Where Does Innovation Stand in The Field of Peritoneal Dialysis Solutions

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November 20th, 2019

PERITONEAL DIALYSIS

A CLINICAL STUDY OF FACTORS GOVERNING ITS EFFECTIVENESS

ACADEMISCH PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE AAN DE UNIVERSITEIT VAN AMSTERDAM, OP GEZAG VAN DE RECTOR MAGNIFICUS, DR. J. KOK, HOOGLERAAR IN DE FACULTEIT DER WIS- EN NATUURKUNDE, IN HET OPENBAAR TE VERDEDIGEN IN DE AULA DER UNIVERSITEIT OP DONDERDAG 26 NOVEMBER 1959, DES NAMIDDAGS TE 4 UUR PRECIES

door

BOEN SAN TJIANG

geboren te Djakarta

To: José Divino
A Good Friend.
Fred A.S. Boen
July 9, 2010

TE ASSEN BIJ

VAN GORCUM & COMP. N.V. - DR. H. J. PRAKKE & H. M. G. PRAKKE

Pat. Toll, 40 yr. female, *fig.* 52 *and* 53. This was the first patient who underwent peritoneal dialysis in the Binnengasthuis.

History: In the last months of her fifth pregnancy, the patient complained of constant headache; hypertension was found, and a salt-free diet was prescribed.

On Nov. [illegible], the patient developed visual disturbances.

On Nov. 16, she was admitted to a hospital in another town as she had lost a great deal of blood from the vagina; solutio placentae occurred, which was followed by anuria.

On Nov. 22, she was transferred to this hospital.

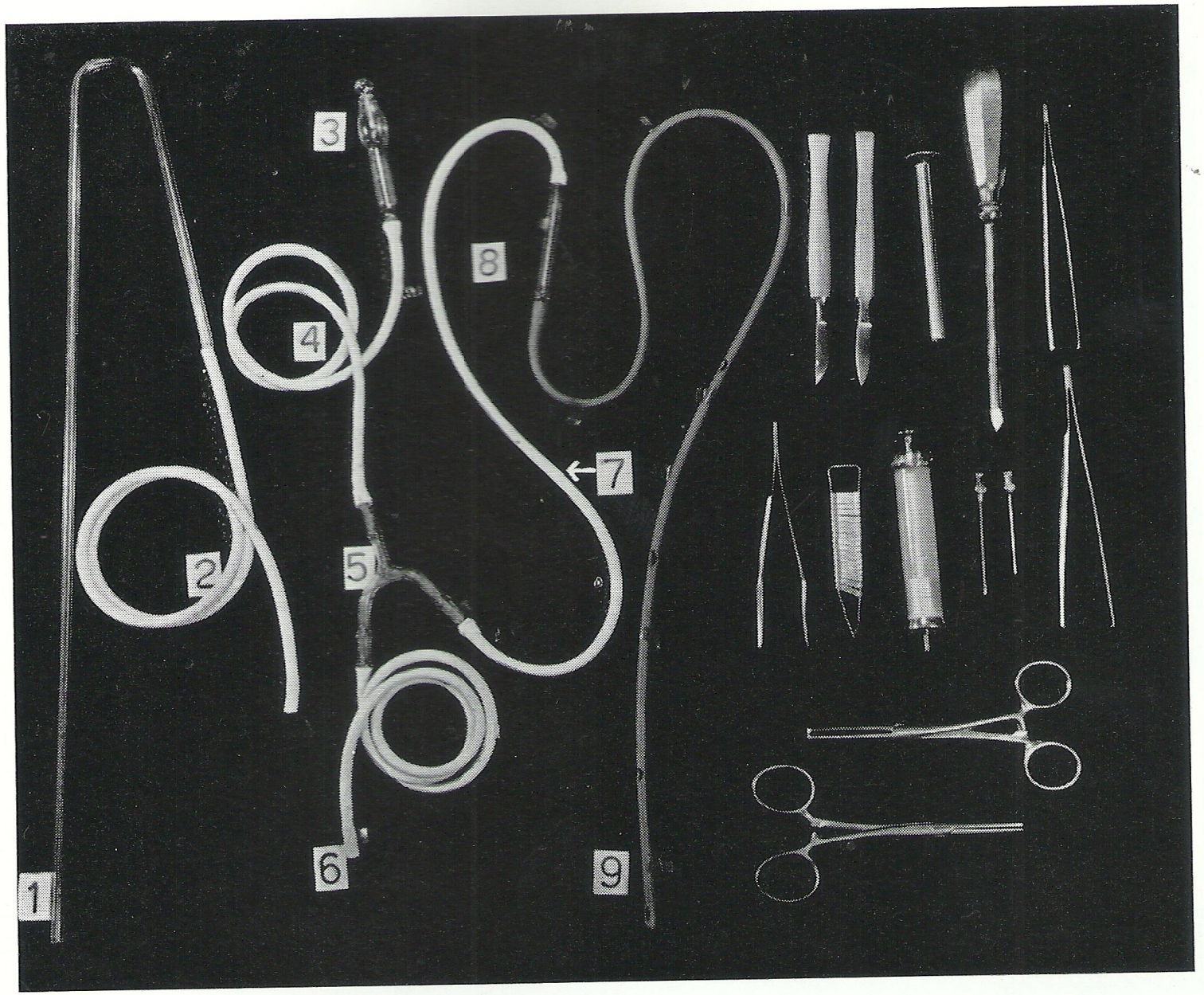

Fig. 49 - Instruments for peritoneal dialysis.

The compositions of the irrigation fluid at different periods are shown in *fig.* 52. The initial composition was: Na 130, K 2.5, Ca 2, Cl 104.5, HCO_3 30 m.eq./L; glucose 2.5 %, heparin 10 mg/L, chloramphenicol 5 mg/L. The glucose concentration in the irrigation fluid was increased later, when the patient had become dyspnoeic and oedematous. The fluid was brought into the abdomen from $\frac{1}{2}$ L bottles.

The flow rate varied from 300 to 800 ml per hour. During a period of 89 hours of dialysis, 81.5 litres fluid were brought into the peritoneal cavity, and 49 litres removed; a great deal of fluid had been lost due to leakage. On the first day a urea concentration of 2 gm/L was found in the outflow fluid with a blood concentration of 4 gm/L. At one point, a rather low urea concentration was found in the outflow fluid, indicating a short-cut between the inflow and the outflow tubes. A total of 109 gm urea was removed at a *peritoneal urea clearance of* 3.6 to 16 ml/min. (average 7.8 ml/min.).

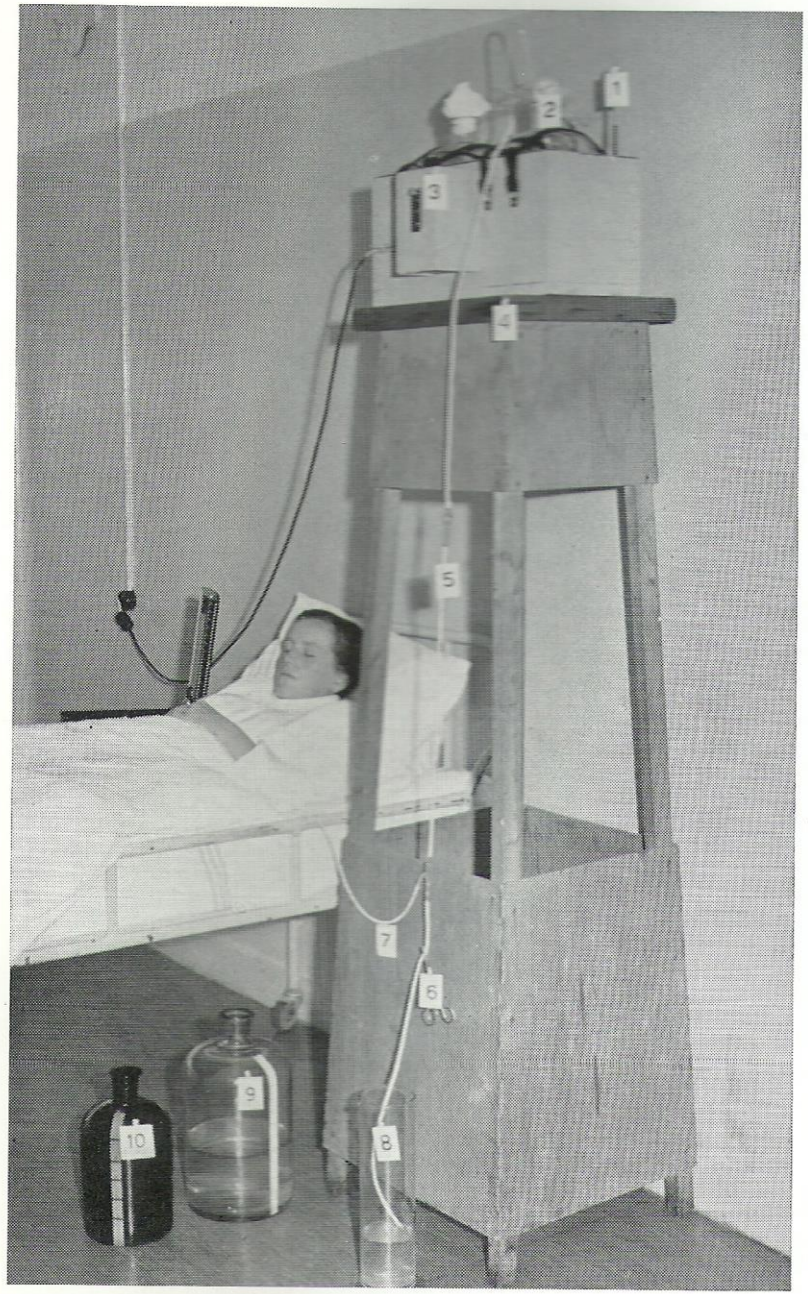

Fig. 50 - Set-up during peritoneal dialysis.

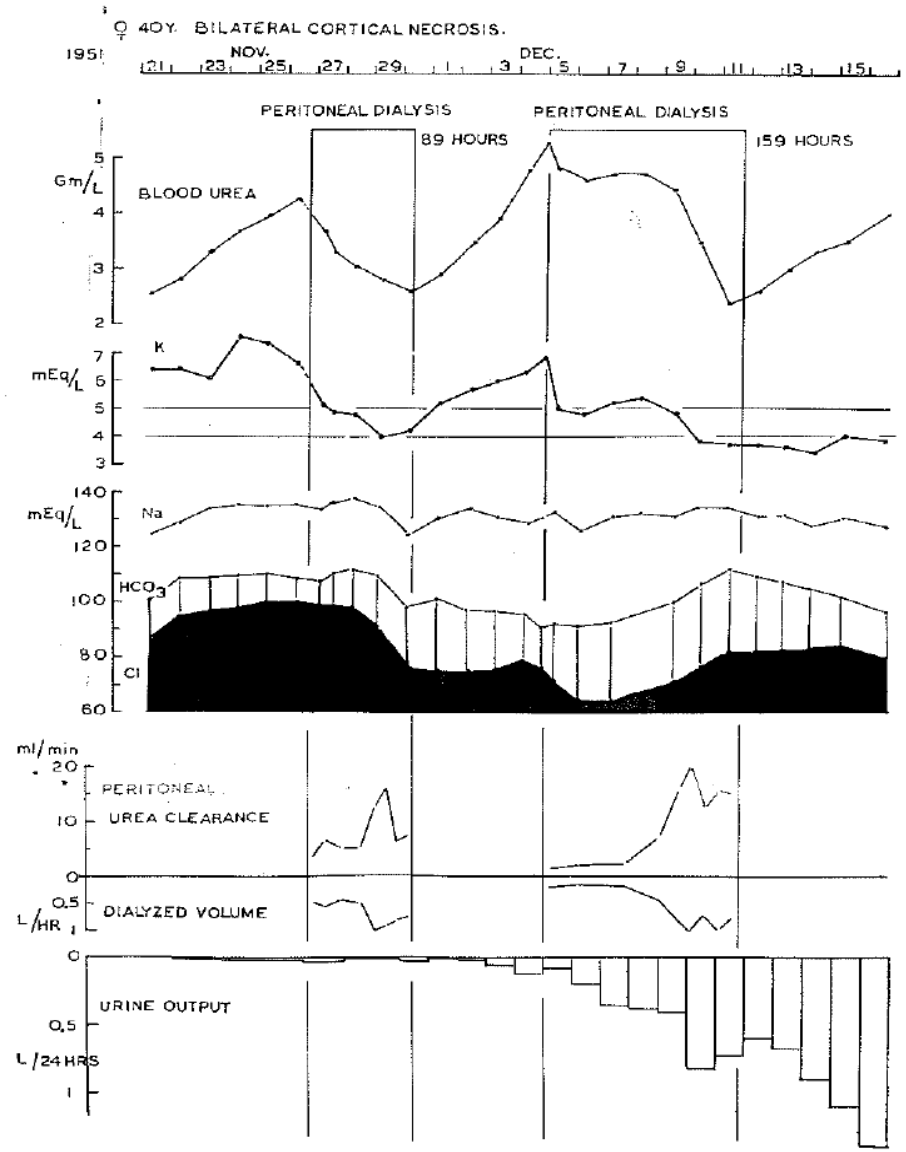

Fig. 53 - Pat. Toll. Blood chemistry, peritoneal urea clearance, urine output.

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PD solutions

Studies of peritoneal dialysis
J Gjessing

Gjessing, J,: Absorption of **ampicillin** from the dialysing fluid during peritoneal dialysis. Opusc. Med., 1968, 13, 215-218

Gjessing, J,: Peritonealdialysens **inverkan pa andningen**, Svenska LäkarTidn., 1967, 64, 26.

Gjessing, J.: Pleural dialysis. Acta Med. Scand., 1967, 182 259-261

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Gjessing, J. Addition of **amino acids** to peritoneal dialysis fluid, Lancet, 1968, ii, 812.

Gjessing, J. & Dencker, H.: Abdominal paracentesis with a dialysis catheter and peritoneal lavage - a diagnostic test in acute abdominal conditions. Acta Chir. Scand., 1968, 134, 351-352.

Gjessing, J.: Peritoneal dialysis in severe **acute haemorrhagic pancreatitis**. Acta Chir Scand., 1967, 133, 645-647.

Evolution of PD Solutions

Before 1990

Solutions for removing uremic toxins and fluid

→

1990/2000 - -

Solutions for nutrition, new osmotic agent for improved UF, and improved biocompatibility

→

2000 -

Glucose sparing **formulations for both systemic and local benefits**

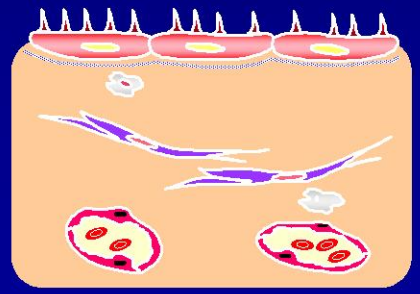
2010 -

Additives to address *systemic inflammation*, *oxidative stress* and *associated morbidities* and *preserve membrane function*

Global biocompatibility in PD

The Patient

The Solutions



The Membrane

Some Approaches to Management of *Peritoneal* Glucotoxicity

Osmotic stress

Iso-osmolar agent

Icodextrin

Polyol pathway

Non-glucose agent

Icodextrin
Amino acids
Glycerol

Protein glycosylation
Amadori adducts
AGE

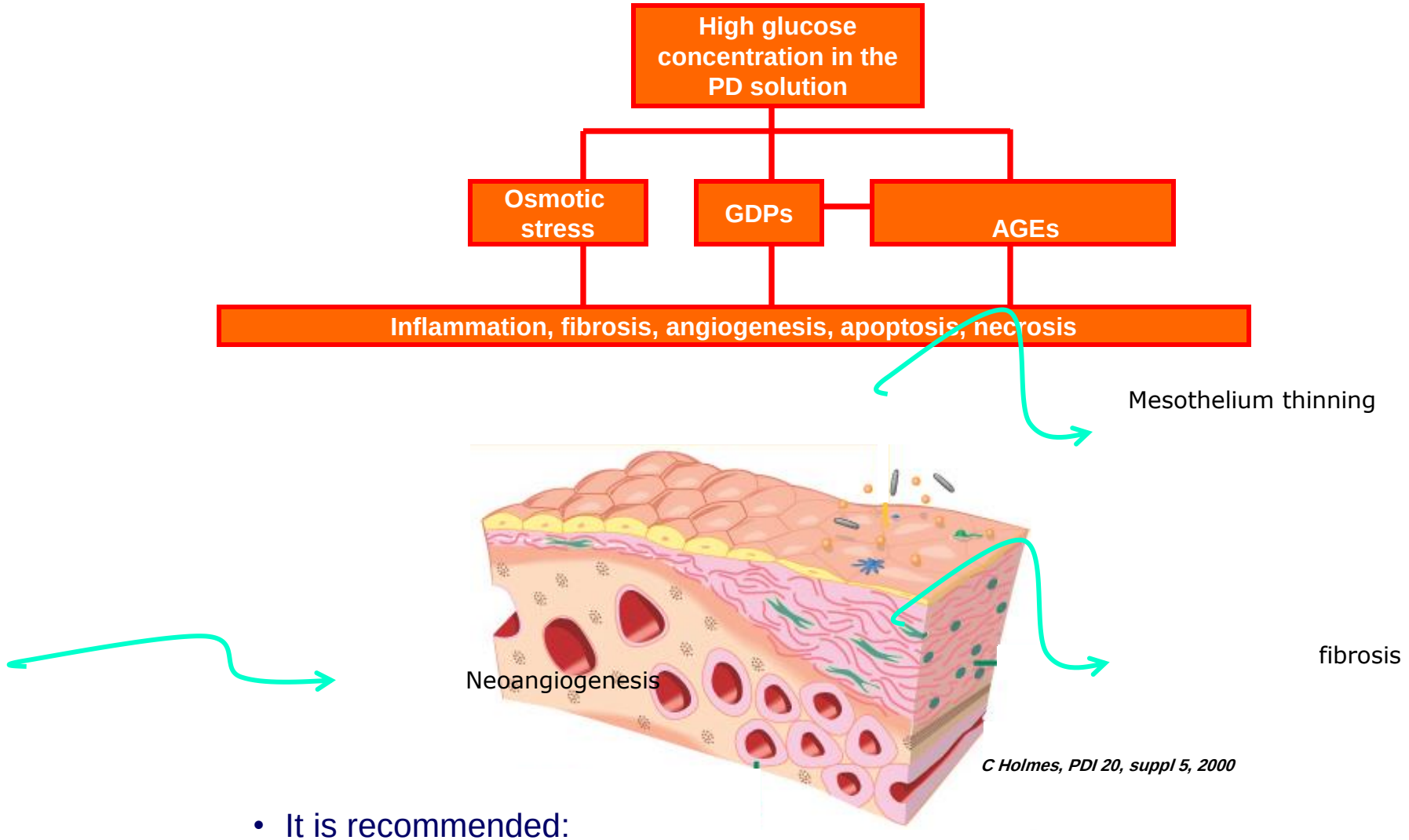
Non-glucose agent

Icodextrin
Amino acids
Glycerol

Glucose degradation products

Non-glucose agent
Low GDP glucose

Icodextrin
Amino acids
Glycerol
Low GDP glucose



- It is recommended:
  - To avoid excessive use of high glucose concentration by using the **new osmotic agents**
  - To utilize the new multicompartment (double or more) PD solutions, w/ low GDPs

Remón C. Diálisis y Trasplante 2006

Glucose Load – Some Context

100gm -300gm glucose absorbed per day

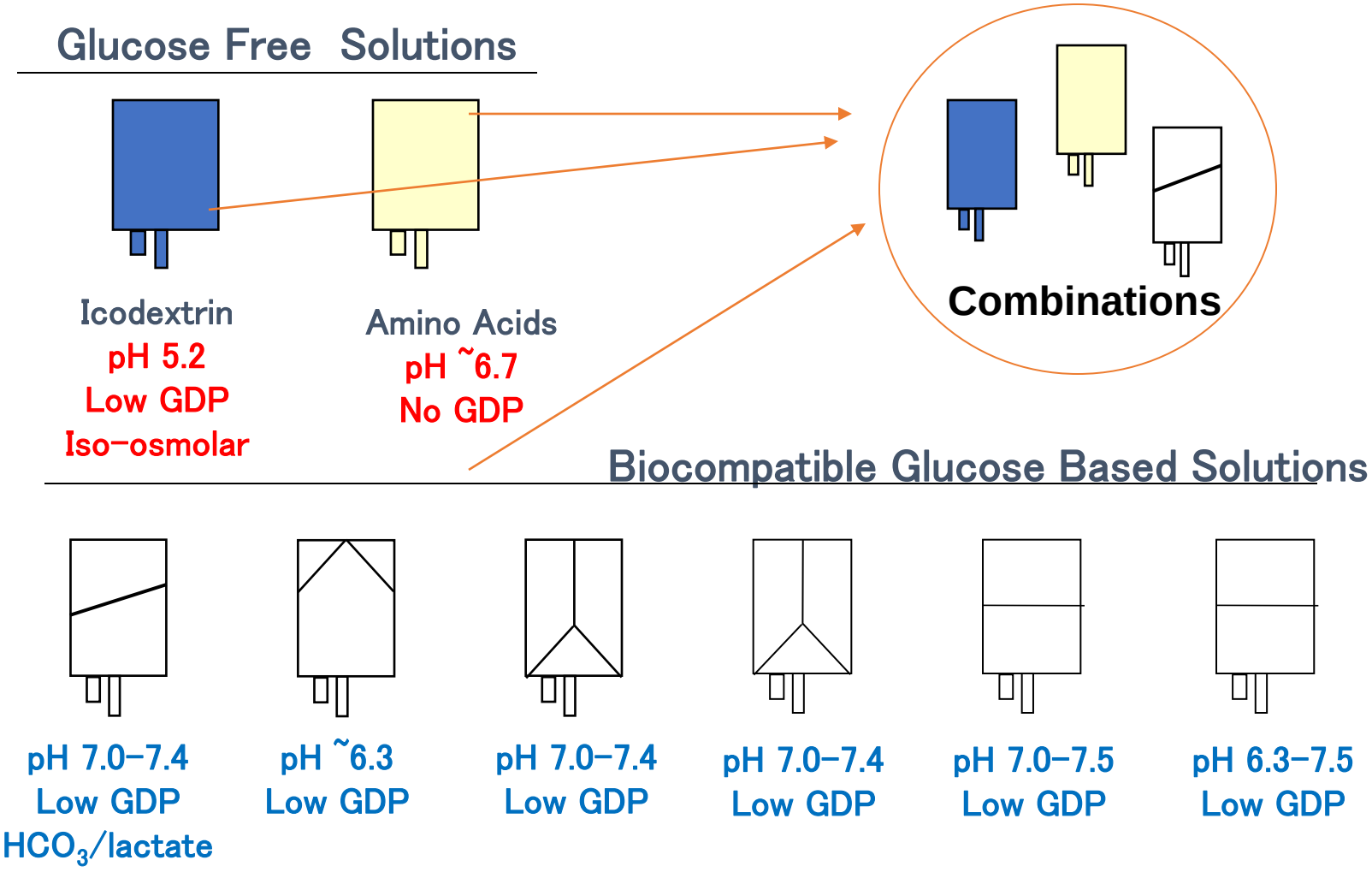
= 3-8 

/day

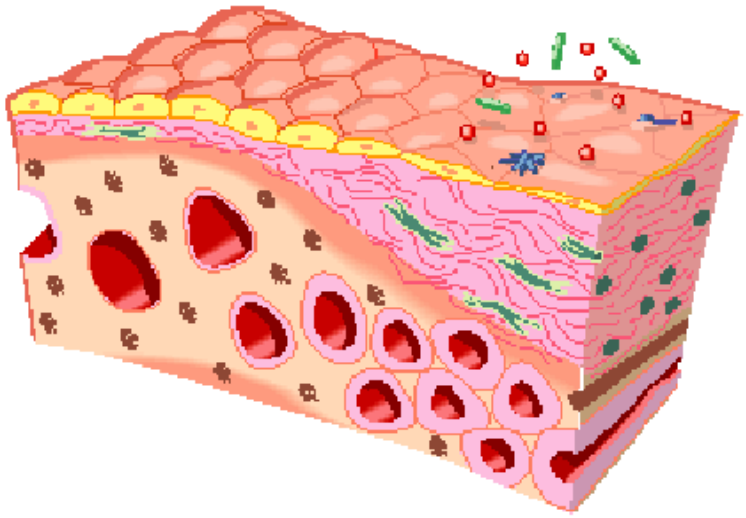
36 to 110 kg/y

100 pounds (45 kg of sugar)

Second generation PD Solutions: Used in new ways



Improving the quality of PD care



Changes to the peritoneal membrane over time

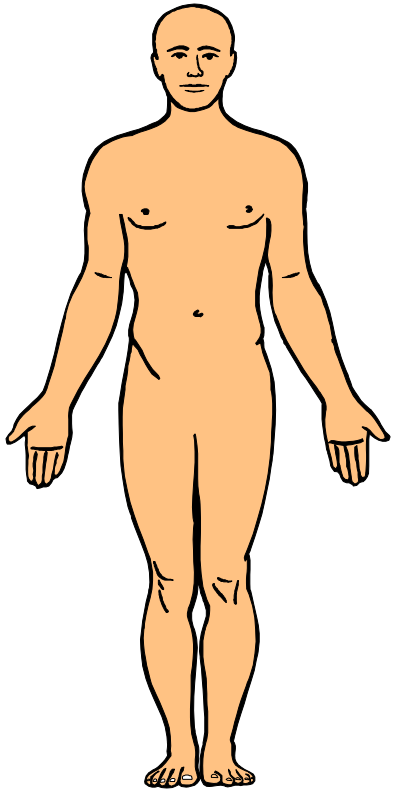
Physioneal, Extraneal and Nutrineal may preserve the membrane functionality for longer by:

- Reducing glucose exposure
- Reducing GDP

Slowing down progression of co-morbidities

Advanced solutions in combination may help to slow down the progression of co-morbidities by:

- **Minimising glucose load**
- **Optimising fluid balance**
- **Delivering 25% of daily protein needs**
- **Improving hyperlipidaemia**
- **Reducing hypertension**
- **Improving blood sugar control**
- **Preserving RRF**



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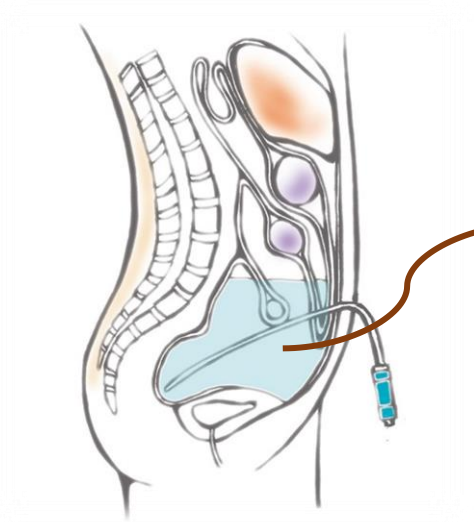
New PD solutions

Metabolic tailoring of peritoneal dialysis solutions, an approach not fully explored

Attributes of an ideal bespoke metabolic tailoring …



Osmometabolic Agents

- Locally & systemically safe
- Active osmotic ingredients (cristalloids & colloidal agents)
- Glucose sparing
- Fully metabolizable to safe final/intermediate products
- Combining active osmotic agents
- Poor insulin secretagoue
- Moderate caloric load
- Addressing comorbidities

Desiderata

- Residual kidney function
- Peritoneal membrane function
- Survival
- Better volume control
- Better glycemic control
- Less peritonitis
- Reduce CVD risk

Outcome of Intraperitoneal Glucose Load

Local effects

Glucotoxicity, GDPs

Changes to peritoneal membrane structure and function

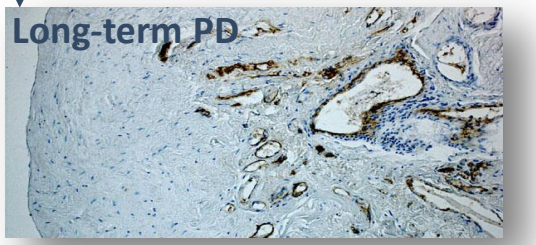
Fluid overload and inflammation

Systemic effects

Glucotox Pathways:
- ✓ Polyol
- ✓ Exosamine
- ✓ PKC
- ✓ AGEs

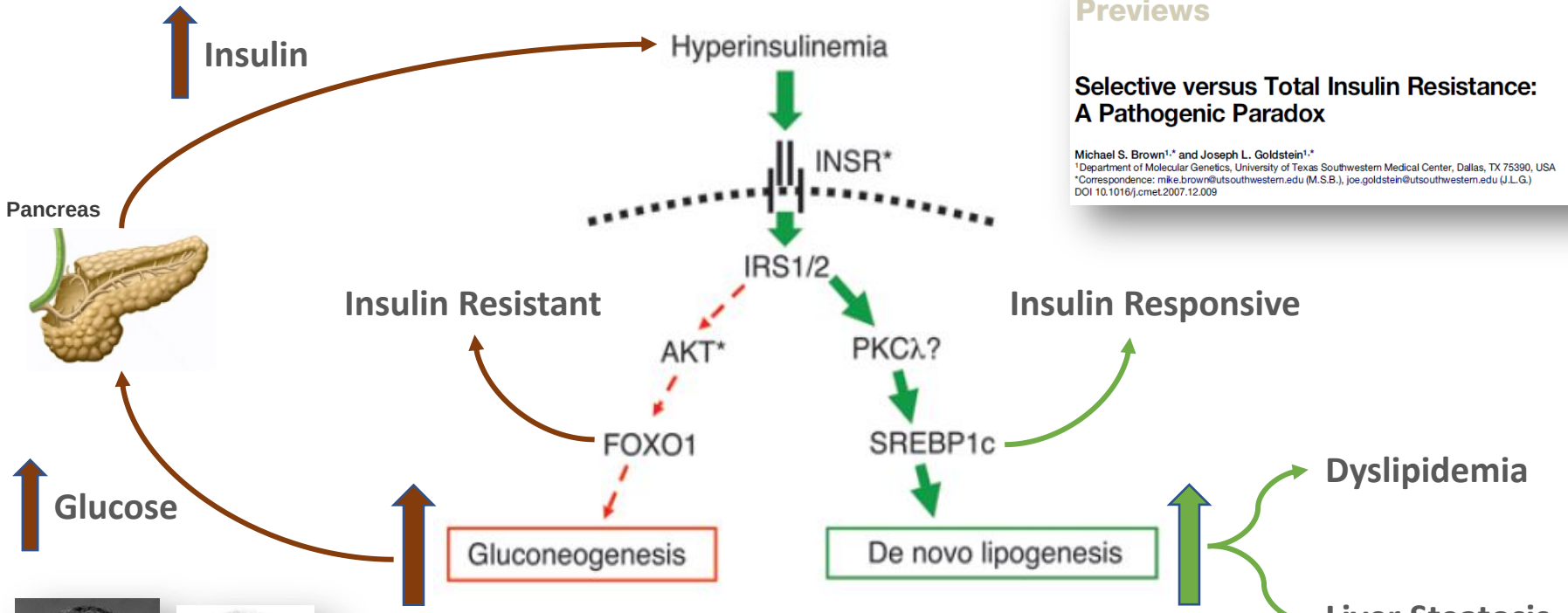
Carbohydrate load:
- ✓ Hyperinsulinemia
- ✓ Selective Insulin Resistance

Increased Cardiovascular Risk



Submesothelial fibrosis Vascular proliferation

Selective Insulin Resistance (Liver)



Michael S. Brown & Joseph L. Goldstein
Nobel Prize in Physiology or Medicine 1985

Cell Metabolism
Previews

Selective versus Total Insulin Resistance: A Pathogenic Paradox

Michael S. Brown[1,*] and Joseph L. Goldstein[1,*]
[1]Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA
*Correspondence: mike.brown@utsouthwestern.edu (M.S.B.), joe.goldstein@utsouthwestern.edu (J.L.G.)
DOI 10.1016/j.cmet.2007.12.009

"In type 2 diabetes, selective insulin resistance has implications for therapy. By "brute force" treatment of type 2 diabetes patients with large doses of insulin, we can overwhelm the insulin resistance and control the blood sugar, but at what price?"

Outcome of Intraperitoneal Glucose Load

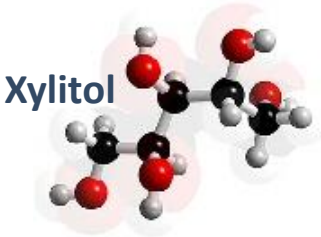
Mitigating the 'Load' in PD patients

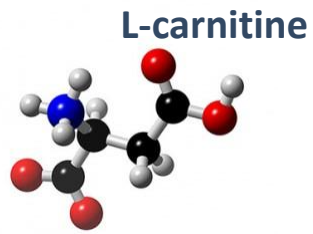
Bioactive Glucose Sparing (soon)

- Local effects
- Systemic effects

→ Increased Cardiovascular Risk

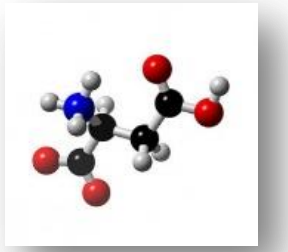
- ✓ To improve biocompatibility and safety
- ✓ To reduced glucose concentration in PD fluid without altering the UF profile
- ✓ To improve glucose homeostasis
- ✓ To limit endogenous/exogenous insulin exposure





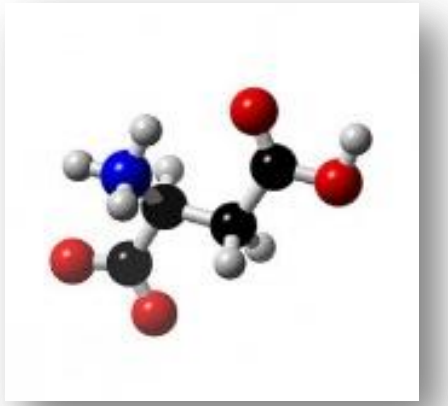
Carnitine based peritoneal dialysis solutions: an “osmo-metabolic” approach

Carnitine’s highlights:



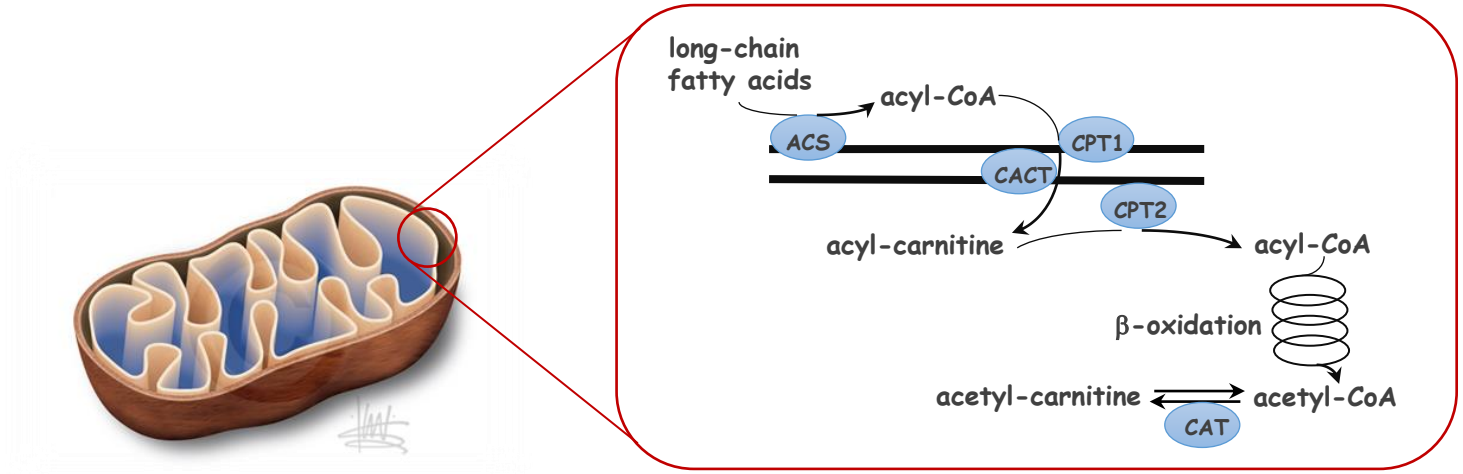
- Naturally occurring compound (MW 160)
- **Extremely stable (no degradation products when steam sterilized)**
- Good osmolar property
- Excellent biocompatibility profile (in vitro) than current osmotic agents for PD
- Well tolerated both locally and systemically
- Excellent safety profile
- **Therapeutic add on values as a conditional drug (i.e., dysmetabolic diseases)**
- Possibility to be combined with other osmotic agents
- Formulation of specific PD solutions (i.e., type II diabetics)

Carnitine's metabolic action



Main metabolic functions of the carnitine system

- Mitochondrial β-oxidation of long-chain fatty acids
- Modulation of the acetyl-CoA/free CoA ratio in mitochondria
- Key role in intermediary metabolism

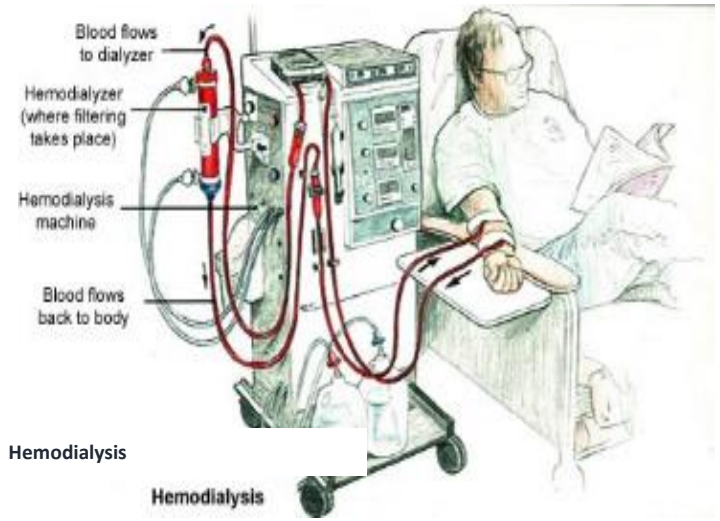


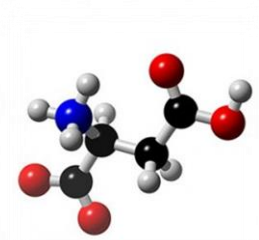
L-carnitine + acyl-CoA ⟷ acyl-L-carnitine + CoA

Keq close to 1

Main therapeutic use of L-carnitine

For the prevention and treatment of carnitine deficiency in patients with end stage renal disease who are undergoing dialysis!



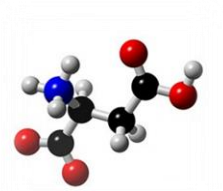


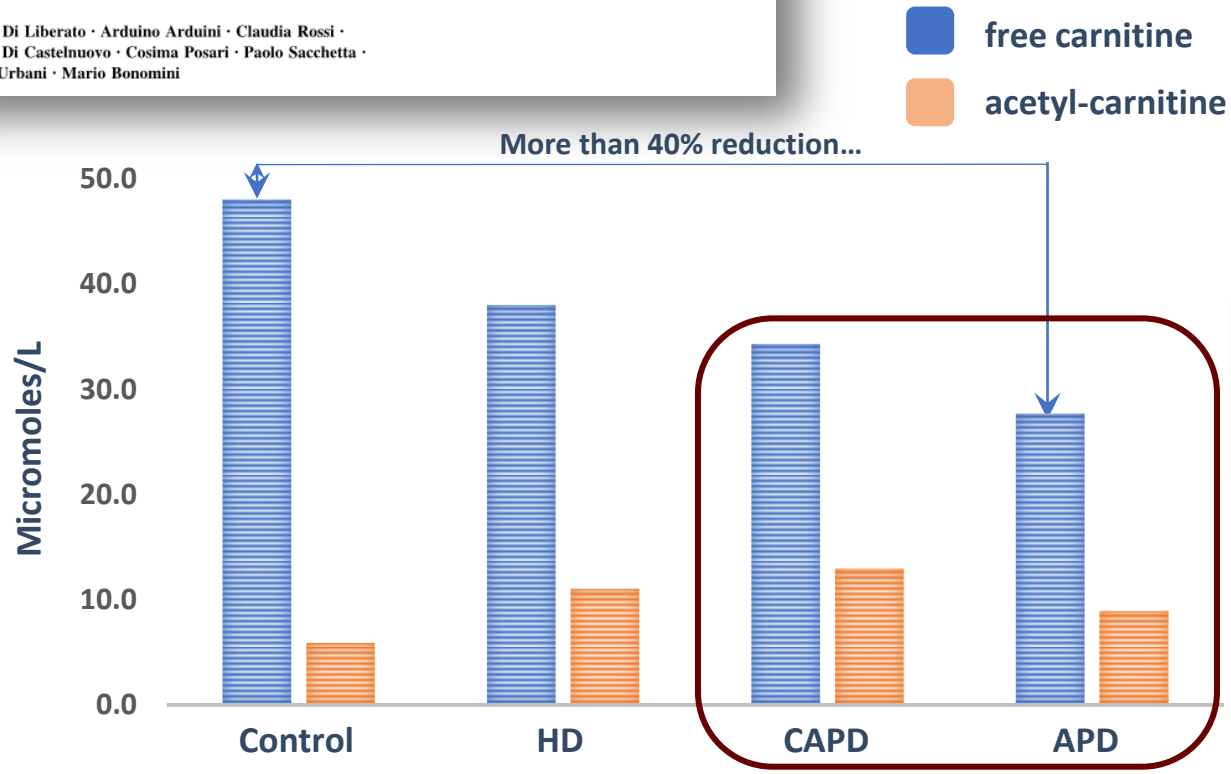
Carnitine levels in healthy subjects and dialysis patients

ORIGINAL ARTICLE

L-Carnitine status in end-stage renal disease patients on automated peritoneal dialysis

Lorenzo Di Liberato · Arduino Arduini · Claudia Rossi · Augusto Di Castelnuovo · Cosima Posari · Paolo Sacchetta · Andrea Urbani · Mario Bonomini

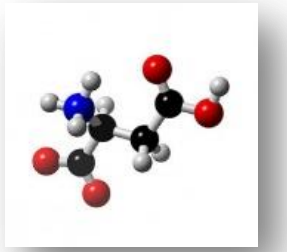




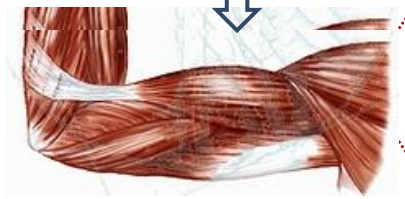
APD patients show the highest carnitine deficiency…

J Nephrol (2014) 27:699-706.

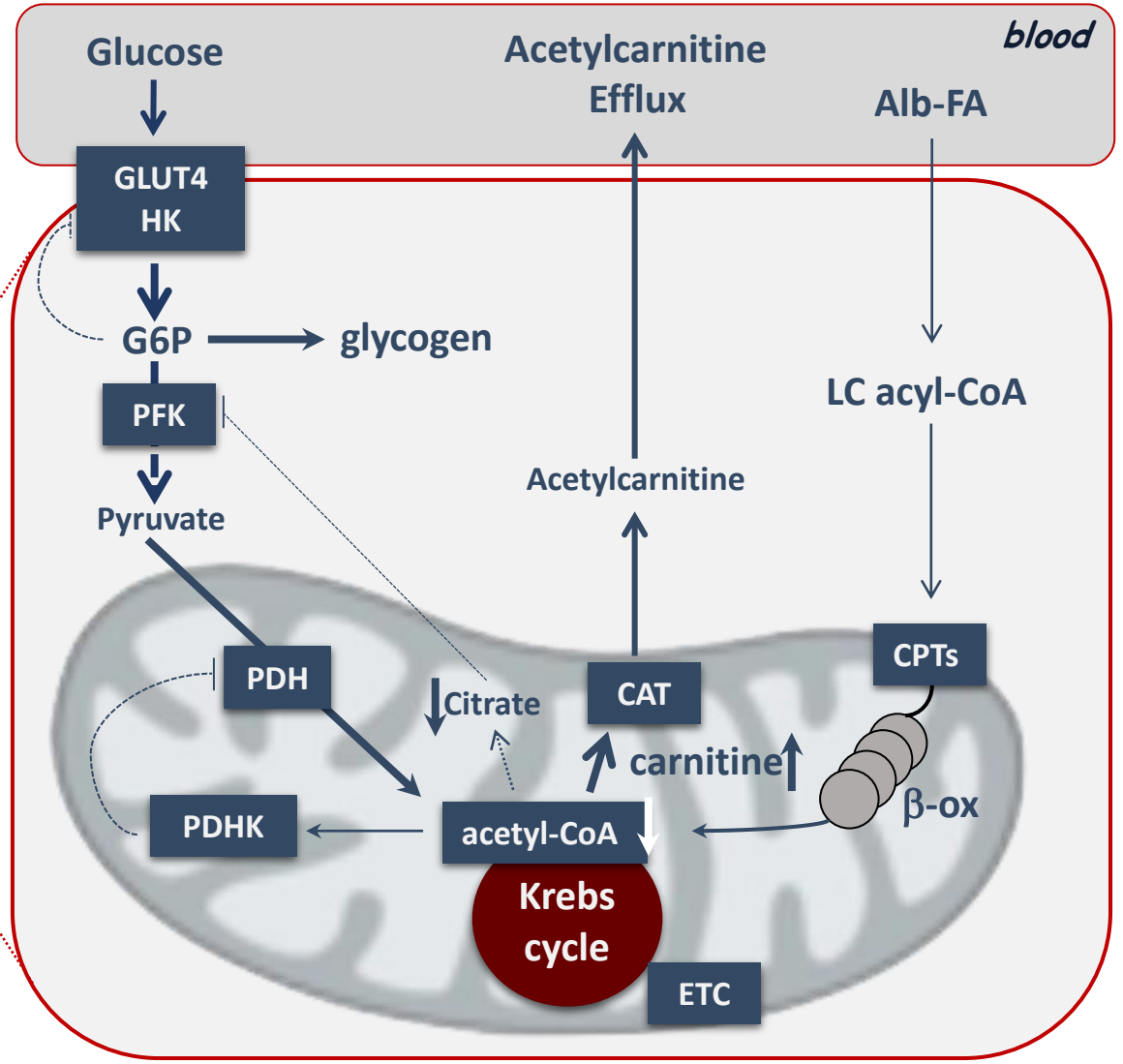
Carnitine overexposure improves muscle glucose homestasis



High carnitine exposure and flux effects

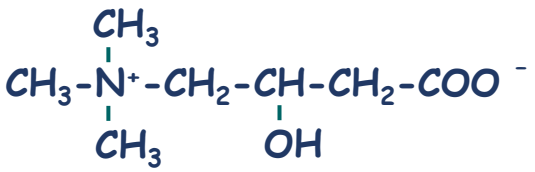


Improvement of insulin sensitivity and glucose disposal



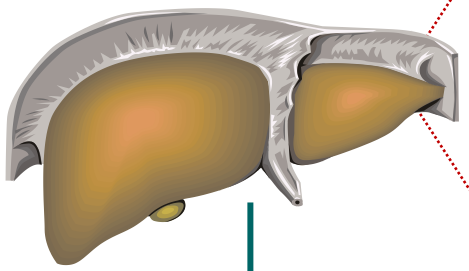
COREQUEST

Liver insulin resistance and glucose production



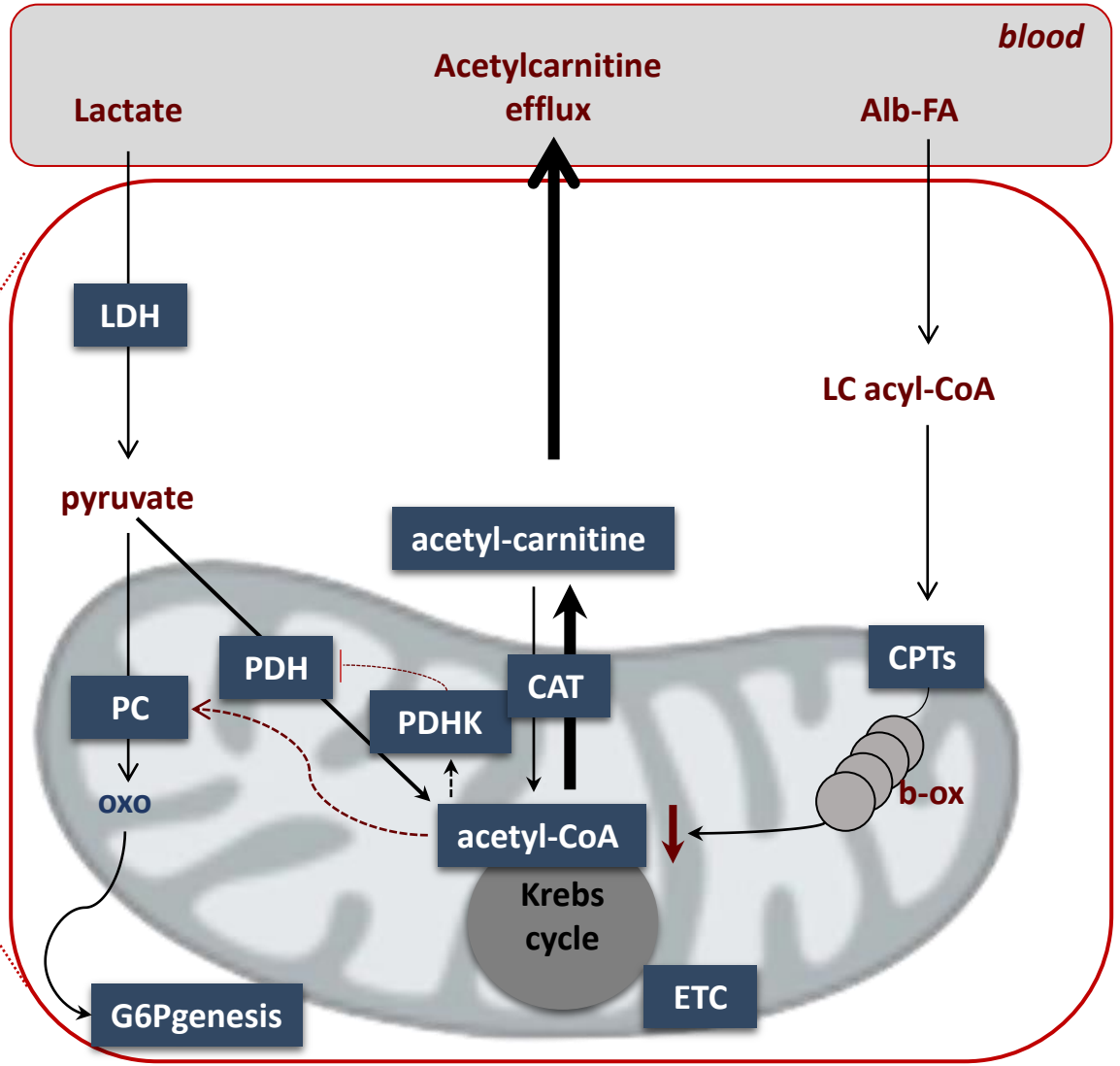
High carnitine exposure

and flux effects



Improvement of insulin sensitivity

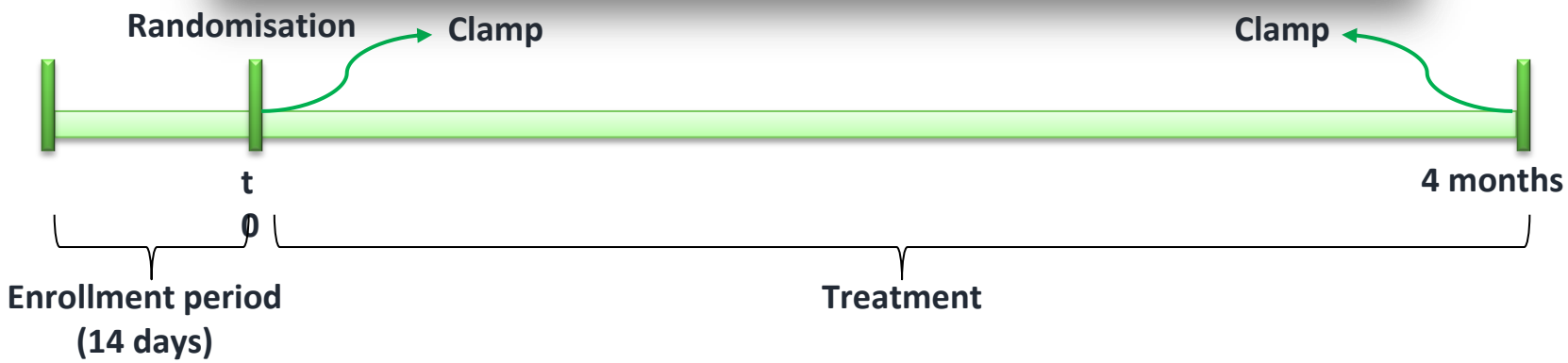
and glucose disposal



AJKD
Original Investigation

Effect of an L-Carnitine–Containing Peritoneal Dialysate on Insulin Sensitivity in Patients Treated With CAPD: A 4-Month, Prospective, Multicenter Randomized Trial

Mario Bonomini, MD,[1] Lorenzo Di Liberato, MD,[1] Goffredo Del Rosso, MD,[2] Antonio Stingone, MD,[3] Giancarlo Marinangeli, MD,[4] Agostino Consoli, MD,[5] Silvio Bertoli, MD,[6] Amedeo De Vecchi, MD,[7] Emanuele Bosi, MD,[8] Roberto Russo, MD,[9] Roberto Corciulo, MD,[9] Loreto Gesualdo, MD,[9] Francesco Giorgino, MD,[10] Paolo Cerasoli, MD,[11] Augusto Di Castelnuovo, PhD,[12] Maria Pia Monaco, MD,[1] Ty Shockley, ScD,[13] Claudia Rossi, PhD,[14] and Arduino Arduini, MD[15]

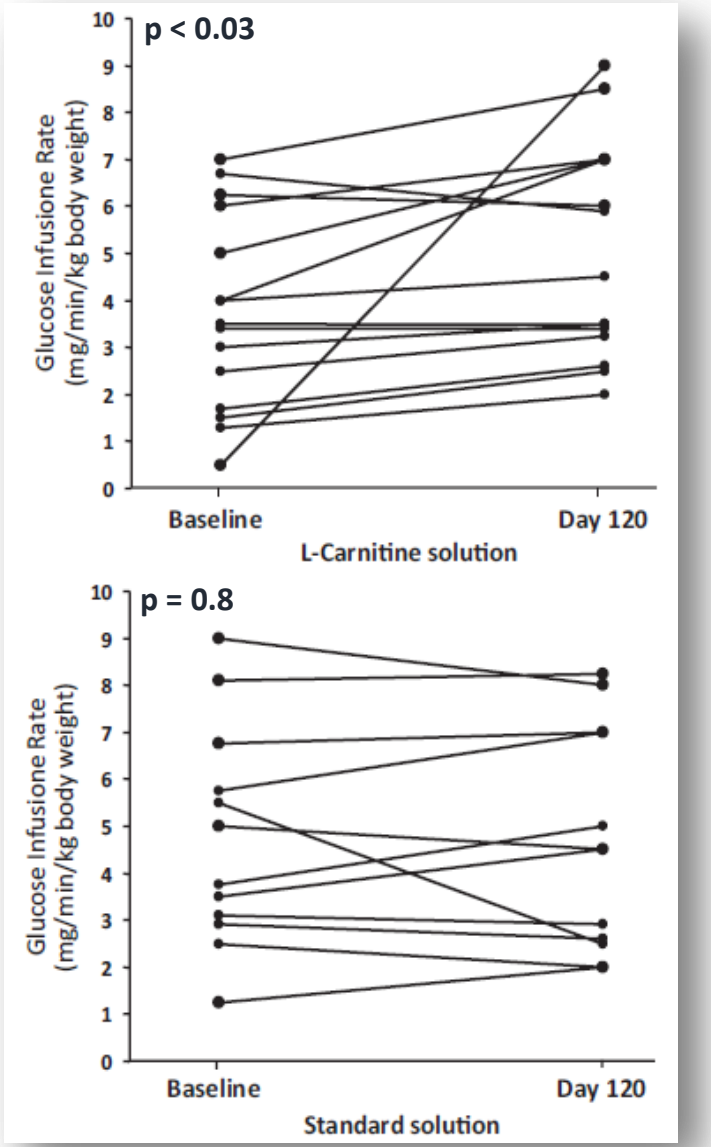


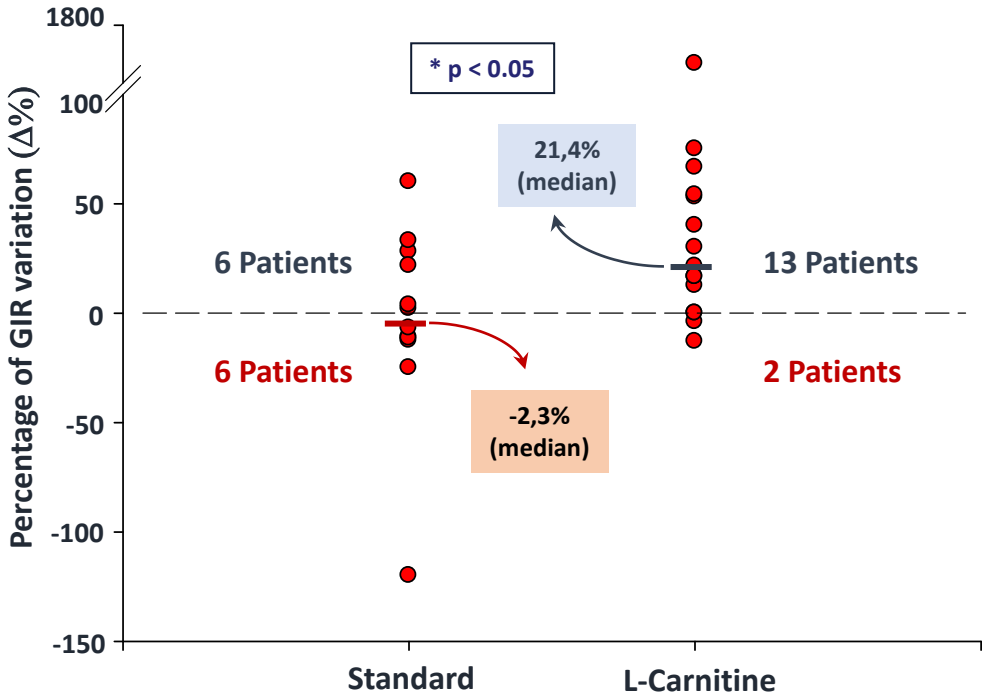
	Active Group	Control Group
Diurnal Dwells	Glucose (1.36 o 2.27%) Plus L-Carnitine (0.1%)	Glucose (1.36 o 2.27%)
Nocturnal Dwell	Icodextrin	

Primary end point: change in insulin sensitivity, evaluated by euglycemic hyperinsulinemic clamp

Am J Kidney Dis (2013) 62:929-38

Insulin sensitivity (clamp) in PD patients treated with glucose- or glucose/carnitine-based PD solution, a proof of concept, prospective randomized trial





Am J Kidney Dis (2013) 62:929-38

CLINICAL DATA FOR L-CARNITINE

Ultrafiltration in PD patients treated for 5 days with glucose/carnitine based PD solutions

http://www.kidney-international.org original article
© 2011 International Society of Nephrology

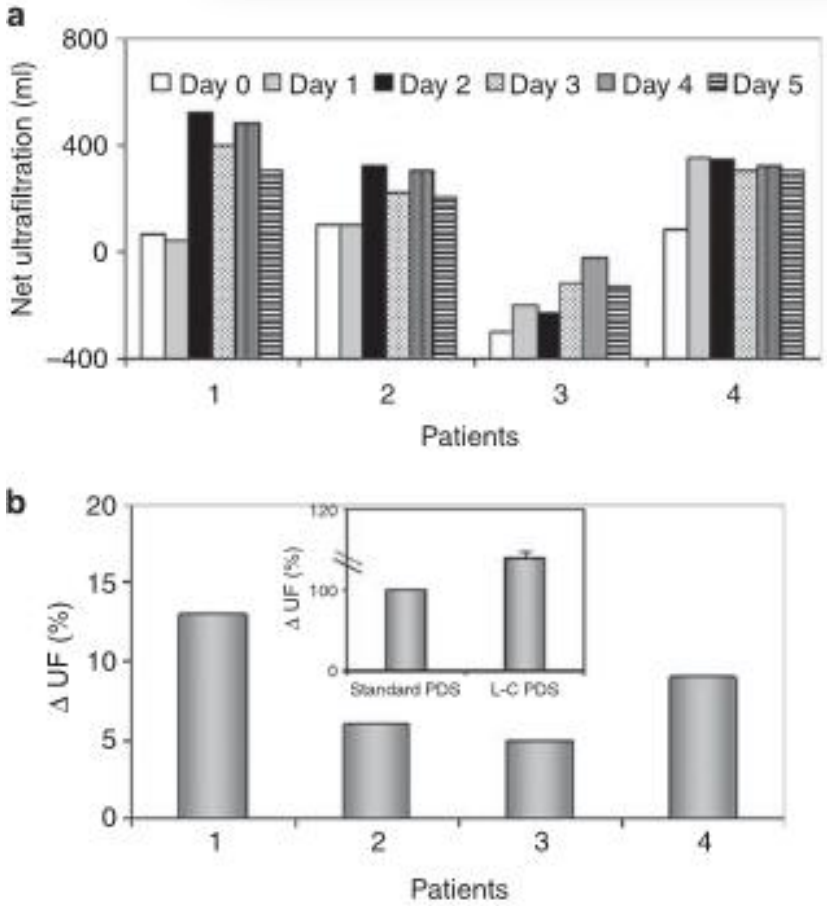
see commentary on page 565

L-Carnitine is an osmotic agent suitable for peritoneal dialysis

Mario Bonomini[1], Assunta Pandolfi[2], Lorenzo Di Liberato[1], Sara Di Silvestre[2], Yvette Cnops[3], Pamela Di Tomo[2], Mario D'Arezzo[1], Maria P. Monaco[1], Annalisa Giardinelli[2], Natalia Di Pietro[2], Olivier Devuyst[3] and Arduino Arduini[4]

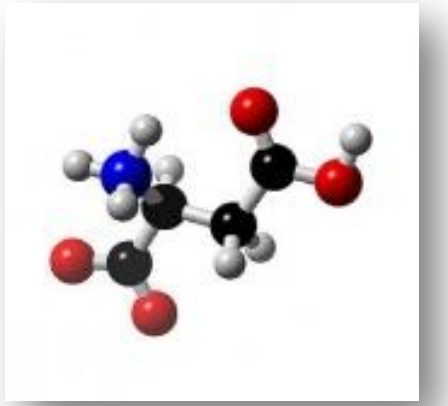
Kidney Int (2011) 80:645-54

In 4 stable CAPD patients, evaluation of tolerability and efficiency of a nocturnal peritoneal dialysis solution containing glucose (1.5%) plus L-carnitine (5 grams; 0.25%) used for 5 consecutive days versus a standard glucose 2.5% solution routinary used for nocturnal dwell.



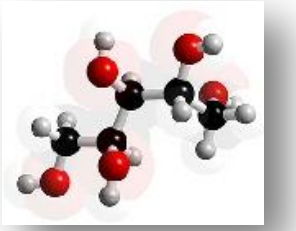
33

Xylitol's metabolic and osmotic actions



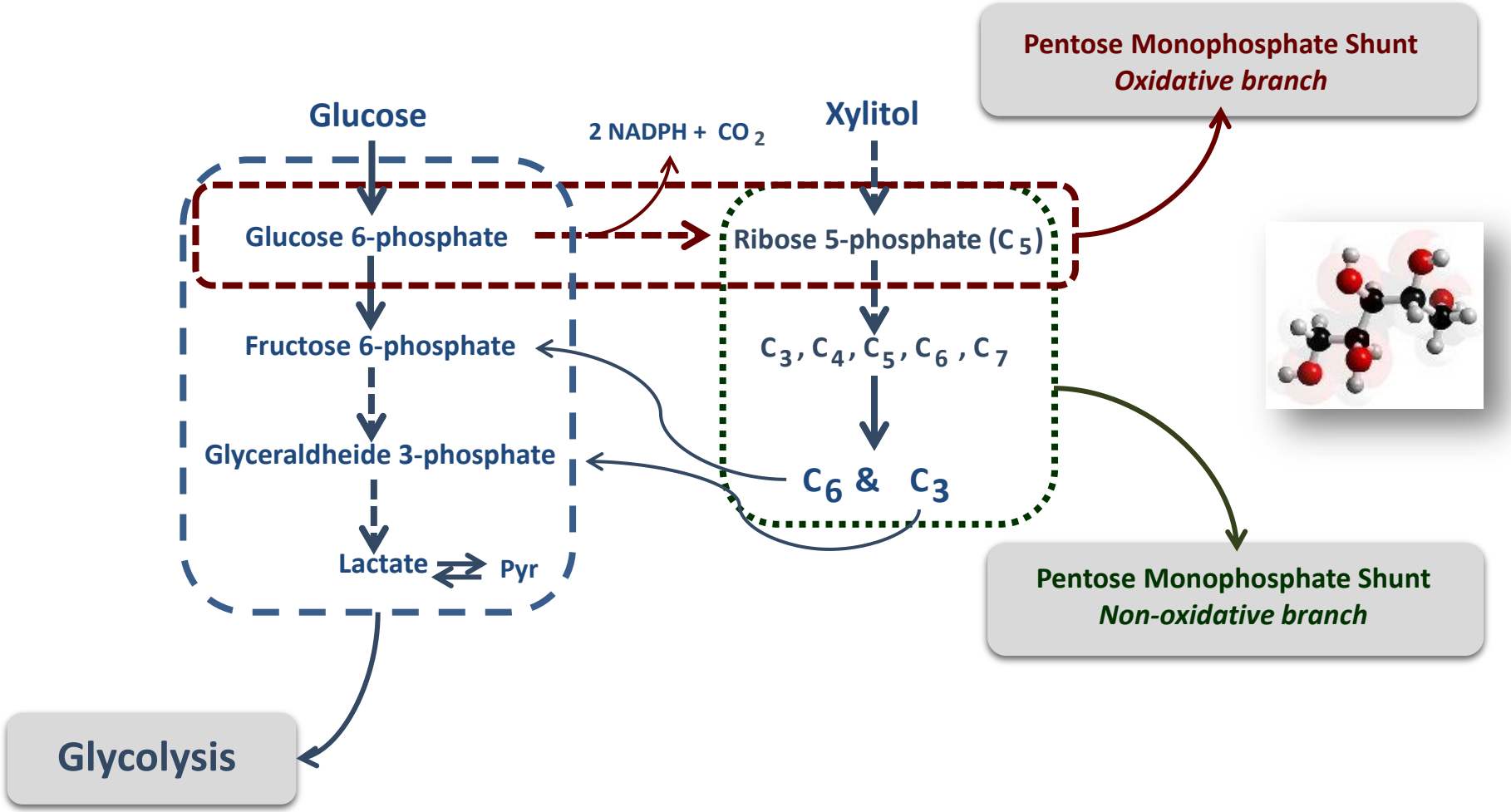
Xylitol-Carnitine based peritoneal dialysis solutions: an "osmo-metabolic" approach

Xylitol highlights:



- Naturally occurring five-carbon sugar alcohol
- Molecular Weight: 152.1
- Extremely stable (no degradation products when steam sterilized)
- Osmotic properties comparable to glucose
- It enters into the Pentose Monohosphate Shunt (PPP)
- Very modest insulin secretagogue
- Several grams of it is produced daily by the liver (5-20gr)
- Mainly metabolised in liver and red blood cells
- Used in total parenteral nutrition (up to 3gr/kg/day)
- Tested as a standalone osmotic agent in diabetic PD patients
- Very low glycemic index

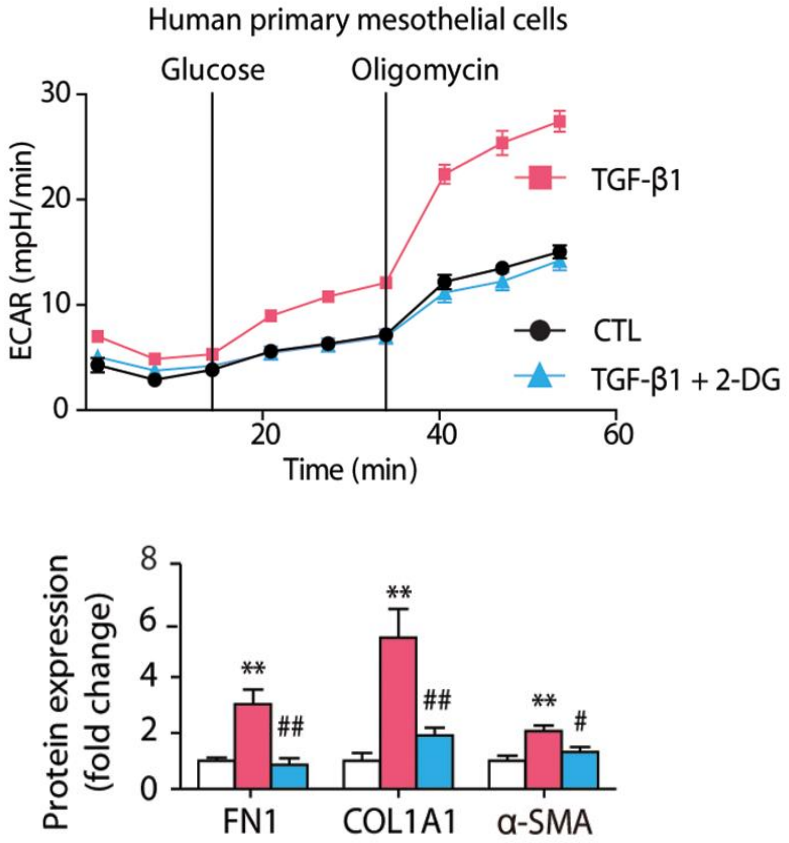
Metabolic fate of xylitol in mammals



FIBROSIS

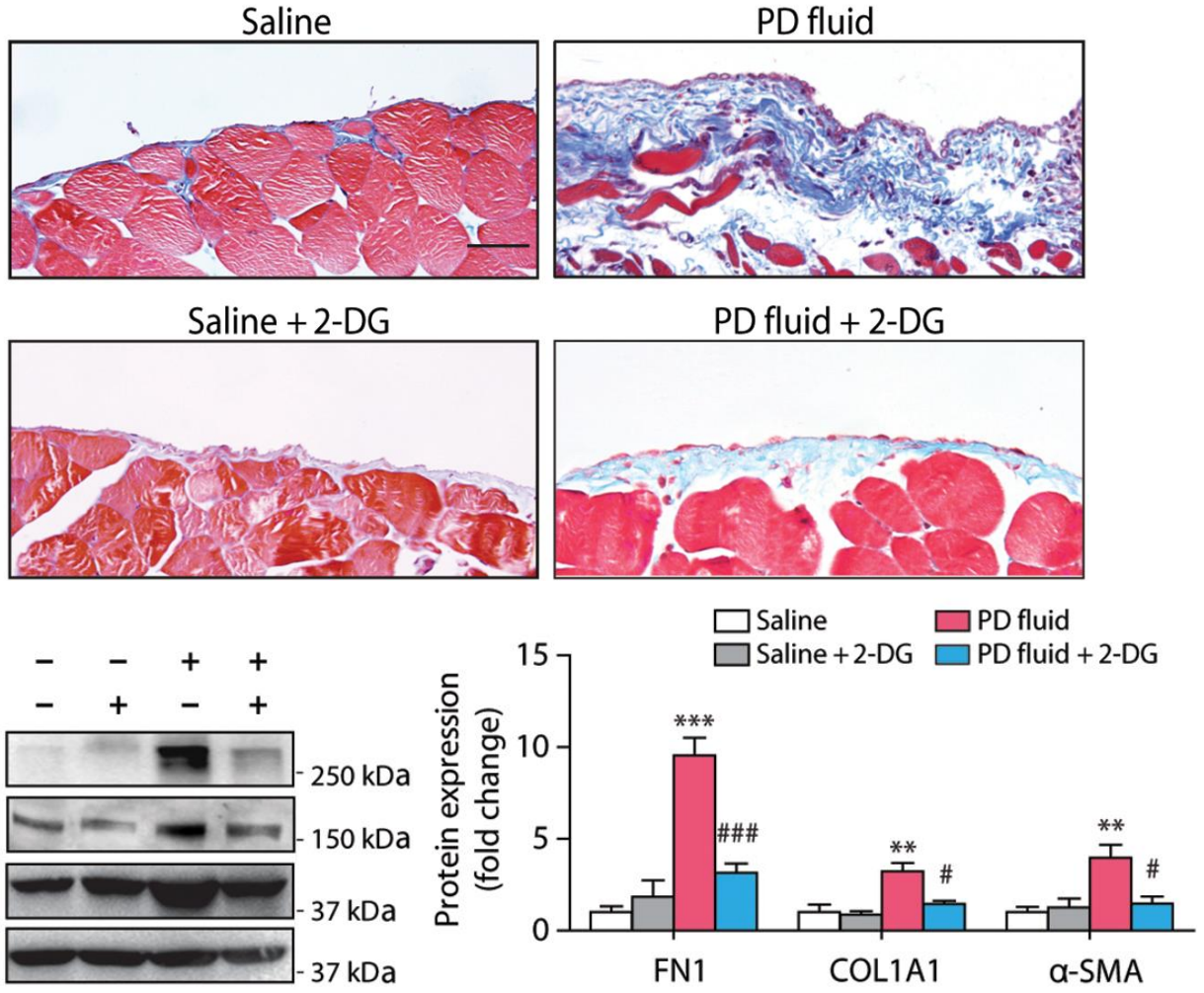
Inhibition of hyperglycolysis in mesothelial cells prevents peritoneal fibrosis

Meijun Si[1,2]*, Qianqian Wang[1,3]*, Yin Li[1]*, Hongchun Lin[1], Dan Luo[1], Wenbo Zhao[1], Xianrui Dou[4], Jun Liu[5], Hui Zhang[5], Yong Huang[6], Tanqi Lou[1], Zhaoyong Hu[2]†, Hui Peng[1]†



Si *et al.*, *Sci. Transl. Med.* **11**, eaav5341 (2019) 5 June 2019

Inhibition of glycolysis attenuates profibrotic phenotype of human mesothelial cells and peritoneal fibrosis in mice

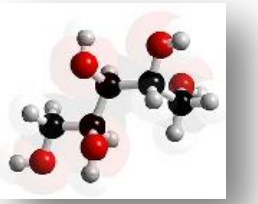


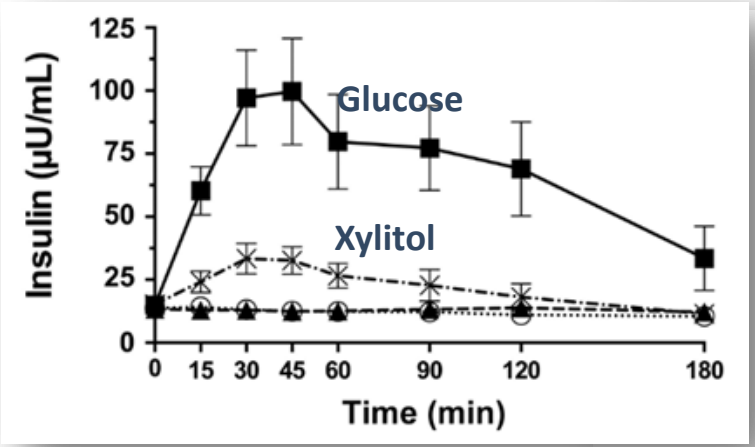
Xylitol, a very modest insulin secretagogue …

Gut hormone secretion, gastric emptying, and glycemic responses to erythritol and xylitol in lean and obese subjects

Bettina K. Wölnerhanssen,[1,2] Lucian Cajacob,[1] Nino Keller,[1] Alison Doody,[3] Jens F. Rehfeld,[4] Juergen Drewe,[5] Ralph Peterli,[6] Christoph Beglinger,[2] and Anne Christin Meyer-Gerspach[1]

[1]Department of Biomedicine of the University Hospital Basel, Basel, Switzerland; [2]Department of Research of the St. Claraspital Basel, Basel, Switzerland; [3]Diabetes Complications Research Centre, Conway Institute University College, Dublin, Ireland; [4]Department of Clinical Biochemistry, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [5]Department of Clinical Pharmacology, University Hospital Basel, Basel, Switzerland; [6]Department of Surgery of the St. Claraspital Basel, Basel, Switzerland





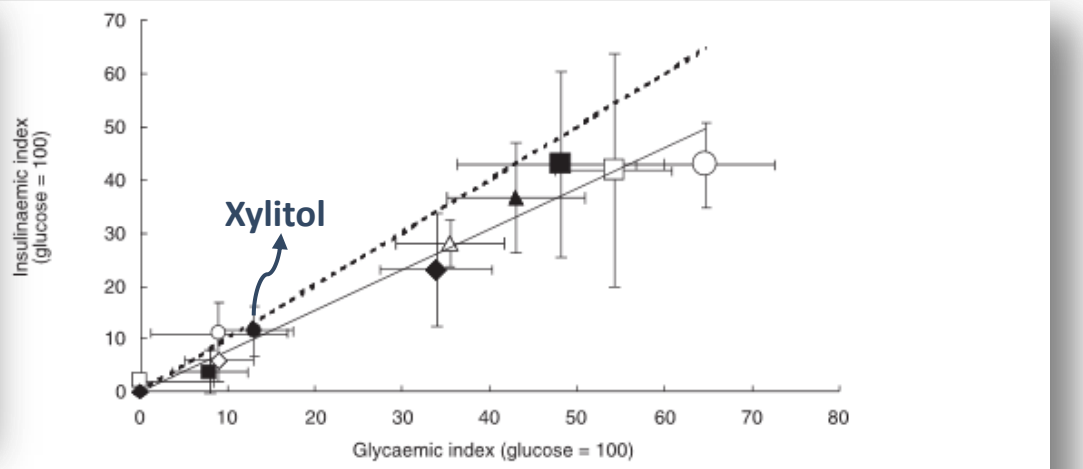


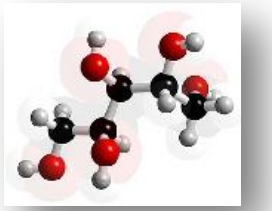
Fig. 4. Relationship (—; Slope = 0·75 (SE 0·05)) of the insulinaemic index to the glycaemic index for polyols and sucrose for untransformed data (a) and square root transformations (b). Data are from Table 5 and are means, with standard errors represented by vertical and horizontal bars (among studies) for sucrose (○), regular-maltitol syrup (□), intermediate-maltitol syrup (■), high-maltitol syrup (▲), polyglycitol (△), maltitol (◆), sorbitol (○), xylitol (●), isomalt (◇), lactitol (■), erythritol (□), and mannitol (◆). (- - -), Unity.

Am J Physiol Endocrinol Metab (2016) 310:E1053-61

Nutr Res Rev (2003) 16:163-91

Use of xylitol in Peritoneal Dialysis

(Bazzato et al.)

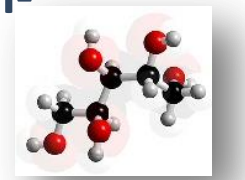


Phase II, exploratory study to test safety and metabolic/ultrafiltration efficacy of a xylitol based PD solution in uremic diabetic patients

- **Patient population: 6 PD patients with poorly controlled type I diabetes**
- **Patients previously treated with a CAPD glucose-based for 5.8±1.55 months (mean±se)**
  - **daily therapeutic program including 4 exchanges of 2 L, 2 of which containing glucose 2.0 % and 2 with glucose 4% (up to 240 gr)**
- **Study plan: from 5 to 11 months treatment with a daily therapeutic program including 4 exchanges of 2 L, 3 of which containing xylitol 1.5% and one with xylitol 3% (up to 150 gr)**

Am Soc Artif Intern Organs (1982) 28:280-86

Biochemical parameters before and after 5 months of xylitol-based PD solution in Type 1 diabetics



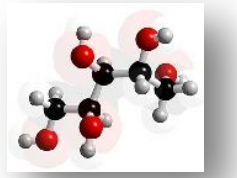
Xylitol load of 150 gr per day

	before	after
BUN (mg/dL)	51.3±15.6	49±18.2
Creatinine (mg/dL)	6.9±1.3	6.7±0.9
Uric acid (mg/dL)	5.6±0.7	9.1±1.0* ↑
Total Protein (g/dL)	6.5±1.1	6.3±0.8
Haemoglobin (g/dL)	12.6±2.8	12.3±2.3
Body weight (Kg)	58.3±12.4	56.4±11.6
MAP (mm Hg)	102±4.2	98±5.3
Blood Glucose (mg/dL)	205±23	193±18
HbA1c (%)	12.9±0.82	10.7±1.08* ↓
Insulin Dosage (UI)	124±16	59±14* ↓
Triglycerides (mg/dL)	316±49	213±42* ↓
Cholesterol (mg/dL)	308±43	245±40* ↓
HDL-Chol (mg/dL)	38±6.6	47±7.3* ↑

	before	after
SGOT (U/L)	21±3.6	24±4.3
SGPT (U/L)	23±5.4	28±4.0
CPK (U/L)	31±9.6	35.4±12
γGT (U/L)	36±5.8	37±7.5
Alk. Phosphat. (U/L)	193±48	208±36
Bilirubin (mg/L)	7.8±1.0	8.2±3.0
Sodium (mEq/L)	139±3.6	138±3.2
Potassium (mEq/L)	4.3±0.8	4.2±0.6
Calcium (mg/dL)	9.5±1.7	9.8±1.4
Phosphorus (mg/dL)	4.3±1.1	2.8±0.7* ↓
Magnesium (mg/dL)	3.1±1.6	2.9±0.7
Bicarbonate (mEq/L)	23.9±3.2	24.1±2.9
Lactic acid (mg/dL)	12.6±3.5	17.5±3.1* ↑

Trans Am Soc Artif Intern Organs (1982) 28:280-86

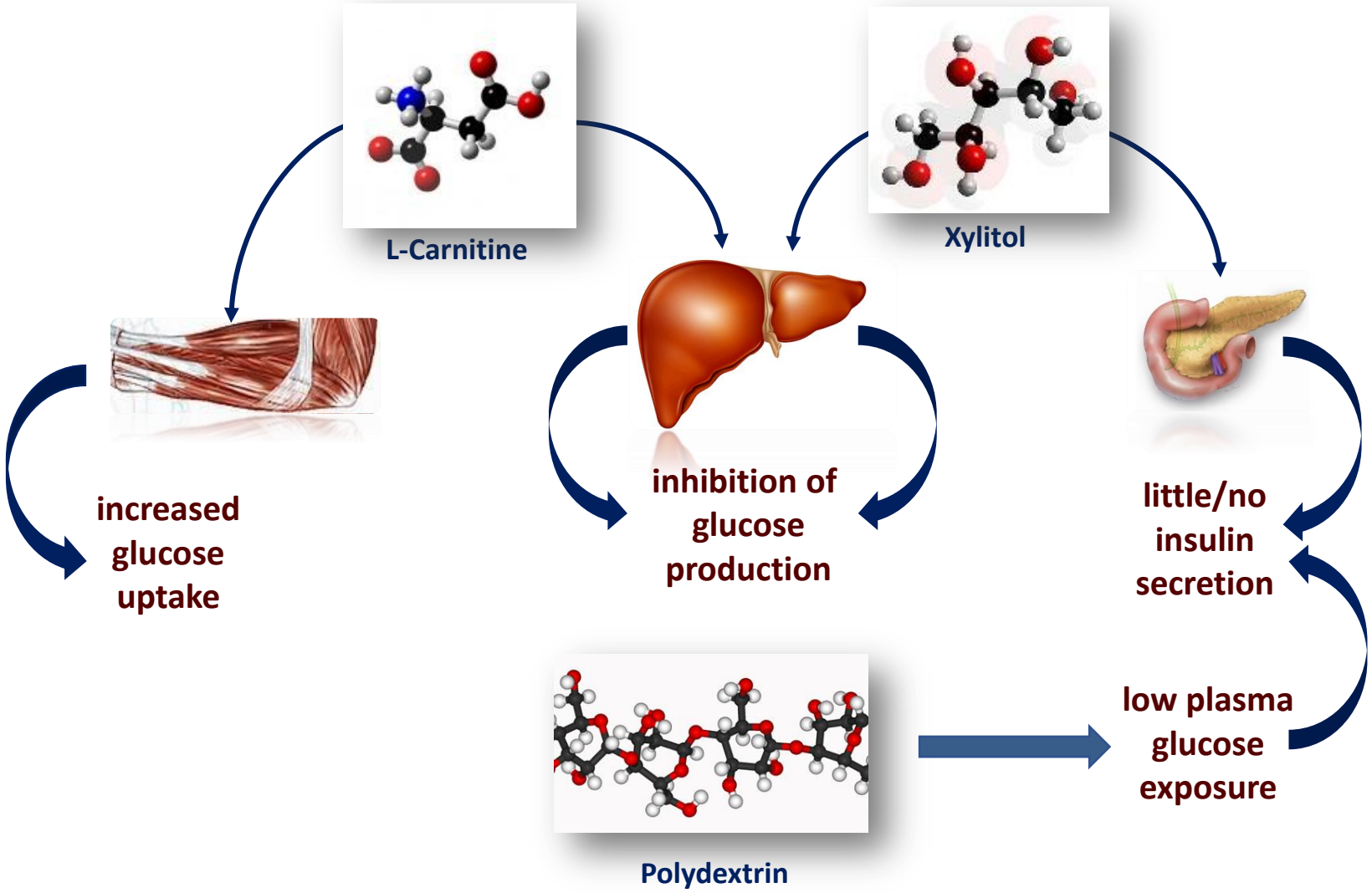
Use of xylitol in Peritoneal Dialysis



Additional Outcomes and Considerations:

- Xylitol-based PD solution was safe and well tolerated over a 6-month period
- Ultrafiltration profile of the xylitol-based PD solution (150 gr per day) was comparable with that of glucose-based PD solution (240 per day)
- No sign of oxalate accumulation
- The amount of xylitol effectively absorbed by PD patients was about 110gr/day, that is much lower than the maximal *iv* dose recommended by German Health Authorities (210gr/day for 70Kg bw)
- Buoncristiani & Di Paolo have treated 11 PD patients with a 2 L PD solution containing glucose (1.5%) and xylitol (2.5%) for more than 5 years [*19° Giornate Nefrologiche Senesi* (Buoncristiani & Di Paolo, eds), pp 303-308; Bios, Italy]

Glucose sparing along with an insulin-independent modulation of glucose disposal/production

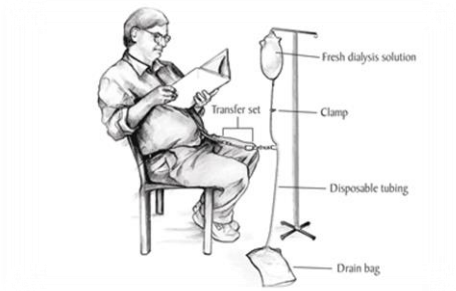


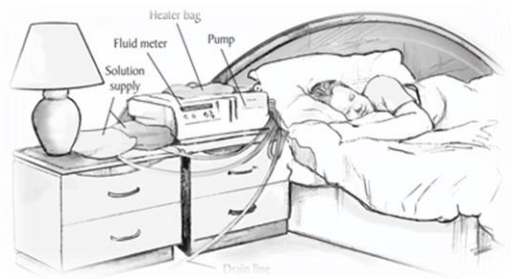
XyloCore
(Xylitol, Glucose and Carnitine)

XyloCore – Composition of three different strengths

Osmotic Strength	Low Strength[a]	Medium Strength[b]	High Strength[c]
Xylitol mmol/L	46 (0.7% w/v)	98.6 (1.5% w/v)	125 (2.0% w/v)
Glucose mmol/L	27.7 (0.5% w/v)		83 (1.5% w/v)
L-Carnitine mmol/L	1.24		
Sodium mmol/L	134		
Calcium mmol/L	1.75		
Magnesium mmol/L	0.5		
Chloride mmol/L	103.5		
Lactate mmol/L	35		
pH	5.5 ± 0.5		
Osmolarity mosmol/L	351.9	404.5	486.2

corresponding to Dianeal containing [a] 1.5%, [b] 2.5% and [c] 4% (w/v) glucose





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ELIXIR

A Study to EvaLuate the EffIcacy and Safety of XyloCore, a Glucose SparIng ExpeRimental Solution for Peritoneal Dialysis

إكسير

Study design:

Randomized, controlled parallel groups, open, multicenter study, comparing the effects of a low glucose PD solution, XyloCore, to Physioneal only regimen, in patients with End-Stage Renal Disease (ESRD) receiving Continuous Ambulatory Peritoneal Dialysis (CAPD), over a 6-month study period. All patients will receive Extraneal (7.5% Icodextrin) for nocturnal (long-dwell) exchange.

Objectives:

The primary objective of this study in CAPD patients is to demonstrate the non-inferiority of XyloCore compared to the Physioneal with regards to safety and efficacy.

Use of xylitol in Peritoneal Dialysis

Additional Outcomes and Considerations:

- Xylitol-based PD solution was safe and well tolerated over a 6-month period
- Ultrafiltration profile of the xylitol-based PD solution (150 gr per day) was comparable with that of glucose-based PD solution (240 per day)
- Significant improvement of glycemic control (HbA1c)
- No sign of oxalate accumulation
- The amount of xylitol effectively absorbed by PD patients was about 110gr/day, that is much lower than the maximal *iv* dose recommended by German Health Authorities (210gr/day for 70Kg bw)
- Buoncristiani & Di Paolo have treated 11 PD patients with a 2 L PD solution containing glucose (1.5%) and xylitol (2.5%) for more than 5 years [*19° Giornate Nefrologiche Senesi* (Buoncristiani & Di Paolo, eds), pp 303-308; Bios, Italy]

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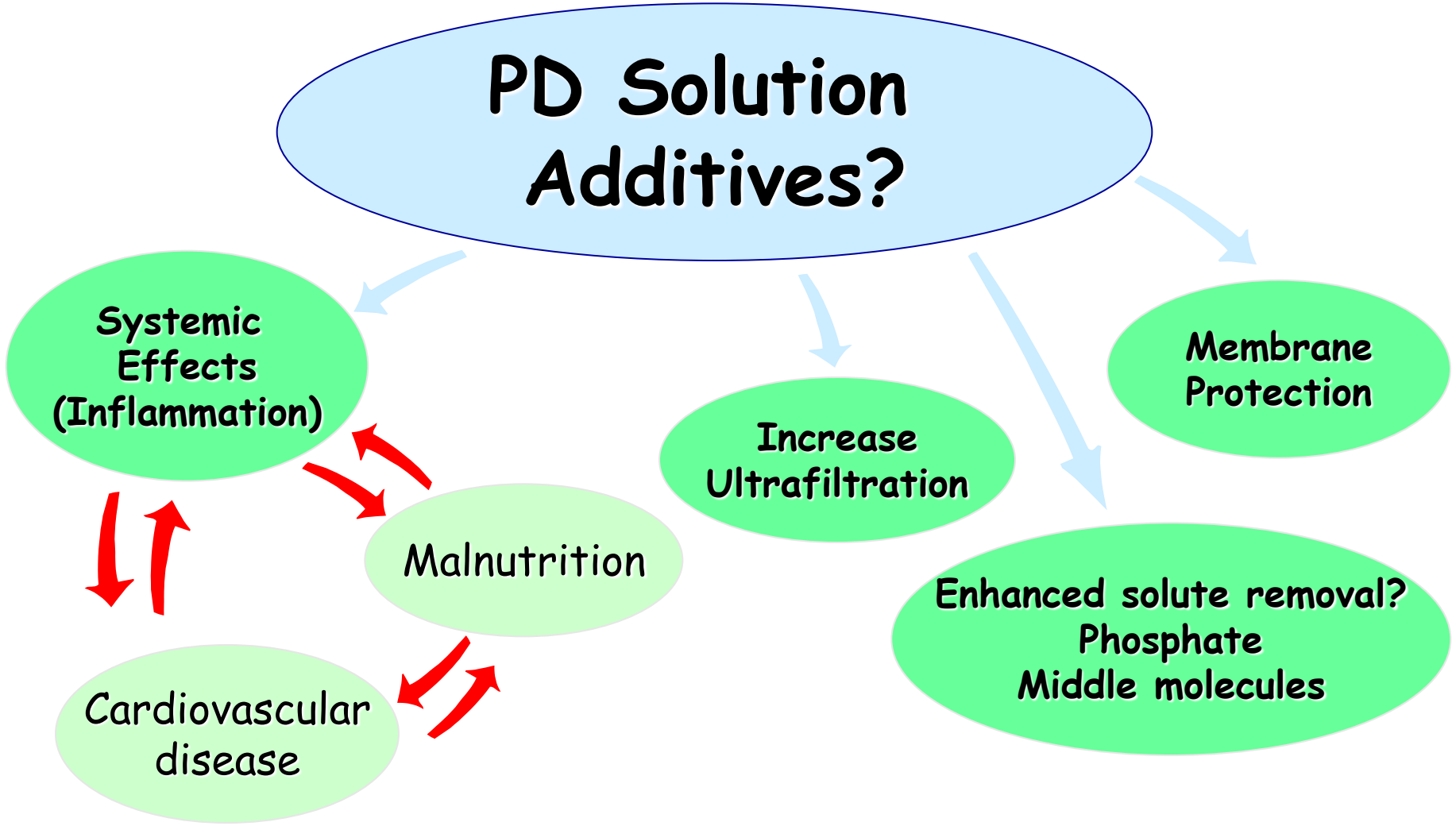

PD Solution Additives?
Systemic Effects (Inflammation)
Malnutrition
Cardiovascular disease
Increase Ultrafiltration
Membrane Protection
Enhanced solute removal?
Phosphate
Middle molecules

PD-protec®: best-in-class product developed to prevent major PD related complications

zytoprotec

Overview

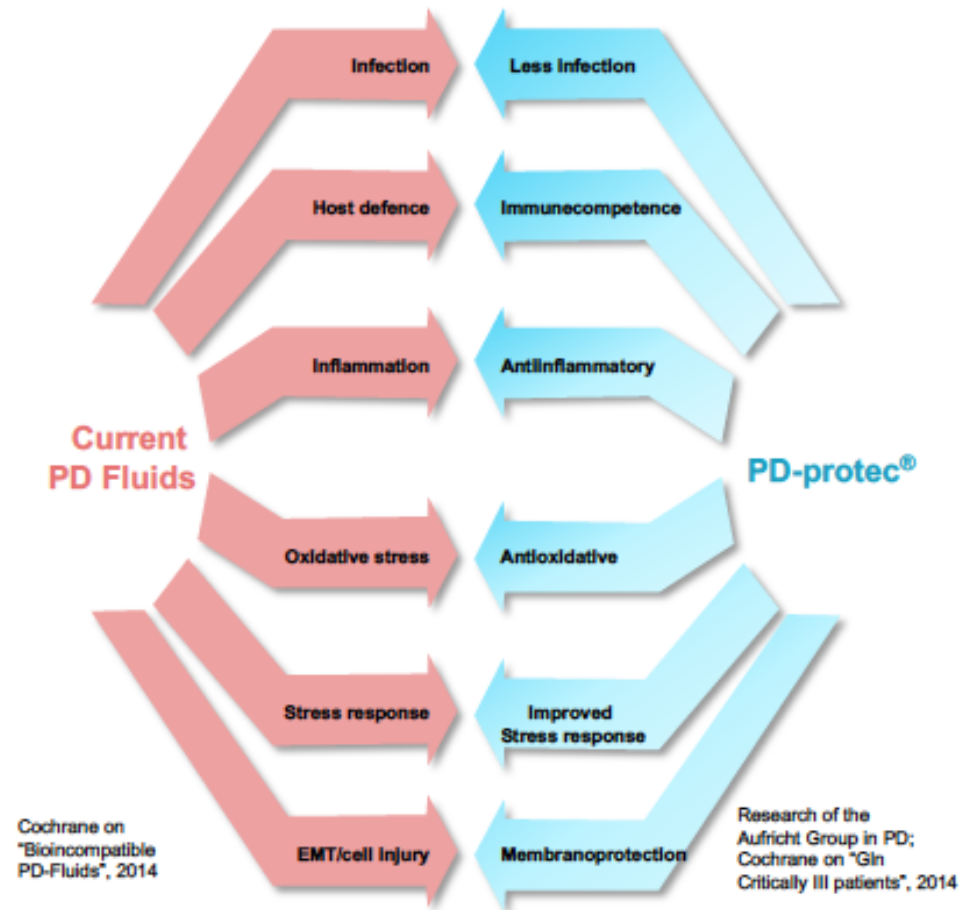
- PD-protec® is a solution for peritoneal dialysis being developed to significantly improve and prolong the survival of patients undergoing PD
- A clinical phase I/II trial and a pilot phase II with PD-protec® demonstrated the clinical safety of PD-protec®
- Early clinical trials provided promising data on beneficial effects in respect to peritoneal membrane protection, peritoneal stress response and peritoneal immunocompetence
- A multi-center placebo controlled, cross-over best-in-class Phase II double blinded clinical trial with PD-protec® met both primary outcome parameters, reflecting improved membrane integrity and increased immune competence, and demonstrated no drug-related adverse events
- Intellectual property

  Granted patents: EU, US, Canada, Hong-Kong and Japan
- Orphan drug designation received by US FDA in Nov 2017

PD-protec® description

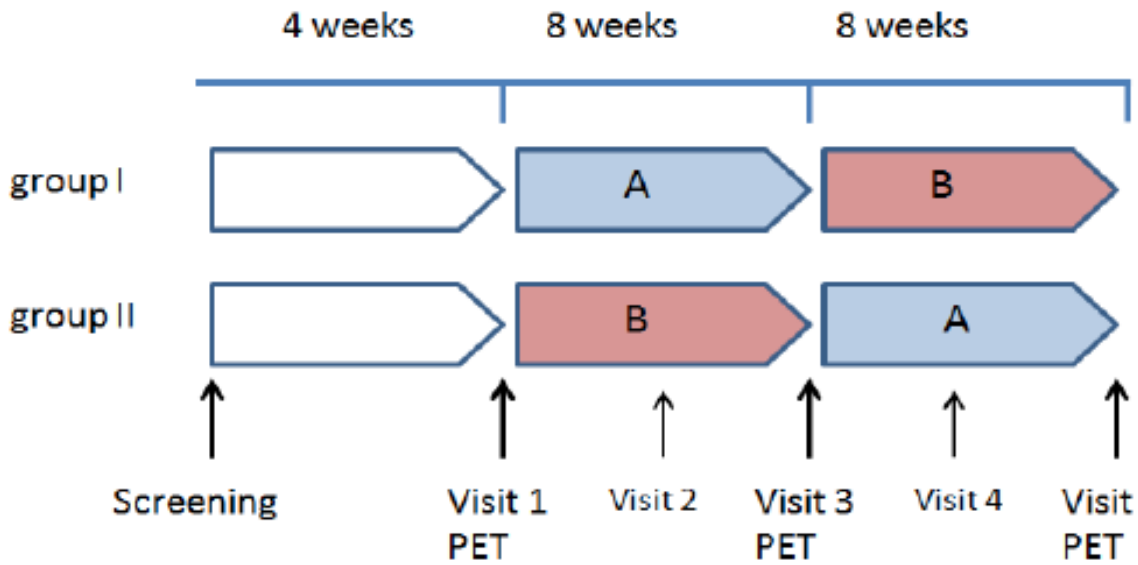
"Novel fluid for peritoneal dialysis designed to avoid the damage that current fluids cause to abdominal tissue by using AlaGln in addition to a glucose PD fluid"

PD-protec® key advantages



Source: Company Information

Phase II Trial Data unblinded.....



A: Standard Physioneal®

B: *PD-protec™* 8mM AlaGln

All Austrian Centers
with >10 Patients invited

54 PD Patients were enrolled
37 completed both treatments

EudraCT No. 2013-000400-42
PI: Prof. Andreas Vychytil, III Med

- **Two Primary Endpoints**
  - **Peritoneal immunocompetence**
  - **Mesothelial cell mass/status**

... and various secondary and exploratory Endpoints covering all Pathomechanisms relevant in PD

MEDIZINISCHE UNIVERSITÄT WIEN

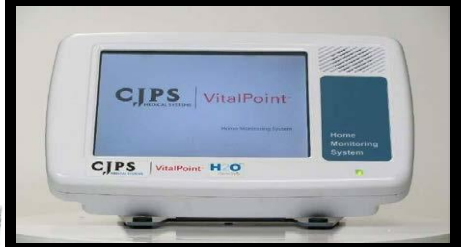
EuTRiPD™
European Training & Research in Peritoneal Dialysis

zytoprotec

Karolinska Institutet

Telemedicine in PD

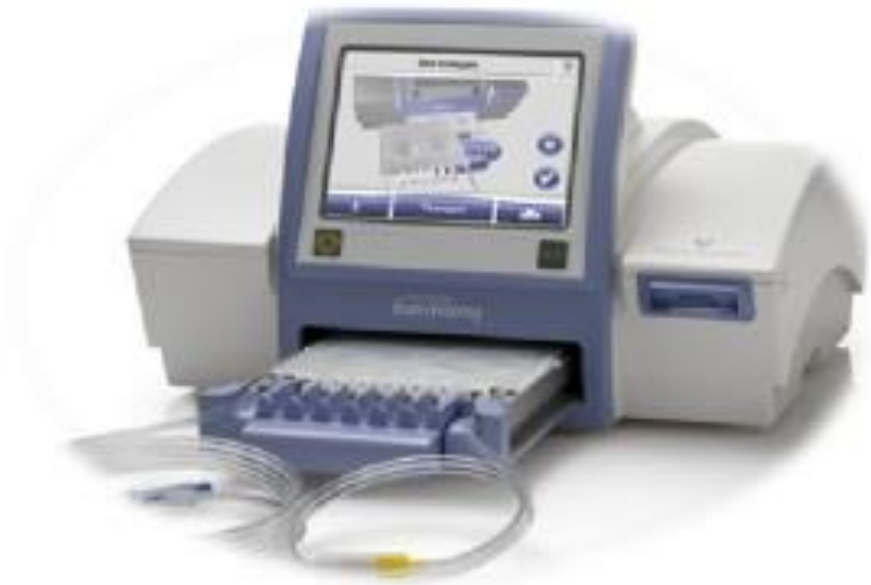
Telemonitoring

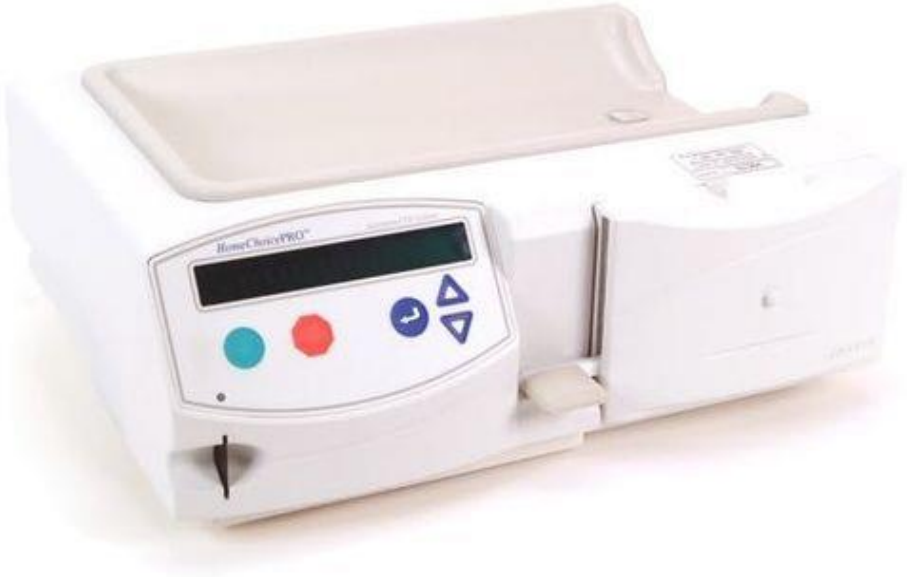


Allows for real-time capture and transmission of numerous physiological variables (pulse, blood pressure, weight, glucose).

Most utilize “Bluetooth” connectivity

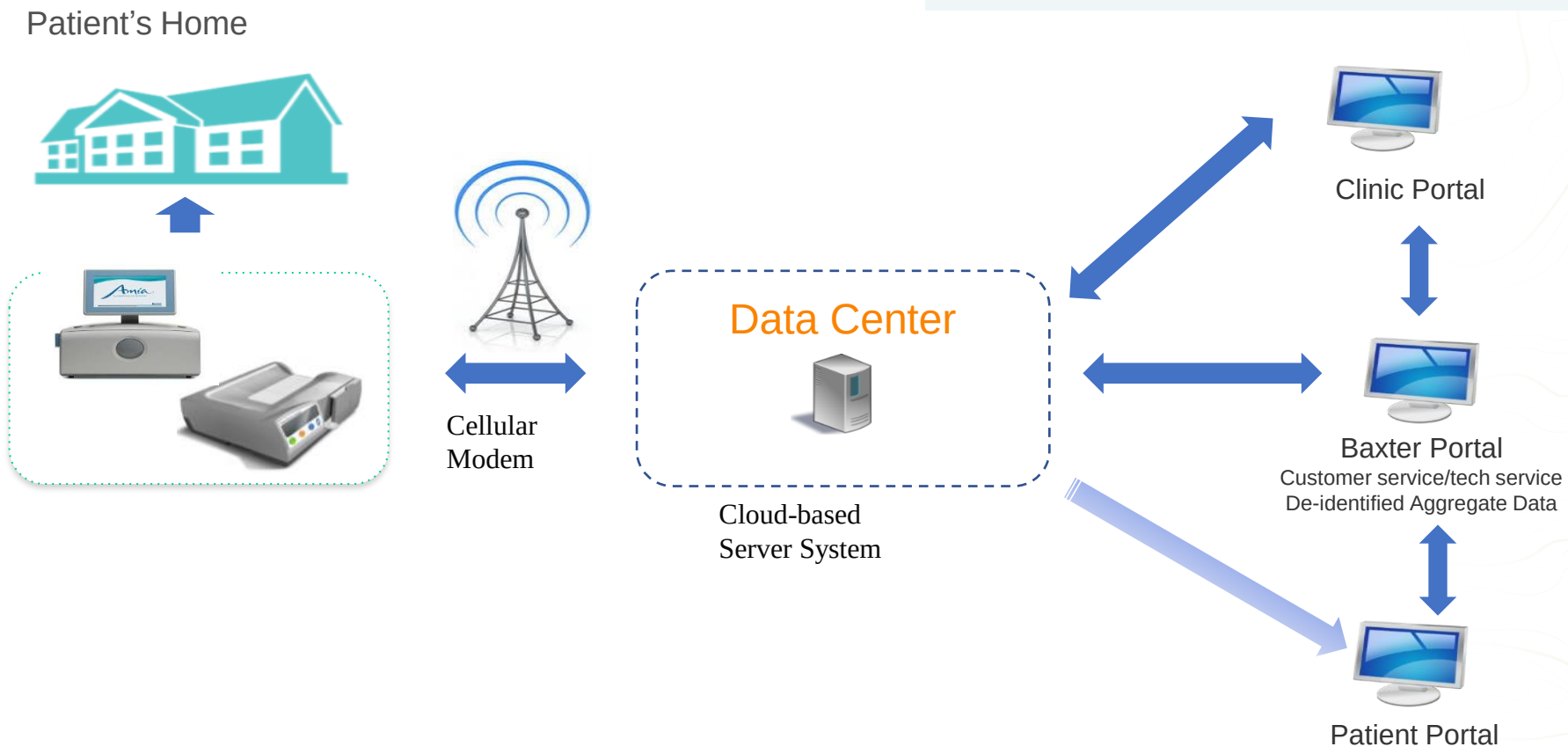
APD Cyclers





adcock ingram critical care

Sharesource



For Patients on Home Dialysis Remote Patient Management

Sharesource

PD-cycler embedded
remote patient management platform

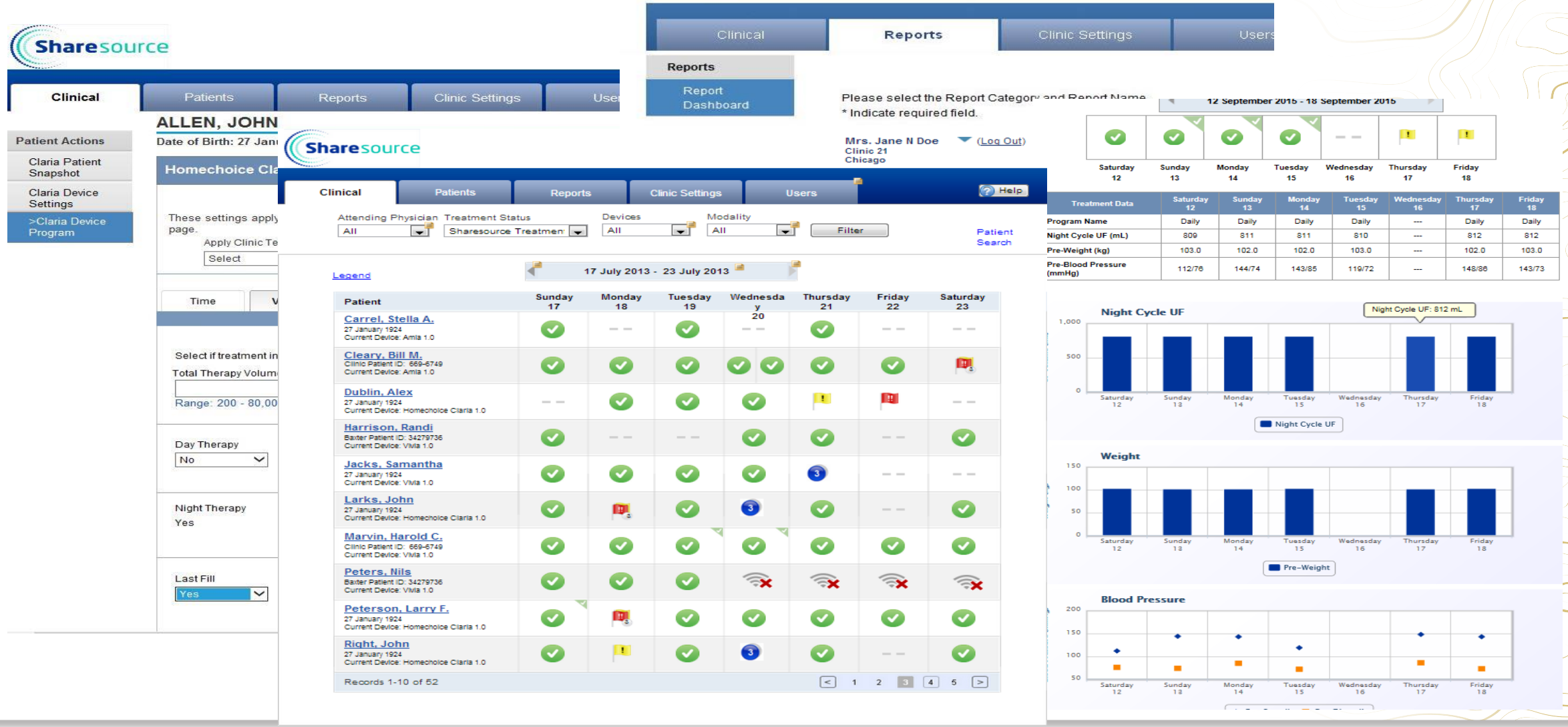
Treatment data is automatically collected after each PD session

Allowing healthcare providers to securely view their patients' recently completed home dialysis-related treatment data

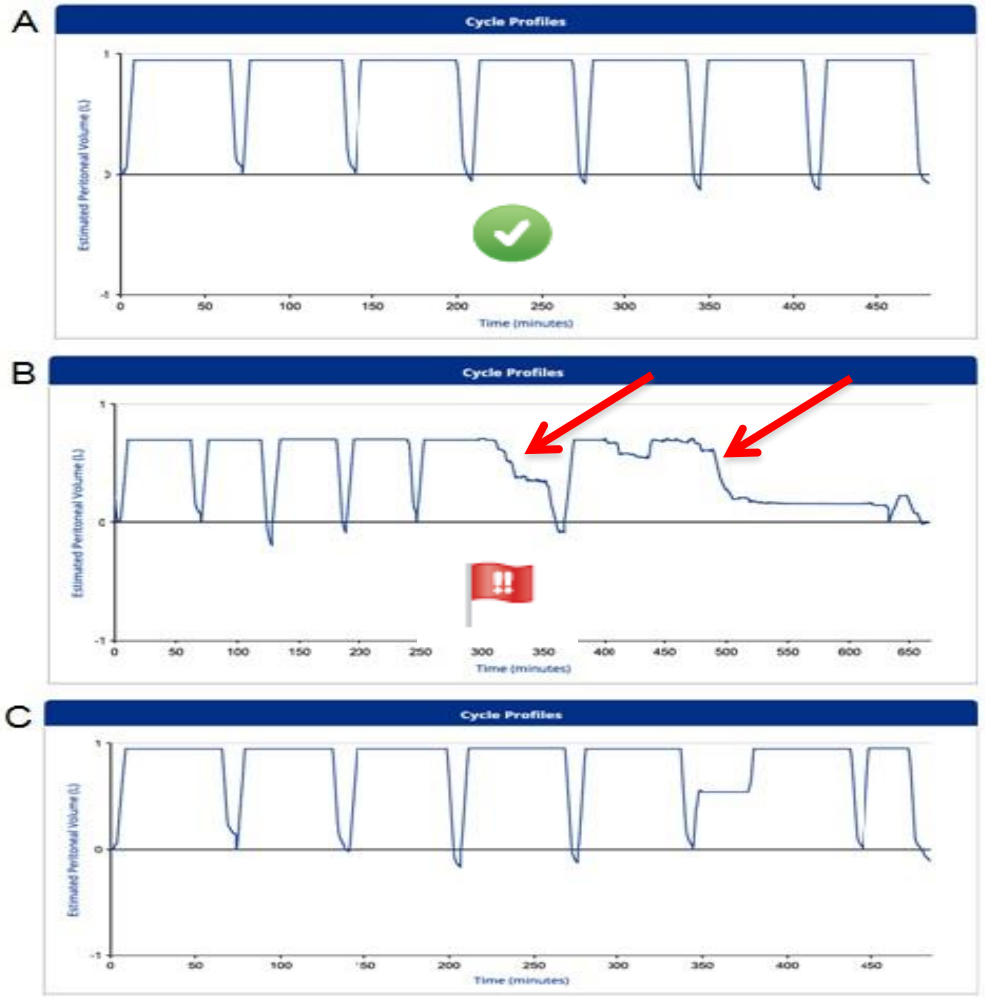
Allowing Healthcare providers to act on this information by directly contacting the patient and/or remotely adjusting their patients' home device settings

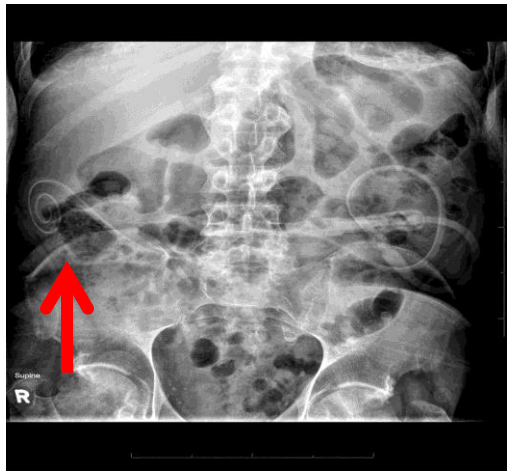
Sharesource Clinician Dashboard:

Slide courtesy James A. Sloand



APD RPM: Early Detection of Catheter Malfunction





Jotterand-Dreppe V, Martin P-Y, Sloand JA. Perit Dial Int 2017.

From Manual to Digital
Modernising Dialysis

The identified “CAPD-challenges”
The Vivatum “Solution”

challenges and unmet needs

Manual therapy lack of digitalisation

Patient based error-prone home therapy

Demanding to HCP(*)

Irregular patient contact

Therapy Outcome

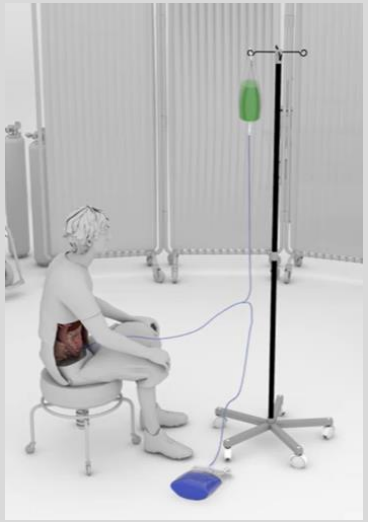
Patient Safety

Quality of life

Affordability

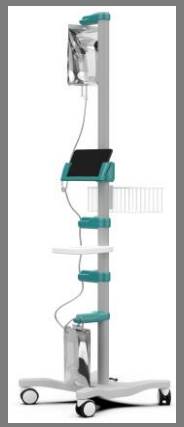
CAPD Therapy “today”

Manual Therapy



The “Solution”

platform based, hardware supported



Integrated remote patient care and therapy analysis platform

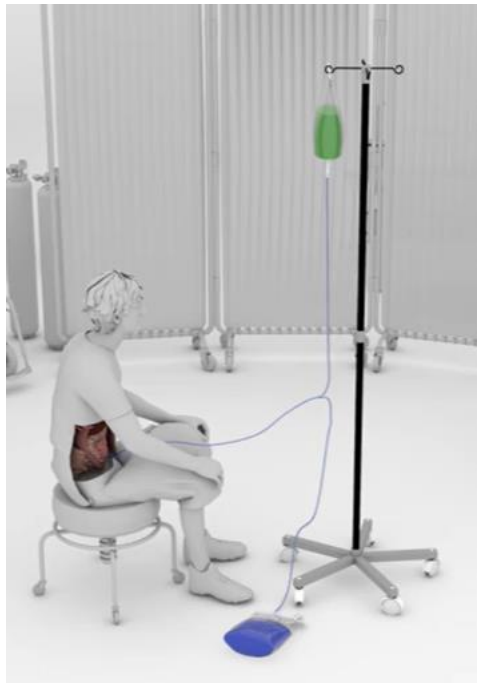
Platform integrated CAPD (home dialysis) hardware

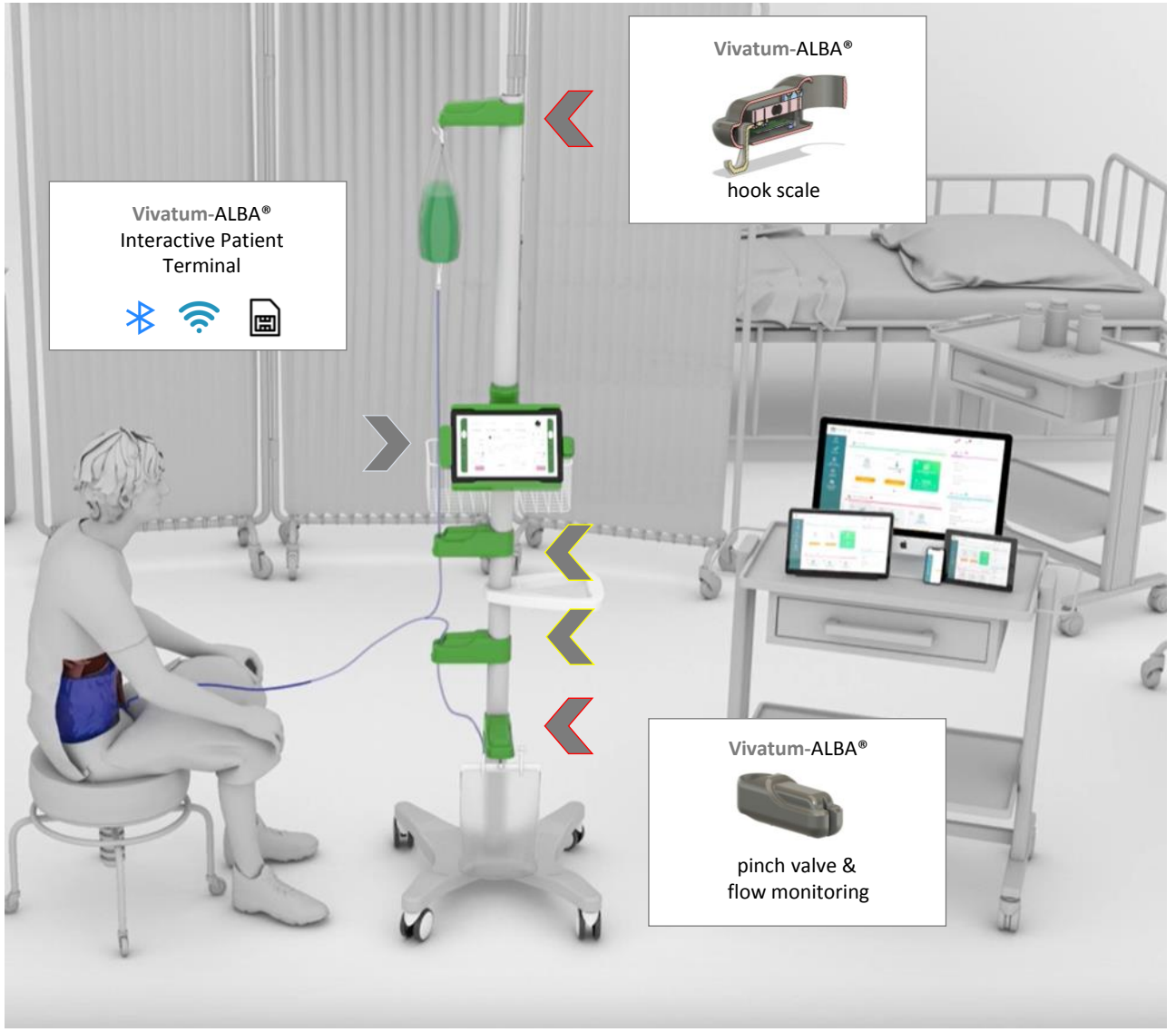
(*) HCP = Healthcare Practitioner

Vivatum “remote patient care” *and* “therapy analytics”

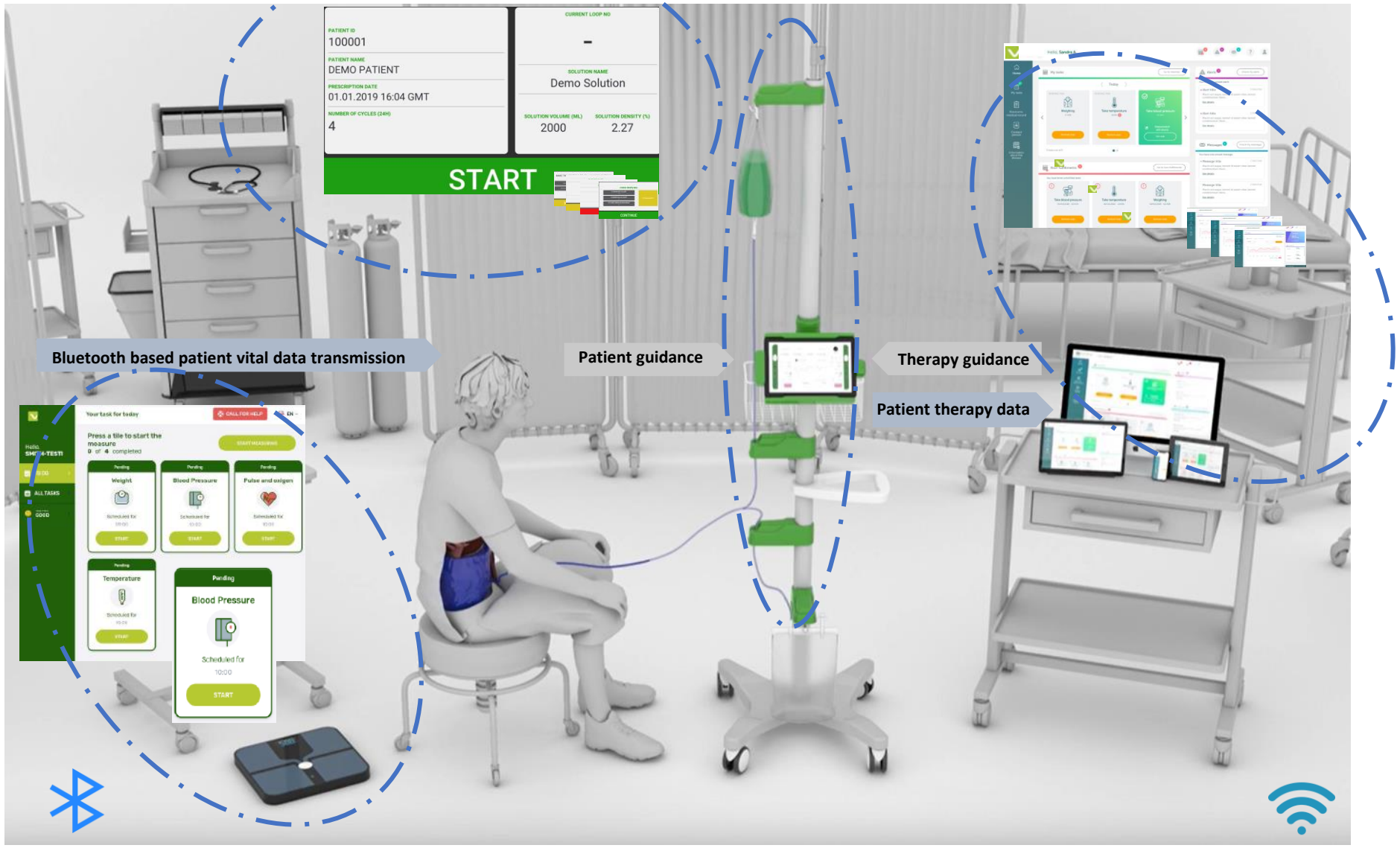
CAPD Therapy “today”

Manual Therapy



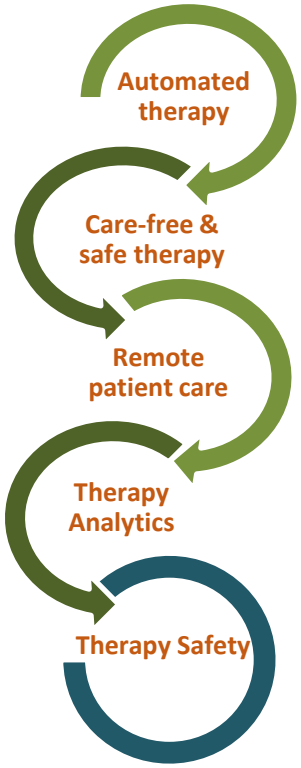


Vivatum “remote patient care” *and* “therapy analytics”



Vivatum **PD ®** Customer Benefit and Congress Feedback

Customer benefits (summary)	
Complementary to all PD dialysates fluid and connector systems	**PD-Solution and Connector independent**
Remote patient care & monitoring	**Dialysate fluid flow guidance to 1ml**
Tailored therapy	**Prescription flexibility**
Patient therapy guidance	**Improved therapy adherence**
Bi-directional communication	**Early detection of complications**
Accurate & automatic therapy data recording	**Real time therapy analytics**
Fewer hospitalisation	**Resource-saving and cost- saving therapy**
Higher therapy accessibility and affordability **Patient therapy retention**	



Feedback and Reactions to Vivatum PD @ EDTA 2019 in Budapest

Quotes:

"Alba modernises CAPD!" Commenting on the Device

"Now I can see catheter function daily!" Commenting on the Pinch Valve Technology allowing measurement to the ml.

"This reduces the stress my team is faced with.!"

"My team can reach out to our patients bidirectionally and the historical patient data is available to the entire team any time." Commenting the remote patient care, therapy analytics and EMR integration.

"This allows us Nephrologist to be closer to the patients." Commenting on the Med.Device integration, the therapy cockpit, the alarm functionality and Communication
"A patient can be managed by the team now"

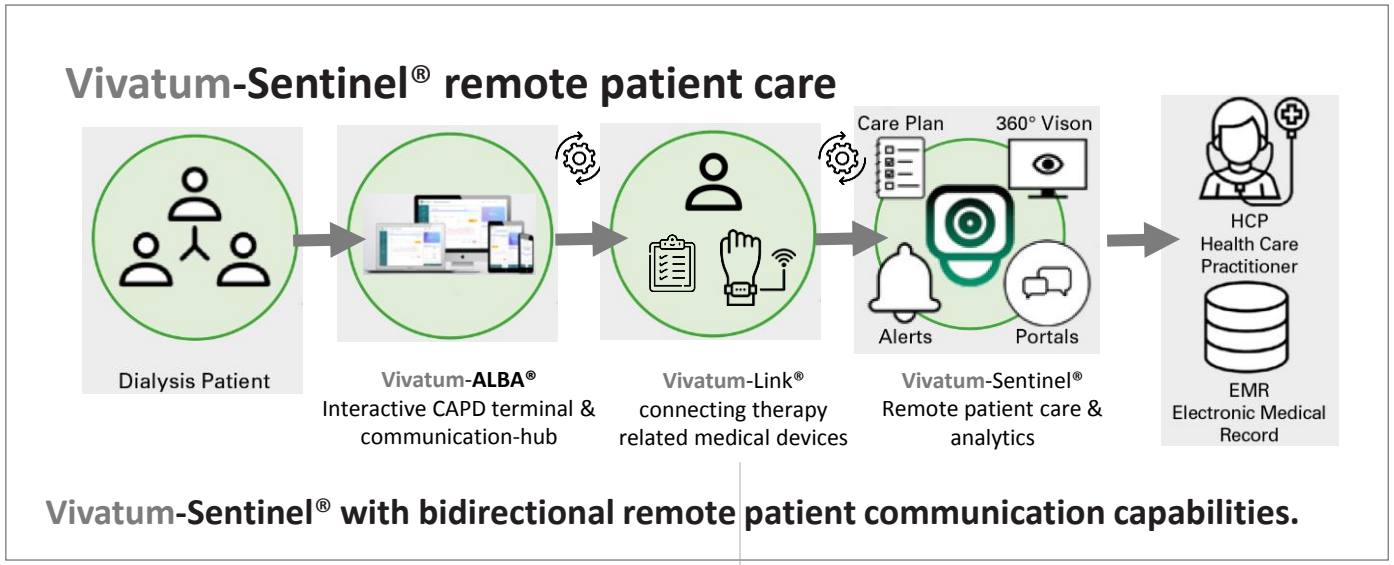
"You have a training function for Patient Training, that's great!"

Something New >> Vivatum-Sentinel®

Vivatum-Sentinel® remote patient care and therapy analysis software

ESRD / RRT remote therapy management, therapy analytics and EMR electronic medical record

- Treatment Plan established by the Nephrologist in Vivatum-**Sentinel®** (Secure Web Access)
- Patient Access via e.g. Vivatum-**ALBA®** CAPD Auto to Vivatum-**Sentinel®** with a verification process to the EMR
- Treatment Plan Tasks Communication to the patient and his device (e.g. Vivatum-ALBA® CAPD Auto, Tablet, Desktop, Smart Phone and others)
- Medical Device connectivity as per Treatment Plan requirements (Vivatum-Link® patient guidance)
- Nurse Management & Reporting by Web or App Portal Access
- Monitoring & Alerts possible to Nurse or Doctor as per established process
- Stand-Alone Option for Dialysis Units for ESRD-therapy options (PD = CAPD & APD & HD) without integrated EMR capability



Vivatum-Link® device examples

Vivatum Remote Patient Care

Vivatum provides tailored solutions for Remote RRT Patient Care and the IT-platform beyond dialysis

Vivatum-Sentinel®
Remote patient care, therapy analytic and EMR IT-platform

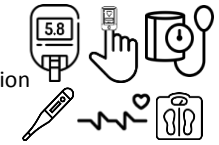
Vivatum IT-Platform (SaaS)

Vivatum-Sentinel® IT based remote patient care (bidirectional).

Vivatum-Link® Designed to managed all ESRD patients. (Therapy / System independent).

Designed to reduce patient based manual therapy steps.

Vivatum-Link®
medical device integration



Vivatum Hardware

Vivatum ALBA® Automated CAPD Patient Care.

Designed to automate the CAPD and manage & support patients remotely.

Designed to eliminate error-prone therapy steps.

Vivatum-**ALBA®**
CAPD Auto

Vivatum-PD®- System Overview

Karolinska Institutet

Other innovative contributing strategies

Minerva Urol Nefrol. 2017 Mar 31. doi: 10.23736/S0393-2249.17.02882-X. [Epub ahead of print]

A systematic review of preclinical studies on therapeutic potential of stem cells or stem cells products in peritoneal fibrosis.

Alatab S[1], Najafi I[2], Atlasi R[3,4], Pourmand G[5], Tabatabaei-Malazy O[6,7], Ahmadbeigi N[8].

Author information

Abstract

INTRODUCTION: Peritoneal fibrosis remains a serious complication of long-term peritoneal dialysis. Stem cell therapy is an innovative field of scientific investigation with potential for clinical application. Here, we systematically reviewed the studies to determine whether stem cell based therapy could improve the peritoneal fibrosis in experimental models of peritoneal fibrosis.

EVIDENCE ACQUISITION: Our systematic search of Pubmed, Scopus, Web of Science, and Cochrane Library yield 5219 article. After screening for eligibility; in-vivo, experimental, interventional studies using stem cells in animal models of peritoneal fibrosis; 1 articles were included. The studies underwent comprehensive review, quality assessment, and data extraction.

EVIDENCE SYNTHESIS: Mesenchymal stem cells were the most used type (90.9%) originated either from bone marrow (70%), adipose tissue (20%), or umbilical cord (10%). In 90.9% of studies, stem cells were injected after peritoneal insult and 63.6% of studies used the intraperitoneal injection route. Eight studies met the ≥ 50% of criteria indicated by ARRIVE recommendation. Information regarding the nature of ethical review permissions, species, strain and gender, dose, route and duration of treatment, was stated by all studies. 81.8% of the studies reported the number of animals in each group. Adverse events were reported in on study. Improvement in histological parameters including attenuation of submesothelial thickness (100%), inflammation (62.5%), angiogenesis (60%), and fibrosis (85.7%) was reported after stem cell therapy. Peritoneal permeability function by assessing the ultrafiltration, glucose transport and solute permeability was improved in all studies. Stem cell treatment resulted in mesothelial recovery in 100% of studies.

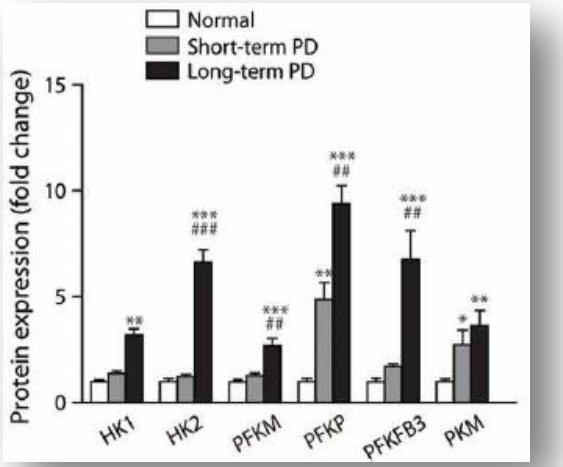
CONCLUSIONS: In preclinical studies, the use of stem cells is associated with improved peritoneal fibrosis. This may provide an important foundation to support future translational clinical research using stem cell therapy to repair the injured peritoneum and modulate immune responses in PD patients.

FIBROSIS

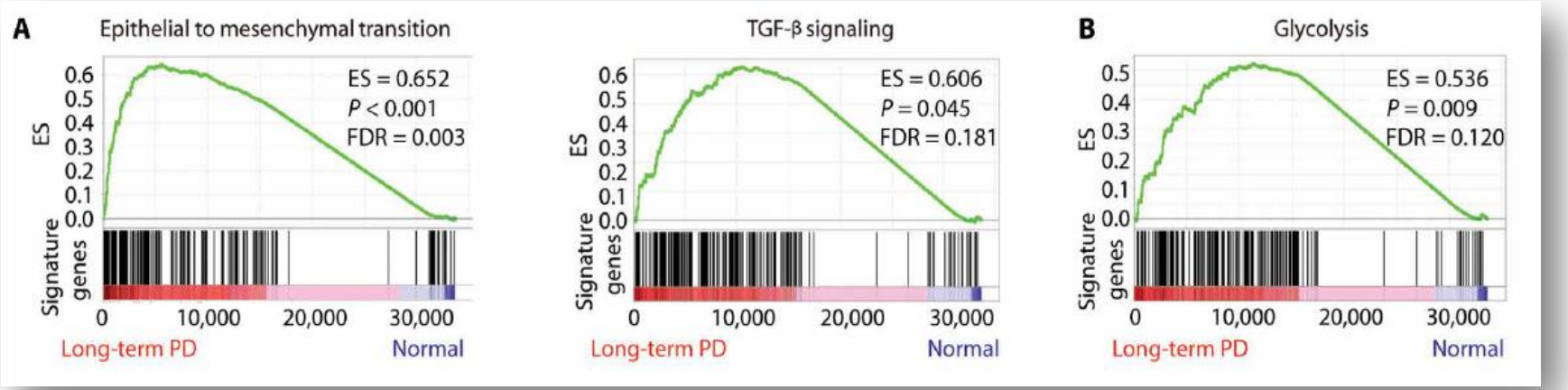
Inhibition of hyperglycolysis in mesothelial cells prevents peritoneal fibrosis

Meijun Si[1,2]*, Qianqian Wang[1,3]*, Yin Li[1]*, Hongchun Lin[1], Dan Luo[1], Wenbo Zhao[1], Xianrui Dou[4], Jun Liu[5], Hui Zhang[5], Yong Huang[6], Tanqi Lou[1], Zhaoyong Hu[2†], Hui Peng[1†]

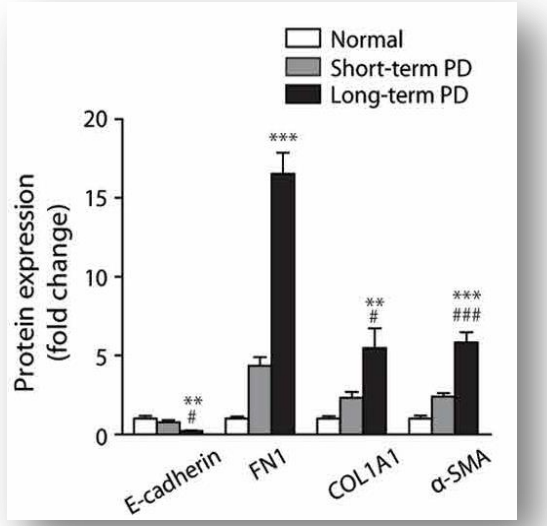
Single-cell transcriptome of mesothelial cells from patients undergoing PD



Quantification of glycolytic enzymes



Gene Set Enrichment Analysis (GSEA)



Quantification of fibrotic proteins

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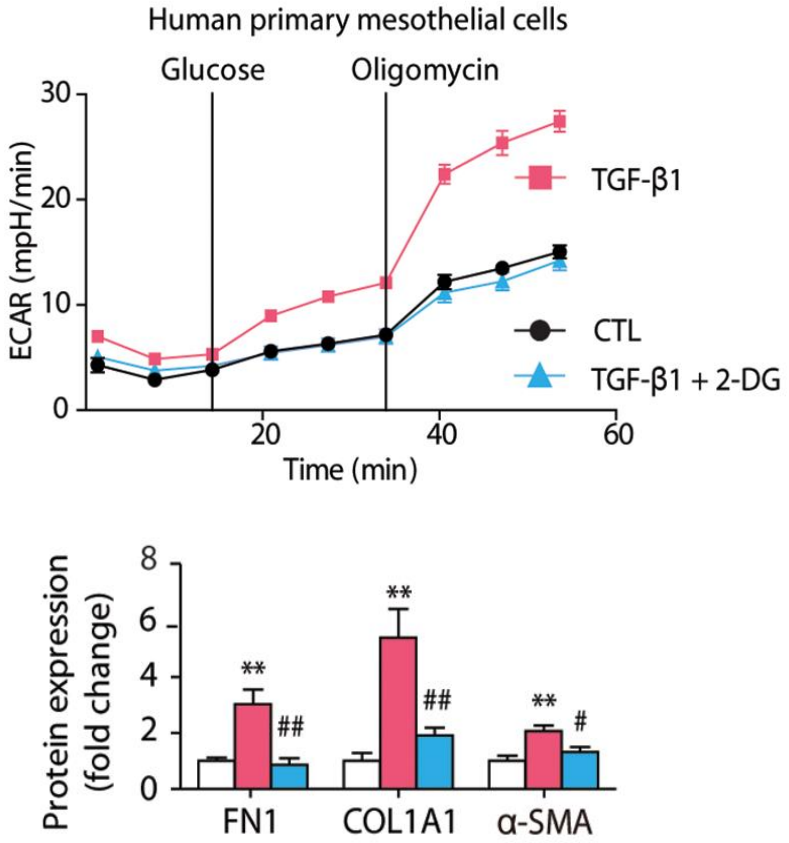
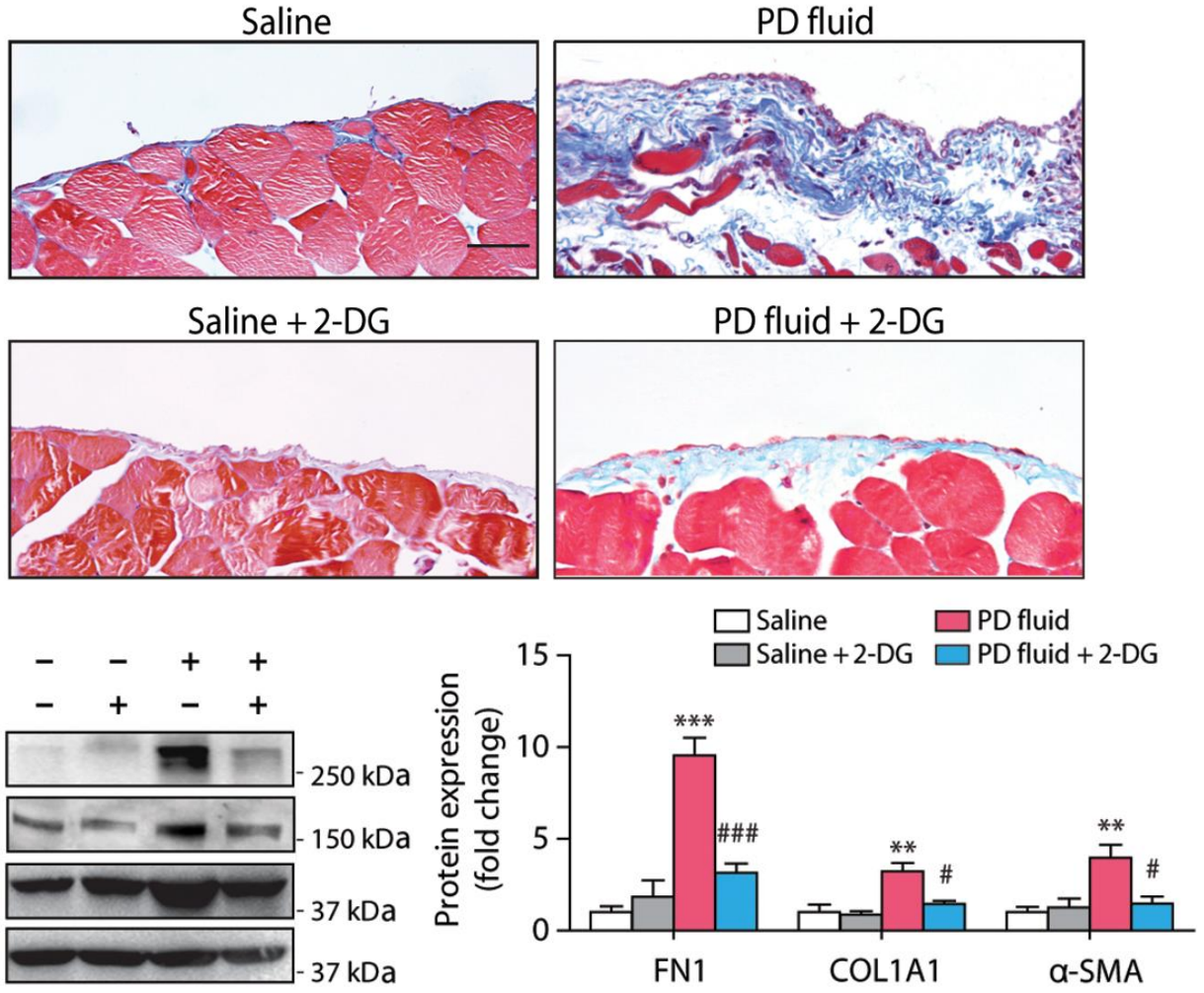


Si *et al.*, *Sci. Transl. Med.* **11**, eaav5341 (2019) 5 June 2019

Inhibition of glycolysis attenuates profibrotic phenotype of human mesothelial cells and peritoneal fibrosis in mice



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Inhibition of hyperglycolysis in mesothelial cells prevents peritoneal fibrosis

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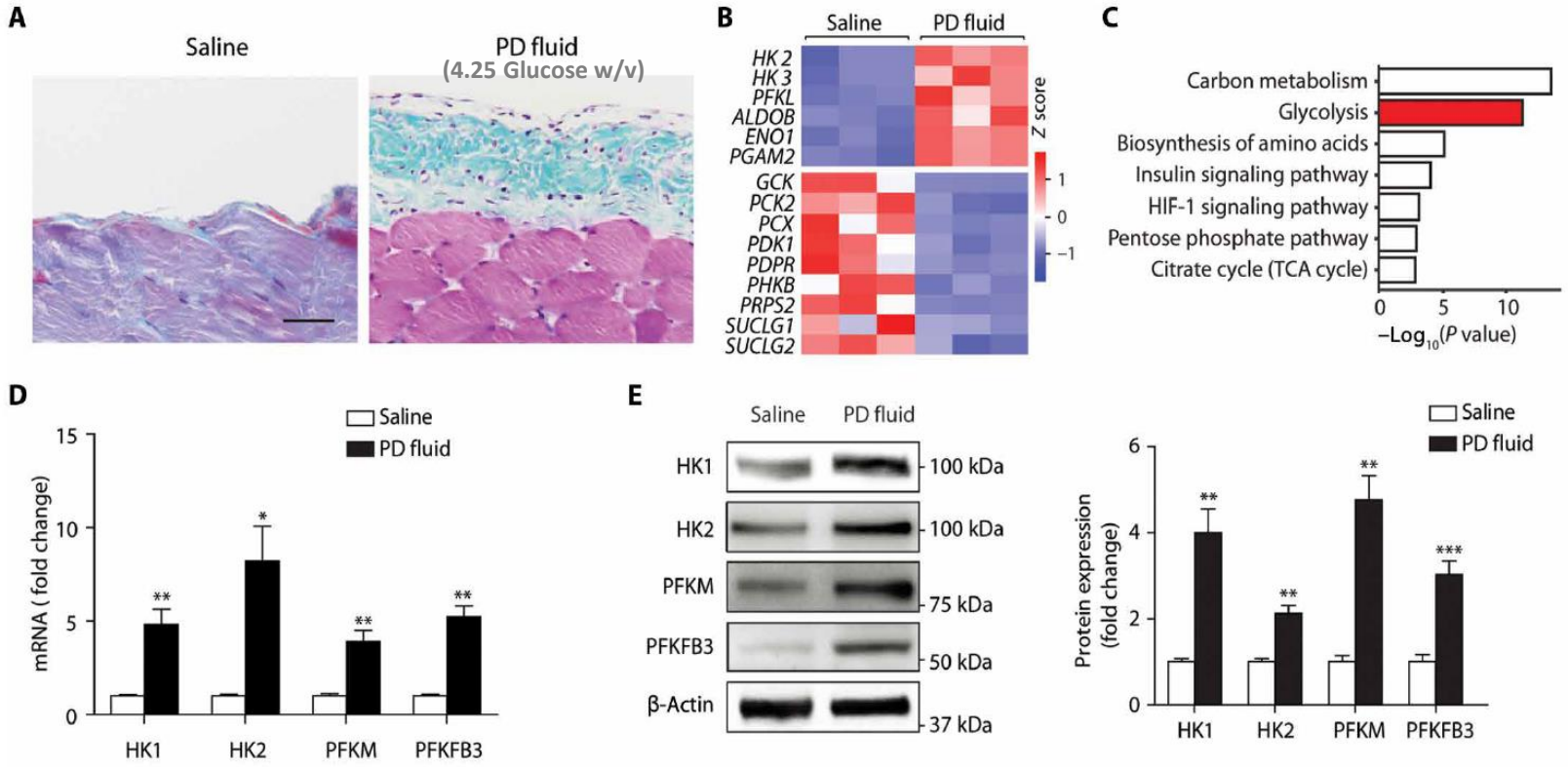
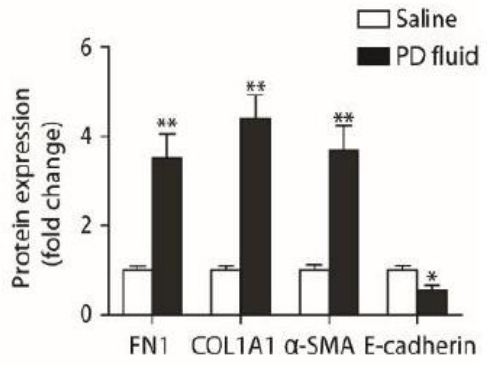
PD fluid enhances glycolysis in mouse peritoneum





Targeting metabolic dysregulation for fibrosis therapy

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Myokine mediated muscle-kidney crosstalk suppresses metabolic reprogramming and fibrosis in damaged kidneys

Hui Peng[1,2], Qianqian Wang[1,2], Tanqi Lou[1], Jun Qin[3], Sungyun Jung[3], Vivekananda Shetty[4], Feng Li[4], Yanlin Wang[2], Xin-hua Feng[5], William E. Mitch[2], Brett H. Graham[6] & Zhaoyong Hu[2]

NATURE COMMUNICATIONS | DOI: 10.1038/s41467-017-01646-6

Proximal Tubular Cell–Specific Ablation of Carnitine Acetyltransferase Causes Tubular Disease and Secondary Glomerulosclerosis

Claudia Kruger,[1] Trang-Tiffany Nguyen,[1] Chelsea Breaux,[1] Alana Guillory,[1] Margaret Mangelli,[1] Kevin T. Fridianto,[2] Jean-Paul Kovalik,[2] David H. Burk,[3] Robert C. Noland,[4] Randall Mynatt,[5] and Krisztian Stadler[1]

Diabetes Volume 68, April 2019