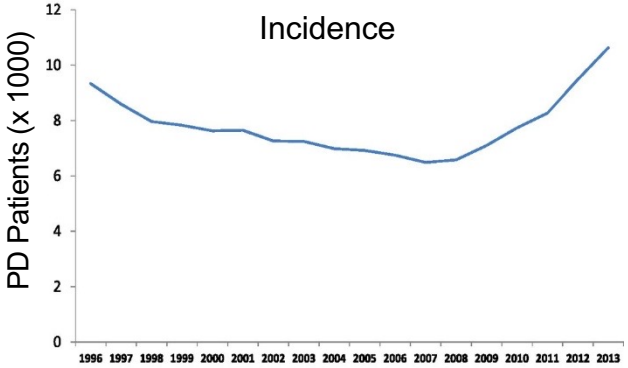
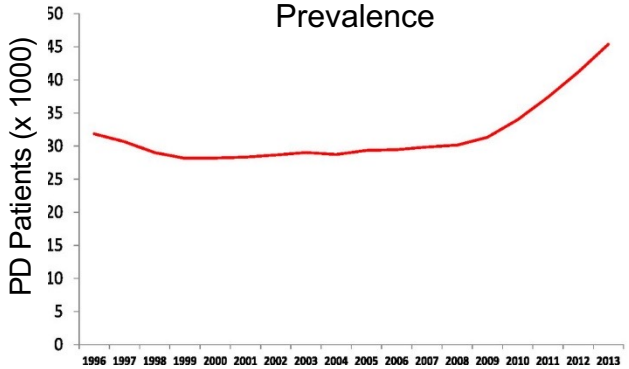
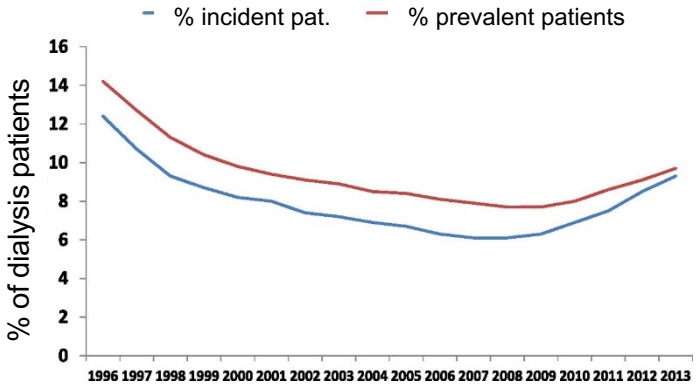
What's new in pediatric PD, a review of the recent literature

Claus Schmitt, Heidelberg

Number of PD Patients, USA 1996 - 2013

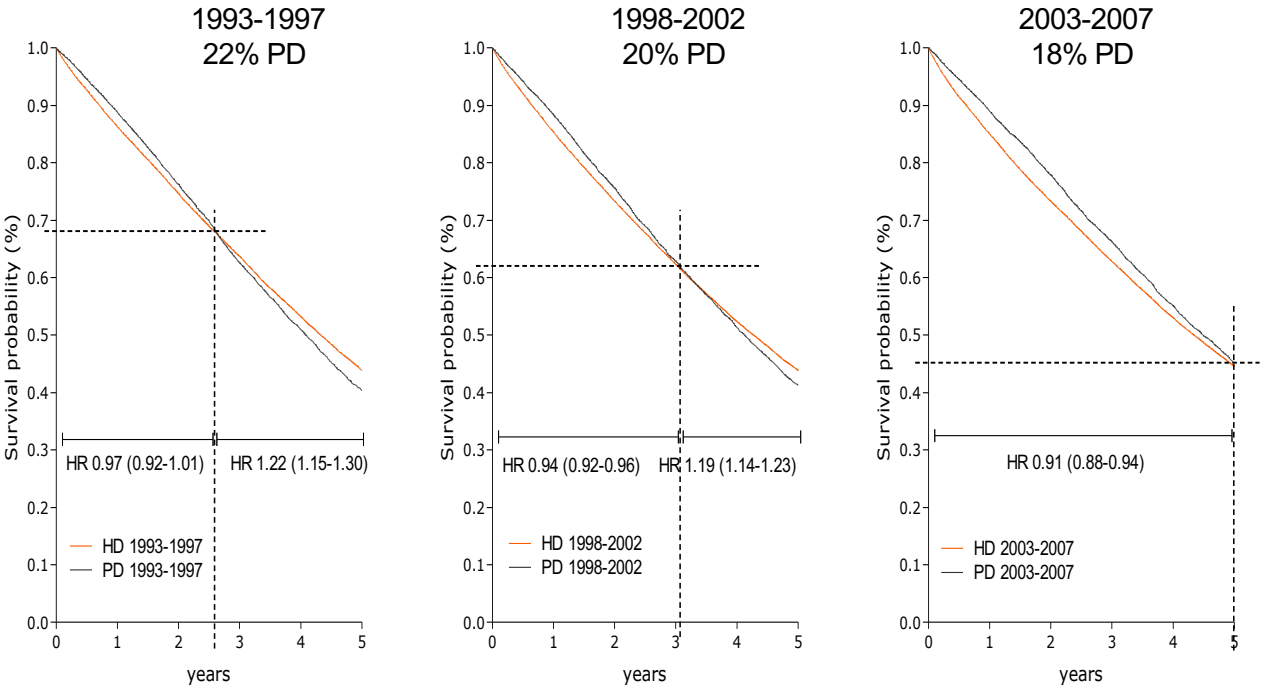






Mehrotra R et al. JASN 2016

ERA-EDTA Registry - Real-Life Data
Superior 5 year survival with PD



5 year patient survival for patients starting dialysis on HD and PD in 1993-1997, 1998-2002, and 2003-2007, adjusted for age, sex, primary renal disease, and country
(n= 29368 – 44726 HD, 8466-9998 PD)

van de Luijtgaarden MW et al, NDT 2016

Special Series/Guidelines

PERITONEAL DIALYSIS INTERNATIONAL

Peritoneal Dialysis International
2021, Vol. 41(4) 352–372

DOI: 10.1177/0896860820982218
journals.sagepub.com/home/ptd
SAGE

ISPD recommendations for the evaluation of peritoneal membrane dysfunction in adults: Classification, measurement, interpretation and rationale for intervention

Johann Morelle[1], Joanna Stachowska-Pietka[2], Carl Öberg[3], Liliana Gadola[4], Vincenzo La Milia[5], Zanzhe Yu[6], Mark Lambie[7], Rajnish Mehrotra[8], Javier de Arteaga[9] and Simon Davies[7]

Lay summary

Peritoneal dialysis (PD) uses the peritoneal membrane for dialysis. The peritoneal membrane is a thin layer of tissue that lines the abdomen. The lining is used as a filter to help remove extra fluid and poisonous waste from the blood. Everybody is unique. What is normal for one person's membrane may be very different from another person's. The kidney care team wants to provide each person with the best dialysis prescription for them and to do this they must evaluate the person's peritoneal lining. Sometimes dialysis treatment itself can cause the membrane to change after some years. This means more assessments (evaluations) will be needed to determine whether the person's peritoneal membrane has changed. Changes in the membrane may require changes to the dialysis prescription. This is needed to achieve the best dialysis outcomes. A key tool for these assessments is the peritoneal equilibration test (PET). It is a simple, standardized and reproducible tool. This tool is used to measure the peritoneal function soon after the start of dialysis. The goal is to understand how well the peritoneal membrane works at the start of dialysis. Later on in treatment, the PET helps to monitor changes in peritoneal function. If there are changes between assessments causing problems, the PET data may explain the cause of the dysfunction. This may be used to change the dialysis prescription to achieve the best outcomes. The most common problem with the peritoneal membrane occurs when fluid is not removed as well as it should be. This happens when toxins (poisons) in the blood cross the membrane more quickly than they should. This is referred to as a *fast peritoneal solute transfer rate* (PSTR). Since more efficient fluid removal is associated with better outcomes, developing a personal PD prescription based on the person's PSTR is critically important. A less common problem happens when the membrane fails to work properly (also called membrane dysfunction) because the peritoneal membrane is less efficient, either at the start of treatment or developing after some years. If membrane dysfunction gets worse over time, then this is associated with progressive damage, scarring and thickening of the membrane. This problem can be identified through another change of the PET. It is called reduced 'sodium dip'. Membrane dysfunction of this type is more difficult to treat and has many implications for the individual. If the damage is major, the person may need to stop PD. They would need to begin haemodialysis treatment (also spelled hemodialysis). This is a very important and emotional decision for individuals with kidney failure. Any decision that involves stopping PD therapy or transitioning to haemodialysis therapy should be made jointly between the clinical team, the person on dialysis and a caregiver, if requested. Although evidence is lacking about how often tests should be performed to determine peritoneal function, it seems reasonable to repeat them whenever there is difficulty in removing the amount of fluid necessary for maintaining the health and well-being of the individual. Whether routine evaluation of membrane function is associated with better outcomes has not been studied. Further research is needed to answer this important question as national policies in many parts of the world and the COVID-19 has placed a greater emphasis and new incentives encouraging the greater adoption of home dialysis therapies, especially PD. For Chinese and Spanish Translation of the Lay Summary, see Online Supplement Appendix 1.

Morelle J et al. PDI 2021

Guideline 1:
A pathophysiological taxonomy: A pathophysiological classification of membrane dysfunction, which provides mechanistic links to functional characteristics, should be used when prescribing individualized dialysis or when planning modality transfer (e.g. to automated peritoneal dialysis (PD) or haemodialysis) in the context of shared and informed decision-making with the person on PD, taking individual circumstances and treatment goals into account. (**practice point**)

Guideline 2a:
Identification of fast peritoneal solute transfer rate (PSTR): It is recommended that the PSTR is determined from a 4-h peritoneal equilibration test (PET), using either 2.5%/2.27% or 4.25%/3.86% dextrose/glucose concentration and creatinine as the index solute. (**practice point**) This should be done early in the course dialysis treatment (between 6 weeks and 12 weeks) (**GRADE 1A**) and subsequently when clinically indicated. (**practice point**)

Guideline 2b:
Clinical implications and mitigation of fast solute transfer: A faster PSTR is associated with lower survival on PD. (**GRADE 1A**) This risk is in part due to the lower ultrafiltration (UF) and increased net fluid reabsorption that occurs when the PSTR is above the average value. The resulting lower net UF can be avoided by shortening glucose-based exchanges, using a polyglucose solution (icodextrin), and/or prescribing higher glucose concentrations. (**GRADE 1A**) Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload. (**GRADE 1A**) Use of automated PD and icodextrin may mitigate the mortality risk associated with fast PSTR. (**practice point**)

Guideline 3:
Recognizing low UF *capacity:* This is easy to measure and a valuable screening test. Insufficient UF should be suspected when either (a) the net UF from a 4-h PET is <400 ml (3.86% glucose/4.25% dextrose) or <100 ml (2.27% glucose /2.5% dextrose), (**GRADE 1B**) and/or (b) the daily UF is insufficient to maintain adequate fluid status. (**practice point**) Besides membrane dysfunction, low UF capacity can also result from mechanical problems, leaks or increased fluid absorption across the peritoneal membrane not explained by fast PSTR.

Guideline 4a:
Diagnosing intrinsic membrane dysfunction (manifesting as low osmotic conductance to glucose) as a cause of UF insufficiency: When insufficient UF is suspected, the 4-h PET should be supplemented by measurement of the sodium dip at 1 h using a 3.86% glucose/4.25% dextrose exchange for diagnostic purposes. A sodium dip ≤5 mmol/L and/or a sodium sieving ratio ≤0.03 at 1 h indicates UF insufficiency. (**GRADE 2B**)

Guideline 4b:
Clinical implications of intrinsic membrane dysfunction (de novo or acquired): in the absence of residual kidney function, this is likely to necessitate the use of hypertonic glucose exchanges and possible transfer to haemodialysis. Acquired membrane injury, especially in the context of prolonged time on treatment, should prompt discussions about the risk of encapsulating peritoneal sclerosis. (**practice point**)

Guideline 5:
Additional membrane function tests: measures of peritoneal protein loss, intraperitoneal pressure and more complex tests that estimate osmotic conductance and 'lymphatic' reabsorption are not recommended for routine clinical practice but remain valuable research methods. (**practice point**)

Guideline 6:
Socioeconomic considerations: When resource constraints prevent the use of routine tests, consideration of membrane function should still be part of the clinical management and may be inferred from the daily UF in response to the prescription. (**practice point**)

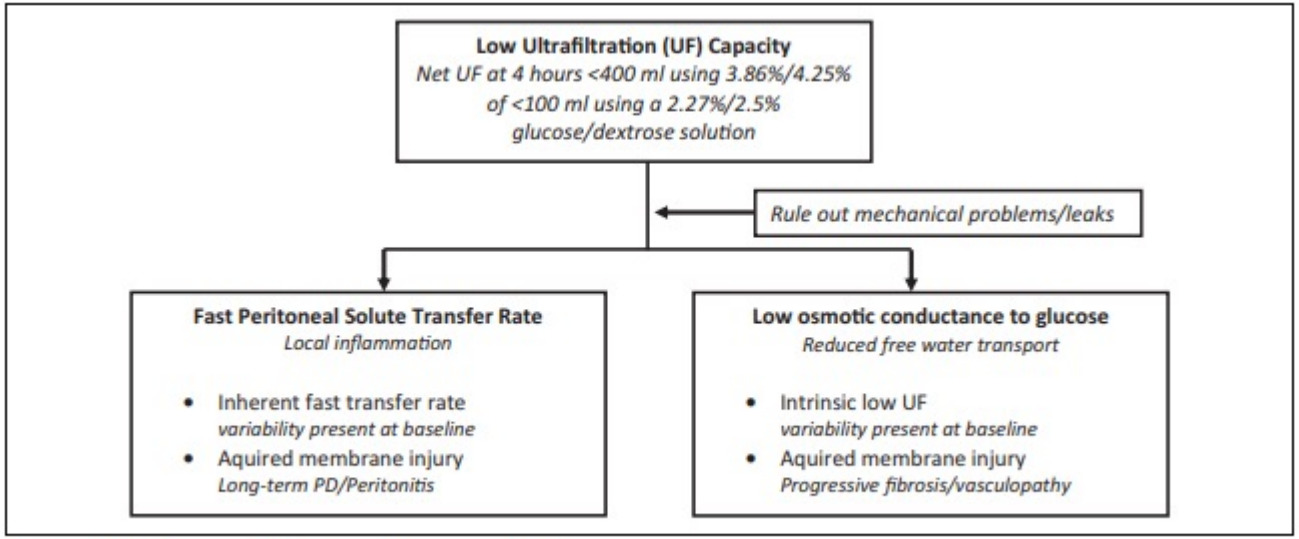


Figure 3. Classification of the causes of membrane dysfunction.

⇒ Classify PD membrane function (4 h PET, D/P Crea)

⇒ A faster Peritoneal Solute Transport Rate is associated with lower survival on PD. (GRADE 1A)

⇒ Icodextrin improves fluid status (GRADE 1A) and probably survival

⇒ Low UF capacity: Net UF from a 4-h PET < 400 ml (3.86% glucose/4.25% dextrose) (GRADE 1B)

⇒ A sodium dip ≤5 mmol/L and/or a sodium sieving ratio ≤0.03 at 1 h indicates UF insufficiency. (GRADE 2B)

⇒ Membrane dysfunction: Consider the risk of encapsulating peritoneal sclerosis and transfer to hemodialysis (practice point)

Morelle J et al. PDI 2021

Original Article

PERITONEAL DIALYSIS INTERNATIONAL

Peritoneal Dialysis International
2020, Vol. 40(5) 446–454

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journals.sagepub.com/home/ptd
SAGE

Single-dwell treatment with a low-sodium solution in hypertensive peritoneal dialysis patients

Simon Davies[1], Börje Haraldsson[2], François Vrtovsnik[3], Vedat Schwenger[4], Stanley Fan[5], Alexandre Klein[6], Saynab Atiye[7] and Adelheid Gauly[7]

- Randomized, prospective, single-blind study in hypertensive patients on PD
- Glucose-compensated, low-Na PD solution (112 mmol/L Na and 2% glucose) compared to a standard Na solution (133 mmol/L Na and 1.5% glucose) in.
- One daily exchange of the standard dialysis regimen was substituted by either of the study solutions

- Both treatment groups showed non-significant decreases of SBP and DBP in 24-h ABPM and office measurements
- patients' self-measurements showed significant decreases of SBP and DBP for low-Na (p = 0.004 and p = 0.008)

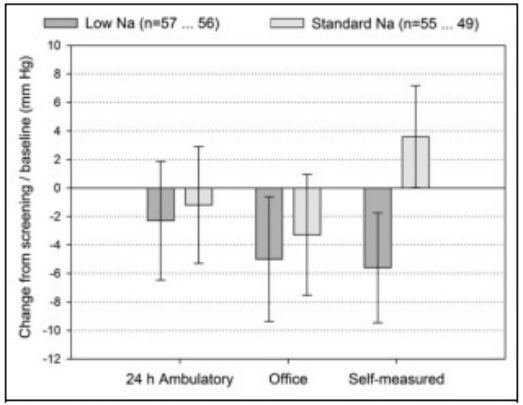


Figure 1. Systolic blood pressure change between screening (24 h) or baseline (office, self-measured) and week 8 (full analysis set; means and 95% confidence intervals).

	Low Na ($n = 60$)	Standard Na ($n = 63$)	Rate difference [95% CI]	p Value
Valid n	58 (100%)	55 (100%)		
Responders	20 (34.5%)	16 (29.1%)	5.4% [−11.6%; 21.9%]	0.512
Response defined by				
(a) Mean 24-h systolic blood pressure decrease from baseline ≥6 mmHg[a]	11 (19.0%)	16 (29.1%)		
(b) Fall in blood pressure requiring medical intervention[b]	9 (15.5%)	0 (0.0%)		

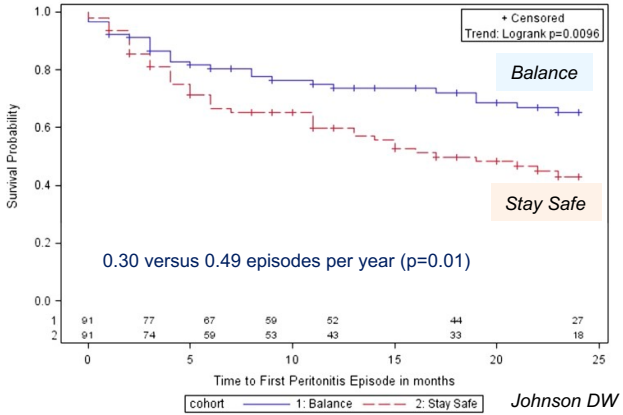
Na: sodium; CI: confidence interval.
[a]Patients without modification of antihypertensive medication only.
[b]For example, a decrease of antihypertensive medication. Fulfilment of this criterion had to be confirmed by the Data Safety Monitoring Board.

?

Davies S et al PDI 2020

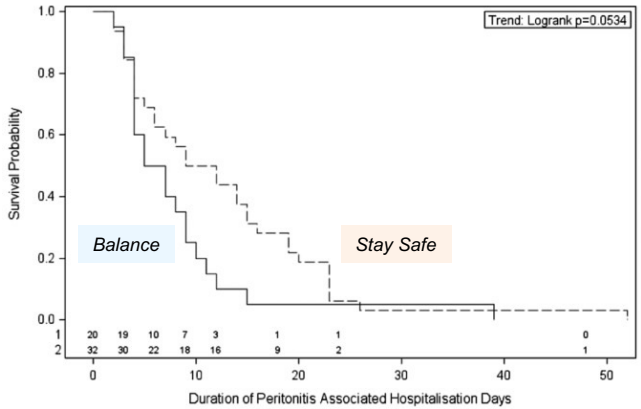
Role of adequately treated peritonitis in PD

Time to first peritonitis



Johnson DW et al, JASN 2012

Duration of peritonitis associated hospitalizations



Johnson DW et al, PDI 2012

Clin J Am Soc Nephrol. 2018 Oct 8; 13(10): 1526–1533.
Published online 2018 Aug 31. doi: 10.2215/CJN.02380218
PMCID: PMC6218832
PMID: 30171050

Biocompatible Solutions and Long-Term Changes in Peritoneal Solute Transport

Emma H. Elphick,[1] Lucy Teece,[1] James A. Chess,[2] Jun-Young Do,[3] Yong-Lim Kim,[4] H. Bahl Lee,[5] Sara N. Davison,[6] Nicholas Topley,[7] Simon J. Davies,[1] and Mark Lambie[1]

Impact of peritonitis on peritoneal solute transport:

Standard solutions (n=169):
D/Pcrea: + 0.020 (95% CI 0.01 to 0.03) per peritonitis episode

Biocompatible solutions (n=29):
no change in D/Pcrea − 0.014 (95% CI, −0.03 to <0.01) per episode

frontiers in Physiology

ORIGINAL RESEARCH
published: 02 April 2019
doi: 10.3389/fphys.2019.00356

Peritoneal Dialysis Vintage and Glucose Exposure but Not Peritonitis Episodes Drive Peritoneal Membrane Transformation During the First Years of PD

Maria Bartosova[1†], Betti Schaefer[1†], Karel Vondrak[2], Peter Sallay[3], Christina Taylan[4], Rimante Cerkauskiene[5], Maria Dzierzega[6], Gordana Milosevski-Lomic[7], Rainer Büscher[8], Ariane Zaloszyc[9], Philipp Romero[10], Felix Lasitschka[11], Bradley A. Warady[12], Franz Schaefer[1], Akos Ujszaszi[13] and Claus Peter Schmitt[1]*

MATCHED

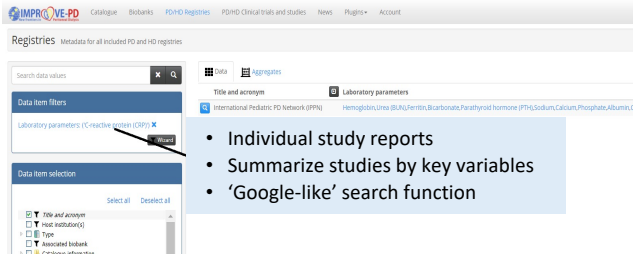
	No peritonitis (n=24)	peritonitis (n=24)	p-value
Age (years)	4.0 (1.8, 9.4)	3.3 (1.5, 10.1)	0.71
Female (%)	46%	58%	0.39
Body surface area (/m²)	0.6 (0.4, 1.2)	0.6 (0.5, 1.0)	0.88
PD duration (months)	11.3 (8.5, 21.4)	12.0 (8.5, 22.4)	0.66
Glucose exposure (mg/day/bsa)	97 (89, 132)	100 (85, 108)	0.64
Absent mesothel layer	46%	38%	0.53
Mesothelial cell coverage (0-6)	0.5 (0.0, 3.5)	1.0 (0.0, 3.0)	0.91
Submesothelial thickness (um)	304 (200, 358)	413 (250, 500)	0.24
Microvessel density (/mm²)	200 (107, 325)	170 (97, 318)	0.82
Microvessel number / mm	59 (32, 75)	82 (30, 116)	0.21
Lymphatic vessel density (/mm²)	39 (23, 56)	33 (22, 46)	0.41
Blood cap. vessel density (/mm²)	176 (71, 238)	139 (66, 362)	0.72
Total endothelial surface area (um²/um³)	10.0 (7.7, 19.0)	10.2 (5.9, 16.4)	0.82
Lym. endothelial surface area (um²/um³)	3.4 (1.8, 5.7)	2.6 (1.3, 4.4)	0.30
Blood cap. endothelial surface area (um²/um³)	8.0 (4.1, 12.8)	6.7 (3.3, 15.7)	0.89
L/V ratio	0.4 (0.2, 0.5)	0.4 (0.3, 0.5)	0.28
ASMA score (0-3)	1 (0, 1)	1 (0, 2)	0.55
CD45 score (0-3)	1 (1, 1.5)	1 (0, 2)	0.89
CD68 score (0-3)	1 (0, 1.5)	2 (1, 2)	0.11
Fibrine (% positive patients)	25%	25%	1.00
Epithelial–Mesenchymal Transition (% pos. Pat.)	46%	42%	0.77
EMT (cells/mm2)	49 (20, 198)	21 (8, 65)	0.34
Diffuse staining (% positive patients)	33%	23%	0.42
VEGF-A (% submesothelial area)	32 (19, 63)	35 (20, 51)	0.50
pSMAD2/3 (% submesothelial area)	18.1 (6.2, 29.1)	20.3 (7.3, 26.7)	0.65

IMPROVE-PD:
- **I**dentification and **M**anagement of **P**atients at **R**isk
- **O**utcome and **V**ascular **E**vents in **P**eritoneal **D**ialysis

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 812699

IMPROVE-PD Finder (IPF): An Integrative Metadata Platform for PD/HD Registries, Biobanks, Clinical Trials and Observational Studies

Metadata + **Aggregated Data** → **Functionalities**



- Individual study reports
- Summarize studies by key variables
- 'Google-like' search function

Registries

- **United Kingdom Renal Registry**
  31 adult and 13 pediatric renal centers
- **Australia & New Zealand Dialysis & Transplant Registry**
  3282 PD patients in Australia / New Zealand
- **The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS)**
  12000 patients (comorbidities, CV events, practice patterns)
- **Int. Ped. PD and HD Registry**
  4000 pediatric PD and 1000 HD patients

Associated partners:

- **Fresenius Medical Care**
- **ERA/EDTA**

Tissue Biobanks

1. **International Pediatric PD Biobank**
2. **The Spanish NEFRONA study**
3. **Wales Kidney Research Tissue Bank**
4. **Louvain Tissue and Fluid Biobank**

Clinical Trial Data & Biobanks

1. **Wales Kidney Research Tissue Bank**
2. **The PD CRAFT study**
3. **The Vienna PD BASE Biobank**
4. **Clinical trial data / samples**

Patient metadata from 121873 patients across more than 41 countries and 900 centers.

A genome-wide association study suggests correlations of common genetic variants with peritoneal solute transfer rates in patients with kidney failure receiving peritoneal

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Cohort and Genotyping

2850 participants

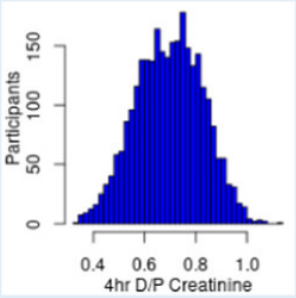
2212 European ancestry
181 African ancestry
109 Asian
348 Admixed-Other

Illumina Omni Genotyping
HRC1.1 Imputation
~7 million variants analyzed

A Polygenic Risk Score was developed which uses 36,357 variants to predict PSTR in 299 participants.

GWAS Phenotype

Peritoneal Solute Transfer Rate (PSTR)



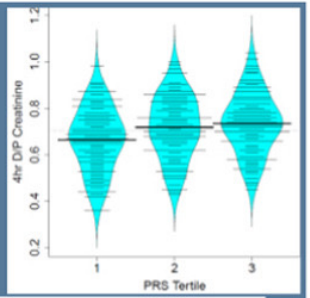
(1. PET)

Ratio of Dialysate to Plasma Creatinine Concentration at 4 hours of dwell time for dialysate in the peritoneal cavity

Findings

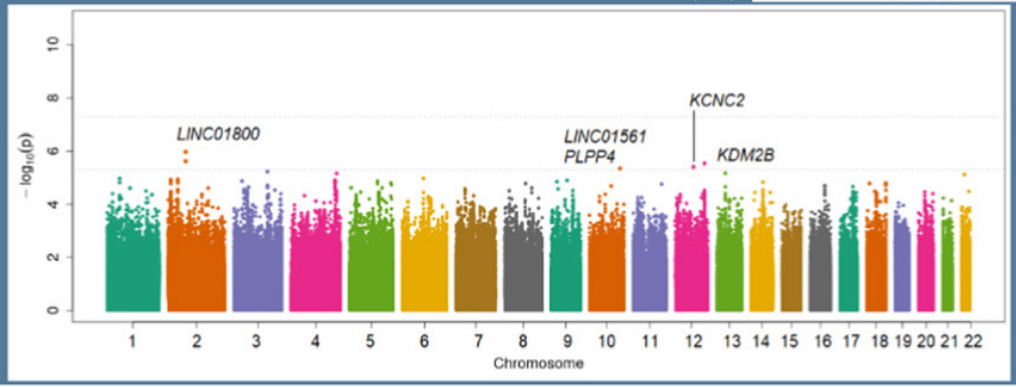
Heritability ~ 19.3%

Polygenic Risk Score associated with PSTR



In meta-analysis across ancestry strata, four loci had suggestive associations with PSTR

KDM2B is an eQTL with the intronic rs28644184 variant with known associations with inflammation *fibrosis, angiogensis (EMT)*



Mehrotra, 2021

CONCLUSION

In this GWAS of a peritoneal dialysis cohort, we did not find any loci with genome wide significance. These data provide the first estimate of heritability of PSTR and significant association with a polygenic risk score. This underscores the contribution of genetic variation to inter-individual variability in PSTR.

N Engl J Med. 2021 Oct 21;385(17):1570-1580. doi: 10.1056/NEJMoa2034279.

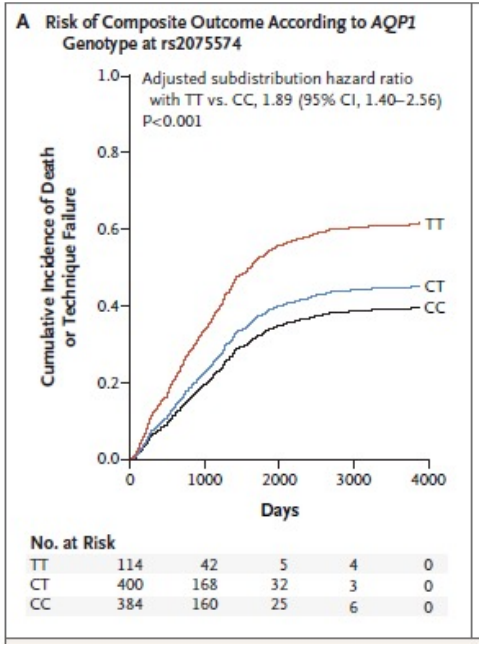
AQP1 Promoter Variant, Water Transport, and Outcomes in Peritoneal Dialysis

Johann Morelle [1], Céline Marechal [1], Zanzhe Yu [1], Huguette Debaix [1], Tanguy Corre [1], Mark Lambie [1], Marion Verduijn [1], Friedo Dekker [1], Philippe Bovy [1], Pieter Evenepoel [1], Bert Bammens [1], Rafael Selgas [1], Maria A Bajo [1], Annemieke M Coester [1], Amadou Sow [1], Nicolas Hautem [1], Dirk G Struijk [1], Raymond T Krediet [1], Jean-Luc Balligand [1], Eric Goffin [1], Ralph Crott [1], Pierre Ripoche [1], Simon Davies [1], Olivier Devuyst [1]

A common variant in AQP1 associated with decreased UF and increased risk of death or technique failure

Carriers of the TT genotype at rs2075574 (10 to 16% of patients) had lower UF than carriers of the CC genotype (35 to 47% of patients):
- 506±237 ml vs. 626±283 ml (discovery phase; P = 0.007)
- 368±603 ml vs. 563±641 ml (validation phase; P = 0.003)

TT carriers had:
- a higher risk of death/technique failure than CC carriers
- a higher risk of death from any cause (24% vs. 15%, P = 0.03).



Multi-Omics Data Warehouse

(Arteries, Arterioles, Peritoneum, Fat …)

Systemic effects

Peritoneal effects

Patients

Tissue material

Methods

Base cohort

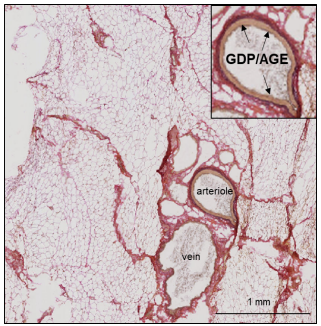
CKD5 n=107
High GDP PD n= 30
Low GDP PD n= 60

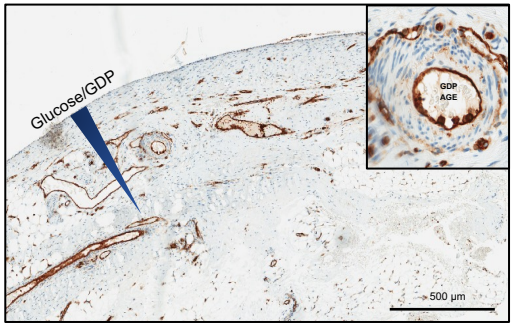
Omics cohort
n=6 / group

Validation cohort
n=10 / per group

Omental arterioles

Peritoneal membrane
Submesothelial arterioles



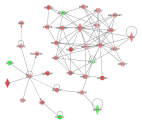


- Transcriptomics
- Proteomics
- Cross omics

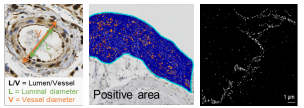
=> *Pathway identification*

- Digital histomorphometry, quantitative IHC
- Single molecule localization microscopy
- *In vitro* endothelial GDP exposure model

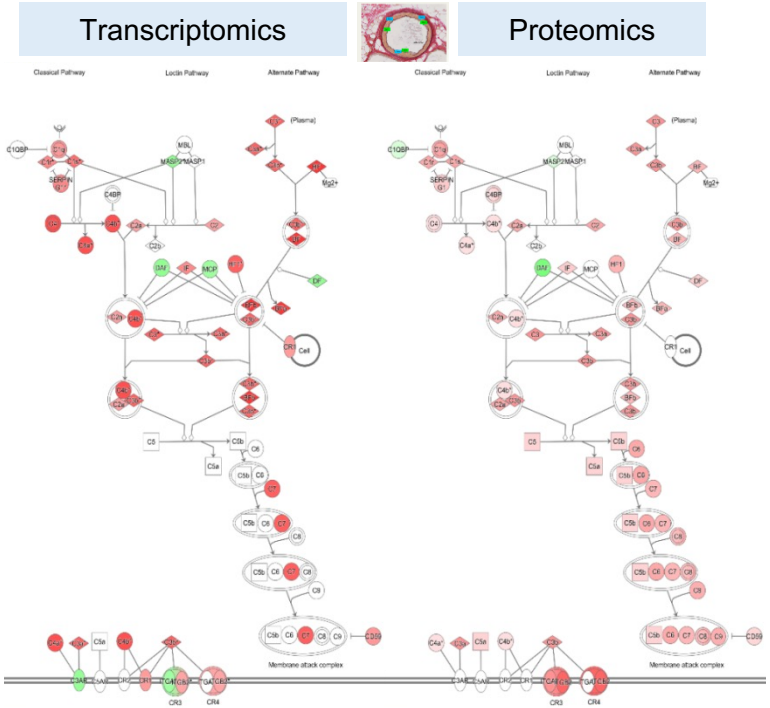
=> *Key pathway validation*

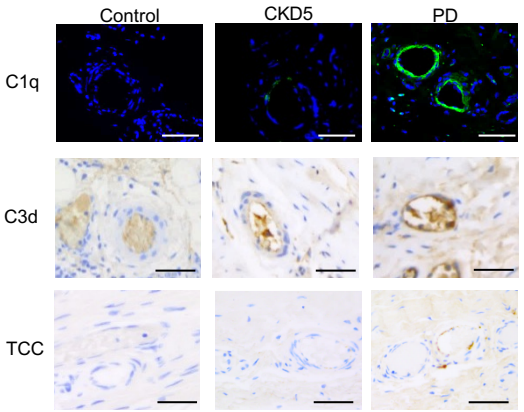


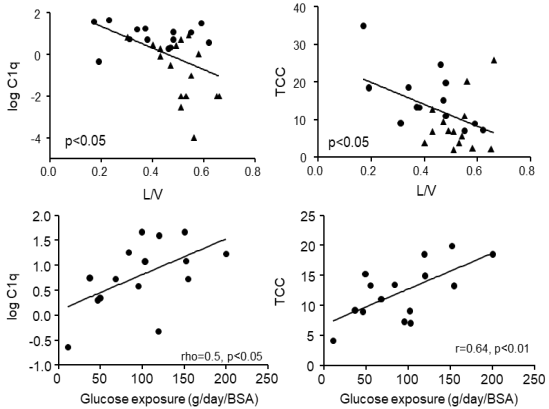
Integrated model of GDP triggered vasculopathy



Low GDP PD: Arteriolar Complement Activation



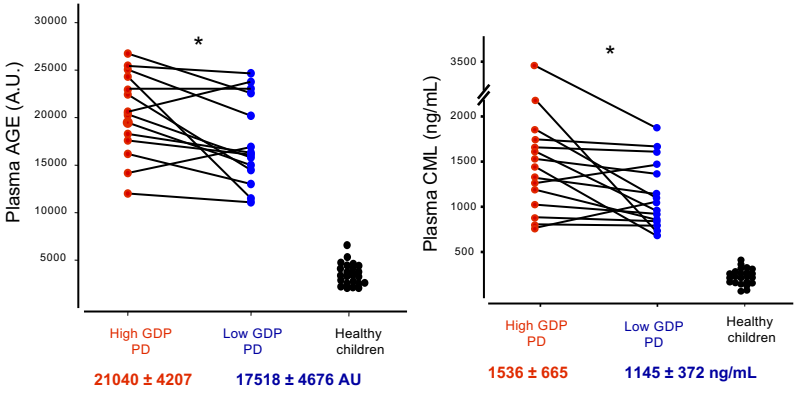




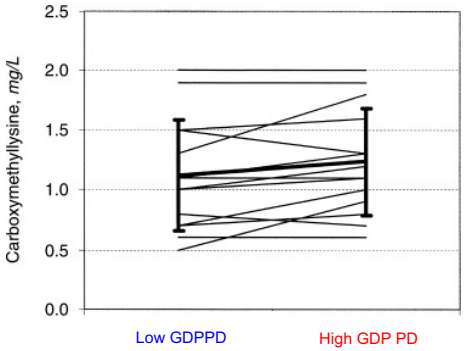
Bartosova M et al. JASN , 2018

Reduced plasma and vascular AGE concentrations with low vs. high GDP PD

Blood AGE concentrations

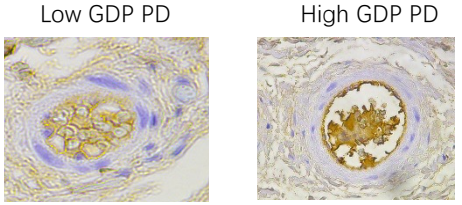


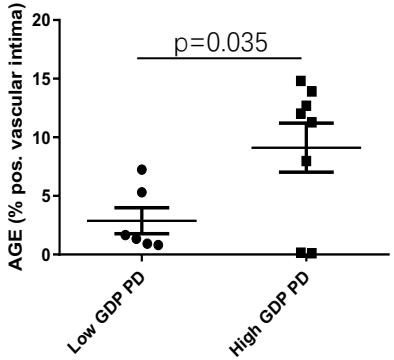
Schmitt CP et al, NDT 2007



Zeier et al. Kidney Int 2003

Arteriolar AGE deposition

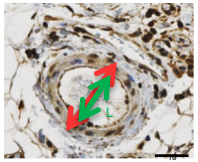




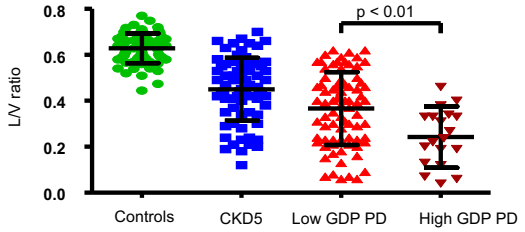
Bartosova M et al. Circ Res 2021

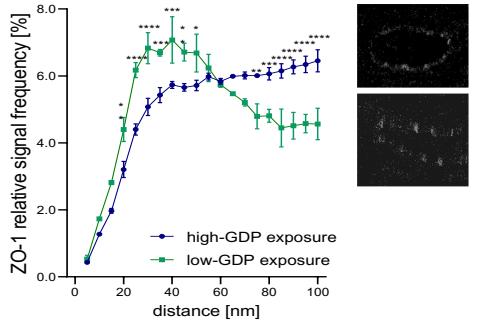
High GDP PD: Increased vascular damage

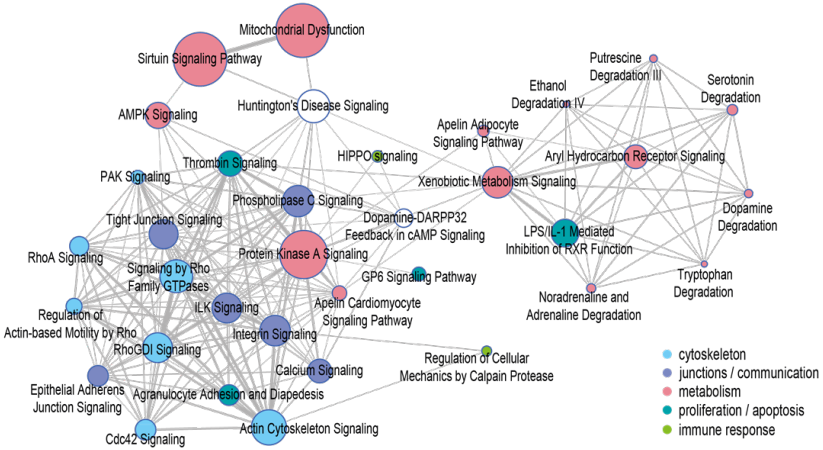
Endothelial Junction Disruption and Apoptosis, vessel lumen narrowing

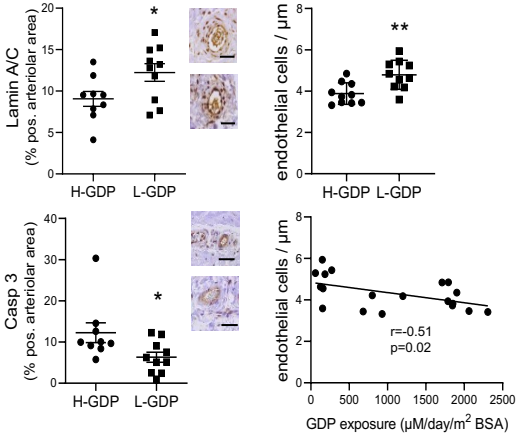


L/V: Lumen/Vessel Ratio
L: Luminal diameter
V: Vessel diameter



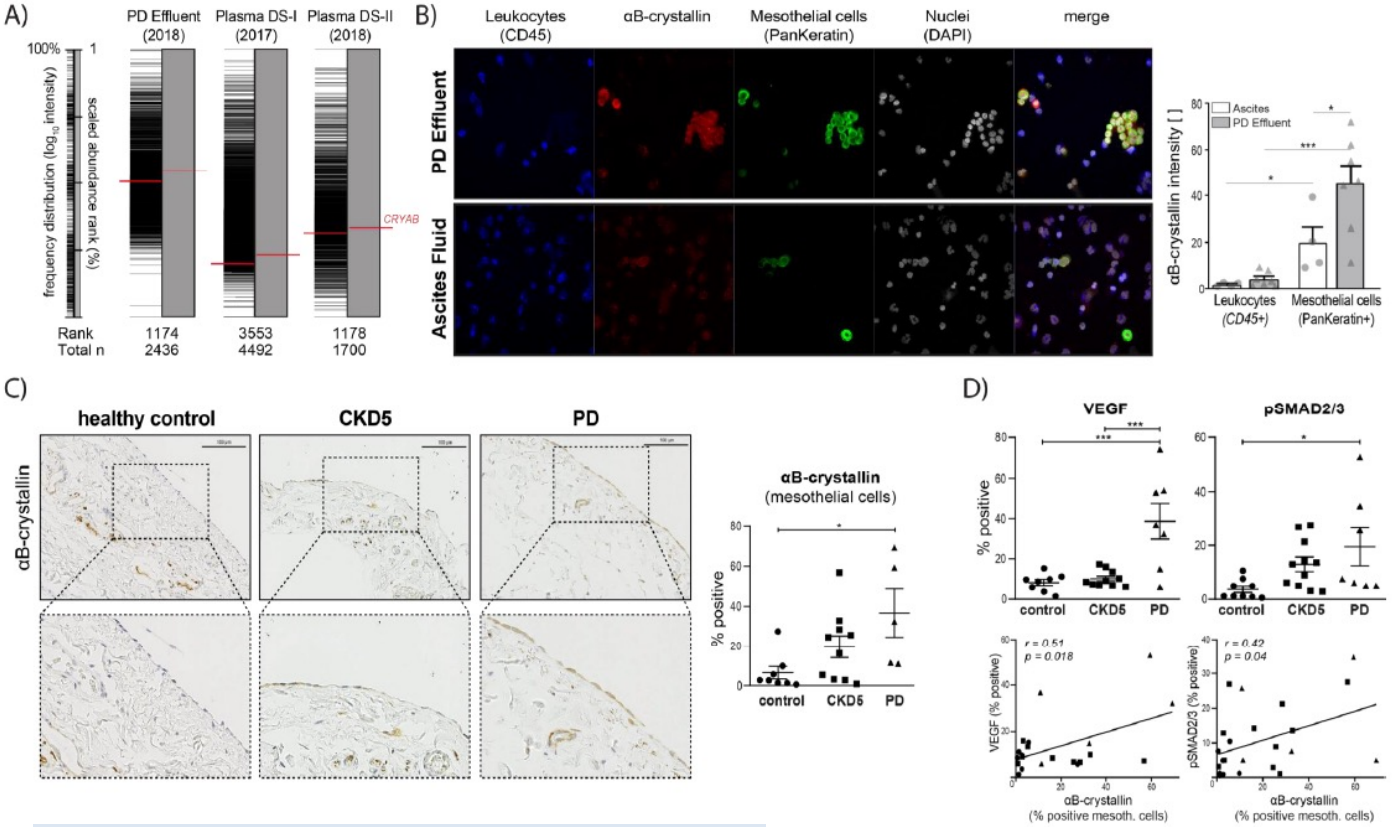






Bartosova M et al. Circ Res 2021

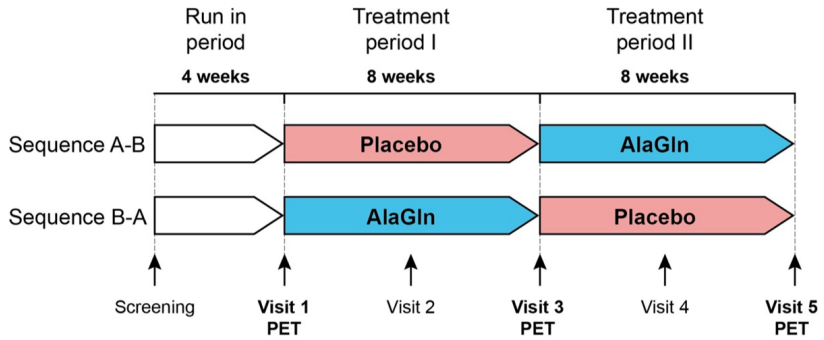
Low GDP-PD + Icodextrin: Induction of αB-crystallin

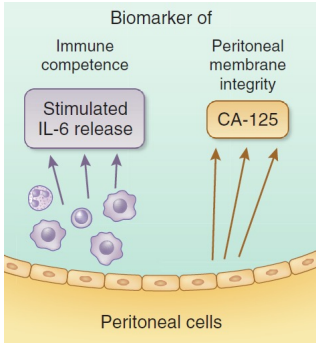


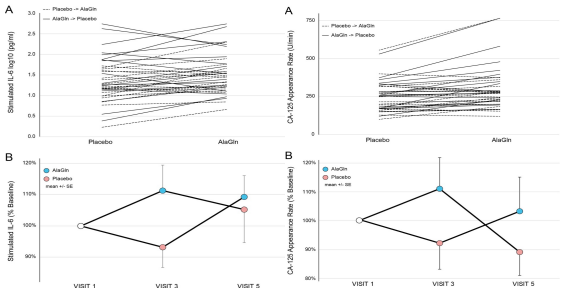
In vitro and in mice, lithium counteracted PDF fluid induced αB-crystalin and fibrosis- and angiogenesis- associated processes

Herzog R et al. Sci Transl Med, 9-2021

AlaGln supplemented pH neutral, low GDP PD Fluid: PD Protec







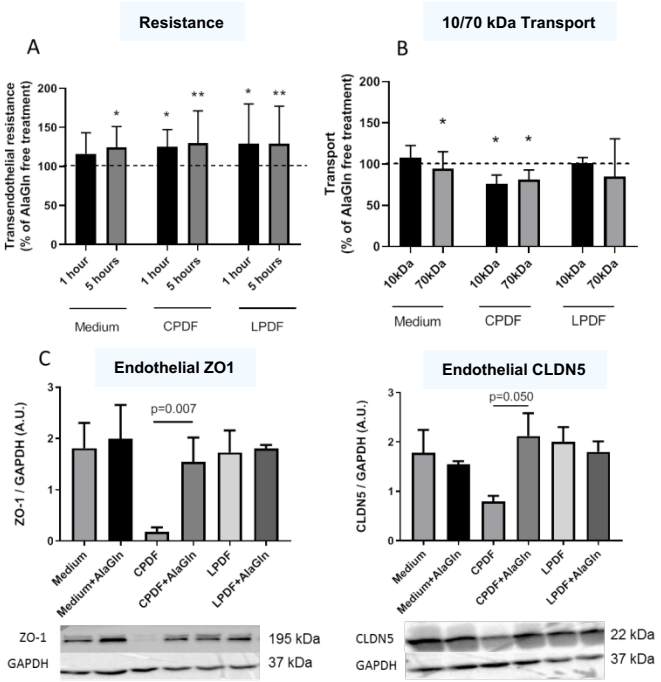
The RCT suggests:

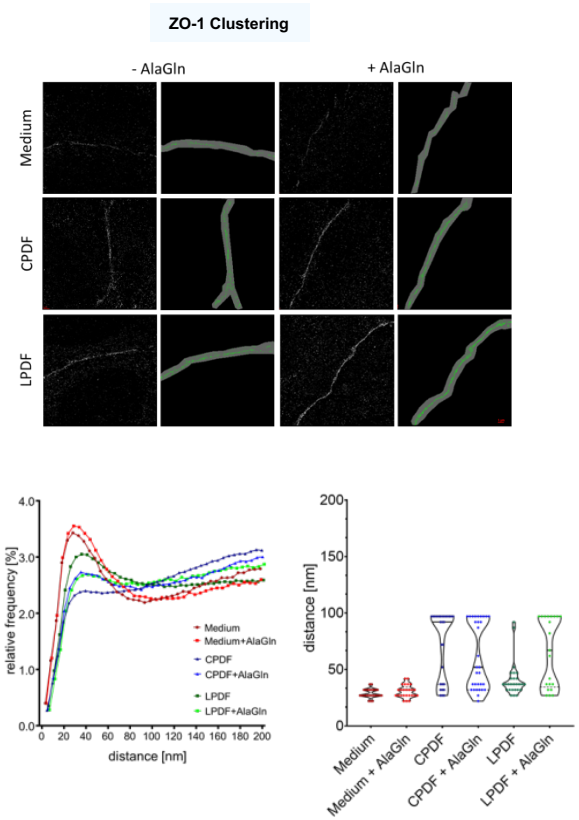
- Improved peritoneal membrane integrity (Ca125)
- Improved local immune competence (IL-6 release)
- Increased semipermeability of the PD membrane
  with higher D/P_{4h} potassium/phosphate/uric acid and less protein losses
- Good tolerance, no safety signals
  Serum HbA1c 0.15% increased, uric acid and IL-8 reduced

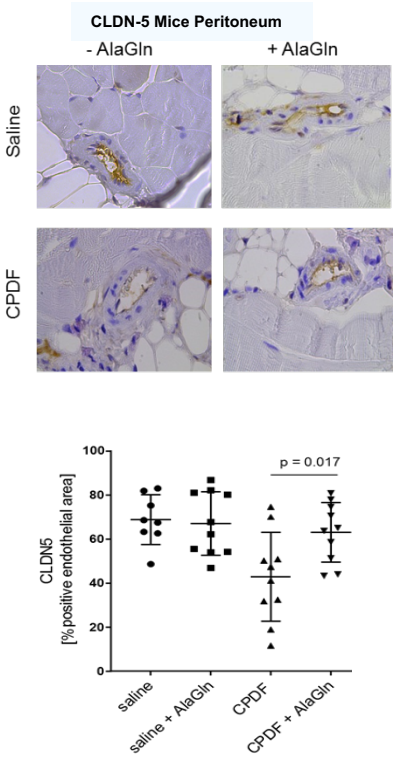
Vychytil A et al., Kidney Int 2018

Addition of AlaGln to PDF improves semipermeability of the PD membrane

(increases endothelial resistance, junction abundance and clustering,
and reduces 10 and 70 kDa protein transport in experimental models of PD)

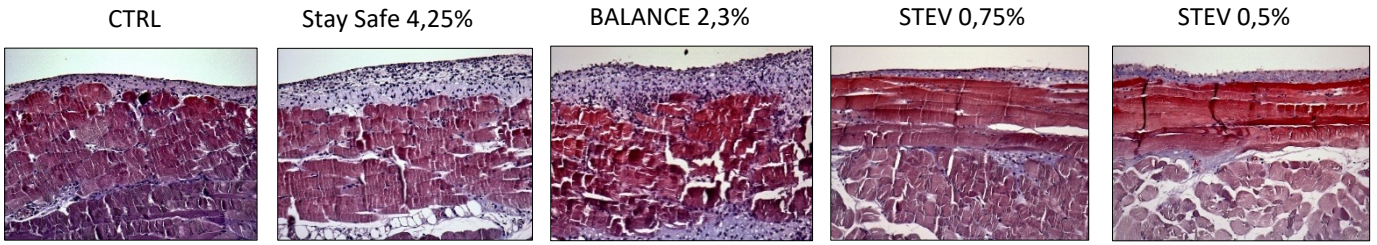




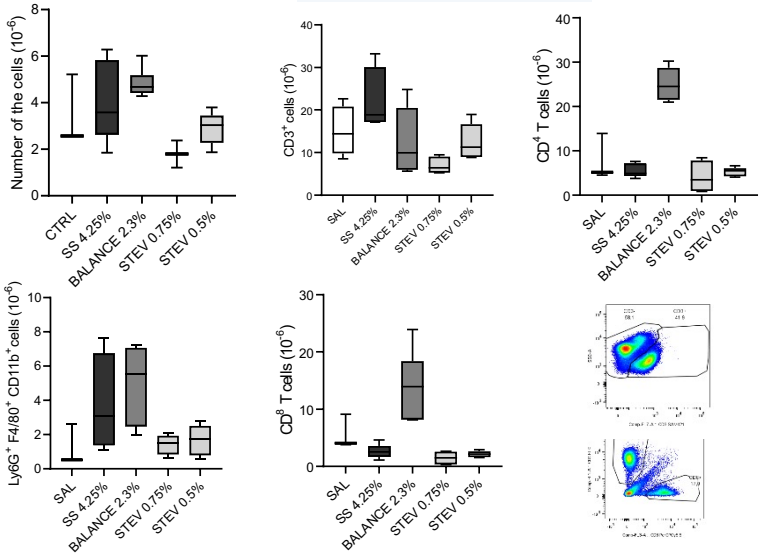


Bartosova M et al., Biomolecules. 2020

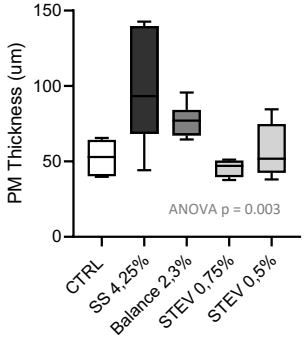
Stevia induces less peritoneal inflammtory cell invasion and fibrosis in experimental PD



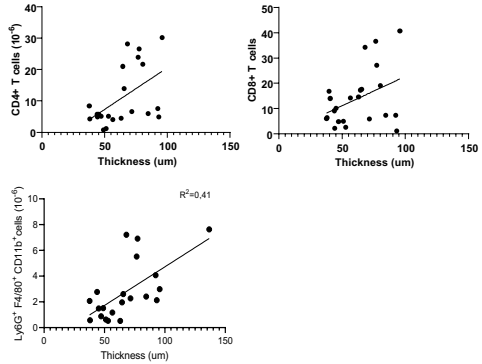
Peritoneal cell infiltration



Peritoneal thickness



Peritoneal infiltration - thickness



Kopytina V, González-Mateo G, Sandoval P, López Cabrera M, Madrid

What does he wants to tell us?

- Standardisation of diagnostics (PET) and valuable treatment recommendations (pediatric clinical practice recommendations)
- Prognostic markers to predict and individualize PD therapy (AQP-1)
- Better understanding and therapeutic targets of PD related local and systemic (vascular) disease
  But - for the moment reduce glucose exposure as much as possible
- Novel supplemented PD fluids are on the horizon, novel osmotic agents
- Still much more to accomplish; you are very welcome to the join scientific groups!

Thank you!

HEIDELBERG UNIVERSITY HOSPITAL

Ivan Damgov, Conghui Zhang, Iva Marinovic, Eszter Levai, Maria Bartosova, Claus Schmitt, Betti Schaefer, Sotirios Zarogiannis

Thank you to all centers contributing to the PD Biobank!

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- Alexander von Humboldt-Foundation
- International Society of Peritoneal Dialysis

DFG Deutsche Forschungsgemeinschaft German Research Foundation

IMPROVE-PD New frontiers in Peritoneal Dialysis

HORIZON 2020

Alexander von Humboldt Stiftung/Foundation

ISPD

MC question

- PET is useful in clinical practice to define PD regime, evidence for improved outcome is scant
- AQP-1 variants predict outcome in adult PD patients
- PD fluids with high GDP concentrations induce significant more vascular damage
- Peritoneal damage of adequately treated peritonitis episodes in patient on pH neutral, low GDP PD fluids is probably low.
- The concept of glucose-compensated, low-sodium PD solution is intriguing, the clinical benefits, however, are uncertain

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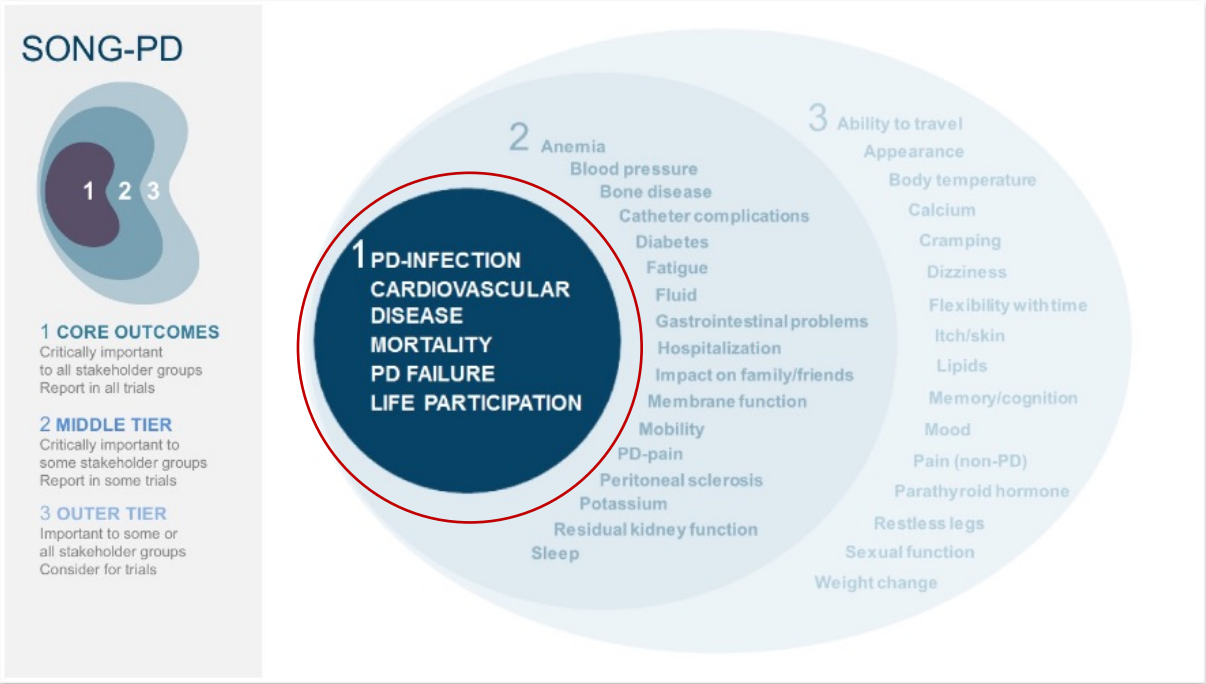
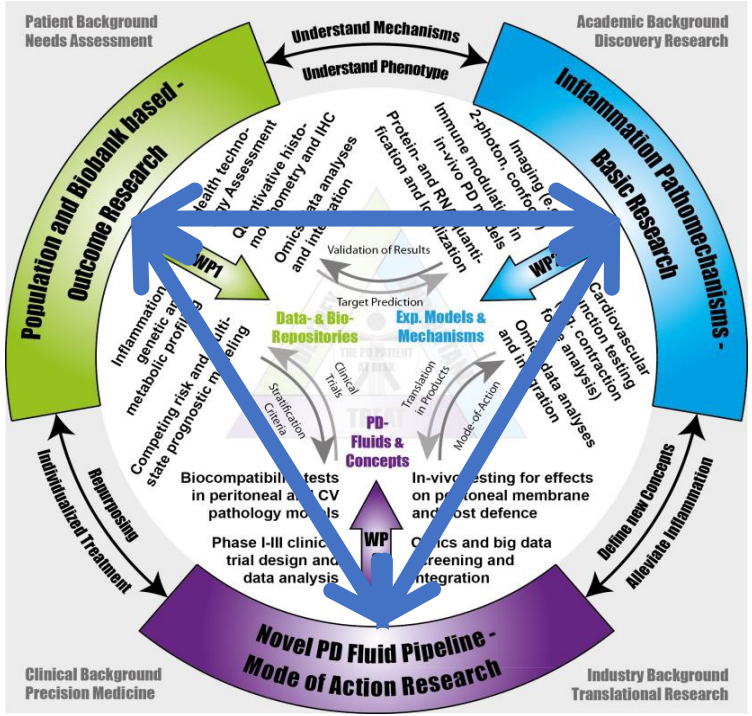


Stakeholders:
- Patients/caregivers
- Health care professionals

Hanson CS et al, KI 2020

The comprehensive approach



1. Create the largest PD patient meta data-platform

2. Provide baseline and long term PD patient (CV) risk profile and risk stratification for a personalized approach
   (profibrotic /EMT phenotype / biomarker links to CV outcomes …)

3. System wide characterization/pathway identification of CKD- and PD-related vascular disease.
   Understand peritoneal - systemic inflammatory interaction
   => Define therapeutic targets

4. Establish novel prototypes of PD fluids

Conclusions

- Optimize PD using PET and IPPM
- Use low GDP fluids whenever possible
- Limited evidence in favour of bicarbonate PD buffer (less angiogenesis)
- Consider Icodextrin
- Low sodium intake to prevent fluid overload – glucose is a major driver of peritoneal damage!
- Repeated and thorough phosphate education, we cannot adequately remove the silent killer with PD