Causes of Peritoneal Membrane Failure

Isaac Teitelbaum, MD
Professor of Medicine
Director, Acute and Home Dialysis Programs
University of Colorado Hospital
Aurora, Colorado
Outline

• Physiology of peritoneal transport
  - Structure of the peritoneum
  - Models of peritoneal transport
  - Inverse relationship between solute transport and ultrafiltration

• Causes of Membrane Failure
  - Pathophysiology
  - Diagnosis
  - Treatment
Structure of the Peritoneal Membrane

- Serous membrane lining the abdominal cavity
- Single layer of mesothelial cells supported by connective tissue
- Capillaries, lymphatics, and nerves are found within connective tissue
Transport Across the Peritoneal Endothelium: 
*The Three Pore Model*

- **Large pores (100 - 200 Å)**
  - few in number (3% of SA)
  - transport macromolecules
  - clefts between endothelial cells

- **Small pores (40 - 60 Å)**
  - most numerous (95% of SA)
  - allow transport of small solutes and water
  - postulated to be clefts in the endothelium; have not been demonstrated anatomically

- **Ultrasmall (transcellular) pores (4 - 6 Å)**
  - many in number (but only 2% of SA)
  - transport water only (Na sieving)
  - **Demonstrated** to be AQP 1
Changes In Dialysate Sodium During Dwell (Sodium Sieving)

Heimburger et al. Kid Int 38: 495, 1990
Ultrafiltration in PD: The Pore-Matrix Model

50% osmotic UF + Na-sieving during hypertonic dwell
Small Solutes

50% osmotic UF + small solute transport

Small solute + protein loss
Protein

Aquaporin (semipermeable membrane)

Dense intercellular fibers restrict transport

Loose intercellular fibers permit transport of macromolecules

Glycocalyx

Flessner M. Contrib Nephrol 163:7, 2009
Ultrafiltration in PD: The Distributed Model
Standard Peritoneal Equilibration Test (2.5% Dextrose)

Ultrafiltration with Different Strengths of Dialysate

Intraperitoneal volume, ml

Time, min

4.25% Dextrose

1.5% Dextrose
Fluid Absorption from the Peritoneal Cavity

- Occurs directly via lymphatics (~ 10%)
- Also via absorption across tissues
- Difficult to measure but ~ 1-2 ml/min
- These processes are “bulk flow” and therefore detract from solute and fluid removal
Balance of Opposing Forces

Absorption
Transcapillary UF
Net UF

Cumulative transport (ml)

Time (min)

Reabsorption from peritoneal cavity

Epithelial to Mesenchymal Transition

Ultrafiltration Failure

• Signs of volume overload
  - In absence of patient non-adherence
  - Stable residual renal function
  - No mechanical disruption of the peritoneal membrane boundary
Causes of Membrane Failure

- Large effective peritoneal surface area (Type 1)
- Low osmotic conduction to glucose (Type 2)
- Low effective peritoneal surface area (Type 3)
- Increased lymphatic reabsorption rate (Type 4)
Large Effective Peritoneal Surface Area

Increased surface area and/or permeability lead to increased glucose absorption and more rapid dissipation of the osmolar gradient.
Diagnosis

• D/P creatinine > 0.81

• Low drain volume
  
  ➢ < 400 mL net UF over 4 hr with 4.25% dextrose (3.86% glucose)
Treatment and Prevention

- Peritoneal “resting”
- Icodextrin
- Inhibitors of the RAAS
- Neutral pH, low GDP PD fluid
Structure of Icodextrin

- Main $\alpha (1\rightarrow 4)$ chain
- $\alpha (1\rightarrow 6)$ branch
Icodextrin Reduces...

- Glucose Toxicity
- Hyperosmolar Stress
- Glucose degradation products (GDPs)
- Advanced glycation end-products (AGEs)

Cooker et al. Kid Int Suppl 81:S34, 2002
Icodextrin Decreases Propensity to Mortality and Technique Failure

• Mortality
  - 14.4% (icodextrin) vs. 20.0% (non-icodextrin)
  - HR 0.69 (95% CI, 0.52-0.90; p=0.004)

• Technique Failure
  - 5.6% (icodextrin) vs. 8.8% (non-icodextrin)
  - HR 0.60 (95% CI, 0.40-0.92; p=0.018)

2163 Korean PD patients on PD using:
  - 641 icodextrin ≥ 50% of time on PD
  - 1522 non-icodextrin

Han et al. Nephrol Dial Transpl 27:2044, 2012
Icodextrin is Not Associated with Longitudinal Change in Membrane Function

Davies SJ et al. Kid Int 67:1609, 2005
EMT: The Role of RAAS

• Peritoneal mesothelial cells
  - Local renin-angiotensin-aldosterone system
  - Contributes to interstitial fibrosis
    - Increases TGF-β
    - Increases fibronectin
    - Increases VEGF

• The peritoneal mesothelial RAAS is up-regulated by:
  - Glucose
  - Low pH
  - Peritonitis

Nessim et al. Kid Int 78:23, 2010
Peritoneal Membrane Small Solute Permeability Over Time

All on PD ≥ 2 years

Control; n= 87

p = 0.05

ACEI/ ARB;

n= 120

Neutral pH, Low GDP Bicarbonate PD Solutions

- Conventional glucose-based PD fluid
  - High concentration glucose degradation products (GDPs)
    - Secondary to heat sterilization
    - Buffered by lactate at low pH 5-6
  - Bioincompatible

- 2 compartment system – more neutral pH
  - Low pH compartment contains glucose
    - Reduces GDPs during sterilization
  - Bicarbonate or lactate/bicarbonate compartment
    - Avoids calcium precipitation

- No convincing evidence of beneficial effect on the peritoneal membrane

Perl et al. Kid Int 79:814, 2011
<table>
<thead>
<tr>
<th></th>
<th>1 Month</th>
<th>2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.62 ± 0.10</td>
<td>0.70 ± 0.08</td>
</tr>
<tr>
<td>Balance</td>
<td>0.67 ± 0.10 *</td>
<td>0.67 ± 0.09 †</td>
</tr>
</tbody>
</table>

* p = 0.002 vs. control
† p = NS vs. control

Low Osmotic Conduction to Glucose

Decrease in function of ultra small pores (aquaporins) leads to decreased osmotic conduction of glucose and inadequate water removal
A Case of Impaired AQP Function

Patient (February 1997)

Patient (March 1996)

Controls (n= 12)

A Case of Impaired AQP Function

1= Control

2= Control

3= Perit biopsy with nl AQP

4= Patient

Pathogenesis

• Functional alteration of aquaporin 1 (AQP1)
  ➢ Risk increases with time on peritoneal dialysis
  ➢ No change in number of AQP1

• Glycation- or NO- mediated process

Fuesshoeller A. Ped Nephrol 23:19, 2008
Diagnosis

- Low drain volume
- High-average or low-average transport are most likely
  - D/P creatinine 0.5 – 0.81
- No drop in dialysate Na concentration
  - No sieving
During a one hour 4.25% dwell, most of the ultrafiltrate will come across the ultrasmall pore (AQP-1).

During this period Na transport across the small pore is due almost entirely to convection.

The degree of AQP-mediated water transport may be assessed by evaluating UF across the small pore (UFSP).

Average free H₂O transport = 46% of total UF; ≤ 26% of total UF suggests AQP-1 deficiency or failure

La Milia et al. Kid Int 68:840, 2005
Calculation of UFSP

Sodium removal (NaR; mmol) =

\[
[\text{Volume}_{\text{dialysate out}} (L) \cdot \text{Na}_{\text{dialysate out}} (\text{mmol/L})] - [\text{Volume}_{\text{dialysate in}} (L) \cdot \text{Na}_{\text{dialysate in}} (\text{mmol/L})]
\]

\[
\text{UFSP (mL)} = \frac{[\text{NaR (mmol) \cdot 1000}]}{\text{Na}_p}
\]

AQP mediated free water transport is equal to UF- UFSP

Average free H\textsubscript{2}O transport = 46% of total UF; \leq 26% of total UF suggests AQP-1 deficiency or failure

La Milia et al. Kid Int 68:840, 2005
Increased AQP1 Function after Kidney Transplantation

Low Effective Peritoneal Surface Area

Severe decrease in surface area and/or permeability leads to restricted transport of fluid and solutes
Clinical Features

- Least common cause of peritoneal membrane failure
- Due to fibrosis/sclerosis, adhesions, compartementalization
- “Simple Sclerosis”
- Sometimes due to the most extreme complication of PD, EPS (encapsulating peritoneal sclerosis)
<table>
<thead>
<tr>
<th></th>
<th>Simple Sclerosis</th>
<th>EPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>Modest</td>
<td>Severe</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Calcification</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Sclerosis (microns)</strong></td>
<td>&lt; 40</td>
<td>&gt; 300</td>
</tr>
</tbody>
</table>

Encapsulating peritoneal sclerosis (EPS) is a clinical syndrome characterized by bowel obstruction (intermittent, recurrent, or persistent) caused by a wide range of adhesions of a diffusely hypertrophied peritoneum.

“Cocoon” Around Bowel Loops

Slingeneyer A. Contrib Nephrol 57: 239, 1987
Encapsulating Peritoneal Sclerosis

Church and Junor NEJM 347: 737, 2002
Frequency of EPS

- Reported frequency ranges from 0- 4.4%
- Highest in Japan and Australia
- Low frequency in US, Canada, Europe
Factors Related to PD

- Duration of PD
- Prior peritonitis
- High transport status
- Withdrawal of PD
- Bioincompatibility (glucose, hypertonicity, low pH)
- Acetate-based dialysate
- Plasticizers
- Chlorhexidine
Incidence of EPS by Duration of PD

Kawanishi et al. Am J Kid Dis 44:729, 2004
Treatment

• Stop PD

• Nutritional support

• Surgery – enterolysis
  ➢ 96% restoration of bowel function but high rate of recurrence and often need post-op immunosuppression

• Immunosuppression (case reports and series)
  ➢ Corticosteroids
  ➢ Azathioprine
  ➢ Mycophenolate mofetil
  ➢ Sirolimus

Korte et al. Nat Rev Nephrol 7:528, 2011
Treatment- 2

• Tamoxifen
  ➢ Used to treat retroperitoneal fibrosis
  ➢ Modest benefit in UK study: median survival (months) -
    - Immunosuppression only (n= 24): 12
    - Tamoxifen only (n= 17): 15
    - Both (n= 13): 21

• ??ACE inhibitors

Korte et al. Nat Rev Nephrol 7:528, 2011
Increased Lymphatic Reabsorption Rate

Increase in lymphatic absorption results in rapid loss of \textit{net} UF
Diagnosis

- Low drain volume
- High-average or low-average transport
  - D/P creatinine 0.5 – 0.81
  - No change in D/P
- Diagnosis of exclusion
  - Difficult to measure lymphatic reabsorption rate
As an Alternative…

- Icodextrin has an average molecular weight of 16 kDa
- It is absorbed from the peritoneal cavity almost exclusively by lymphatics
- Even very rapid transporters will ordinarily achieve good UF with icodextrin
- Failure to achieve UF with icodextrin over an 8-10 hour dwell may be taken as indirect evidence for excessive lymphatic reabsorption
Treatment

• Bethanechol chloride
  ➢ Cholinergic properties (similar to phosphatidylcholine)
  ➢ Enhances contraction of subdiaphragmatic lymphatic stomata thereby decreasing lymphatic flow

• Clinical utility – small study
  ➢ 9 patients, 5 days
    - Bethanechol chloride (0.27 mg/k/day; max 50 mg daily) divided, prior to each exchange
    - 18.4% improvement in 4 hour drain volume (p <0.05) with no change in solute transport characteristics

Alternative Method to Reduce Excessive Lymphatic Reabsorption - Speculative

- Certain dihydropyridine CCBs have been reported to cause chylous peritoneal fluid, presumably by slowing peritoneal lymphatics. Might these be beneficial?
  - Manidipine
  - Benidipine
  - Nisoldipine
  - Nifedipine
  - Lercanidipine
### Evaluation of UF Failure

<table>
<thead>
<tr>
<th>Condition</th>
<th>UF</th>
<th>Change in PET</th>
<th>Solute clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessively rapid transport</td>
<td>↓</td>
<td>↑</td>
<td>↔ or ↓</td>
</tr>
<tr>
<td>Impaired AQP function</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Decreased permeability</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Increased lymphatic absorption</td>
<td>↓</td>
<td>↔</td>
<td>↔ or ↓</td>
</tr>
</tbody>
</table>
Outline

- Physiology of peritoneal transport
  - Structure of the peritoneum
  - Models of peritoneal transport
  - Inverse relationship between solute transport and ultrafiltration

- Causes of Membrane “Failure”
  - Pathophysiology
  - Diagnosis
  - Treatment
THANK YOU