings</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA-125</td>
<td>Mesothelial cell</td>
<td>Effluent levels correlate with mesothelial cell mass</td>
<td>Koomen et al(^{47})</td>
</tr>
<tr>
<td></td>
<td>loss</td>
<td>Dialysate CA125 decreases during time on PD</td>
<td>Ho-dac-Pannekeet et al(^{48})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Higher CA125 levels with biocompatible solutions at baseline and during follow-up evaluation</td>
<td>Williams et al(^{25})</td>
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<tr>
<td>IL-6</td>
<td>Inflammation</td>
<td>Effluent levels increased markedly during peritonitis</td>
<td>Pecoits-Filho et al(^{49})</td>
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<tr>
<td>TGF-β</td>
<td>Fibrosis</td>
<td>Dialysate IL-6 levels are decreased with biocompatible solution use</td>
<td>Cooker et al(^{52})</td>
</tr>
<tr>
<td></td>
<td>Angiogenesis</td>
<td>No relationship between effluent levels and time on PD</td>
<td>Zweers et al(^{57})</td>
</tr>
<tr>
<td>VEGF</td>
<td>Angiogenesis</td>
<td>Similar levels with conventional and biocompatible PD solutions</td>
<td>Jones et al(^{122})</td>
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<tr>
<td></td>
<td></td>
<td>Increases with PD duration</td>
<td>Zweers et al(^{58})</td>
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<tr>
<td></td>
<td></td>
<td>Increased dialysate VEGF concentrations associated with high peritoneal solute transport</td>
<td>Pecoits-Filho et al(^{49})</td>
</tr>
<tr>
<td>MMP-2</td>
<td>Fibrosis</td>
<td>Dialysate levels are related to peritoneal fibrosis in animal models</td>
<td>Lopes Barreto et al(^{56})</td>
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<tr>
<td></td>
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<td>MMP-2 levels in the drained dialysate correlate with D/P Cr</td>
<td>Hirahara et al(^{55})</td>
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<tr>
<td></td>
<td></td>
<td>Not related to PD duration</td>
<td></td>
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<tr>
<td>CCI-18</td>
<td>Fibrosis</td>
<td>Effluent CCL18 correlates with high peritoneal transport and development of EPS</td>
<td>Ahmad et al(^{53})</td>
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<tr>
<td></td>
<td></td>
<td>Higher effluent CCL18 levels found in patients with UFF and in patients who develop EPS</td>
<td>Bellón et al(^{54})</td>
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<tr>
<td>HA</td>
<td>Fibrosis</td>
<td>Increased dialysate levels are associated with both high peritoneal transport and time on PD</td>
<td>Yamagata et al(^{62})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower effluent concentrations with biocompatible PD solutions</td>
<td>Rippe et al(^{63})</td>
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<tr>
<td>PAI-1</td>
<td>Fibrosis</td>
<td>Tendency to increase with PD duration</td>
<td>Lopes Barreto et al(^{56})</td>
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<tr>
<td></td>
<td></td>
<td>Correlates with peritoneal transport parameters</td>
<td></td>
</tr>
<tr>
<td>CTGF</td>
<td>Angiogenesis</td>
<td>Increased CTGF levels in PD patients with high peritoneal transport</td>
<td>Mizutani et al(^{61})</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Angiogenesis</td>
<td>No difference between conventional and biocompatible PD fluids</td>
<td>Williams et al(^{25})</td>
</tr>
</tbody>
</table>

Abbreviations: CCL18, CC chemokine ligand 18; D/P Cr, dialysate/plasma creatinine ratio; MMP-2, matrix metalloproteinase-2; CCl-18, chemokine ligand 18; PAI-1, plasminogen activator inhibitor-1; CTGF, connective tissue growth factor; TNF-α, tumor necrosis factor α.
Therapeutic measures....anything new?
Biocompatible solutions

- Neutral pH low GDP solution
- Icodextrin and low glucose regimen
- Peritoneal resting
<table>
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<th>Therapeutic Agents</th>
<th>Patients and Study Design</th>
<th>Parameters Studied</th>
<th>Outcomes</th>
<th>Reference</th>
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<tr>
<td><strong>Low-GDP solutions</strong></td>
<td>Patients allocated to use standard PD fluids (n = 20) or low-GDP solution (Balance) (n = 13) for 24 months</td>
<td>Human peritoneal MC isolated from PD effluent and peritoneal function evaluation</td>
<td>The degree of EMT was less with low-GDP solutions; peritoneal functional parameters were similar in both groups</td>
<td>Bajo et al.</td>
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<td></td>
<td>Patients randomly assigned to use either a neutral pH low-GDP fluid (BicaVera; n = 13) or standard PD fluid (n = 20) (both from Fresenius, Fresenius Medical Care, Bad Homburg, Germany)</td>
<td>Human peritoneal MC isolated from PD effluent</td>
<td>A trend to gain and maintain an epithelioid phenotype with fewer fibrogenic characteristics</td>
<td>Fernández-Perpén et al.</td>
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<tr>
<td></td>
<td>10 patients randomly assigned to use conventional or low-GDP PD solutions</td>
<td>PMO</td>
<td>Improvement in PMO function</td>
<td>Jones et al.</td>
</tr>
<tr>
<td></td>
<td>60 new PD patients were randomized to use low-GDP or standard PD solutions for 12 months</td>
<td>Culture of HPMCs drained from PD effluent.</td>
<td>Rapid remesothelialization and less fibroblastoid change in the peritoneum with time on PD</td>
<td>Do et al.</td>
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<td></td>
<td>11 patients on PD for at least 3 years</td>
<td>Peritoneal biopsies</td>
<td>Less progression of peritoneal interstitial fibrosis and hyalinizing vasculopathy</td>
<td>Ayuzawa et al.</td>
</tr>
<tr>
<td></td>
<td>24 PD patients treated with standard solutions or neutral pH solution with low GDP</td>
<td>Peritoneal specimens</td>
<td>Less peritoneal membrane fibrosis and vascular sclerosis; however, blood capillary density was increased in the neutral group</td>
<td>Kawanishi et al.</td>
</tr>
<tr>
<td></td>
<td>23 PD patients treated with biocompatible solutions compared with 23 patients, matched for time on PD, treated with conventional solutions</td>
<td>Peritoneal biopsies</td>
<td>Better-preserved mesothelial cell layer, less thickening of submesothelial compact zone, and near absence of hyalinizing vasculopathy</td>
<td>Del Peso et al.</td>
</tr>
<tr>
<td><strong>Icodextrin</strong></td>
<td>16 PD patients using glucose-based or icodextrin PD solutions</td>
<td>HPMCs isolated from the nocturnal peritoneal effluent</td>
<td>MCs taken from icodextrin effluent showed greater ex vivo proliferation than those taken from glucose effluent</td>
<td>Bajo et al.</td>
</tr>
<tr>
<td></td>
<td>A prospective cohort of 177 anuric patients treated with APD</td>
<td>Ultrafiltration capacity and small-solute transport</td>
<td>Icodextrin use was associated with less damage in membrane function</td>
<td>Davies et al.</td>
</tr>
<tr>
<td><strong>Low-glucose PD regimen</strong></td>
<td>A prospective study of 63 new CAPD patients randomized to either a standard or a low-glucose PD regimen</td>
<td>Clinical and laboratory determinations</td>
<td>Lower daily glucose load, less decrease in CA125 levels in efflent, and higher D/P creatinine levels</td>
<td>Le Poole et al.</td>
</tr>
<tr>
<td></td>
<td>80 incident PD patients randomized to use either a low-glucose PD regimen or standard glucose-based PD solutions for 12 months</td>
<td>Effluent biomarkers and peritoneal function parameters</td>
<td>Effluent dialysate levels of CA125, decorin, HGF, IL-6, adiponectin, and adhesion molecules were significantly higher in the low-glucose PD group; a higher D/P creatinine ratio was observed in the low-glucose PD group</td>
<td>Yung et al.</td>
</tr>
<tr>
<td><strong>Peritoneal resting</strong></td>
<td>16 patients with UFF</td>
<td>Peritoneal function parameters</td>
<td>Urea and creatinine MTAC decreased and UF increased significantly after peritoneal resting</td>
<td>De Alvaro et al.</td>
</tr>
<tr>
<td></td>
<td>11 patients with type I UFF</td>
<td>Peritoneal function parameters</td>
<td>66.6% recovered UF; better results if the pause was initiated soon after diagnosis</td>
<td>Rodrigues et al.</td>
</tr>
<tr>
<td></td>
<td>35 patients with UFF compared with 49 controls</td>
<td>Peritoneal function parameters</td>
<td>Patients with UFF showed decreased D/P creatinine, decreased creatinine MTAC, and increased UF capacity after resting</td>
<td>De Sousa et al.</td>
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</table>
The effect of low glucose degradation product, neutral pH versus standard peritoneal dialysis solutions on peritoneal membrane function: the balANZ trial

David W. Johnson¹,², Fiona G. Brown³, Margaret Clarke⁴, Neil Boudville⁵, Tony J. Elias⁶, Marjorie W.Y. Foo⁷, Bernard Jones⁸, Hemant Kulkarni⁹, Robyn Langham¹⁰,¹¹, Dwarakanathan Ranganathan²,¹², John Schollum¹³, Michael G. Suranyi¹⁴, Seng H. Tan¹⁵,¹⁶,¹⁷, David Voss¹⁸ and on behalf of the balANZ Trial Investigators

The effect of low glucose degradation product

Fig. 1. Change in D/P Cr 4 h over time in the balance (A) and control (B) groups over 2 years. Grey lines represent individual patient measurements while solid lines represent predicted gradients. The difference in gradients between the two groups was statistically significant (P < 0.001).
The effect of low glucose degradation product, neutral pH versus standard peritoneal dialysis solutions on peritoneal membrane function: the balANZ trial

David W. Johnson1,2†, Fiona G. Brown3†, Margaret Clarke4, Neil Boudville5, Tony J. Elias5, Marjorie W.Y. Foo6, Bernard Jones6, Hemant Kulkarni6, Robyn Langham6,11, Dwarakanathan Ranganathan6,12, John Schollum13, Michael G. Suranyi14, Seng H. Tan15,16,17, David Voss18 and on behalf of the balANZ Trial Investigators

Fig. 5. Change in peritoneal UF over time in the Balance (A) and control (B) groups over 2 years. Grey lines represent individual patient measurements while solid lines represent predicted gradients. The difference in gradients between the two groups was statistically significant (P = 0.002).

Fig. 6. Change in peritoneal UF, normalized for peritoneal glucose exposure, over time in the Balance (A) and control (B) groups over 2 years. Grey lines represent individual patient measurements while solid lines represent predicted gradients. The difference in gradients between the two groups was statistically significant (P = 0.004).
BIOCOMPATIBLE DIALYSIS SOLUTIONS PRESERVE PERITONEAL MESOTHELIAL CELL AND VESSEL WALL INTEGRITY. A CASE-CONTROL STUDY ON HUMAN BIOPSIES

Gloria del Peso,1 José Antonio Jiménez-Heffernan,2 Rafael Selgas,3 César Remón,3 Marta Ossorio,1 Antonio Fernández-Perpén,4 José Antonio Sánchez-Tomero,4 Antonio Cirugeda,5 Erika de Sousa,7 Pilar Sandoval,6 Raquel Díaz,4 Manuel López-Cabrera,6 and María Auxiliadora Bajo1

Figure 3 — Peritoneal biopsies from patients receiving biocompatible solutions (a,c,e) showed better mesothelial cell preservation, less submesothelial thickness and hyalinizing vasculopathy when compared with patients treated with conventional fluids (b,d,f). Grade 1 hyalinizing vasculopathy lesions are seen on image b (arrow). A clear contrast among mesothelial cell preservation is evident on all images (a,b,c,d: hematoxylin and eosin, ×200). Immunohistochemistry for cytokeratins reveals a modified, superficial mesothelial cell (arrow) that contrasts with the well preserved layer seen on a biocompatible patient (e,f: immunoperoxidase, ×400).

RAS blockade

Losartan and captopril inhibit glucose-induced TGF-\(\beta\) and fibronectin expression in culture human peritoneal MC

– Attenuation of overproduction of VEGF due to proinflammatory cytokines

– Enalapril treated rats, decrease sub-mesothelial thickness, this correlated with decrease dialysate TGF-\(\beta\) concentration

In humans

• Patients on RAAS blockade: slower rate of UF reduction

• Lower fibronectin, TGF-\(\beta\) 1 and VEGF in PD effluent and prevents the increased in MTAC

  Jing et al. Nephrology 2010;15:27-32
  Kolesnyk I et al PDI 2007;27: 446-53
Spironolactone to Prevent Peritoneal Fibrosis in Peritoneal Dialysis Patients: A Randomized Controlled Trial

20 incident cases
• Spironolactone 25mg x 6 month
• Peritoneal biopsy at the start and end of follow up
• IHC for collagen IV, CD20 and CD3

Primary outcome: Peritoneal fibrosis
Secondary outcome: inflammatory markers, hyperkalemia and peritonitis episodes

Table 2. Peritoneal Characteristics Between Groups at Follow-up

<table>
<thead>
<tr>
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<th>Spironolactone (n = 9)</th>
<th>Placebo (n = 9)</th>
<th>P Between Groups</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Catheter Placement</td>
<td>End of Follow-up</td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td>18,451 [11,451-19,431]</td>
<td>19,561 [15,761-24,123]</td>
<td>0.07</td>
</tr>
<tr>
<td>Thickness</td>
<td>865 [762-1,238]</td>
<td>1,342 [1,281-1,781]</td>
<td>0.05</td>
</tr>
<tr>
<td>CD20</td>
<td>11 [9-15]</td>
<td>29 [28-39]</td>
<td>0.008</td>
</tr>
<tr>
<td>CD3</td>
<td>7 [5-12]</td>
<td>16 [12-25]</td>
<td>0.008</td>
</tr>
<tr>
<td>Collagen IV</td>
<td>108 [101-121]</td>
<td>147 [146-156]</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Note: Data shown as median [25th-75th percentile]. Values are given in pixel units, except for thickness, which is given in μm.

Heparin and Glycoaminoglycans (GAG)

**GAG:** Long unbranched polysaccharides
- Produced by MC
- Highly polar and hydrophilic, good lubricant reduces friction and adhesions

**Heparin**
- Has immunomodulatory effects and effects on ECM
- Anti-inflammatory, anti-proliferative, anti-fibrotic

**LMWH**
- Inhibit VEGF and fibroblast growth factor activity

*Del Peso G et al.*
- 95 PD patients, one daily IP bemiparin for 16 weeks
  
  **Conclusion:** no significant improvement in transport status or UF capacity but a time-limited improvement in UF in a subgroup with overt UFF

**Hyaluronan acid**

*Moberly et al.*
- Effects of intraperitoneal hyaluronan on peritoneal fluids and solute transport in peritoneal dialysis *PDI 2003:23:63-73*
- Randomised cross over 13 patients, IP administration of HA ...negative study

**Sulodexide:** a mixture of GAGs, fast moving heparin and dermatan sulphate with anticoagulant and anti-thrombotic effects
- Results in humans and rats were encouraging on both morphological and functional properties of the PM
Agents targeting EMT and mesothelial cells

- **TGF-beta 1**
  - Cannot be used in human,
  - plays an important role in modulation functions and inflammatory responses..
  - target signaling pathways involve in EMT offers more specific strategies with fewer side effects

- **BMP-7 ameliorate**
  - Natural blockers of EMT induced by high glucose
  - IP BMP-7 in rats - reduction in EMT fibrosis and angiogenesis, no human studies

- **Tamoxifen**
  - Effective in fibrotic diseases due to this effect on TGF- \( \beta \), clinically has been used to treat EPS with some success
    - *De Sousa-Amorium et al…PDI 2014;34:582-93*
    - *Korte MR et al…Dutch multicenter EPS study. NDT 2011;26;691-7*

- **Statins**
  - Inhibits EMT changes on MC in rats
  - Effective stimulator of mesothelial fibrinolytic capacity, suppress procoagulant activity under normal and inflammatory conditions
    - *Haslinger et al .KI 2003;63:265-74*
Additive to PD solution

• Agents that targets inflammation
• Alanyl-glutamine (Ala-Gln) added to cultured mesothelial cells increased O-linked N-acetylglucosamine (O-GlcNAc)
  – Restoration of cytoprotective stress proteome increase MC integrity to PDF exposure
  – First clinical evidence for peritoneal immune-modulation by an alanyl-glutamine containing peritoneal dialysis solution

Kratochwill et al PDI 2014;24 (Suppl 3):S72
Alternative osmotic agent

L-Carnitine

- Soluble and stable and physiological pH
- PDF with L carnitine showed superior cell growth, enhance secretion of prostaglandin E2, less release of LDH, less apoptosis and better conservation of cell morphology
- Prevention of peritoneal sclerosis
  - A new proposal to substitute glucose with carnitine dialysis solution (biocompatibility testing in vitro and in rabbits).

  Bonomini et al. KI 2011;80:645-54

Taurine, regulates osmotic balance ion transport

  Nishimura Het al  PDI 2009;29:204-16
Other therapeutic agents

Celecoxib-cyclooxygenase 2
- No human studies
- Animal studies showed reduced peritoneal inflammation, angiogenesis and fibrosis

Paricalcitol (selective VDR agonist)
- VDR: a nuclear hormone that modulates inflammation, fibrosis, angiogenesis and immune response
- Rats experiments IP paricalcitol: prevents PM deterioration, reduce fibrosis and UF failure
- Mechanism of action: dependent increased in T regulatory cells and reduction of IL-17 production

Rosiglitazone: Peroxisome proliferator-activated receptor –γ agonist (PPARγ)

- Reduces GDPs and formation of AGEs
- Anti-inflammatory with possible anti-EMT activity
- In mice, diminish accumulation of AGEs, preservation of mesothelial monolayer, reduced fibrosis and angiogenesis
- Anti-inflammatory effects were mediated by increase peritoneal levels of IL-10 and recruitment of CD4+, CD 25+, FoxP3+ cells and D3+ lymphocytes
Other therapeutic agents

- **Benfotiamine**
  - Fat soluble vitamin B1
  - Anti-oxidant properties, reduction of AGEs accumulation
  - Animal studies:
    - Improvement in peritoneal fibrosis, AGE accumulation, neo-angiogenesis, inflammatory markers and with peritoneal transport status
    - No human studies
Peritoneal Resting

Figure 1 — Evolution of peritoneal functional data before and after peritoneal rest in the control and ultrafiltration failure groups. (A) Creatinine MTAC (mL/min), (B) Urea MTAC (mL/min), (C) D/P-Cr and (D) UF/4 h (mL). The p value in bold expresses the differences between groups in the comparison of the gradients. Posthoc analysis showed statistically significant (p<0.05) differences in all parameters evaluated when the 2 groups were compared. Cr-MTAC = mass transfer area coefficient creatinine; U-MTAC = mass transfer area coefficient urea; D/P Cr = dialysate/plasma creatinine ratio; UF/4h = ultrafiltration capacity; PR = peritoneal rest; UFF = ultrafiltration failure; NS = not significant.
Peritoneal resting enabled patients with UFF to continue on PD for a median time of 23 months (range, 13 – 46 months).

Figure 2 — Evolution of peritoneal functional data before and after peritoneal rest in ultrafiltration failure patients, with and without a previous history of peritonitis. (A) Creatinine MTAC (mL/min), (B) Urea MTAC (mL/min), (C) D/P-Cr and (D) UF/4 h (mL). The p value in bold expresses the differences between groups in the comparison of the gradients. Posthoc analysis showed no statistically significant (p<0.05) differences in all the parameters evaluated when the 2 groups were compared. Cr-MTAC = mass transfer area coefficient creatinine; U-MTAC = mass transfer area coefficient urea; D/P Cr = dialysate/plasma creatinine ratio; UF/4 h = ultrafiltration capacity; PR = peritoneal rest; NS = not significant.
Summary

• **Dietary and fluid intervention.**
  – Low salt and restrict fluid
  – Maximize use of diuretics
  – =minimize glucose exposure

• **Biocompatible solution**

• **Medication**
  – RAAS blockade with spironolactone, ACEis or ARBs
  – PPAR - γagonist, statins
  – Diuretics

• **Other maneuvers**
  – Peritoneal rest
  – In fibrosis/ sclerosis: tamoxifen / IS e.g. rapamycin
Thank You