Enhancing outcomes in PD: recent developments and future directions

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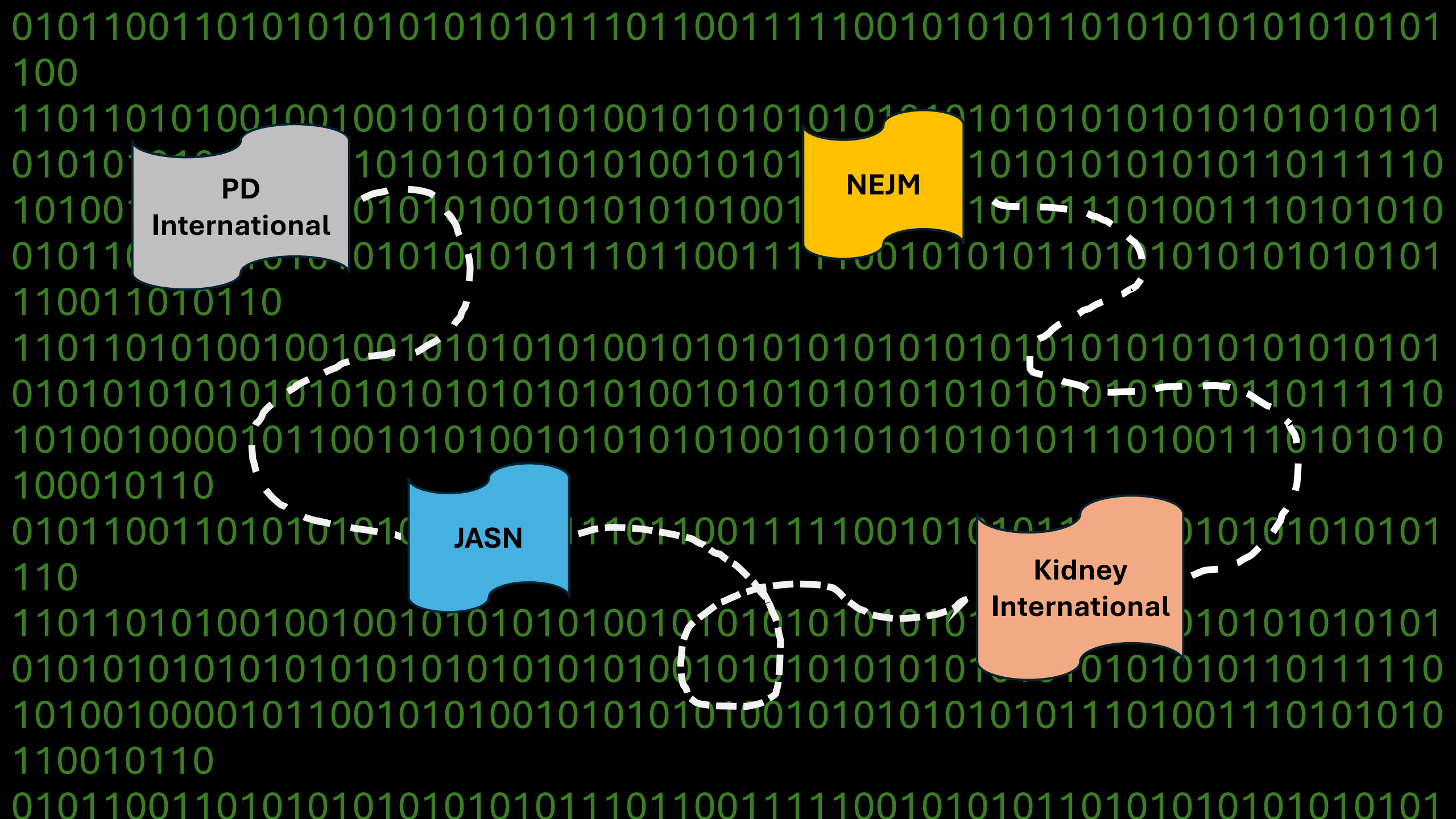
Aim

- To find the most exciting developments that has the potential to ***change the future*** of PD


PD International
NEJM
JASN
Kidney International

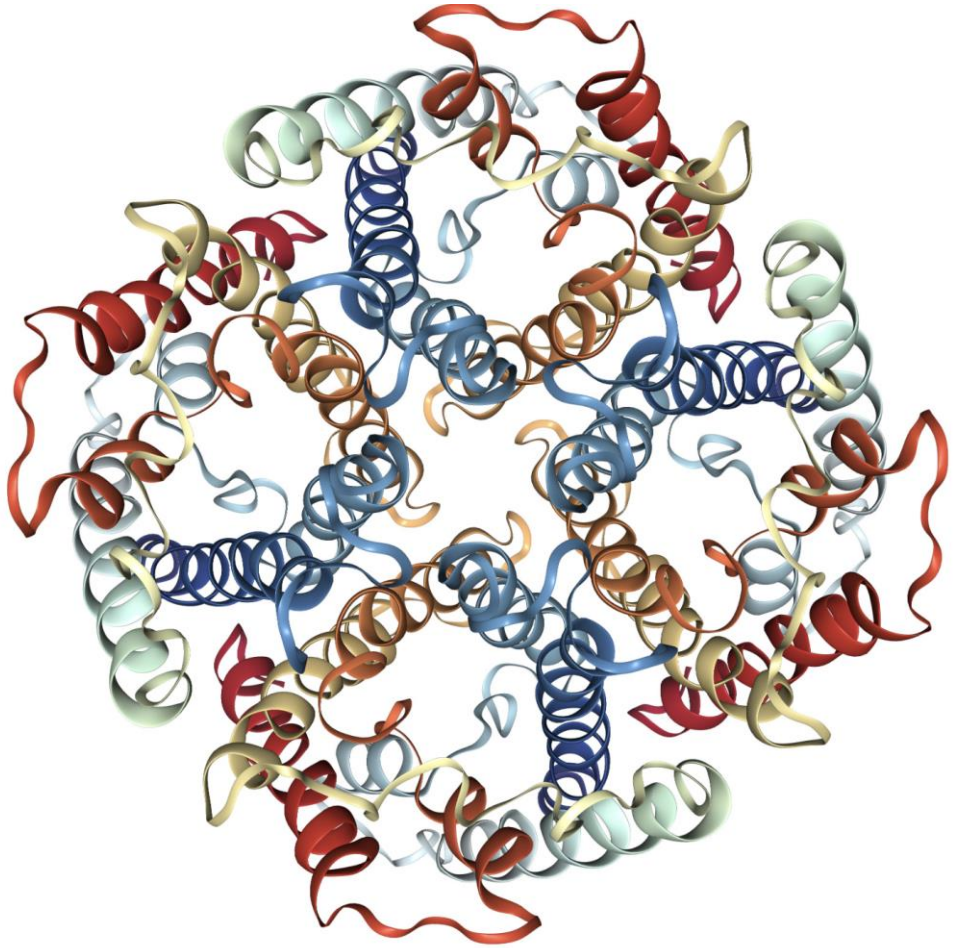
Top picks for 2024

AQP1 variant & PD outcomes

Glucose transport inhibitor in PD

Green(er) PD

AQP1 variant & PD outcomes



Murata K et. al. Available from https://sinobiological.com

Volume control in PD

- A key component of successful PD is fluid removal

- Based on Rippe's 3 pore model[1], ultrafiltration (UF) occurs via:
  - Osmosis, through aquaporins (ultra-small pores)
  - Convection (small pores)

- Poor UF is associated with worse patient outcomes[2,3]

1. Rippe B et al. Kidney Int. 1991;40:315-325
2. Lin X et al. Nephrol Dial Transplant 2010;25:2322-2327
3. Brown E et al. J Am Soc Nephrol 2003;14(11):2948-2957

Determinants of UF

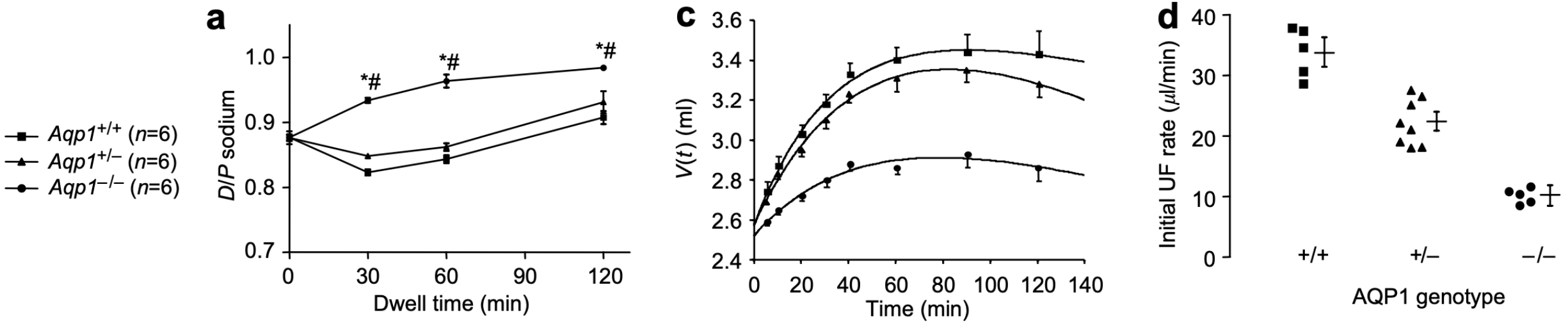
- Trans-capillary fluid movement
  - Osmotic gradient (tonicity of PD fluid)
  - Oncotic gradient
  - Hydrostatic pressure
- Lymphatic re-absorption
- Peritoneal membrane surface area
- Peritoneal membrane permeability (D/P creatinine)

- ***?Genetics***

Aqp1 KO mouse model of PD

To improve our understanding of aquaporin function in PD

- Modified PET-test in *Aqp1*$^{+/+}$, *Aqp1*$^{+/-}$ and *Aqp1*$^{-/-}$ mice
- KO mice could not concentrate urine, needed 2.7x fluid intake



Ni J. et al. Kidney Int. 2006;69:1518-1525

Aqp1 KO mouse model of PD

- Validates Rippe's modelling of ultrasmall pores
  - Ultrasmall pores = aquaporins
  - Contributes to sodium sieving
  - Confers ~50% of UF when using hypertonic PD solutions

- *So, how does this translate in humans?*
  - Case reports of rare *Aqp1* homozygous deletion[1]

1. King L. et al. N Engl J Med 2001;345:175-179

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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

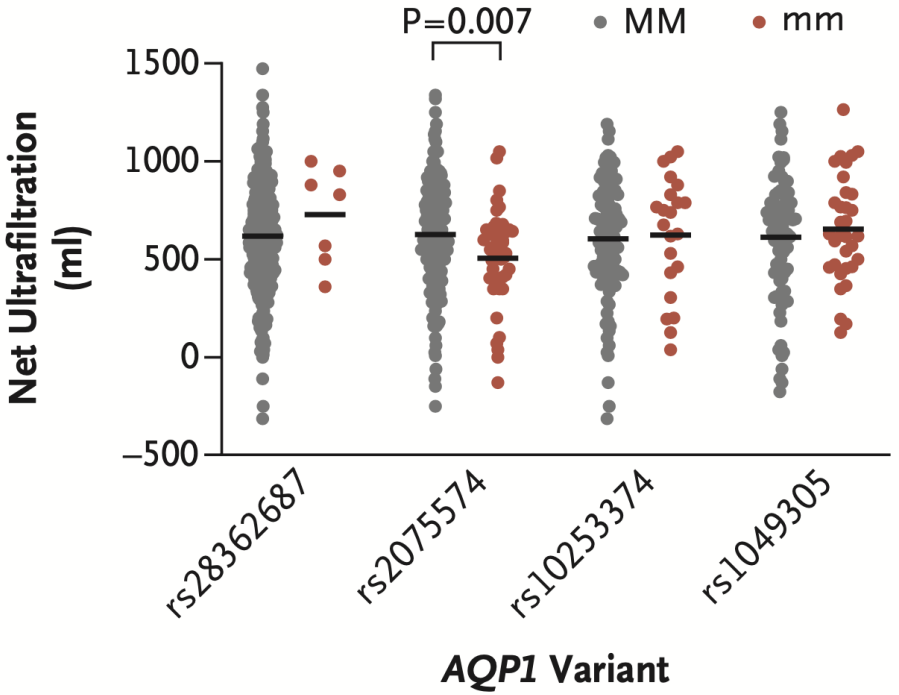
Morelle J. et al. N Engl J Med 2021;385:1570-1580

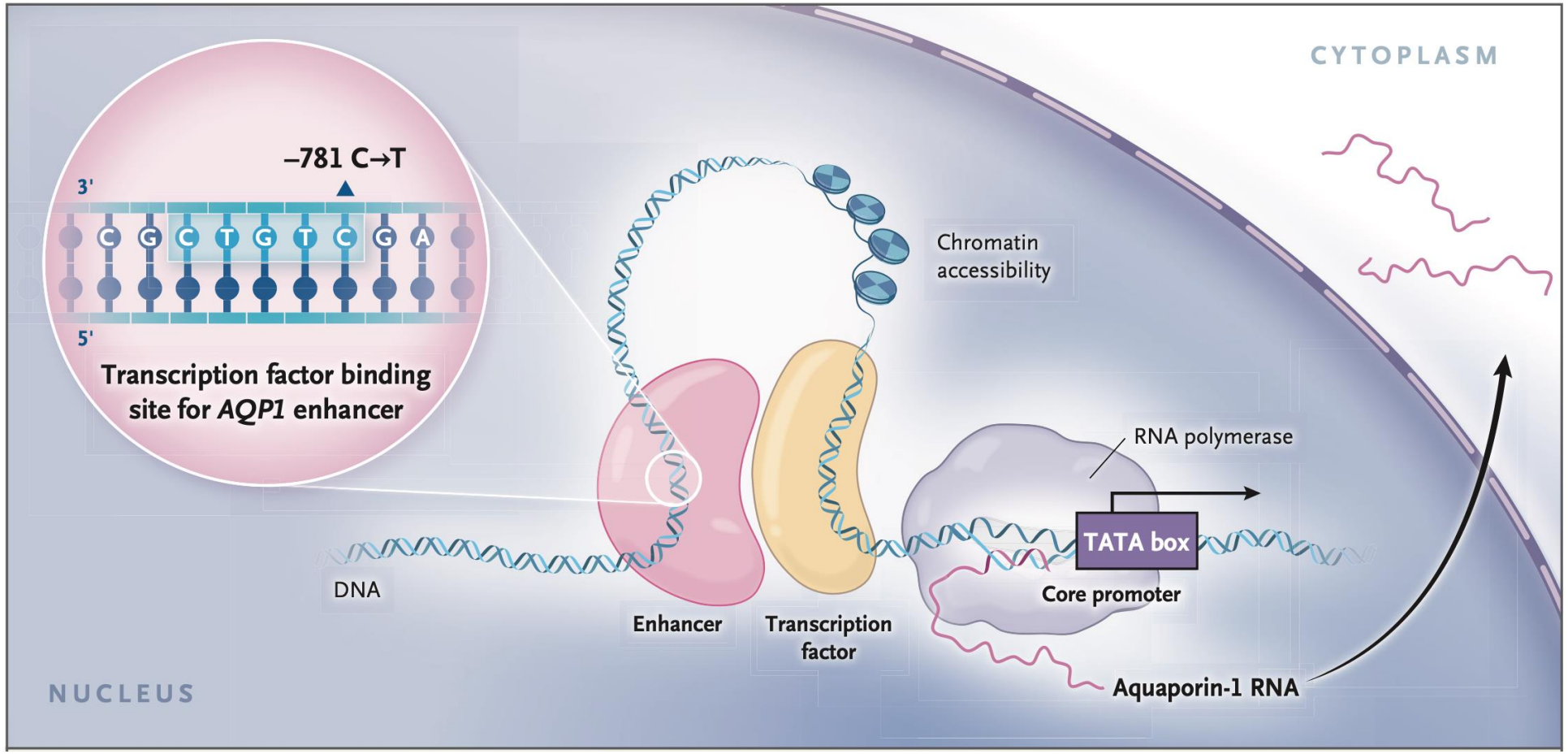
AQP1 promoter variant

A multi-national cohort study of 1851 PD patients

- Netherlands, Belgium, Spain, UK and China
- DNA material stored, PET test results and outcome data
- Mutations with minor allele frequency >10% at *AQP1* were genotyped
- Compared differing genotypes with PET and patient outcomes
- Explorative cohort followed by validation (UK & China)

- Among different variants, rs207574 (c.781C→T) was a/w ultrafiltration





Bichet D. N Engl J Med 2021;385(17):1617-1619

Cohort characteristic	Overall (N = 1851)
Age	54 ± 16
Female gender (%)	695 (38)
BMI	24.5 ± 4.9
Racial background (%) European African Asian Other	 1372 (75) 22 (1) 421 (23) 18 (1)
Diabetes (%)	426 (24)
Daily urine volume, mL	948 ± 771
Peritoneal D/P creatinine	0.68 ± 0.13
PET ultrafiltration, mL	611 ± 280
AQP1 genotype at rs2075574 (%) CC CT TT	 758 (41) 842 (45) 251 (14)

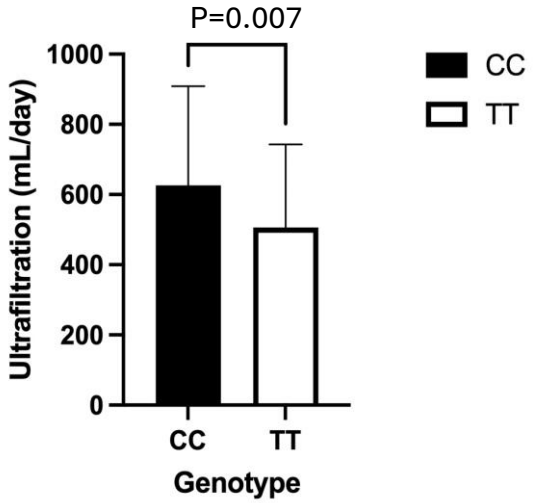
Morelle J. et al. N Engl J Med 2021;385:1570-1580

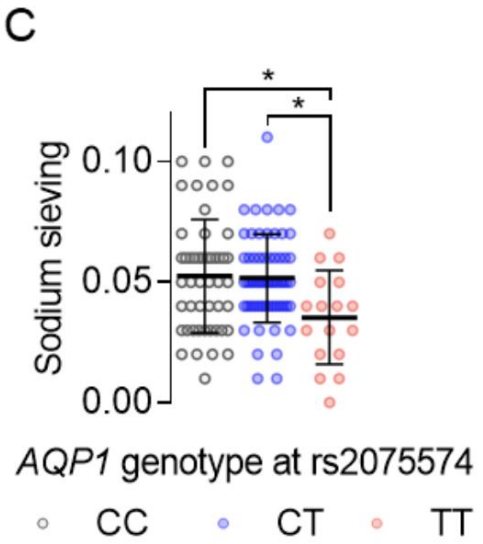
AQP1 variant - ultrafiltration

Compared to the CC genotype, TT genotype was associated with:

- Lower ultrafiltration by ~20%
  - 626 vs. 506 mL/day (explore)
  - 563 vs. 368 mL/day (validate)
- Lower sodium sieving

- Lower peritoneal expression of
  - AQP1 mRNA expression by 27%
  - AQP1 protein by 37%

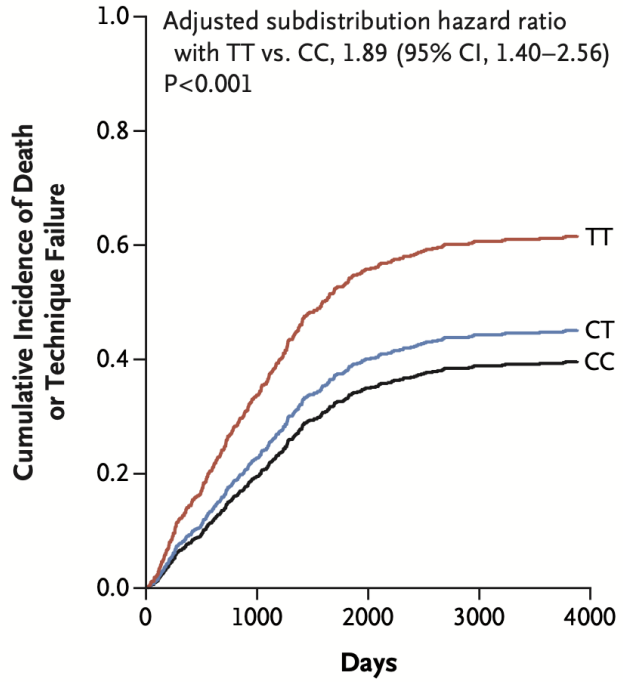




Adapted from Morelle J. et al. N Engl J Med 2021;385:1570-1580

AQP1 variant - clinical outcomes

A **Risk of Composite Outcome According to *AQP1* Genotype at rs2075574**



No. at Risk

TT	114	42	5	4	0
CT	400	168	32	3	0
CC	384	160	25	6	0

B **Subgroup Analysis**

Subgroup	No. of Patients	Subdistribution Hazard Ratio for Death or Technique Failure with TT vs. CC (95% CI)
Age		
<50 yr	381	1.75 (1.01–3.06)
≥50 yr	517	1.58 (1.12–2.25)
Sex		
Male	561	2.10 (1.44–3.07)
Female	337	1.21 (0.75–1.95)
Diabetes		
Absent	673	1.59 (1.11–2.27)
Present	193	2.25 (1.28–3.95)
Cardiovascular disease		
Absent	641	1.40 (0.95–2.07)
Present	207	2.90 (1.77–4.75)
Body-mass index		
<25	475	1.72 (1.09–2.71)
≥25	423	1.62 (1.09–2.40)
Dialysate:plasma creatinine ratio at 4 hr		
<0.80	612	1.57 (1.08–2.28)
≥0.80	286	1.84 (1.12–3.01)

Morelle J. et al. N Engl J Med 2021;385:1570-1580

AQP1 variant – summary

- Variations in the *AQP1* promoter is associated with differing UF, transfer to HD and patient survival.

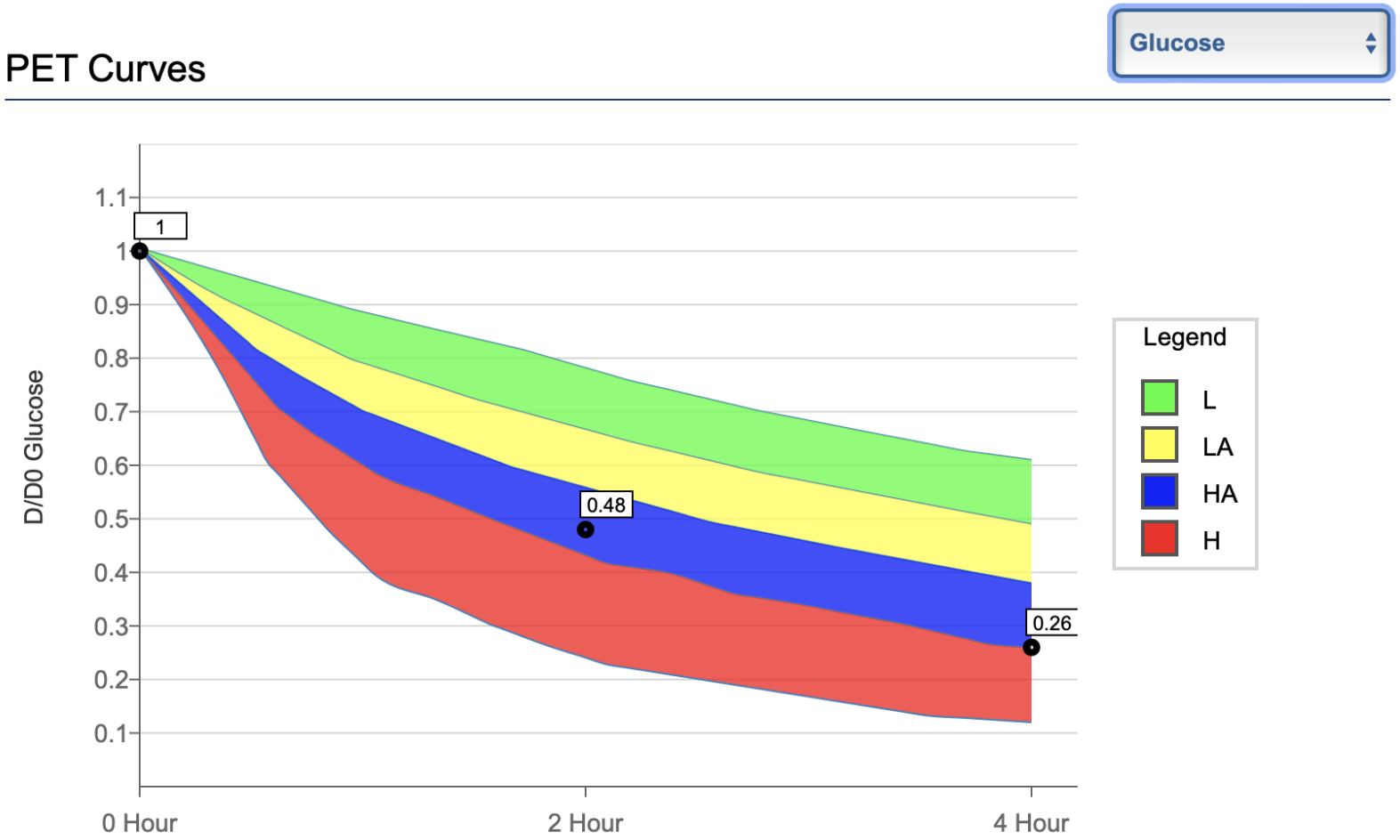
- Impact is 100-200 mL/day difference between TT vs. CC rs207574 genotypes
  - Little relevance in those with residual kidney function
  - Significant in anuric PD patients

- Effect is driven by osmosis through aquaporin; convective UF is not affected

- Do we genotype our PD patients & reconsider PD prescription?

Glucose transport inhibitor in PD

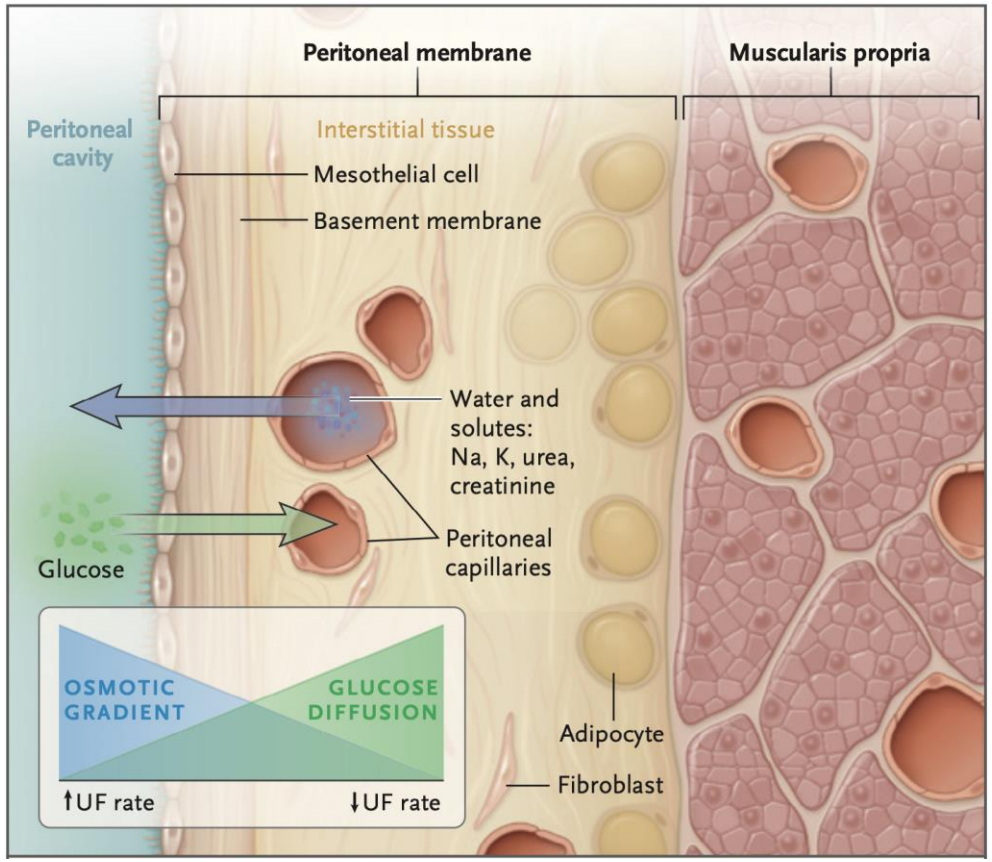
Rapid dissipation of glucose from the peritoneum



Dextrose absorption causes complications:

- **Locally**
- **Systemically**
- **Reducing ultrafiltration**

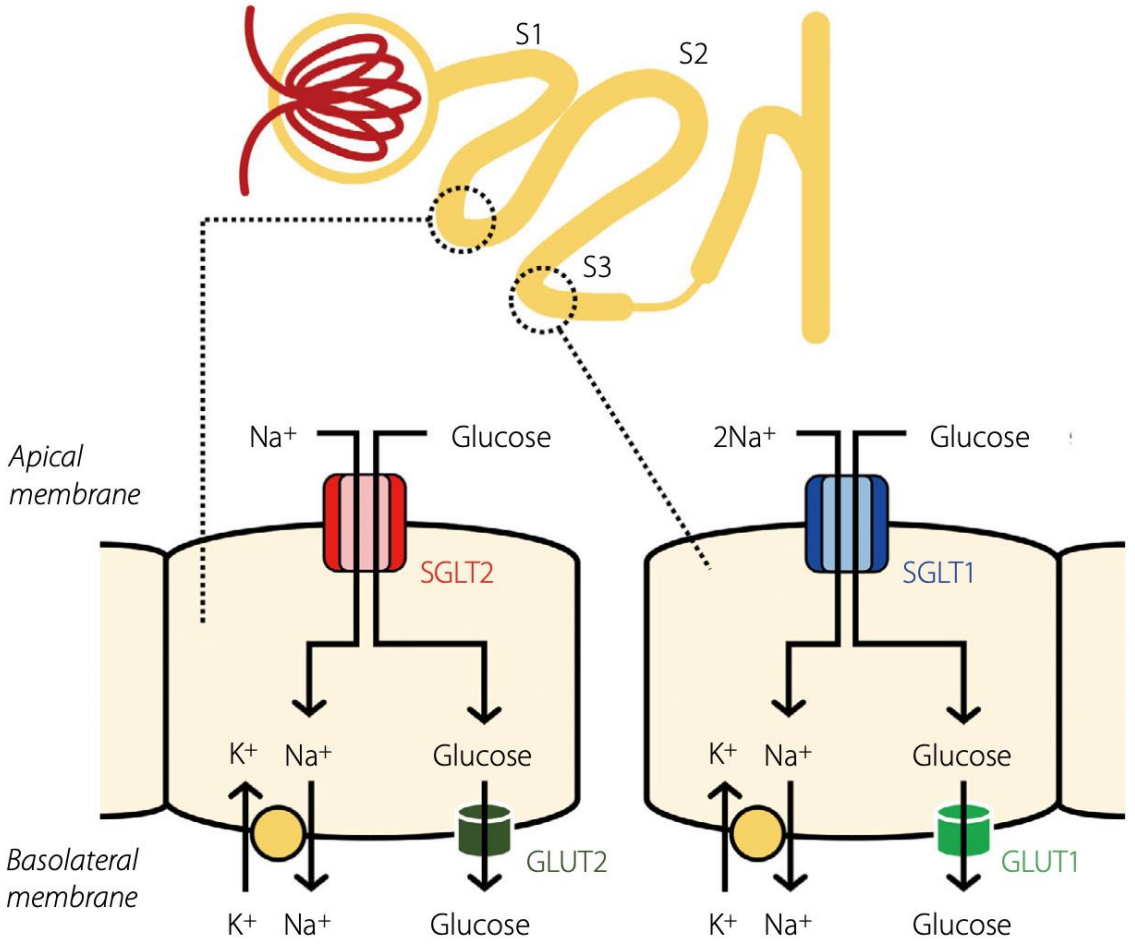
Can we lower dextrose absorption?



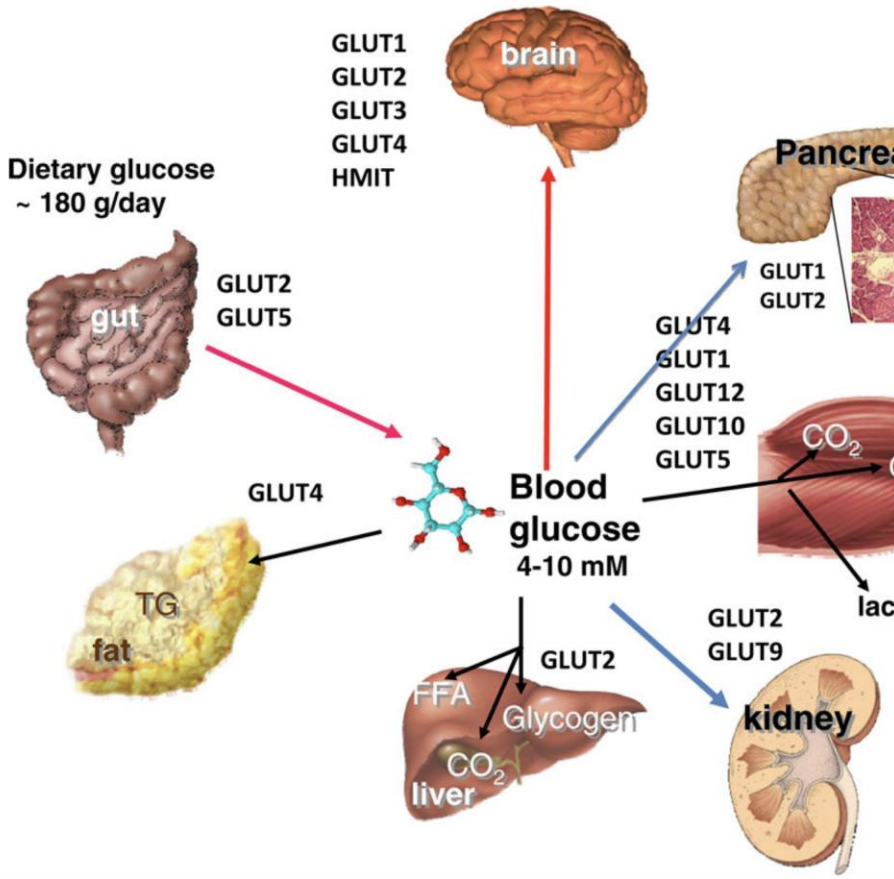
Teitelbaum I. New Engl J Med. 2021;385:1786-1795

Intracellular movement of glucose

- Sodium glucose cotransporter
  - 6 isoforms, 2 main subtypes
- Facilitated diffusion via GLUT transporters
  - Encoded by SLC2 gene
  - Up to 14 different GLUT proteins



Sano R et al. J Diabetes Investig. 2020;11:770-782



Mueckler M and Thorens B. Mol Aspects Med. 2013;34(0):121-138

What about the peritoneal membrane?

- Are there glucose transporters in the peritoneal membrane?
- If so, what is their purpose?
- Can we exploit this system for peritoneal dialysis?

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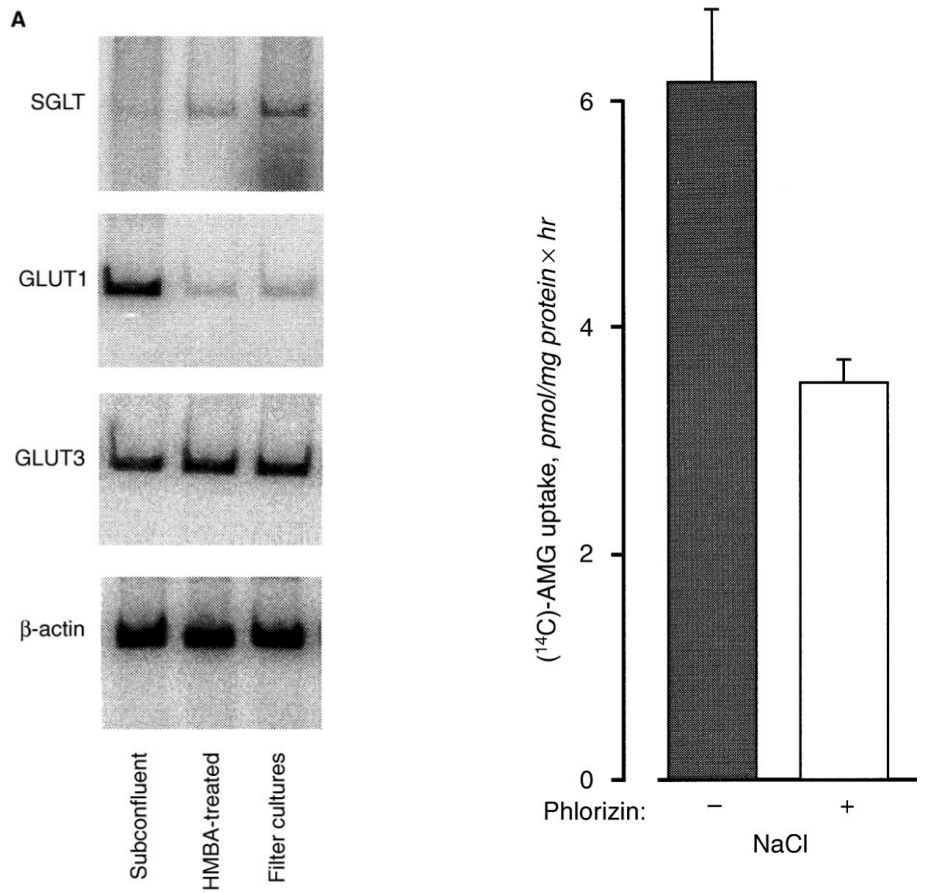
Human mesothelial cells express glucose transporters

- SGLT1, GLUT1 and GLUT3 are detected on human mesothelial cell culture
- Phlorizin, a competitive SGLT1 inhibitor, reduced cellular glucose uptake by 30-45%



Schroppel B et al. Kidney Int. 1998;53:1278-1287

Data from human peritoneal membrane biopsies

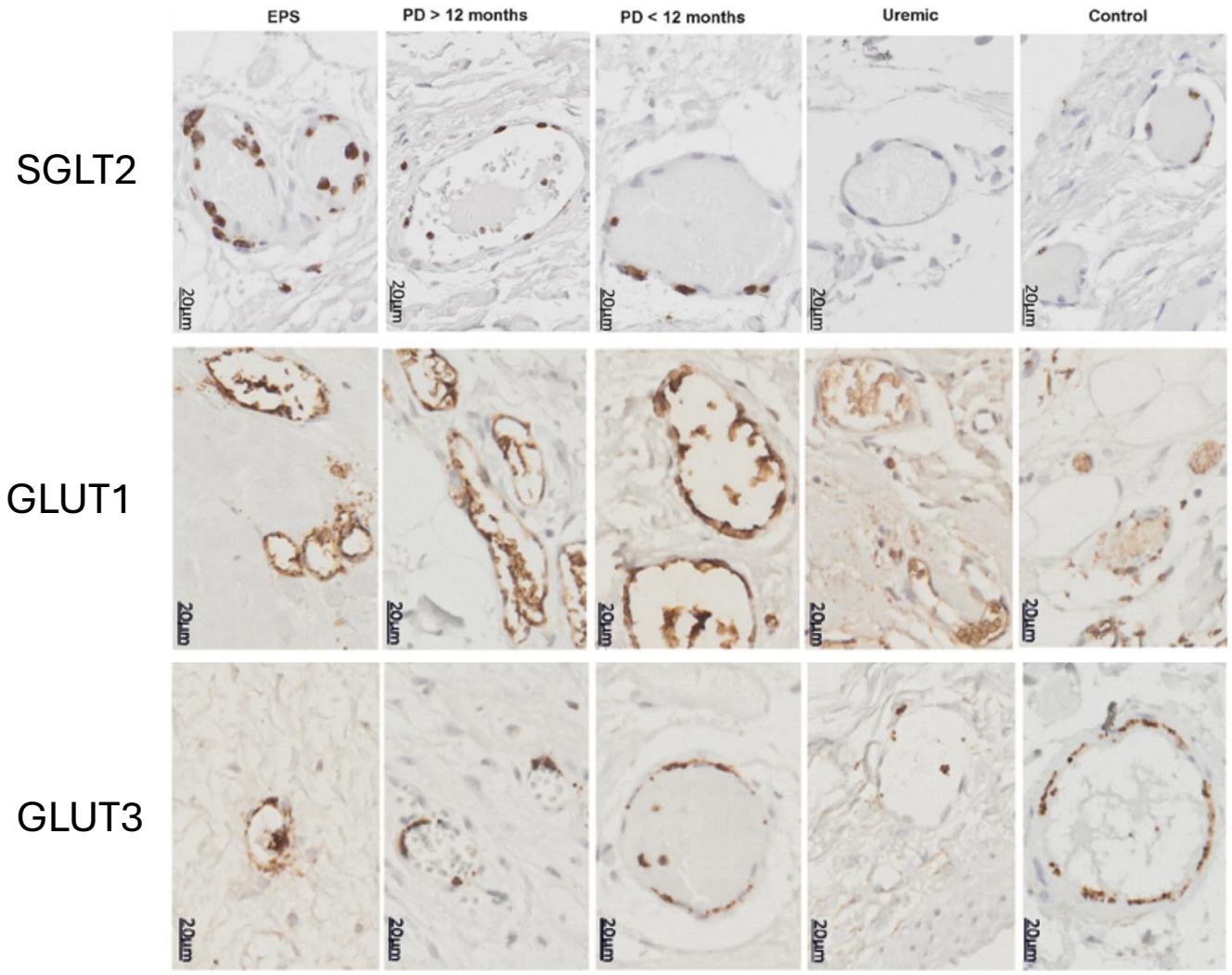
Opportunistic peritoneal biopsies from:

- Controls – surgical indication, i.e. hernia repair, cholecystectomy
- Uraemic – pre-dialysis at Tenckhoff insertion
- PD <12 and >12 months – at time of catheter reposition/removal
- Encapsulating peritoneal sclerosis

Table 2. Clinical data of study patients

Variable	Control	Uremic	PD <12 months	PD >12 months	EPS
N	8	11	18	23	12
Age, years					
Median	64.5	65.0	64.0	62.0	51.5
IQR	55.5–70.8	49.0–75.0	53.0–69.3	46.0–71.0	45.3–58.8
Female/male	6/2	3/8	4/14	9/14	3/9
PD duration, months					
Median			10.5	44.0	70.0
IQR			6.0–11.25	29.0–52.0	55.5–99.5
Diabetes, *n* (%)	1 (13)	3 (27)	8 (44)	8 (35)	0 (0)
Hypertension, *n* (%)	1 (13)	9 (82)	14 (78)	23 (100)	11 (92)
Smokers, *n* (%)	1 (13)	3 (27)	7 (39)	8 (35)	2 (17)

Schricker S et al. Kidney Blood Press Res. 2022;47:125-134

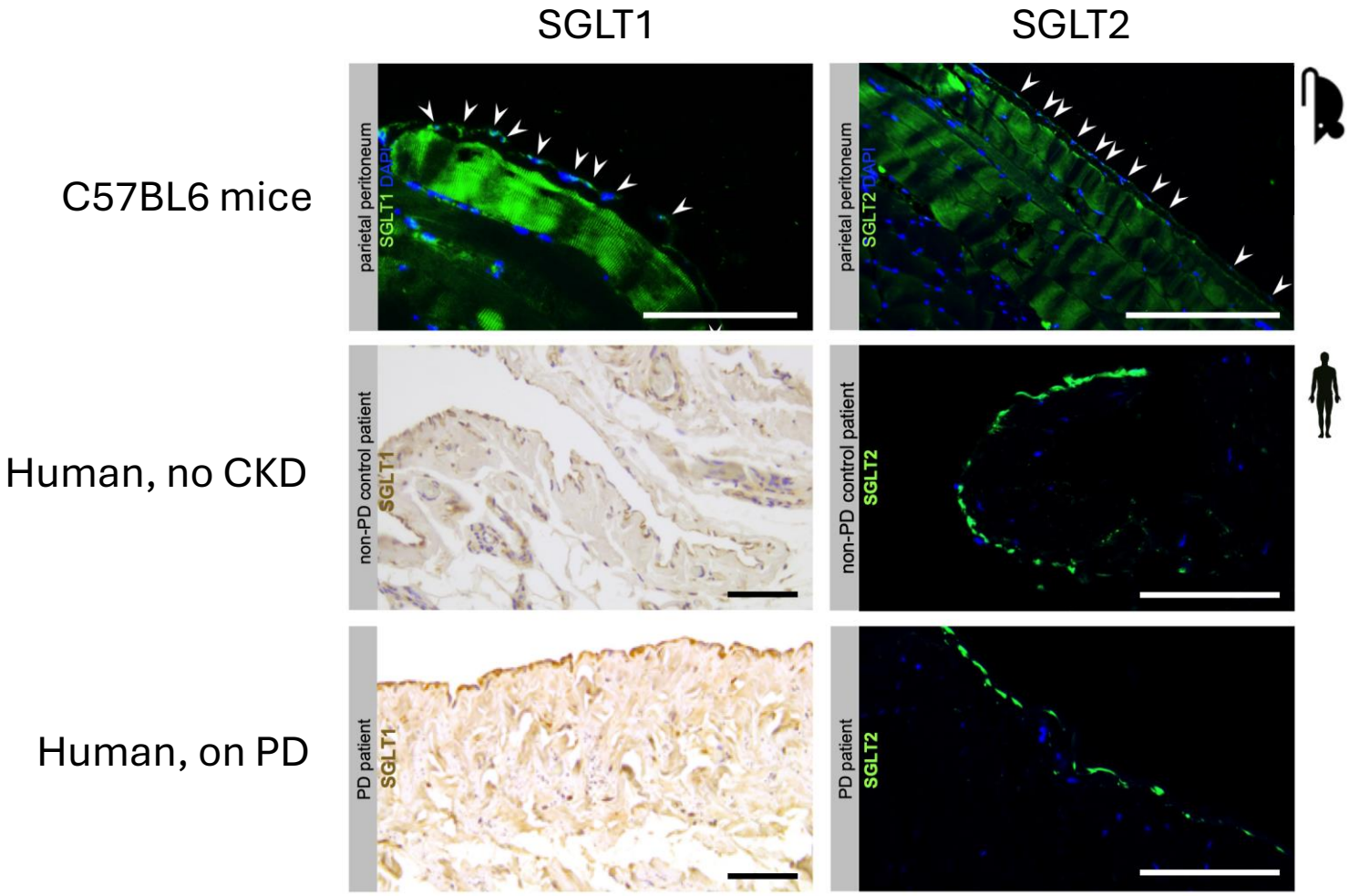


Schricker S et al. Kidney Blood Press Res. 2022;47:125-134

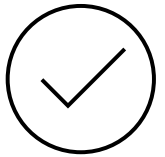
SGLT2, GLUT 1 and 3 were detected by qPCR and immunostaining

- Stronger detection was associated with PD vintage, i.e. strongest with EPS
- Peri-vascular location

SGLT1&2 conserved across species



Balzer M et al. Biomolecules. 2020;10:1573. DOI:10.3390/biom10111573

- Are there glucose transporters in the peritoneal membrane? 
- If so, what is their purpose?
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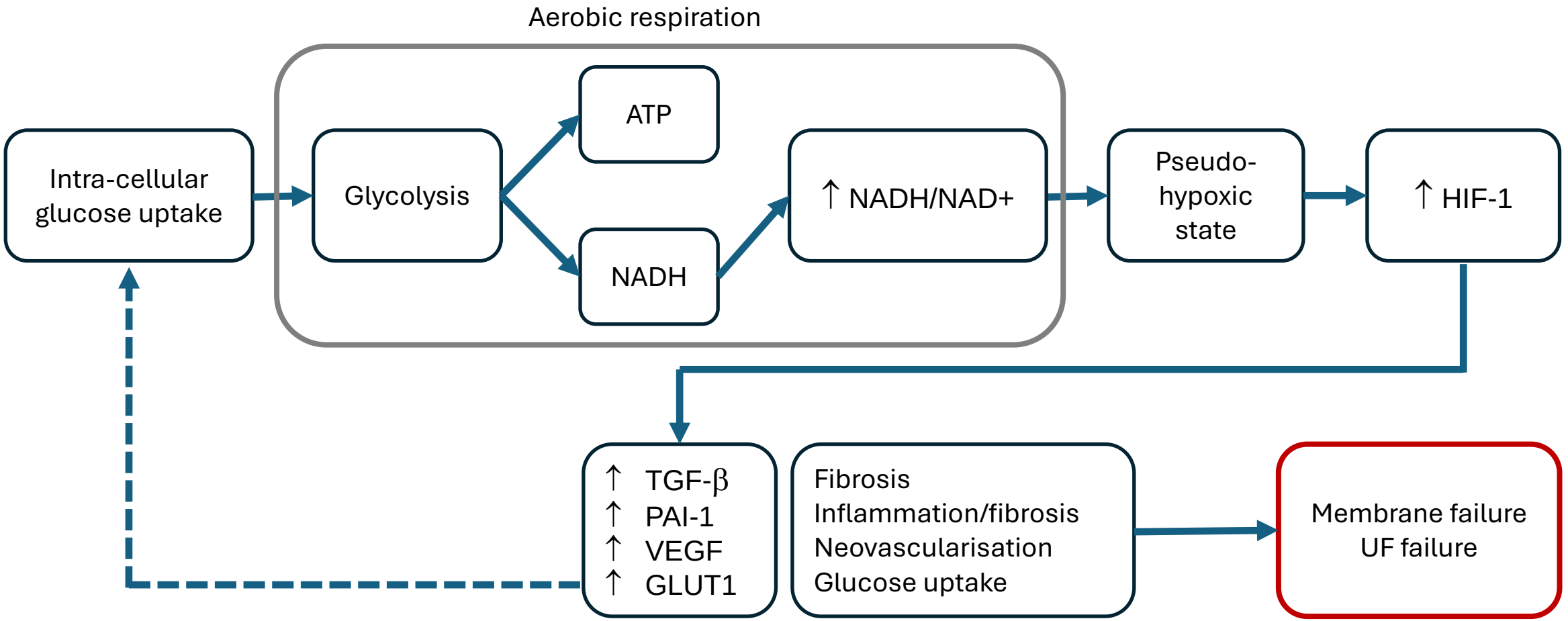
Glucose transporters in the peritoneum

Uncertain role…

- Sodium and glucose are not expected in the peritoneum
- Possibly related to glucose uptake and cellular function; GLUT & SGLTs are almost ubiquitous
- Expression of SGLT and GLUT are increased in diabetic humans and rats
- The beginnings of a “pseudohypoxic” cascade

Schricker S et al. Kidney Blood Press Res. 2022;47:125-134
Krediet R. J Am Soc Nephrol. 2021;32:2408-2415

Glucose-driven pseudohypoxia hypothesis



Adapted from Krediet R. J Am Soc Nephrol. 2021;32:2408-2415

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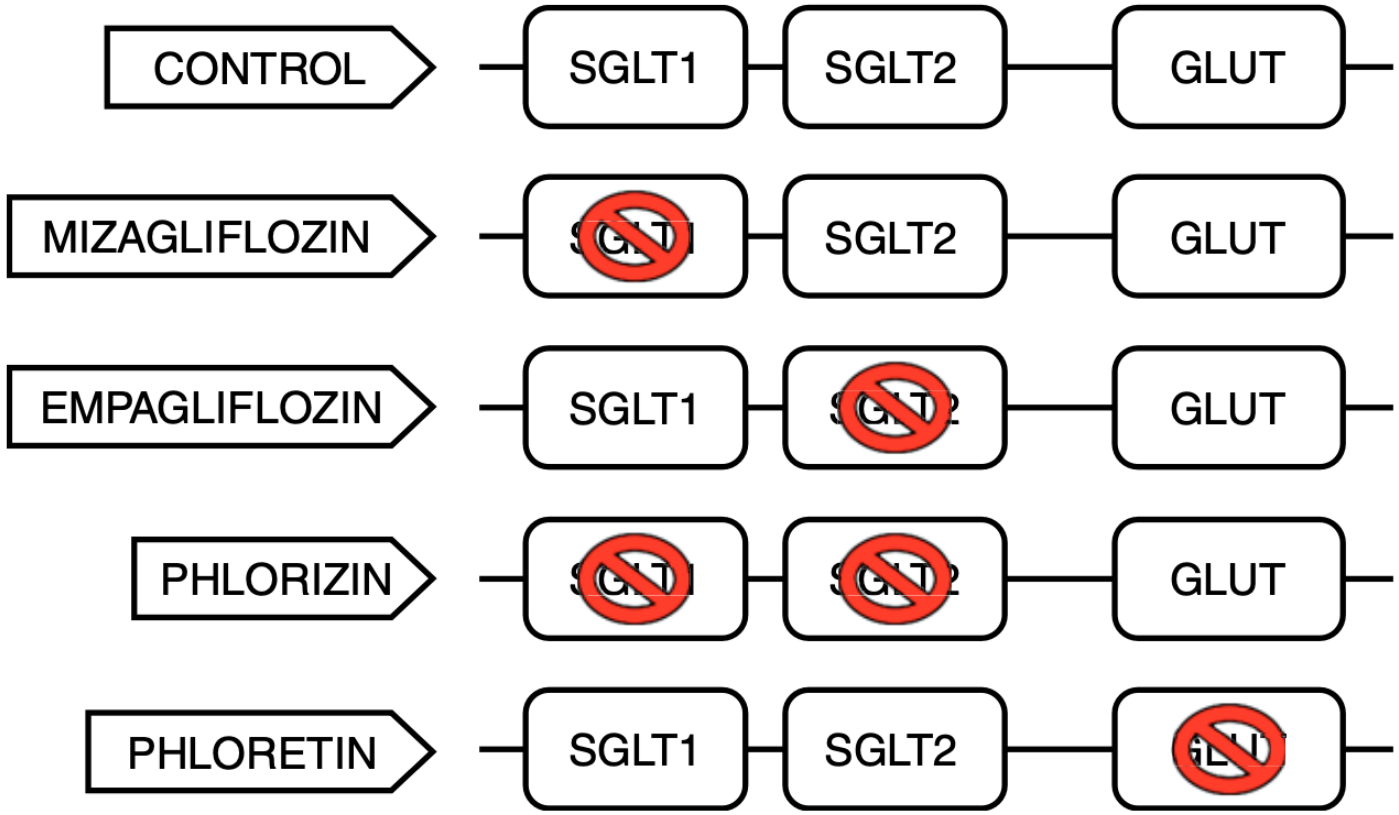
Exploiting glucose transporters for PD

- In theory, inhibition of glucose transporters at the peritoneum may be associated with:
    - Reduced glucose dissipation; maintain UF
    - Reduced systemic glucose absorption
    - Reduced pseudo-hypoxia and peritoneal membrane damage
    - Possible residual kidney benefit (SGLT2i)
    - Possible cardiovascular benefit (SGLT2i)

Inhibitors of glucose transporters



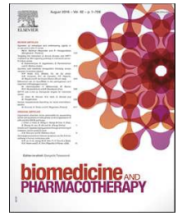
Bergling K. et al. J Am Soc Nephrol. 2022;33:1857-1863

SGLT2 inhibition in a rat model of PD & HPMC culture

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha



SGLT-2 inhibitors reduce glucose absorption from peritoneal dialysis solution by suppressing the activity of SGLT-2

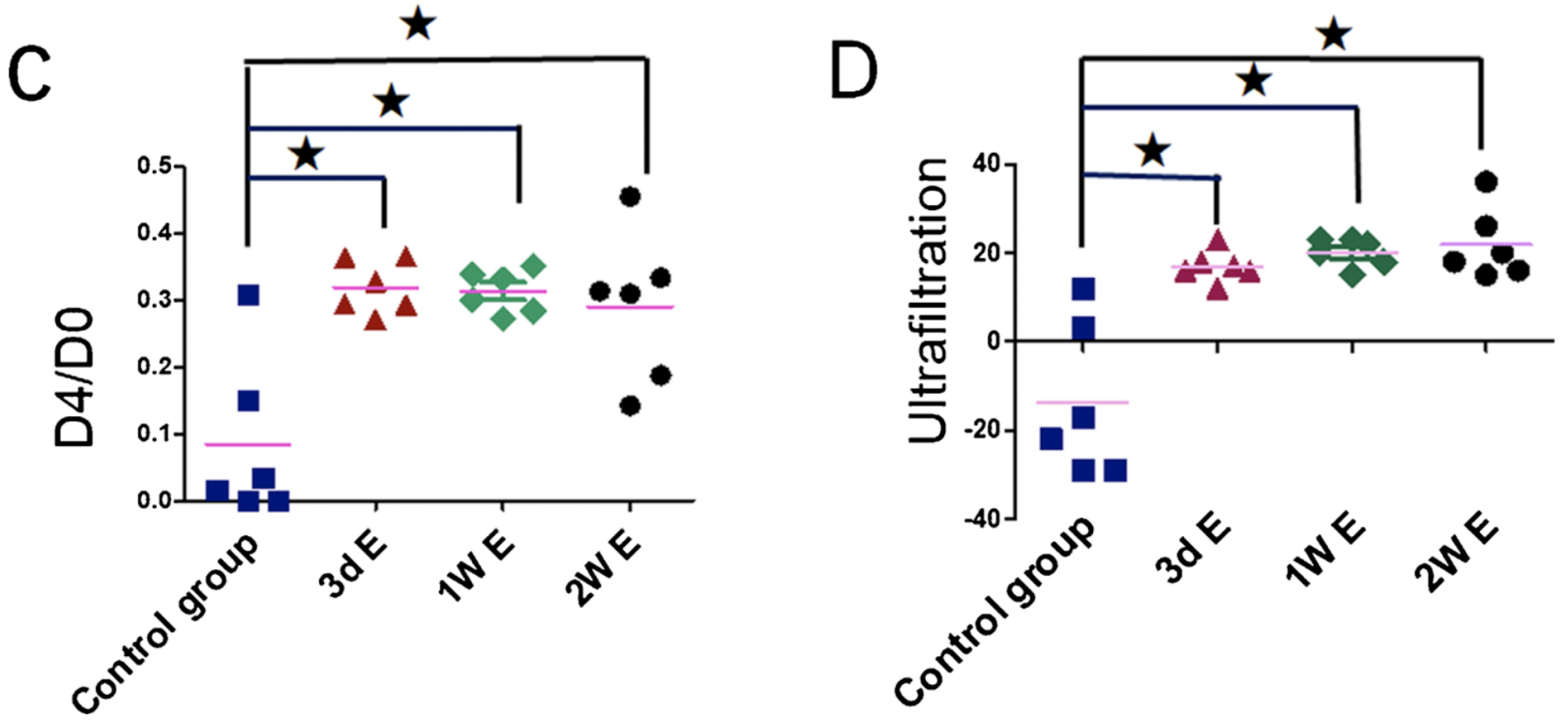
Ying Zhou[a,b,c,1,2], Jinjin Fan[b,c,1,2], Chenfei Zheng[a,1,2], Peiran Yin[b,c], Haishan Wu[b,c], Xiaoyan Li[b,c], Ning Luo[b,c], Xueqing Yu[a,b,c], Chaosheng Chen[a,*]

- Sprague-Dawley rat model of PD
  - Modified-PET, using 4.25% dextrose PD solution
  - Glucose D4/D0 +/- empagliflozin
- Human mesothelial cell culture
  - Intracellular uptake of tracer-labelled glucose +/- empagliflozin

Empagliflozin reduced glucose absorption and maintained UF

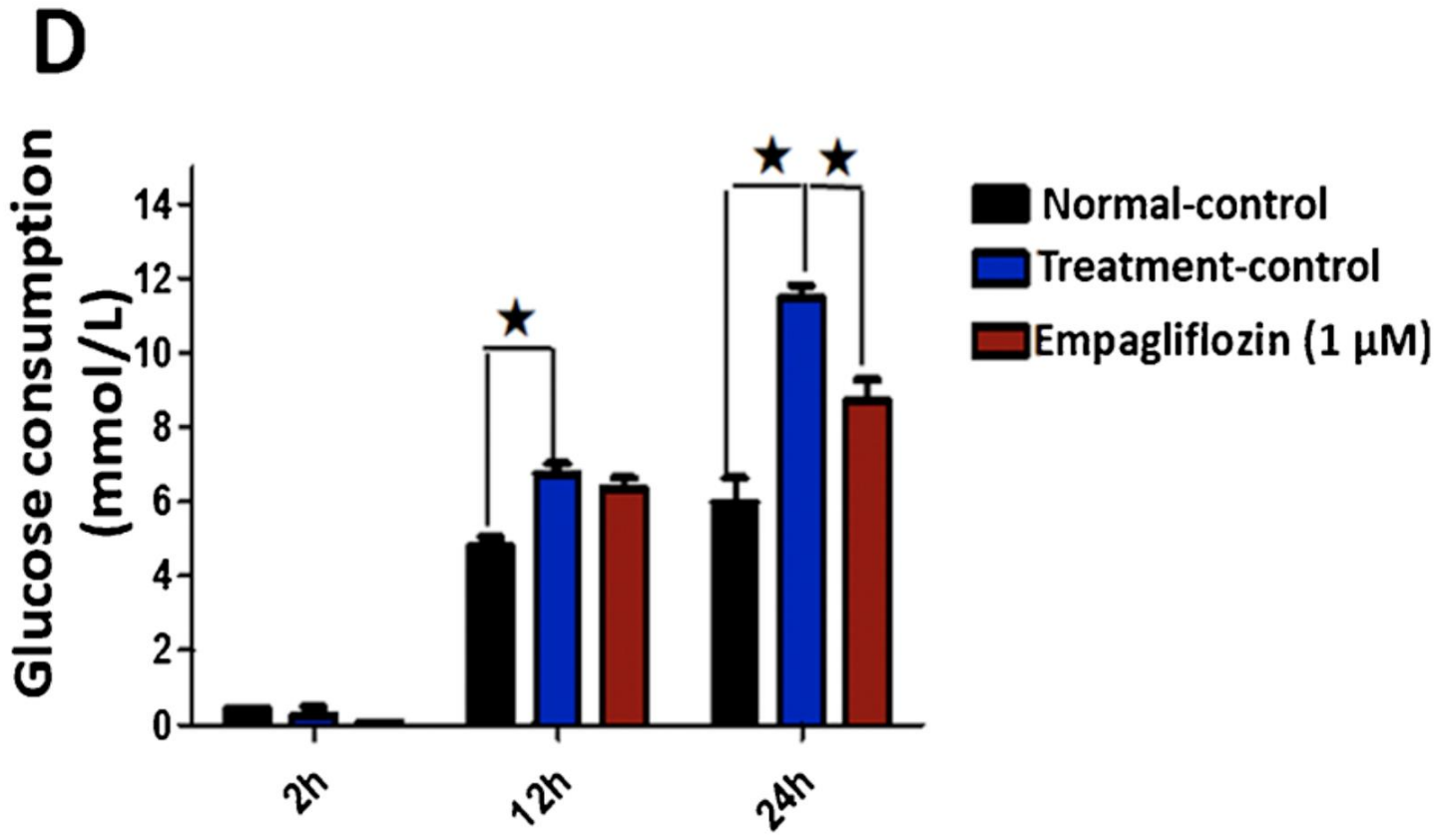
Reduced glucose absorption

Maintained ultrafiltration



Zhou Y, Fan J et al. Biomed Pharmacotherapy 2019;109:1327-1338

Empagliflozin reduced intra-cellular uptake of glucose in HPMC



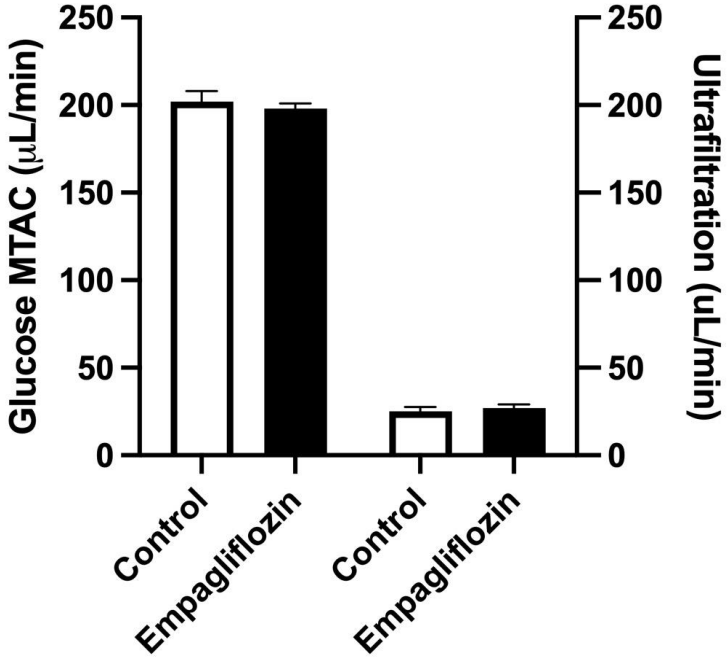
Zhou Y, Fan J et al. Biomed Pharmacotherapy 2019;109:1327-1338

Results were not consistent

In another Sprague-Dawley Rat model of PD

- 2-hour dwell of dextrose PD solution
- Control vs. IV empagliflozin
- Intervention group had glucosuria and increased urine output

- Empagliflozin had no effect on glucose diffusion or UF rate

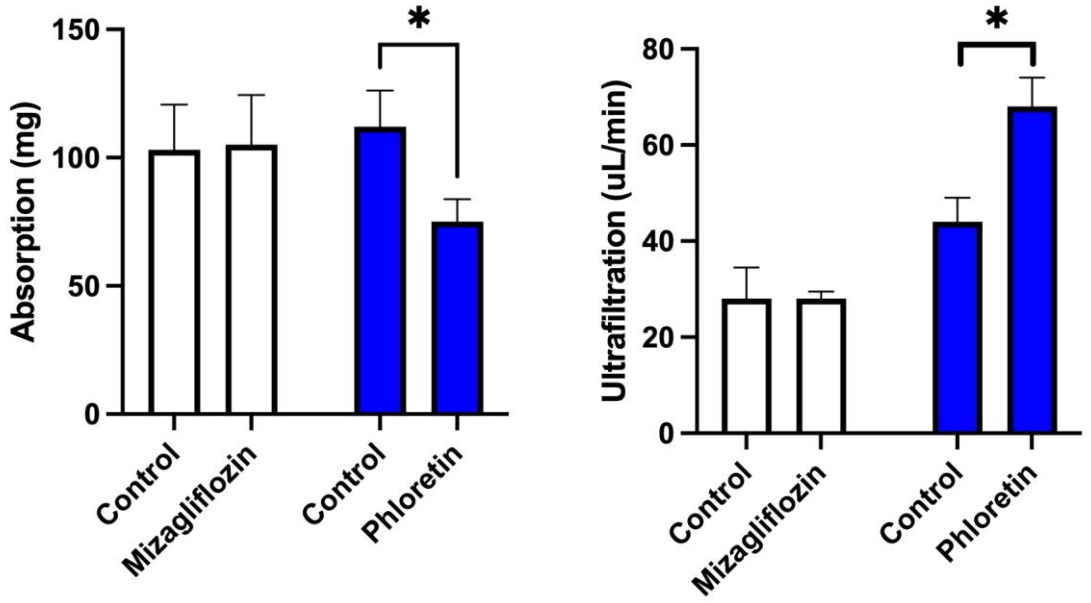


Adpated from Martus G. et al. Perit Dial Int. 2021;41(4):373-380

Blocking SGLT1 and GLUT

Rat model of PD, modified-PET:

- GLUT inhibition (using phloretin, blue bars)
  - reduced glucose diffusion by 30%
  - maintained UF rate by 50%
- SGLT1 inhibition (mizagliflozin, white bars) had no effect



Adpated from Bergling K. et al. J Am Soc Nephrol. 2022;33:1857-1863

Mouse model of chronic PD

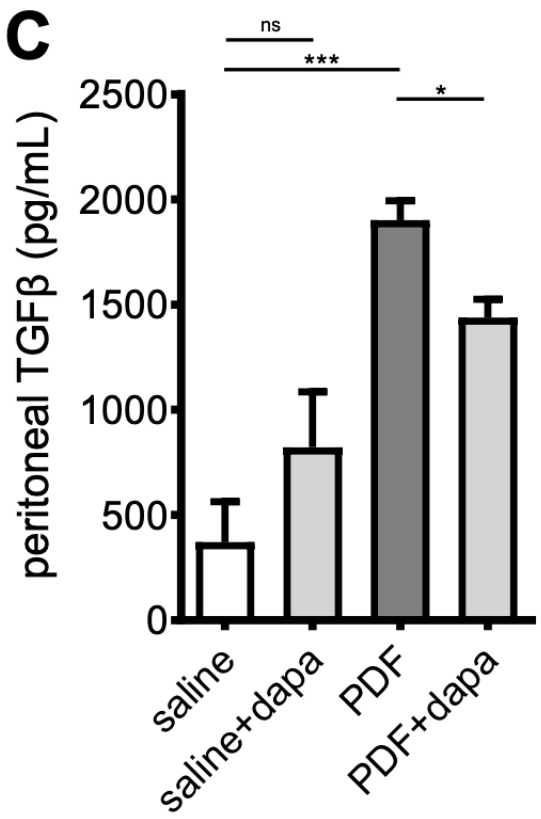
- C57BL6 mice, 5 weeks of PD using 4.25% dextrose

- Use of dapagliflozin (SGLT2 inhibitor) was a/w:

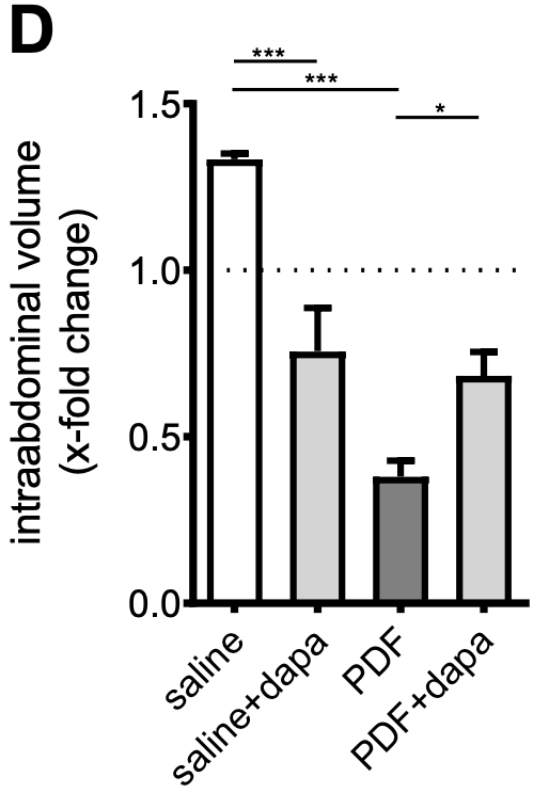
    - Improved ultrafiltration volume
    - Reduced effluent TGFβ-1 concentration
    - Reduced submesothelial thickness
    - Reduced peritoneal membrane fibrosis (collagen deposition)

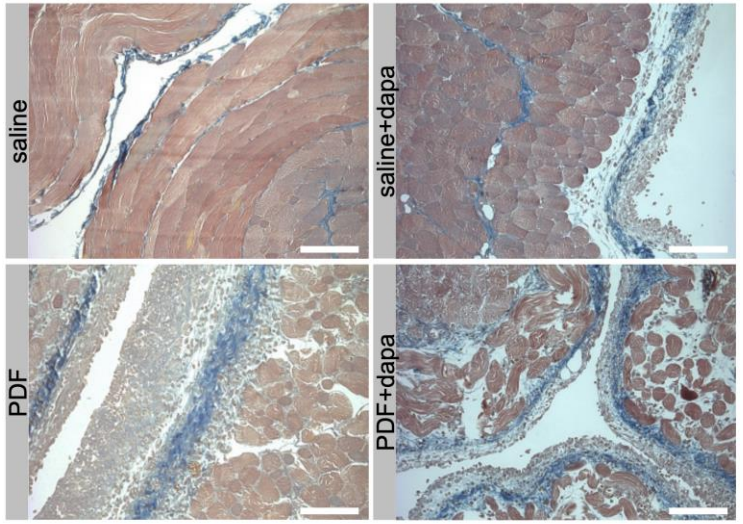
Balzer M et al. Biomolecules. 2020;10:1573. DOI:10.3390/biom10111573

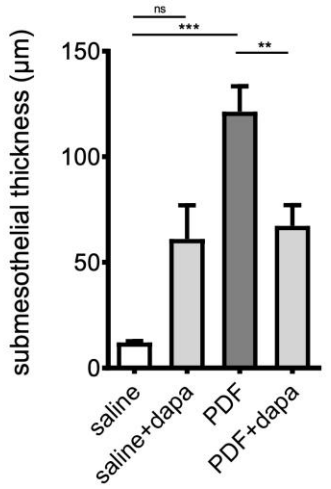
PD effluent TGFβ by ELISA

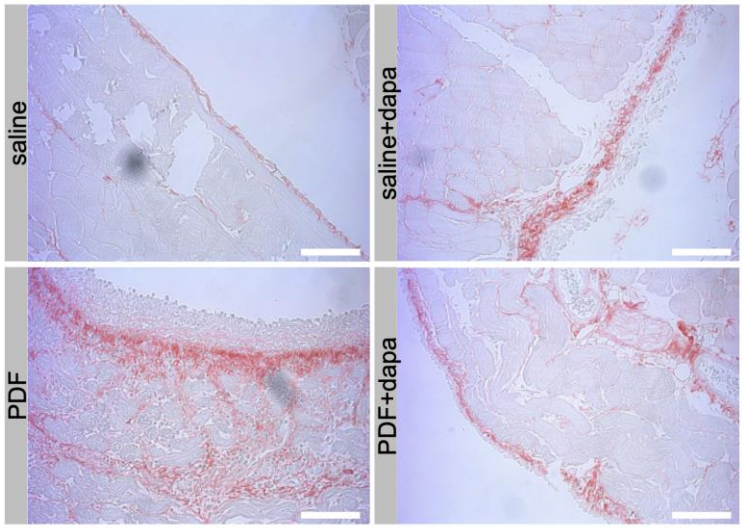


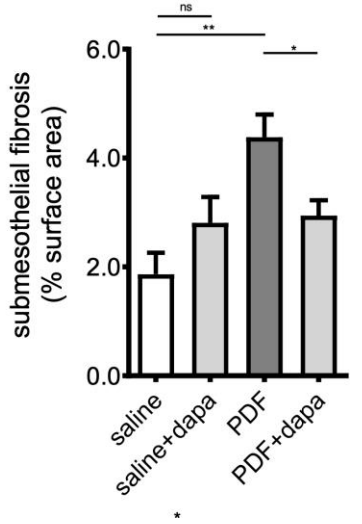
2-hr Mini-PET, 4.25%











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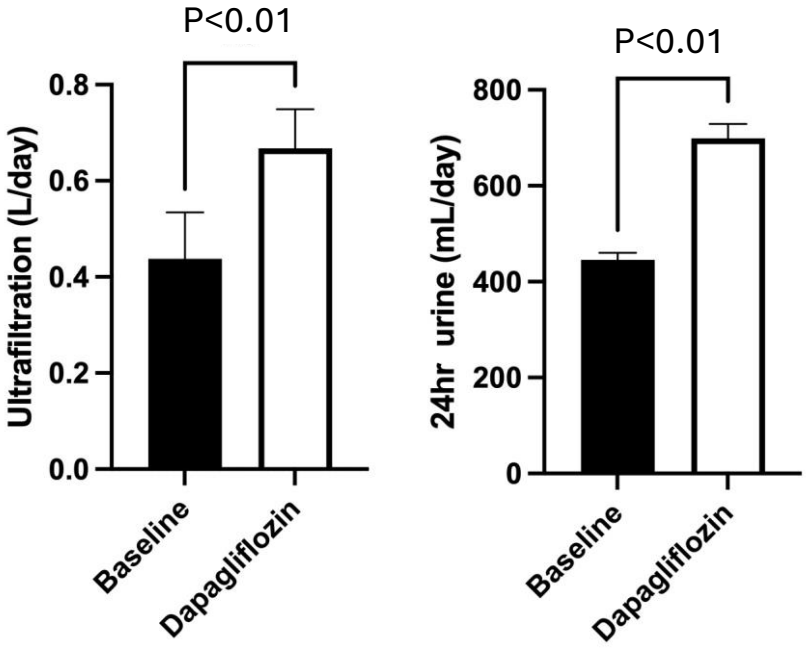
Clinical studies using SGLT/GLUT inhibitors

- No human data on GLUT inhibitors

- Sparse data on SGLT2 inhibitor in ESKD
  - Case reports

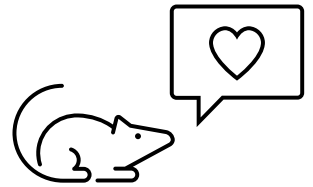
  - Cohort study from Saudi Arabia
    - n=50 diabetic PD patients given dapagliflozin 10mg
    - Observed for 6 months. Un-controlled study.

    - UF and 24hr urine volume improved
    - Mean weight loss 2.6 kg
    - Adverse events or deaths not reported



Adapted from Alhwiesh A. et al. Arch Nephrol Urol. 2022;5(1):1-8

- Are there glucose transporters in the peritoneal membrane?
- If so, what is their purpose?
- Can we exploit this system for peritoneal dialysis?



Potential risks of using SGLT & GLUT inhibitors in ESKD

- Hypoglycaemia (combination blockade)
- Euglycaemic ketoacidosis
- Impact on infections, including mycotic
- CKD-MBD
- Amputation
- Diarrhoea, GI symptoms (SGLT1 inhibition)

GLUT & SGLT inhibitors in ESKD

More clinical trials, including RCTs, are coming

Study	Trial registry
Reduction of Peritoneal Glucose Uptake With the Use of SGLT2 in Humans Undergoing Peritoneal Dialysis Treatment	NCT05250752
Mechanisms and Safety of SGLT2 Inhibition in Peritoneal Dialysis	NCT05715814
The Effect of Dapagliflozin on Ultrafiltration Among Peritoneal Dialysis Patients	NCT04923295
Effect of Empagliflozin on Peritoneal and Kidney Function in End Stage Renal Disease (EMPA-PD)	NCT05671991
The effects of empagliflozin on ultrafiltration in patients with peritoneal dialysis	jRCTs051230081

Glucose transport inhibitors in PD – summary

- Targeting glucose transporters in the peritoneum may reduce
  - toxicity of dextrose-based PD solutions to preserve peritoneal membrane function
  - Dissipation of glucose, improving ultrafiltration

- SGLT2 inhibitor use may preserve residual kidney function, reduce cardiovascular disease

- Clinical trials are needed to prove efficacy and safety. It is a brave new world in PD!

Green(er) PD

Carbon footprint of dialysis in Australia

- Healthcare uses a disproportionate amount of energy and generates significant waste[1]
  - VIC hospitals use 60% of the State's energy
  - Generates waste equivalent to 200,000 households per year

- Haemodialysis contributes significantly to waste & CO_2 emission[1]
  - A 6-chair satellite haemodialysis unit generated 122 tonne CO_2-equivalent/year
  - 10.2 tonne CO_2-equivalent/patient

- Carbon footprint of PD in Australia has not been quantified… until now

1. Lim A. et al. Aus Health Rev 2013;37:369-374

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CLINICAL RESEARCH: DIALYSIS

The Carbon Footprint of Peritoneal Dialysis in Australia

McAlister, Scott[1,2]; Talbot, Ben[3,4]; Knight, John[3,5]; Blair, Susan[6]; McGain, Forbes[2,7,8]; McDonald, Stephen[9,10,11]; Nelson, Craig[12,13,14,15]; Knight, Richard[6]; Barraclough, Katherine A.[15,16]

Author Information

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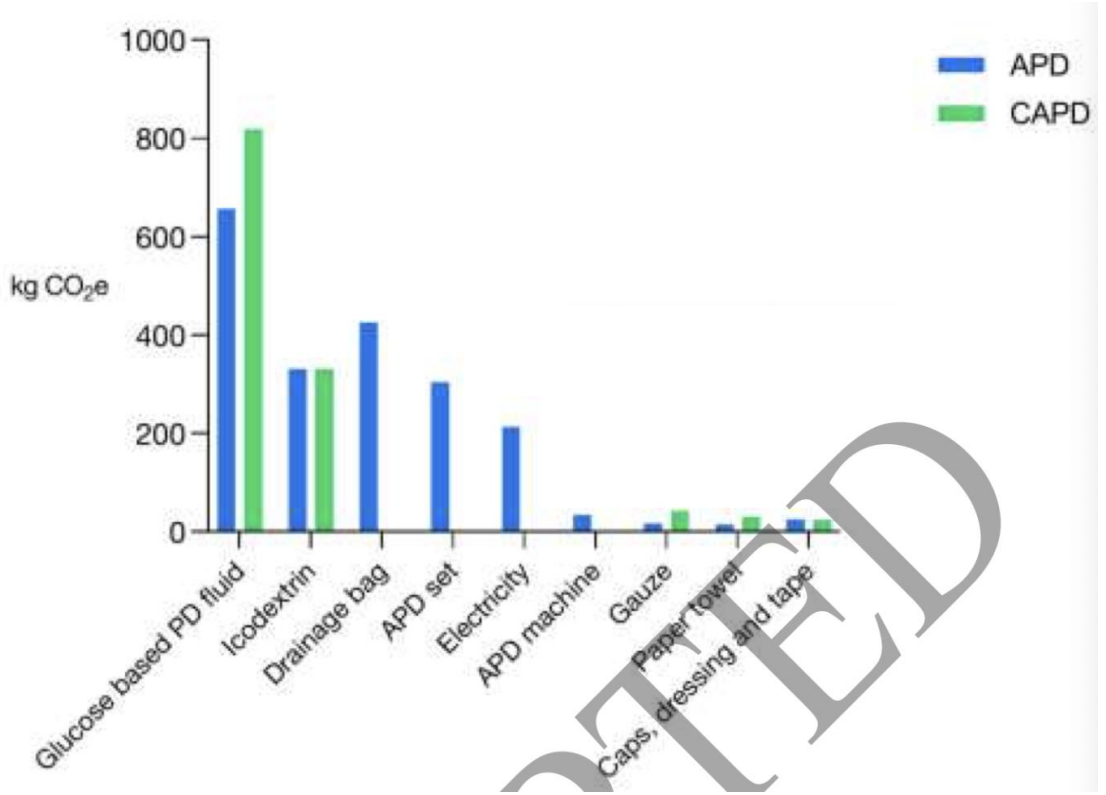
Carbon footprint of PD

- Comprehensive “life cycle analysis” of PD:
  - raw material extraction
  - manufacture (power/water usage)
  - transportation
  - waste generation/recycling

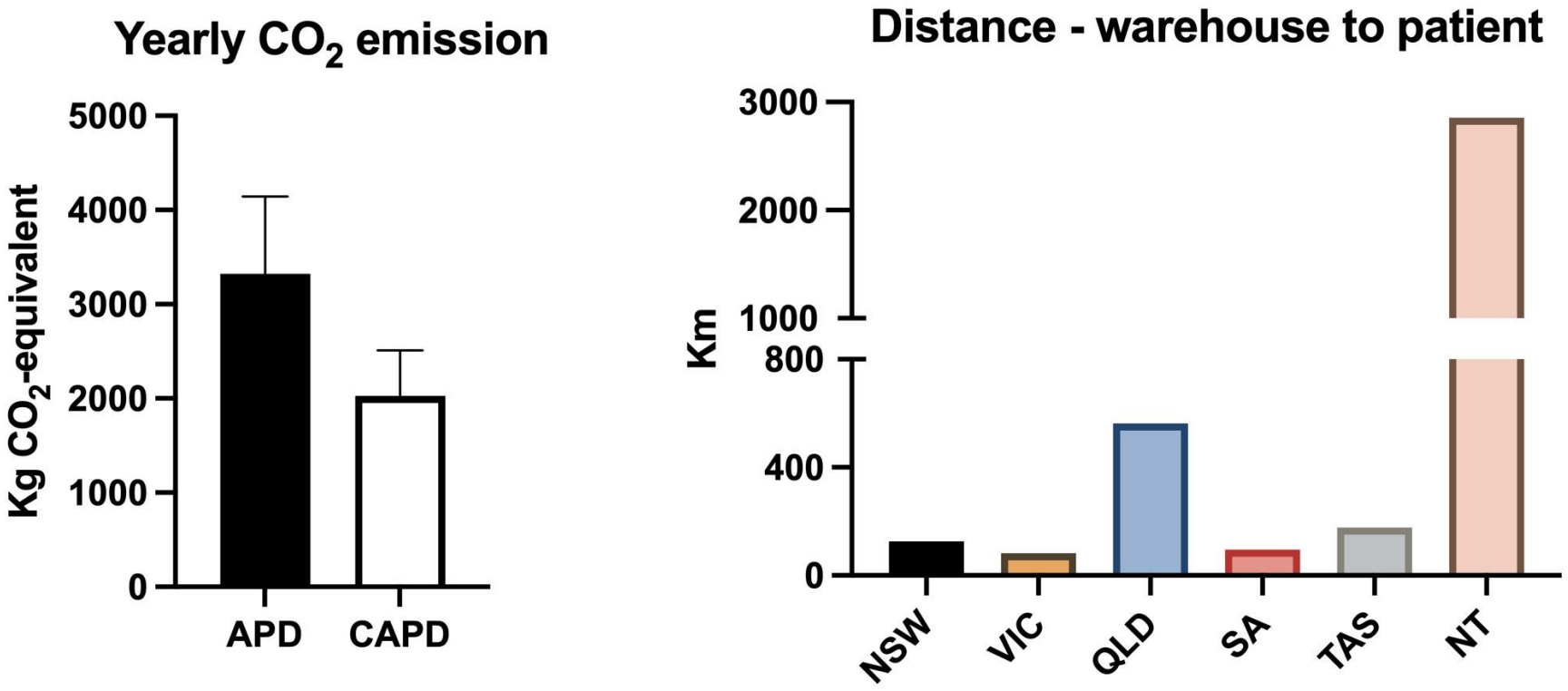
- Modelling based on 67 “typical” PD patient
  - 45 on APD, 22 on CAPD

Component	APD	CAPD
2 x 6L 2.5% dextrose	656	-
3x 2L 2.5% dextrose	-	818
2L icodextrin	331	331
15L drain bag	425	
4 prong cassette	304	-
Minicap	3	11
Opticap	11	-
Paper towel	15	31
Tape	2	4
Primapore	9	9
Gauze	17	42
APD machine	34	-
Electricity	213	-
Total emission (Kg CO_2)	**1992**	**1245**



Adapted from Scott M. et al. J Am Soc Nephrol 2024. In-press

Carbon emission



Adapted from Scott M. et al. J Am Soc Nephrol 2024. In-press

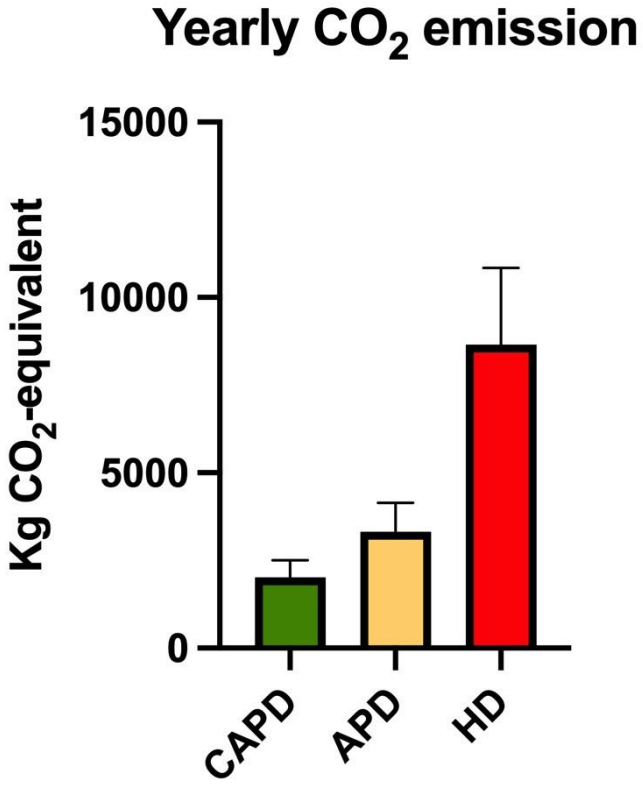
Green(er) PD - summary

Both forms of PD have significant carbon footprint

- CAPD < APD < Haemodialysis

Opportunities to reduce waste

- Drum, instead of drainage bag
- PVC recycling
- Point of care dialysate generation
- Incremental PD



Adapted from Scott M. et al. J Am Soc Nephrol 2024 (In-press) and Lim A. et al. Aus Health Rev 2013;37:369-374

Questions