Monitorización del paciente en DP. Marcadores en efluente y en sangre: ¿son útiles? NO

From biomarkers to clinical practice

Anabela Rodrigues
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UMIB /ICBAS/UP
Ideal biomarker

- derived from intraperitoneal production
- readily measurable in peritoneal fluid effluent
- involved in membrane pathology
- have a high sensitivity and specificity for the clinical outcome of interest, such as encapsulating peritoneal sclerosis (EPS)

*Helbert Rondon, MD*
Biomarkers and CKD: a never ending story

**CV disease**
- Endothelin
- Nitric oxide
- Troponin
- Cistatin C
- AGE/RAGE

**Nutrition**
- Albumin
- pre albumin
- PNA
- BCM®

**Metabolic syndrome**
- hgA1C
- vitD
- Adipokines

**Volume**
- Pro BNP
- ECW/TBW (BCM®)

**Peritoneal Membrane**
Lesion processes in peritoneal dialysis

Nature Reviews Nephrology 8, 542-550 (September 2012)
Lesion processes in peritoneal membrane

Comorbidity
- Rapid residual renal function loss
- Diabetes
- Uremia

Glucose exposition
- Solutions biocompatibility

Peritonitis

EMT

Local RAS activation

inflammation

VEGF

VEGF-C lymphangiogenesis

TGF-β

IL6
Macrophages
IL-17a
Biomarkers and peritoneal membrane

Candidate biomarkers look like ...

- **Ca125**  
  (mesothelium)

- **VEGF**  
  (angiogenesis)

- **PAI-1**  
  (fibrinolysis)

- **CCL18**  
  (alternative macrophages activation)

- **IL17a**  
  (T cells role)

- **MMP-2**  
  (matrix remodelling)

- **VEGF-c**  
  (lymphangiogenesis)

- **HGF**  
  (fibrosis counteraction)

- **Others?**
IL6

CV disease
IL6

Nutrition
IL6

Metabolic Syndrome
IL6

Volume
IL6

Peritoneal membrane
Effluent IL6
Peritoneal fast transport in incident peritoneal dialysis patients is not consistently associated with systemic inflammation

Evaluation of Peritoneal Transport and Membrane Status in Peritoneal Dialysis: Focus on Incident Fast Transporters

Anabela S. Rodrigues, Margarida Martins, Johanna C. Korevaar, Sandra Silva, José C. Oliveira, Antonio Cabrita, João Castro e Melo, Raymond T. Krediet

Departments of *Nephrology and Clinical Pathology, Hospital Geral de Santo António, University of Porto, Porto, Portugal; †Department of Clinical Epidemiology and Biostatistics and *Division of Nephrology, Department of Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands
Trends in D/P creat and effluent IL6
IL6 independently related with increasing D/P creatinine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean estimate $\times 10^{-4}$</th>
<th>95% CI</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Univariate</strong></td>
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<td></td>
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<tr>
<td>VEGF model</td>
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<td></td>
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<tr>
<td>Effluent VEGF, pg/min</td>
<td>22</td>
<td>12–32.4</td>
<td>&lt;0.0001</td>
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<tr>
<td>IL-6 model</td>
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<tr>
<td>Effluent IL-6, pg/min</td>
<td>0.16</td>
<td>0.09–0.23</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>Multivariate</strong></td>
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<td></td>
</tr>
<tr>
<td>VEGF-IL6 model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effluent VEGF, pg/min</td>
<td>0.82</td>
<td>0.82–2.46</td>
<td>0.3</td>
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<tr>
<td>Effluent IL-6, pg/min</td>
<td>0.12</td>
<td>0.04–0.23</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Dependent variable: D/P creatinine ratio.
Independent Effects of Systemic and Peritoneal Inflammation on Peritoneal Dialysis Survival

Lambie M et al, on behalf of the Global Fluid Study Investigators

• n=959 patients, with up to 8 years of follow-up
• systemic inflammation was associated with age and comorbidity and independently predicted patient survival
• intraperitoneal inflammation was the most important determinant of PSTR but did not affect survival

Effluent CA125 reduced in UFF

Hepatocyte growth factor signalizes peritoneal membrane failure in peritoneal dialysis

Ana Paula Bernardo, José C Oliveira, Olivia Santos, Maria J Carvalho, António Cabrita and Anabela Rodrigues.
Biomarkers to evaluate membrane status

**Hypothesis-driven** peritoneal biomarker research

- Inflammation
  - IL6, TH17

- Interstitium
  - HGF, PAI-1

**Nonhypothesis-driven** peritoneal biomarker research

- Mesothelium
  - Ca125

- Oxidative stress
  - AOPP

**Omics**

Biomarker research: consensus of the European Training and Research in Peritoneal Dialysis (EuTRiPD) network
**Biomarker research: consensus of the European Training and Research in Peritoneal Dialysis (EuTRiPD) network**

The diagram outlines the approaches to biomarker research in Peritoneal Dialysis (PD), categorizing them into hypothesis-driven, clinical phenotype, and open “Omics” approaches. It highlights the need for validation of known candidate biomarkers reflecting pathomechanisms in PD.

- **Hypothesis-driven approach**
  - Inflammation: IL-6, IL-8, IL-17, M1/M2, Th17/Treg, inflammation signature
  - Ex vivo stimulated cytokine release
  - Infection: WBC, (culture), pathogen fingerprint
  - Membrane remodeling: PET, CA-125, MMT signature, AOPP, oxidative stress signature

- **Clinical phenotype**
  - Inflammation phenotype: Acute peritonitis, Post peritonitis
  - Membrane phenotype: Effluent cell MMT, Functional PET changes

- **Open “Omics” approach**
  - Phenotype-associated molecular signatures (PAMSs)

**Need for validation of known candidate biomarkers reflecting pathomechanisms in PD**

**Need for candidate biomarker development and validation**
Biomarker research: consensus of the European Training and Research in Peritoneal Dialysis (EuTRiPD) network
EARLY DIAGNOSTIC MARKERS FOR ENCAPSULATING PERITONEAL SCLEROSIS: A CASE-CONTROL STUDY

Denise E. Sampimon,¹ Mario R. Korte,² Deirisa Lopes Barreto,¹ Anniek Vlijm,¹ Rudy de Waart,³ Dirk G. Struijk,¹,⁴ and Raymond T. Krediet¹

[Graph showing data with EPS markers]
## Predictive biomarkers for EPS

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>sensitivity</th>
<th>specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR-CA125 &lt;33 U/min</td>
<td>70%</td>
<td>66%</td>
</tr>
<tr>
<td>AR-IL-6 &gt;350 pg/min</td>
<td>80%</td>
<td>50%</td>
</tr>
<tr>
<td>AR-CA125 &lt;33 U/min and AR-IL-6 &gt;350 pg/min</td>
<td>70%</td>
<td>89%</td>
</tr>
<tr>
<td>AR-CA125 &lt;33 U/min and AR-IL-6 &gt;350 pg/min in UFF patients</td>
<td>70%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Limitations

• Biomarker levels may reflect mere changes of distribution between compartments
  • leakage from intracellular into extracellular or spill over from systemic into local compartments by altered clearance

• Major age-specific particularities

• Methodological issues
  • OMICS
    • High-abundance proteins that originate from plasma mask low-abundance proteins, such as cytokines
    • When focusing on these low-abundance biomarker candidates, depletion strategies are required such as affinity chromatographic separation or semispecific precipitation of proteins.
What do we aim for but have not achieved yet?

association with clinically relevant outcomes remain to be tested

validation is mandatory

clinical trials to test the proof of concept and confirm the usefulness
Validation as predictors of Major outcomes

- DEATH
- EPS
Relevant outcomes

• **Overhydration** is probably the most important risk factor for **DEATH** in peritoneal dialysis patients.

• **Duration of PD** is by far the major determinant of the risk for the development of **EPS**.
  • But the prevalence of EPS after eight years of PD treatment in Japan has fallen to 2.3%.

NAKAYAMA et al. NOVEMBER 2014 - VOL. 34, NO.7 PDI
Does any biomarker predict cognitive function loss?

Peritoneal dialysis is associated with better cognitive function than hemodialysis over a one-year course

Denise Neumann, Wilfried Mau, Andreas Wienke and Matthias Girndt
Which marker is more relevant? Lab or clinic?

- MCP-1, IL-6 and CCL15 were found at higher levels in the dialysate of patients who subsequently developed EPS
- But
- **dialysate levels of these cytokines do not improve prediction of future EPS above a model using known clinical risk factors**
  - Duration of PD
  - D/P creat

The predictors of EPS are duration of PD and D/P creatinine. The area under the curve is 0.886.
Task force to improve outcomes biomarkers versus clinical judgement

**Integrated judgment of BCM parameters (%OH)**

- Fluid BALANCE
- Renal protection
- UF rate (updated PD prescription)
  - Low GDPs solutions
  - Well prescribed APD

**Water transport measurement**

- FWT
- high discriminative power of 0.82
  - A cut-off value of FWT < 75 ml in the first 60 minutes of a 3.86% glucose dwell is the best predictor of EPS

Conclusions

• Biomarkers may sign lesion processes but are individually unable to testimony precise cell damage

• Complex network of cytokines and proteins in a dynamic pathophysiologic process can hardly be expressed by a single measurement

• Hard clinical outcomes in PD are predicted strongly by other tools such as fluid balance and water transport

• Integrated information is needed: combined clinical and biomarker panel to make prognosis more accurate