LE SOLUZIONI PER LA DIALISI PERITONEALE

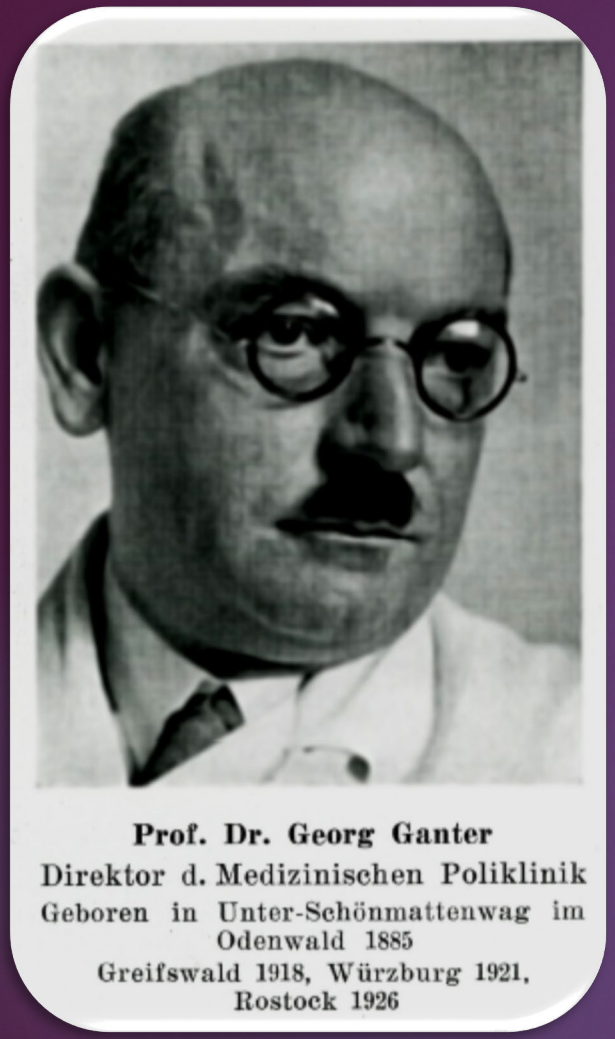
VINCENZO TERLIZZI

ASST SPEDALI CIVILI BRESCIA

PROGRAMMA

- Storia
- Soluzioni standard
- Soluzioni biocompatibili
- Icodestrina
- Aminoacidi
- Teoria Osmo-metabolica
- Studi in corso
- Conclusioni

▶**1744,** physiologist and physicist Stephen Hales joined forces with surgeon and fellow Englishman Christopher Warrick to lay the foundation for peritoneal dialysis in humans. They attempted to treat a 50-yearold patient with ascites by first removing the excess abdominal fluid from the woman before using a leather tube to introduce ***a solution consisting of 50% water and 50% wine into her abdomen.***



Wurtzburg, Germany, 1923

instilled saline solutions in volumes of approximately 50 mL

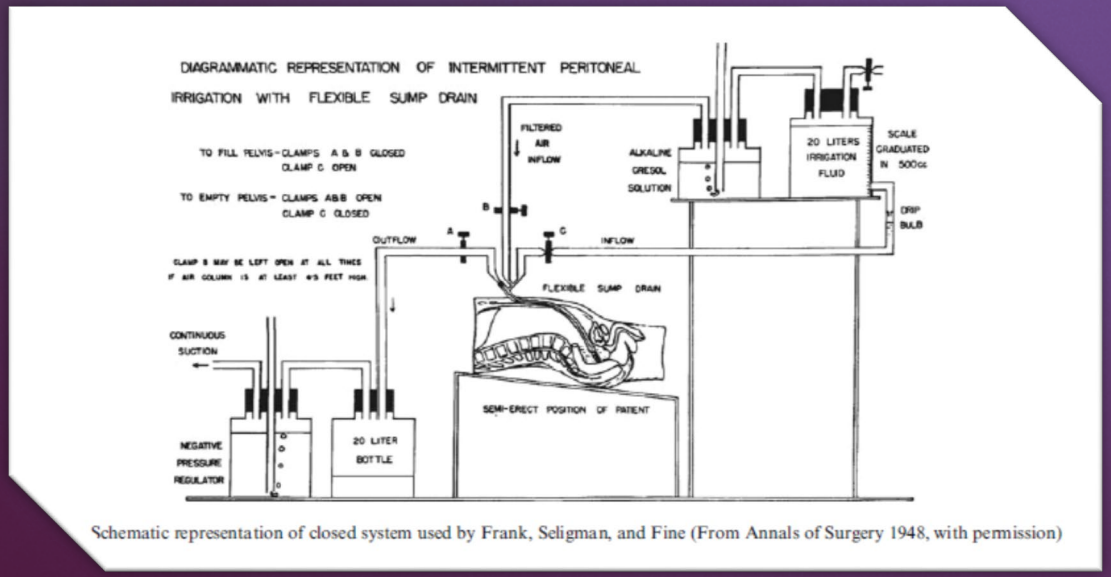
Between 1923 and 1948: 14 different types reported: different concentrations of
sodium chloride and dextrose solutions, Ringer's, Rhoads', Hartmann's two modified Tyrode's, "A," "P," modified "P" solutions, Kolff's and two unknown.

Of the papers published after World War II, the most important are considered to be those of doctors Howard Frank, a surgical intern, Arnold Seligman, trained in chemistry, and Jacob Fine.
The irrigation fluid used was Ringer's solution
containing glucose, which was later changed to a Tyrode's solution, in their search for the right solution.

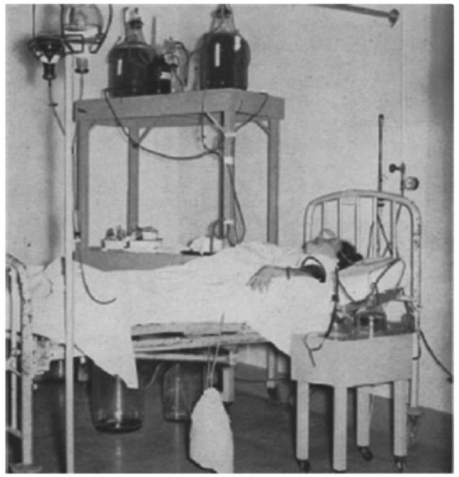
They improved the irrigation fluid by **decreasing the sodium chloride concentration to 0.74% to reduce the risk of hyperchloremia**, added gelatin, and **increased the glucose concentration to increase the fluid tonicity** so they were able to control edema.

Bicarbonate was used in the irrigation fluid to combat acidosis. The bicarbonate solution was sterilized separately and **added to the solution before irrigation was initiated**.

The dialysis **solution was sterilized and administrated from special 20-L Pyrex bottles**, which required a large autoclave and were difficult to manipulate.



Schematic representation of closed system used by Frank, Seligman, and Fine (From Annals of Surgery 1948, with permission)


Closed system used by Frank, Seligman, and Fine (From Annals of Surgery, 1948 with permission)

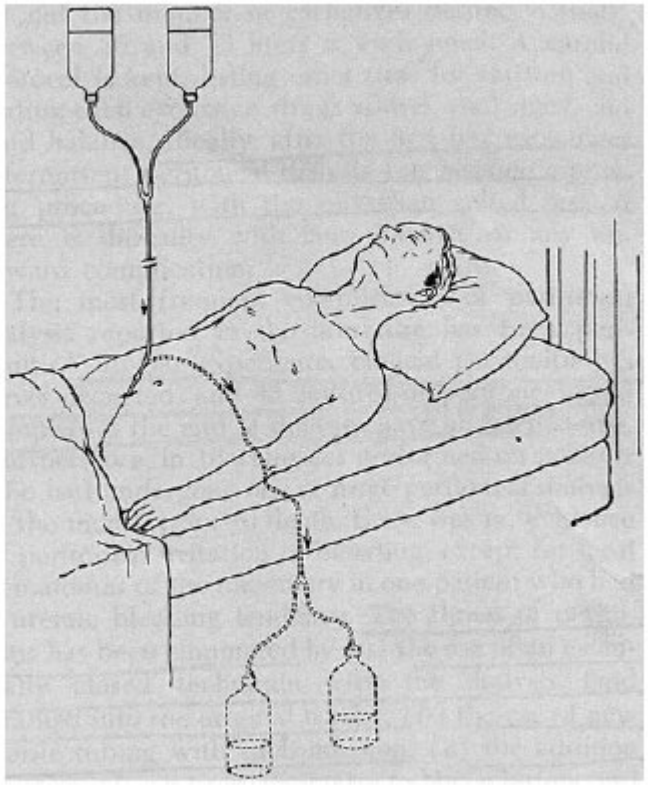


Fig. 1.3 Maxwell's paired bottle technique (From JAMA 1959, with permissio

1959, Toronto, Canada
The new dialysis solution contained

- Na 140 mEq/L
- Cl 101 mEq/L
- Ca 4mEq/L
- Mg 1.5 mEq/L
- Dextrose 15 g/L
- **Lactate 45mEq/L**

The lactate was replacing bicarbonate in the dialysis solution, eliminating the problem of precipitation of calcium salts. Potassium was excluded from the commercial dialysis solution because most of the patients with acute renal failure had hyperkalemia, but, if needed in patients with low serum potassium levels, it could be added to one of the **1 L bottles** using a hypodermic syringe.

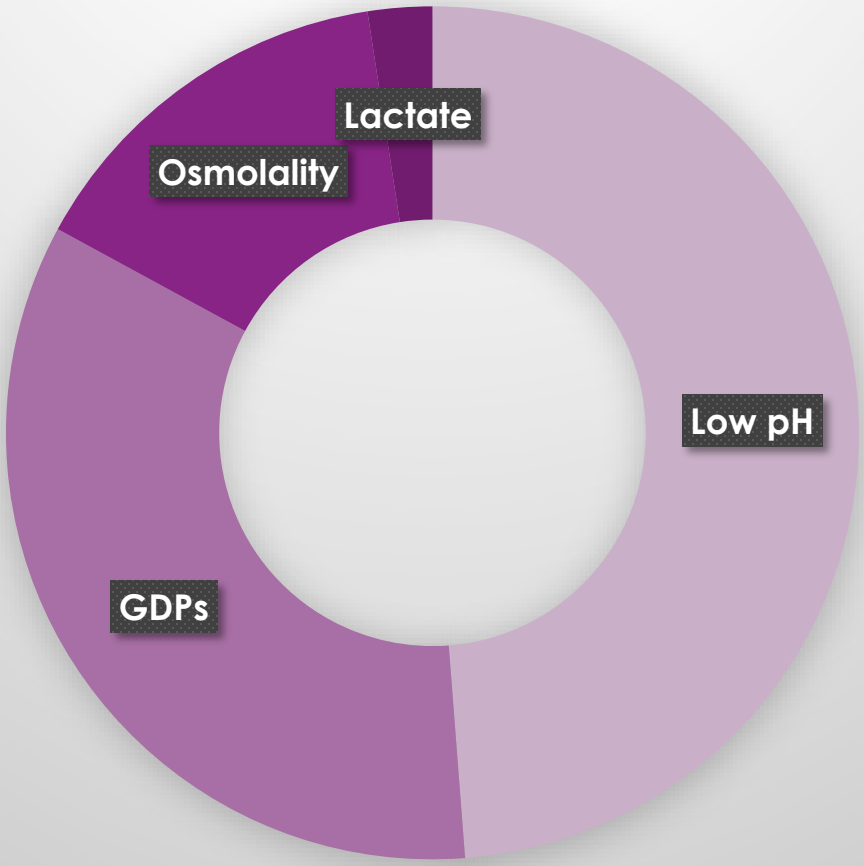
Standard peritoneal dialysis solution

Osmotic agent
- ✓ Cheap
- ✓ Safe
- ✓ Effective

Na	132-134 mmol/l
K	0-2-4 mmol/l
Ca	1,25-1,75 mmol/l
Mg	0,25-0,75 mmol/l
Cl	95-106 mmol/l
Lactate	35-40 mmol/l
Glucose	1,36/1,5-3,86/4,25 g/dl
Osmolality	347-486
pH	5,2-5,5

Cytotoxicity

Cytotoxicity



Mariano Feriani JNEPHROL 2013; 26(Suppl 21): S76-S82

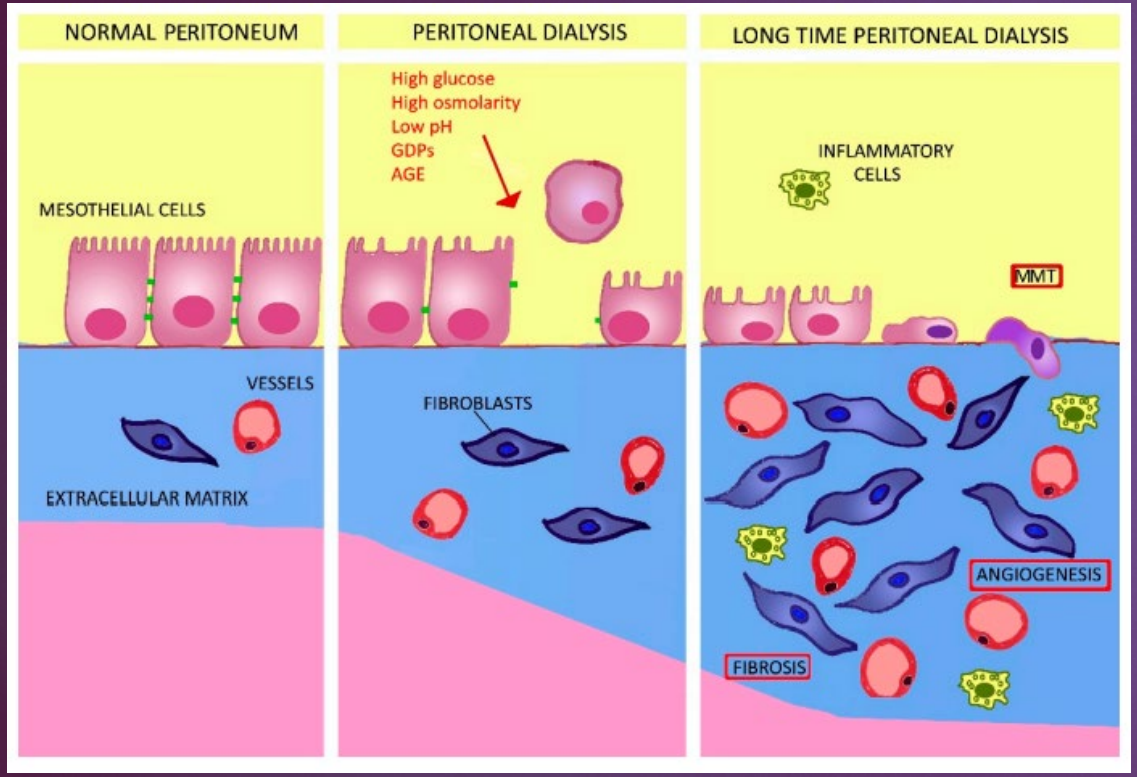
Wieslander A, et al. PDI 2001;21(suppl. 3):119-124

Proinflammatory cytokines

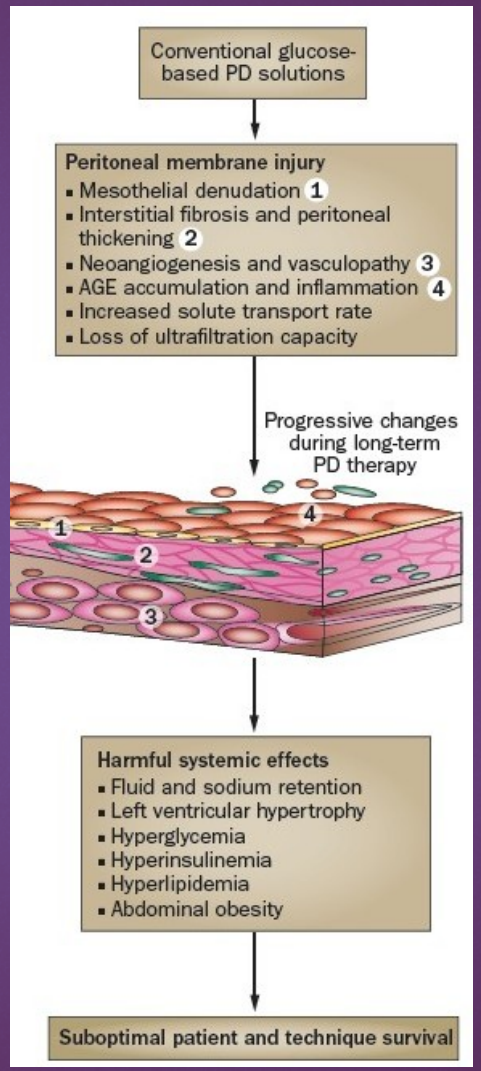
HIF-1a

TGF-beta

VEGF



Metabolic mechanisms (glycolytic, fatty acid and pyruvate metabolism),



impairment of mesothelial cell viability adverse effects on leukocyte recruitment accelerated angiogenesis and vascular proliferation low-grade inflammation epithelial-to-mesenchymal transition fibrosis and thickening of the peritoneal membrane formation of advanced glycation end products (AGEs)

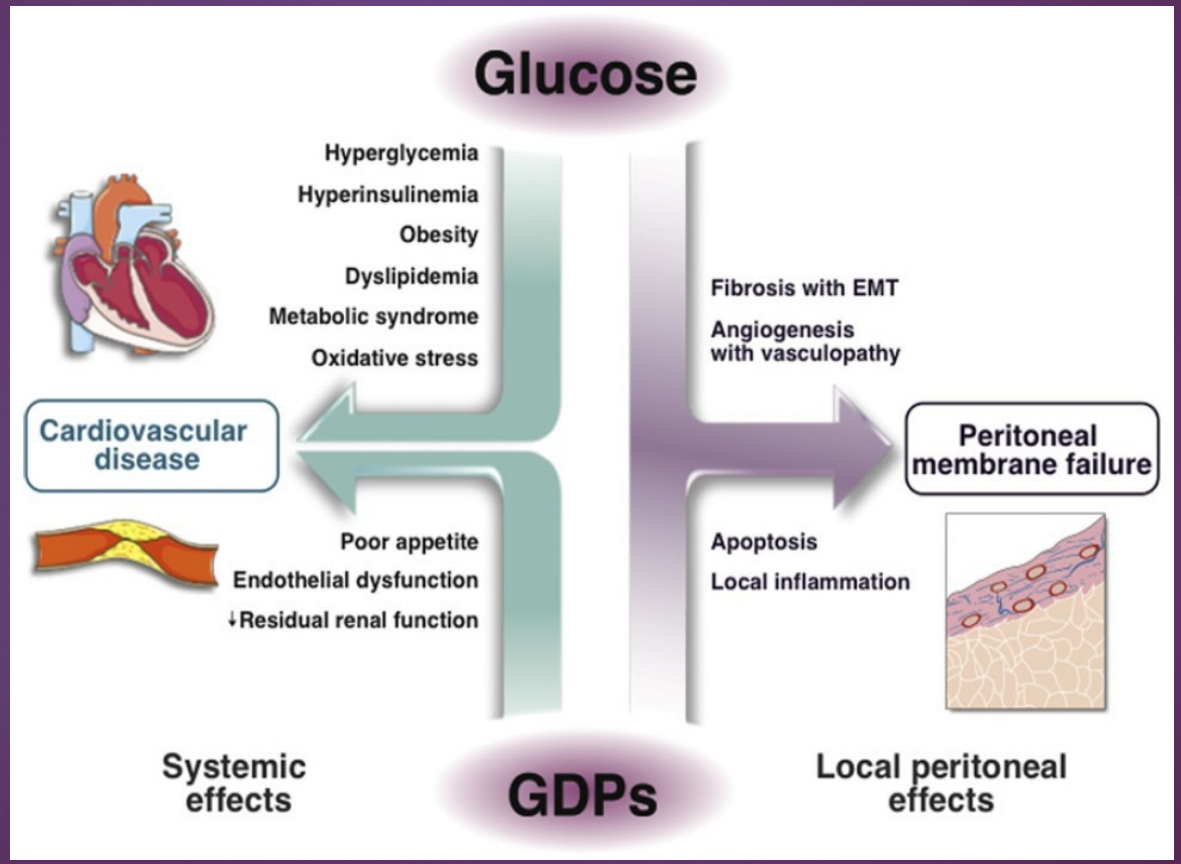
partial loss of peritoneal ultrafiltration capacity fluid retention left ventricular hypertrophy, heart failure increased risk of cardiovascular morbidity

worsening of metabolic and nutritional problems impaired glucose tolerance, insulin resistance hyperlipidemia (atherogenic lipid profile) abdominal obesity

Bonomini et al. Int. J. Mol. Sci. 2021, *22*(15), 7955
García-López, E. *et al. Nat. Rev. Nephrol. 2012;8:224-233*

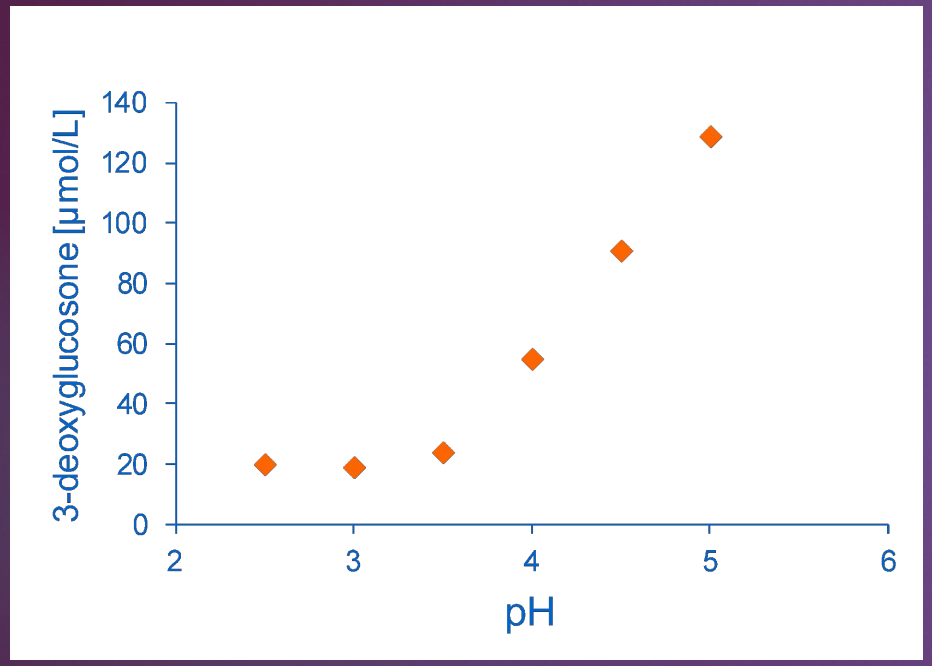
Systemic and Local Impact of Glucose and Glucose Degradation Products in Peritoneal Dialysis Solution

Yong-Lim Kim, MD, Jang-Hee Cho, MD, Ji-Young Choi, MD, Chan-Duck Kim, MD, and Sun-Hee Park, MD



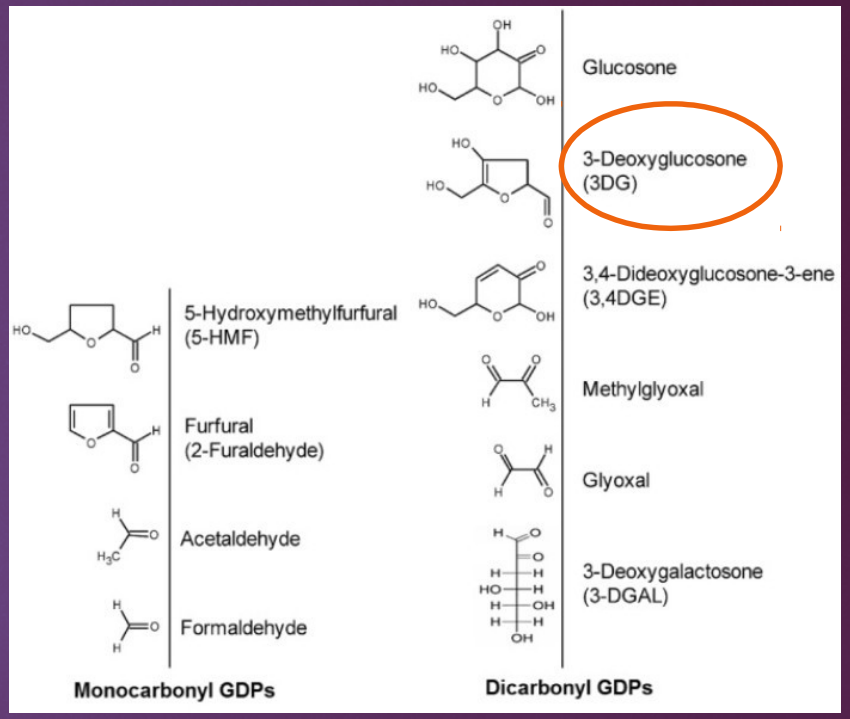
Journal of Renal Nutrition, Vol 23, No 3 (May), 2013: pp 218-222

pH dependent formation of 3-DG (3-deoxyglucosone)



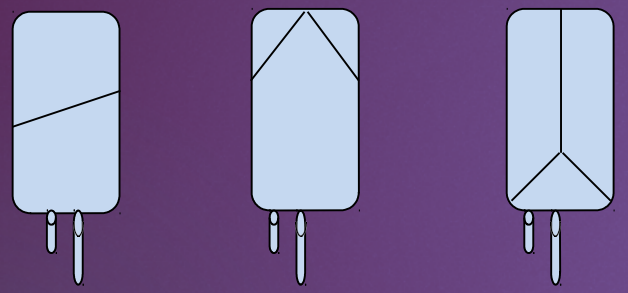
GDPs

AGEs



A "New" Generation of PD Solutions

Glucose based solutions

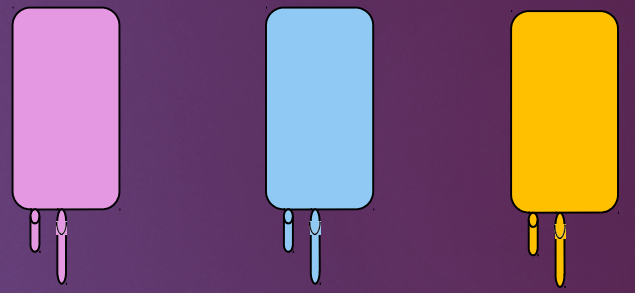


pH 7.0-7.4
Low GDPs
HCO3/Lactate

pH 6.3
Low GDPs
Lactate

pH 7.0-7.4
Low GDPs
HCO3

Alternative osmotic agents



Icodextrin

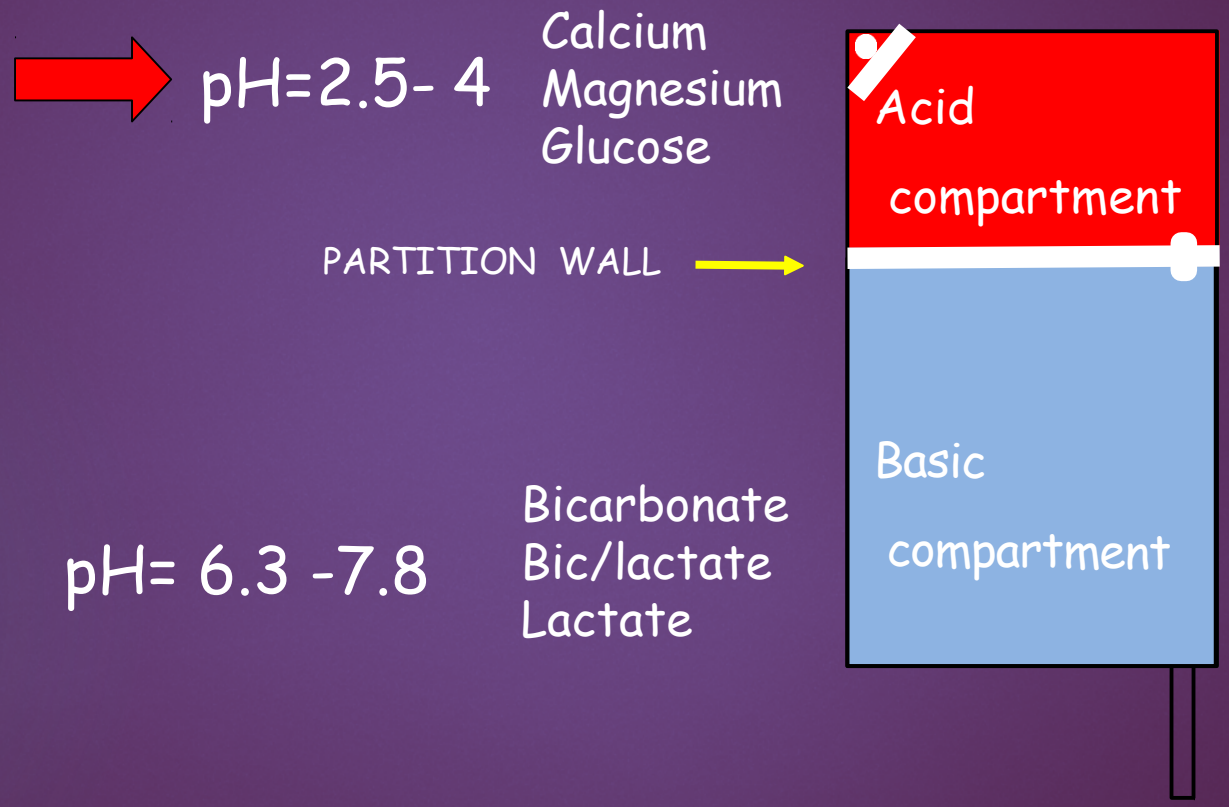
pH 5.6
Low GDPs
Iso-osmolar

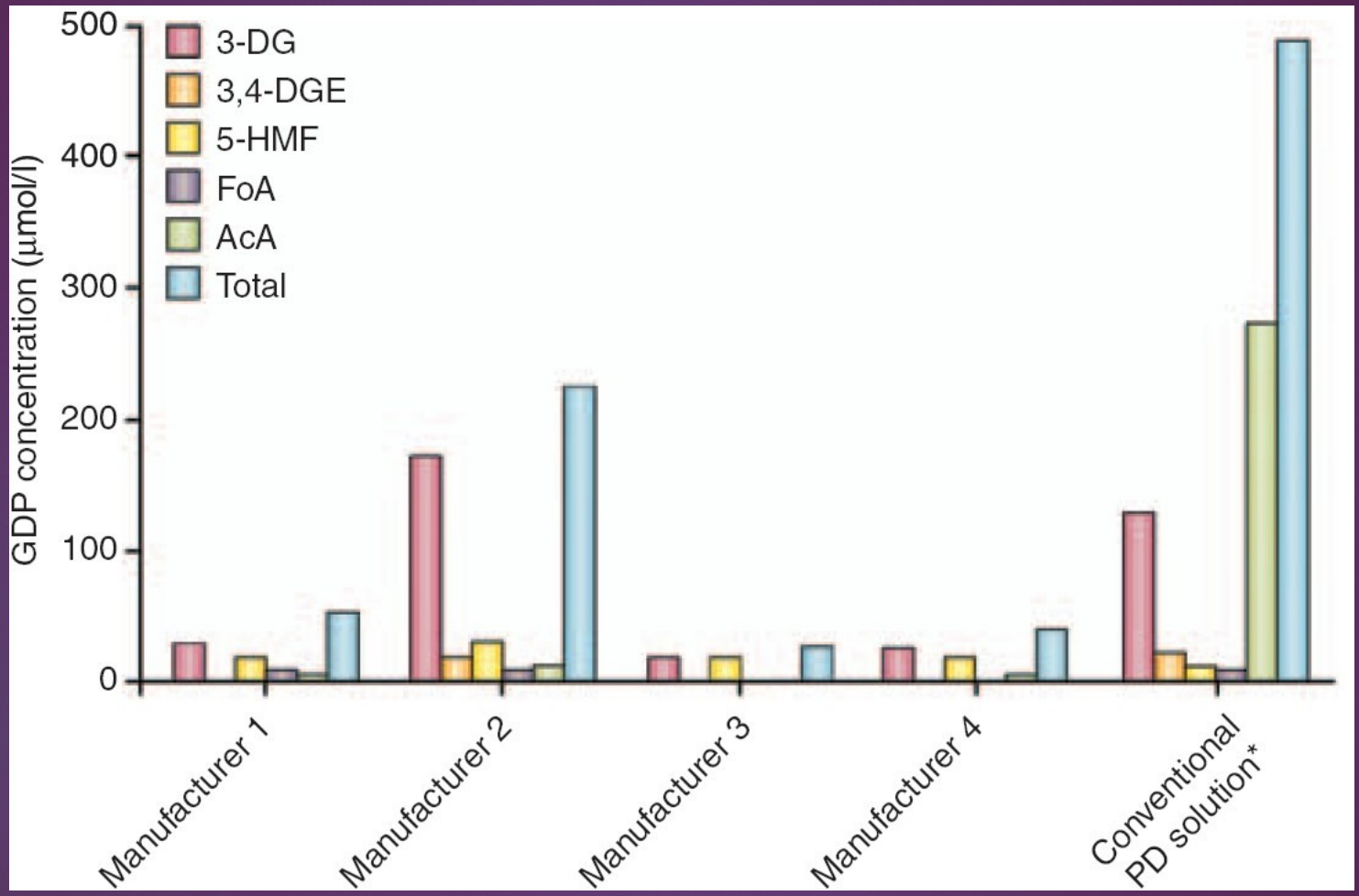
Amino Acids

pH 6.6
No GDPs
Glucose free

Others

Multicompartment bag system





J Perl et al Kidney Int 2011;79:814–824

An update on peritoneal dialysis solutions

Table 1 | Selected peritoneal dialysis solutions currently available in Europe

Solution (manufacturer)	pH	Chambers	Buffer	Osmotic agent	GDPs	Advantages	Disadvantages
Dianeal® (Baxter*)	5.2	Single	Lactate	Glucose	High	Easy to manufacture; low cost	Low pH; poor peritoneal membrane biocompatibility; infusion pain; contains lactate
Extraneal® (Baxter*)	5.6	Single	Lactate	Icodextrin	Low	Sustained ultrafiltration; reduced hyperglycemia; improved metabolic profile and body composition	Contains lactate; low pH; single daily use only; hypersensitivity
Nutrineal® (Baxter*)	5.5	Single	Lactate	Amino acids	No	Avoids glucose exposure; peritoneal membrane protection; enhanced nutrition	Contains lactate; low pH; single daily use only
Physioneal® (Baxter*)	7.4	Double	Lactate/ bicarbonate	Glucose	Low	Improved biocompatibility; preserved membrane defense; reduced infusion pain	Local and systemic glucose exposure; reduced peritoneal lactate exposure
Stay-safe® (Fresenius‡)	5.5	Single	Lactate	Glucose	High	Ease of manufacture; low cost	Low pH; poor peritoneal membrane biocompatibility; infusion pain; contains lactate
Balance® (Fresenius‡)	7.0	Double	Lactate	Glucose	Low	Improved biocompatibility; preserved membrane defense; reduced risk of peritonitis?	Higher but not neutral pH; local and systemic glucose exposure; contains lactate
BicaVera® (Fresenius‡)	7.4	Double	Bicarbonate	Glucose	Low	Improved biocompatibility; preserved membrane defense; improved correction of acidosis	Local and systemic glucose exposure
Gambrosol® Trio (Fresenius‡)	6.5	Triple	Lactate	Glucose	Low	Improved biocompatibility; preserved membrane defense	Higher but not neutral pH; local and systemic glucose exposure; contains lactate

*Deerfield, IL, USA. ‡Bad Homburg, Germany. Abbreviation: GDPs, glucose degradation products.

	Glucose based
Glucosio anidro - monoidrato	1,36 – 1,5 2,27 – 2,3 3,86 – 4,25
Sodio (mEq/L)	**132**
Potassio (mEq/L)	**0**
Cloruro (mEq/L)	96
Calcio (mmol/L)	**1,25** – 1,75
Magnesio (mEq/L)	0.5
Lattato (mEq/L)	35/0/15
Bicarbonato (mEq/L)	0/34/25
Osmolalità (mOsm/kg)	346-485
pH	**7,4**

García-López, E. *et al. Nat. Rev. Nephrol. 8, 224–233 (2012)*

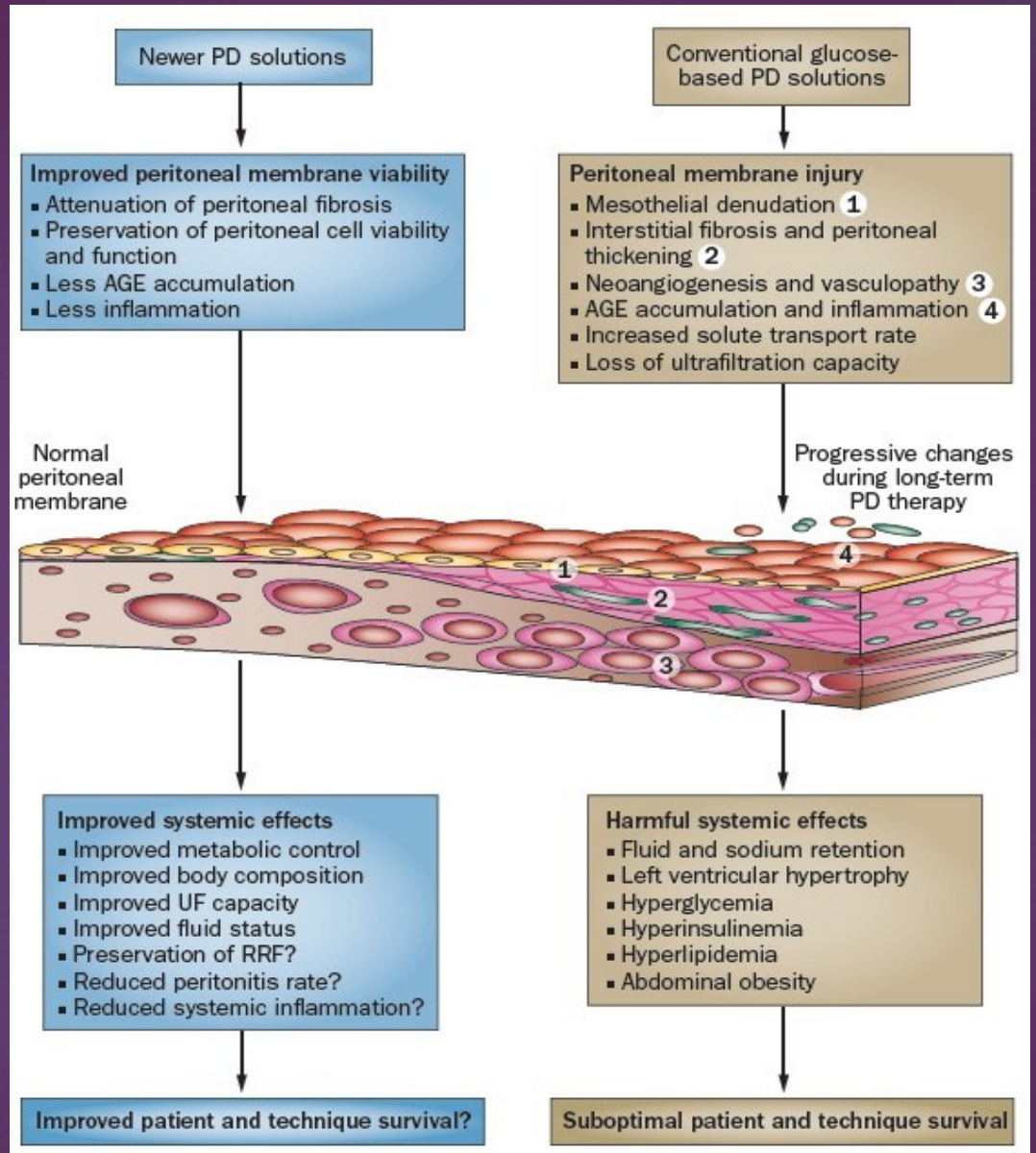


Figure 1 | A schematic presentation of the potential beneficial effects of newer peritoneal dialysis solutions. Abbreviations: AGE, advanced glycation end product; PD, peritoneal dialysis; RRF, residual renal function; UF, ultrafiltration.

García-López, E. *et al. Nat. Rev. Nephrol. 2012;8:224-233*

Cochrane Library

Cochrane Database of Systematic Reviews

Biocompatible dialysis fluids for peritoneal dialysis (Review)

Htay H, Johnson DW, Wiggins KJ, Badve SV, Craig JC, Strippoli GFM, Cho Y 2018

42 eligible studies (3262 participants

29 studies (1971 participants) compared neutral pH, low GDP PD solution with conventional PD solution

13 studies (1291 participants) compared icodextrin with conventional PD solution

Studies of amino acid-based dialysis fluids were excluded

11 studies (1034 participants)

Peritoneal Dialysis International, Vol. 34, pp. 724–731
doi: 10.3747/pdi.2012.00331

0896-8608/14 $3.00 + .00

EFFECT OF BIOCOMPATIBLE PERITONEAL DIALYSIS SOLUTION ON RESIDUAL RENAL FUNCTION: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

Eun-Young Seo,[1] Sook Hee An,[2] Jang-Hee Cho,[3] Hae Sun Suh,[4] Sun-Hee Park,[3] Hyesun Gwak,[1] Yong-Lim Kim,[3] and Hunjoo Ha[1]

Graduate School of Pharmaceutical Sciences,[1] College of Pharmacy, Ewha Global Top5 Program, Ewha Womans University, Seoul, Korea; Department of Pharmacy,[2] Wonkwang University, Iksan City, Jeonbuk, Korea; Division of Nephrology and Department of Internal Medicine,[3] Kyungpook National University Hospital, Daegu, Korea; and College of Pharmacy,[4] Pusan National University, Korea 2012

RRF

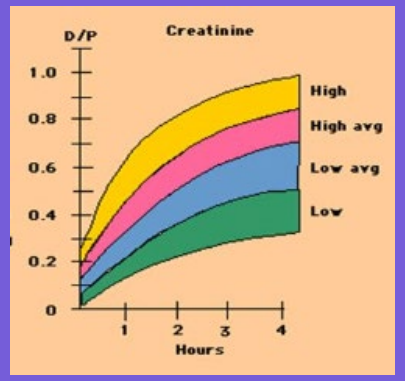
once follow-up reached 12 to 24 months

Urine Volume

Once the study duration exceeded 12 months

ClCr

wKt/V



Peritoneal ultrafiltration

D/P creatinine ratio

Hospitalisation

Peritonitis

Technique survival

Death

There is controversy in the literature regarding the mechanism by which biocompatible solutions preserves the RRF.

One is a direct beneficial effect of biocompatible solutions with lower level of GDP inducing apoptosis of renal tubular cell.

The other is an indirect effect which comes from less effective ultrafiltration and consequent hypervolemia.

Editorial › Nephrol Dial Transplant. 2009 Sep;24(9):2620-2. doi: 10.1093/ndt/
Epub 2009 Jun 23.

Preserving residual renal function in peritoneal dialysis: volume or biocompatibility?

Simon J Davies

Comment › Kidney Int. 2013 Nov;84(5):864-6. doi: 10.1038/ki.2013.303.

Biocompatible peritoneal dialysis solutions: many questions but few answers

Peter G Blake [1], Arsh K Jain, Sechelle Yohanna

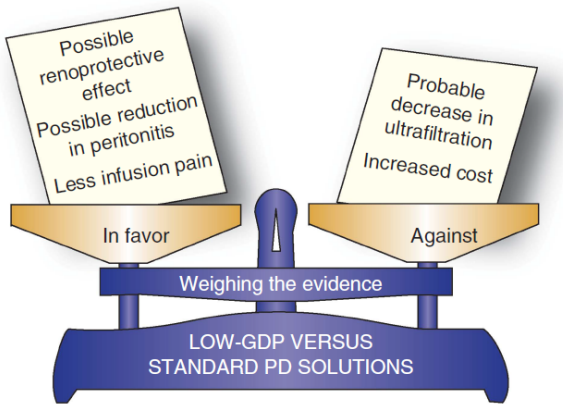


Figure 1 | Weighing the evidence on biocompatible peritoneal dialysis solutions.
GDP, glucose degradation product; PD, peritoneal dialysis.

Guidelines

PERITONEAL DIALYSIS INTERNATIONAL

Peritoneal Dialysis International
2020, Vol. 40(3) 310–319

DOI: 10.1177/0896860819895356
journals.sagepub.com/home/ptd
SAGE

International comparison of peritoneal dialysis prescriptions from the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS)

Angela Yee-Moon Wang[1], Junhui Zhao[2], Brian Bieber[2], Talerngsak Kanjanabuch[3], Martin Wilkie[4], Mark R Marshall[5], Hideki Kawanishi[6], Jeffrey Perl[7], Simon Davies[8]; and PDOPPS Dialysis Prescription and Fluid Management Working Group

Table 4. Urea clearance (dialysis and residual kidney) and PD solution type by country and PD modality.

	A/NZ		Canada		Japan		Thailand		UK		US	
	APD	CAPD	APD	CAPD	APD	CAPD	APD	CAPD	APD	CAPD	APD	CAPD
Number of patients	213	111	269	107	195	337	26	521	149	72	2199	458
Total *Kt/V* urea	2.17 (0.76)	2.08 (0.91)	1.94 (0.94)	1.72 (0.89)	1.84 (0.57)	1.91 (0.78)	2.39 (0.67)	2.26 (0.93)	2.26 (0.70)	2.27 (0.61)	2.29 (0.62)	2.37 (0.72)
Residual *Kt/V* urea	0.88 (0.74)	0.85 (0.86)	0.71 (0.73)	0.54 (0.55)	0.75 (0.52)	0.79 (0.86)	0.59 (0.59)	0.53 (0.81)	0.89 (0.73)	1.23 (0.68)	0.74 (0.77)	0.90 (0.94)
Peritoneal *Kt/V* urea	1.29 (0.46)	1.19 (0.60)	1.23 (0.57)	1.18 (0.64)	1.09 (0.51)	1.16 (0.44)	1.75 (0.86)	1.73 (0.59)	1.35 (0.57)	1.04 (0.44)	1.55 (0.50)	1.47 (0.55)
24-h urine volume per BSA (L/1.73 m^2)	0.83 (0.64)	0.72 (0.65)	0.76 (0.61)	0.82 (0.60)	0.90 (0.73)	0.84 (0.61)	0.67 (0.65)	0.58 (0.69)	0.74 (0.54)	1.41 (0.70)	0.65 (0.63)	0.77 (0.79)
Anuric[a] (%)	7%/18%	13%/21%	16%/25%	11%/22%	8%/40%	6%/36%	33%/54%	28%/76%	8%/34%	3%/21%	23%/24%	20%/23%
PD solution type[b]												
Icodextrin	44%	53%	55%	65%	40%	46%	17%	0%	47%	78%	25%	16%
Nutrineal	1%	0%	1%	7%	0%	0%	0%	0%	0%	6%	0%	0%
Calcium > 3.5 mEq/L	7%	11%	20%	20%	40%	39%	13%	19%	14%	15%	42%	51%
Neutral pH low GDP	21%	44%	8%	15%	99%	98%	0%	0%	29%	24%	0%	0%
PD solution glucose concentration[b]												
Without any 2.27% or 3.86% use	15%	22%	21%	26%	75%	65%	88%	72%	50%	57%	4%	6%
Use of 2.27% but not 3.86%	77%	76%	70%	55%	25%	35%	8%	19%	48%	44%	51%	50%
Use of any 3.86%	8%	3%	9%	19%	0%	0%	4%	9%	2%	0%	45%	44%

www.kidney-international.org clinical trial

Neutral pH and low–glucose degradation product dialysis fluids induce major early alterations of the peritoneal membrane in children on peritoneal dialysis

see commentary on page 246

Betti Schaefer[1,28], Maria Bartosova[1,28], Stephan Macher-Goeppinger[2], Peter Sallay[3], Peter Vörös[3],

106 peritoneal biopsy samples from 82 children on PD, all treated with low-GDP fluids

lacking is a control group of children treated with conventional solutions

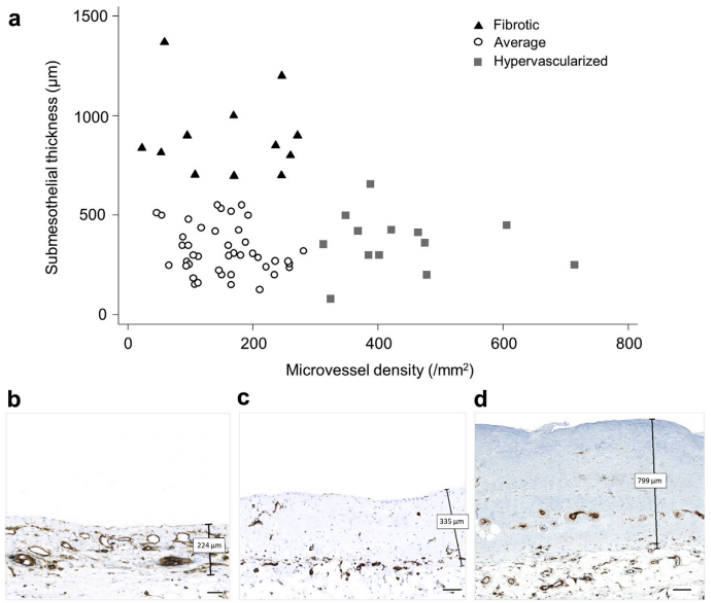


Figure 2 | Cluster analysis of patients treated with low–glucose degradation product peritoneal dialysis (PD) based on submesothelial thickness and microvessel density. Fibrotic type had increased submesothelial thickness with average microvessel density. (**a**) Hypervascularized peritoneum had increased microvessel density with average submesothelial thickness. For details on the 3 different clusters, please see Supplementary Table S2. Representative CD31 stainings of patients with (**b**) predominant hypervascularization, (**c**) average findings, and (**d**) predominant fibrotic changes after 8, 72, and 109 months of PD, respectively. Bar = 100 µm. To optimize viewing of this image, please see the online version of this article at www.kidney-international.org.

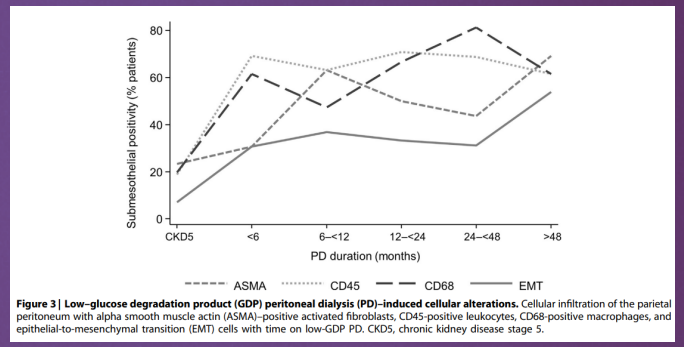


Figure 3 | Low–glucose degradation product (GDP) peritoneal dialysis (PD)–induced cellular alterations. Cellular infiltration of the parietal peritoneum with alpha smooth muscle actin (ASMA)–positive activated fibroblasts, CD45-positive leukocytes, CD68-positive macrophages, and epithelial-to-mesenchymal transition (EMT) cells with time on low-GDP PD. CKD5, chronic kidney disease stage 5.

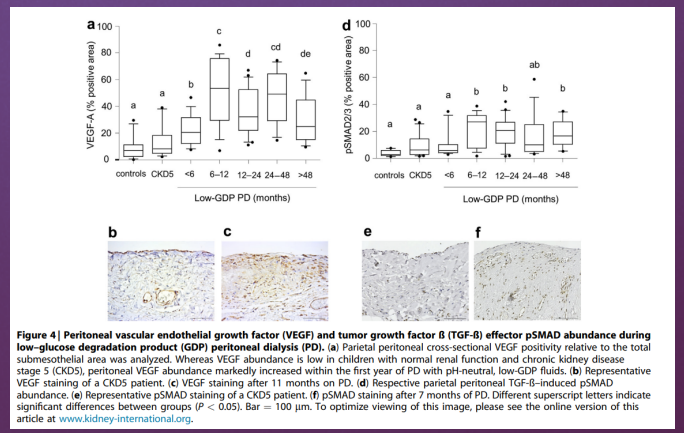


Figure 4 | Peritoneal vascular endothelial growth factor (VEGF) and tumor growth factor ß (TGF-ß) effector pSMAD abundance during low–glucose degradation product (GDP) peritoneal dialysis (PD). (**a**) Parietal peritoneal cross-sectional VEGF positivity relative to the total submesothelial area was analyzed. Whereas VEGF abundance is low in children with normal renal function and chronic kidney disease stage 5 (CKD5), peritoneal VEGF abundance markedly increased within the first year of PD with pH-neutral, low-GDP fluids. (**b**) Representative VEGF staining of a CKD5 patient. (**c**) VEGF staining after 11 months on PD. (**d**) Respective parietal peritoneal TGF-ß–induced pSMAD abundance. (**e**) Representative pSMAD staining of a CKD5 patient. (**f**) pSMAD staining after 7 months of PD. Different superscript letters indicate significant differences between groups ($P < 0.05$). Bar = 100 µm. To optimize viewing of this image, please see the online version of this article at www.kidney-international.org.

Early peritoneal angiogenesis : increase of blood microvessel density and endothelial surface exchange

Submesothelial inflammation leukocytes, macrophages

EMT cells

Kidney International (2018) 94, 419–429

Comment > Kidney Int. 2018 Aug;94(2):246-248. doi: 10.1016/j.kint.2018.04.014.

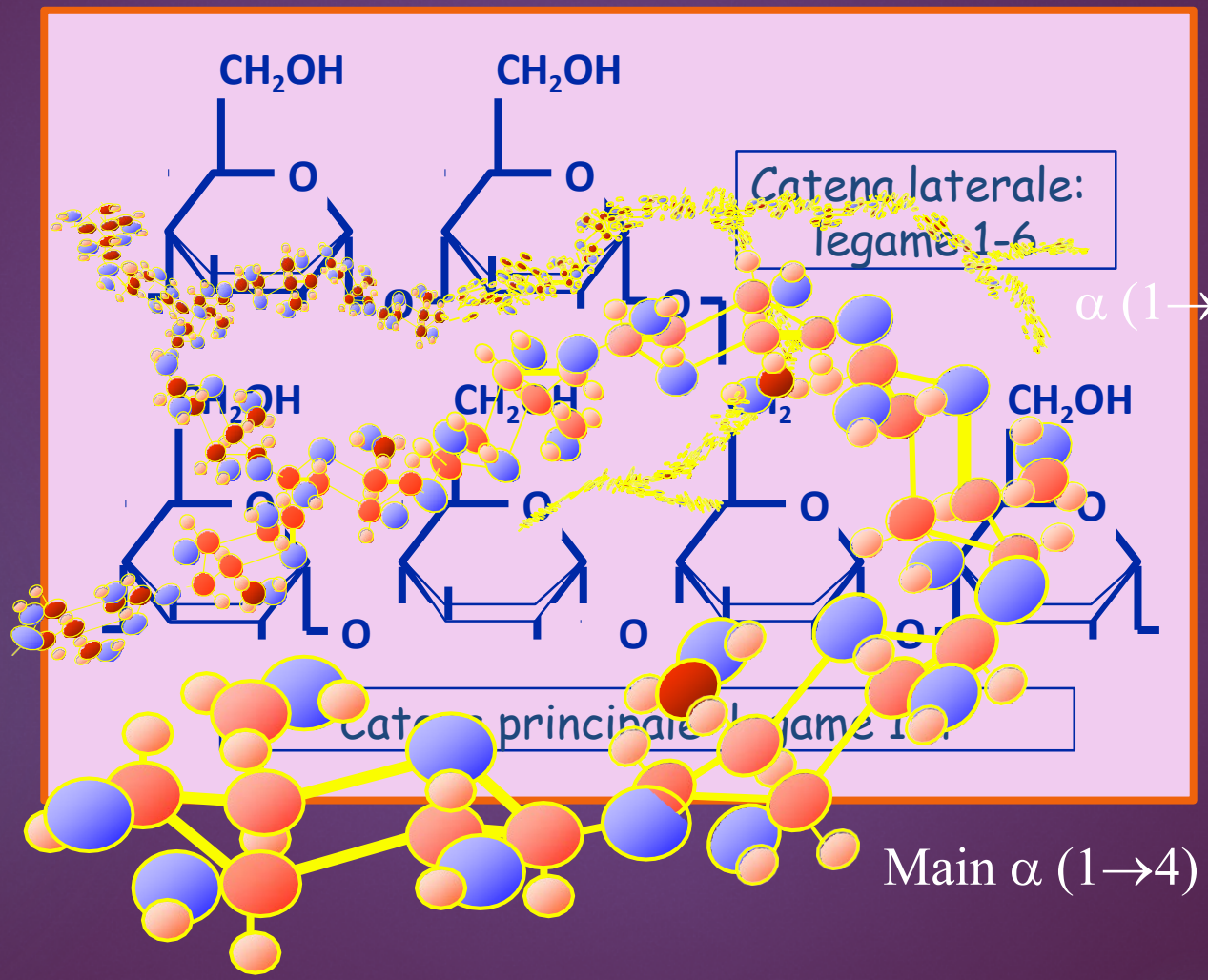
Is the peritoneal dialysis biocompatibility hypothesis dead?

Peter G Blake [1]

*"Where does this leave clinical practitioners of PD? If they have not been persuaded to use biocompatible fluids by now, the evidence from the Schaefer study will strengthen this view. If they have already been using the solutions, it has been a **leap of faith**, unsupported by high-level clinical evidence, and this will continue to be the case."*

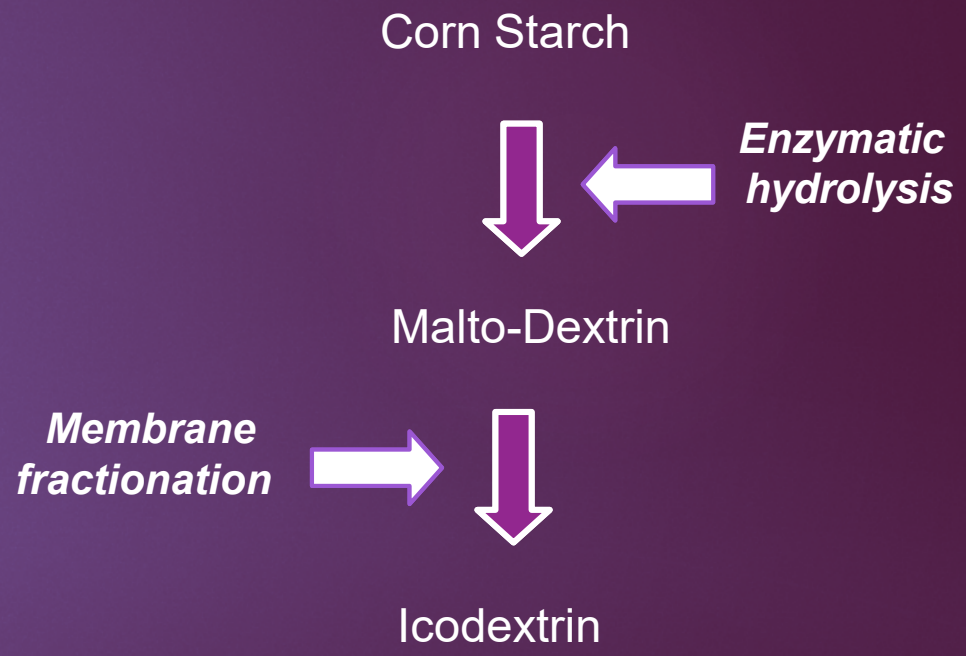
"It does suggest that the **glucose** that is present in both low-GDP as well as standard fluids is now the **best candidate to be the cause of the morphological changes** that occur with both types of solution. The replacement of glucose by **an alternative osmotic agent** may be more likely to attenuate these changes and their functional consequences."

ICODEXTRIN

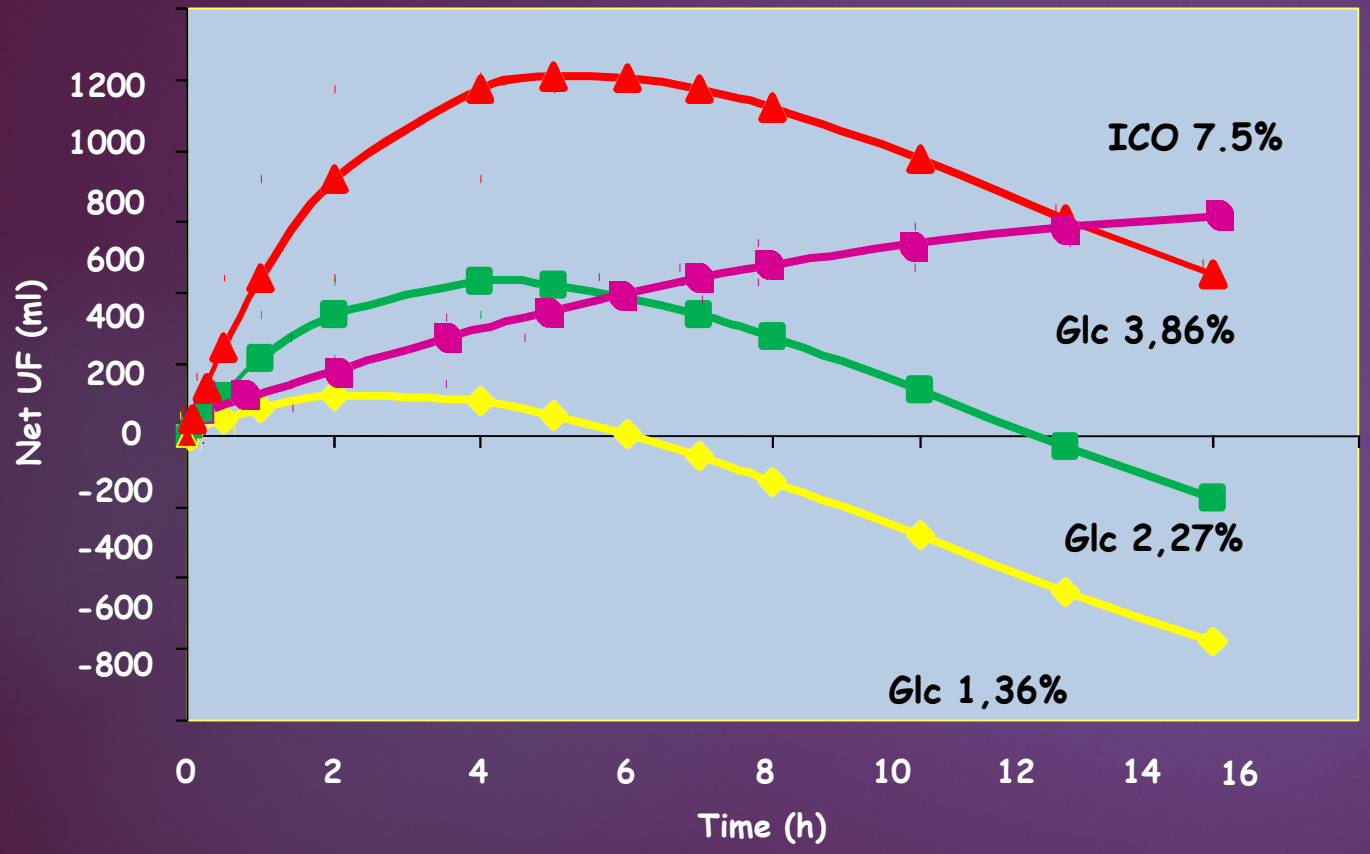

CH2OH
CH2OH
O
Catena laterale:
legame 1-6
α (1→6) branch
Main α (1→4) chain

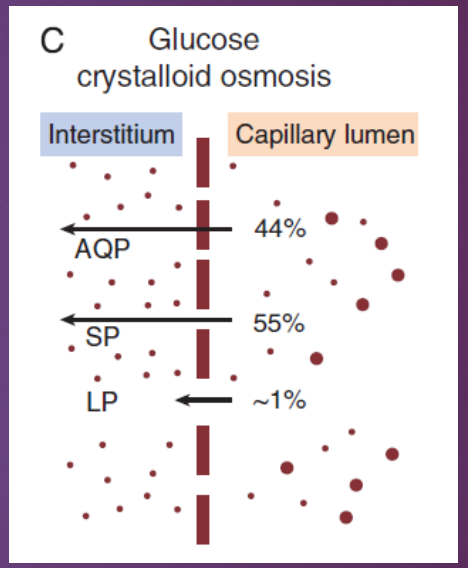
FEATURES OF ICODEXTRIN

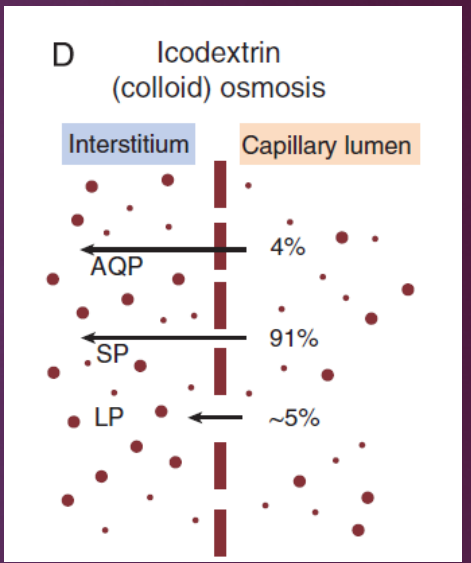
- Gluco-pyranose polymer (glucose chains)
- Produced by hydrolysis of starch and fractionation by membrane separation technique
- Distribution of oligopolysaccharides with chains of variable length
- Glucose polymer with average MW around 16,000 Da (MW = 12-20 kDa)
- Effects ultrafiltration through the numerous small intercellular pores (reflection coefficient = 1.0).



UF PROFILE: GLUCOSE vs ICODEXTRIN

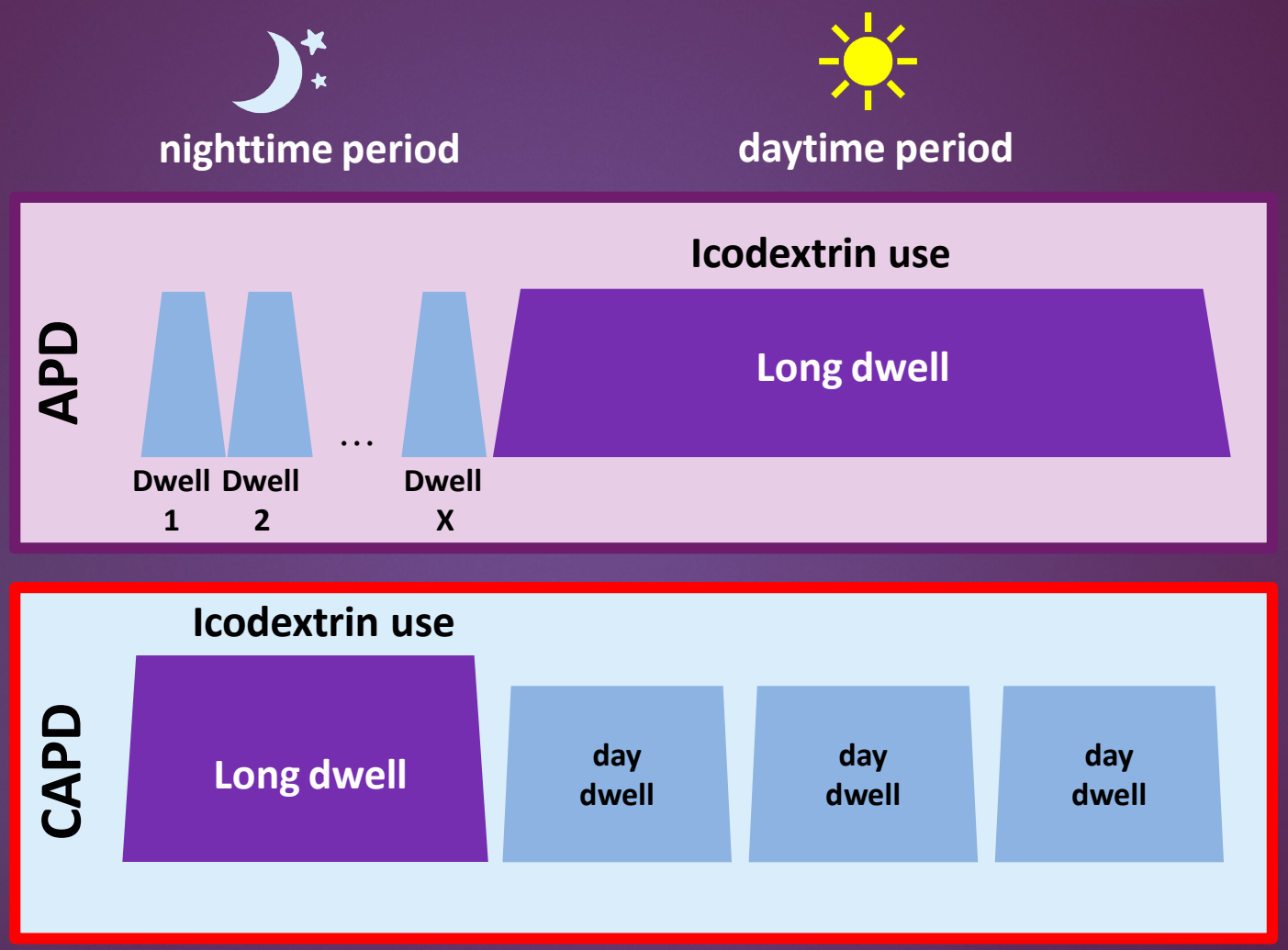






Ho-Dac-Pannekeet et al, Kidney Int 1996; 50:979-86
Douma et al, Kidney Int 1998; 53:1014-21

The long dwell



SOLUTION

	Glucose based	Icodestrina
Glucosio	1,36 2,27 3,86	**0**
Poliglucosio (g/dL)	---	7.5
Sodio (mEq/L)	132-134	132
Cloruro (mEq/L)	96	96
Calcio (mmol/L)	1,25	**1,75**
Magnesio (mEq/L)	0.5	0.5
Lattato (mEq/L)	15	**40**
Bicarbonato (mEq/L)	25	0
Osmolalità (mOsm/kg)	346-485	**284**
pH	7,4	**5.2**

Yamaguchi N, Miyamoto K, Murata T, Ishikawa E, Horiuchi T. Newly developed neutralized pH icodextrin dialysis fluid: nonclinical evaluation. Artif Organs 2016; 40:E158-E166.
Higuchi C, Kuriyma J, Sakura H. Effect of neutral pH icodextrin peritoneal dialysis fluid on mesothelial cells. Ther Apher Dial 2018; 22:656-661.

Original Article

ndt
Nephrology Dialysis Transplantation

Impact of icodextrin on clinical outcomes in peritoneal dialysis: a systematic review of randomized controlled trials

No significant differences in

- Peritonitis
- Hospitalization
- Technique survival
- Patient survival
- Adverse events (rash)

11 trials that enrolled 1222 participants

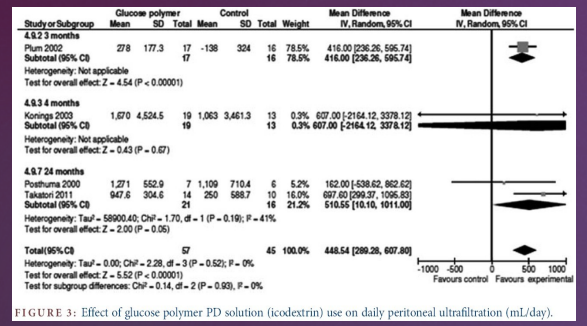


FIGURE 3: Effect of glucose polymer PD solution (icodextrin) use on daily peritoneal ultrafiltration (mL/day).

Peritoneal ultrafiltration
MD 448.54 mL/day,
95% CI 289.28–607.80, P < 0.01

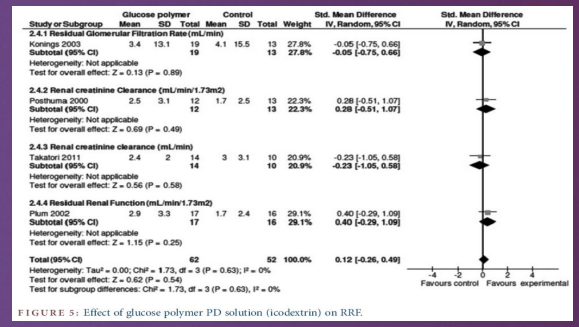


FIGURE 5: Effect of glucose polymer PD solution (icodextrin) on RRF.

Residual renal clearance
SMD 0.12, 95% CI −0.26 to 0.49,
P = 0.5

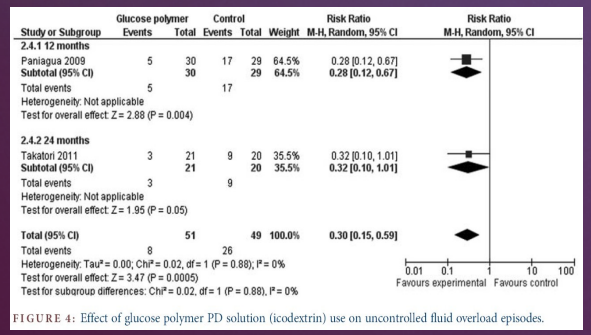


FIGURE 4: Effect of glucose polymer PD solution (icodextrin) use on uncontrolled fluid overload episodes.

Episodes of uncontrolled fluid overload
RR 0.30,95%
CI 0.15–0.59, P < 0.01

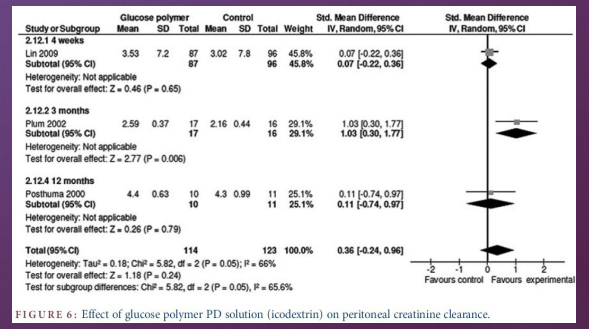


FIGURE 6: Effect of glucose polymer PD solution (icodextrin) on peritoneal creatinine clearance.

Peritoneal creatinine clearance
SMD 0.36, 95% CI −0.24 to 0.96
P = 0.2

Y. Cho et al. NDT, 2013

AJKD

Original Investigation

Icodextrin Versus Glucose Solutions for the Once-Daily Long Dwell in Peritoneal Dialysis: An Enriched Systematic Review and Meta-analysis of Randomized Controlled Trials

Käthe Goossen, Monika Becker, Mark R. Marshall, Stefanie Bühn, Jessica Breuing, Catherine A. Firanek, Simone Hess, Hisanori Nariai, James A. Sloand, Qiang Yao, Tae Ik Chang, JinBor Chen, Ramón Paniagua, Yuji Takatori, Jun Wada, and Dawid Pieper

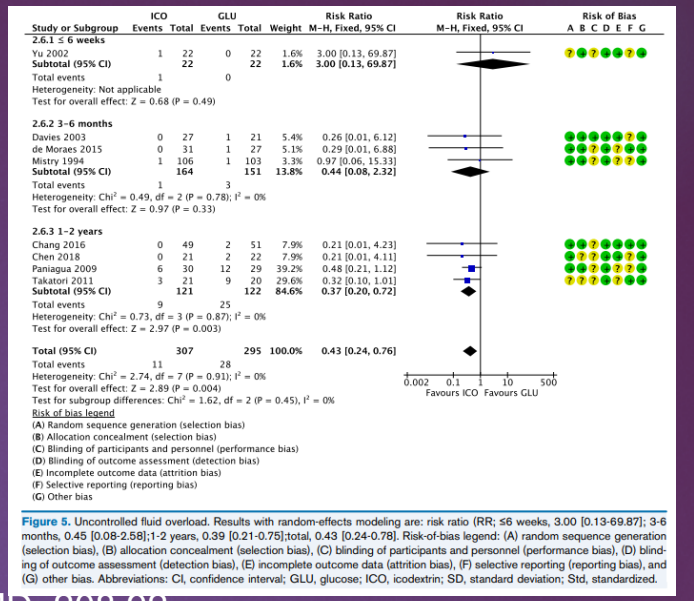


Figure 5. Uncontrolled fluid overload. Results with random-effects modeling are: risk ratio (RR; ≤6 weeks, 3.00 [0.13-69.87]; 3-6 months, 0.45 [0.08-2.58];1-2 years, 0.39 [0.21-0.75];total, 0.43 [0.24-0.78]. Risk-of-bias legend: (A) random sequence generation (selection bias), (B) allocation concealment (selection bias), (C) blinding of participants and personnel (performance bias), (D) blinding of outcome assessment (detection bias), (E) incomplete outcome data (attrition bias), (F) selective reporting (reporting bias), and (G) other bias. Abbreviations: CI, confidence interval; GLU, glucose; ICO, icodextrin; SD, standard deviation; Std, standardized.

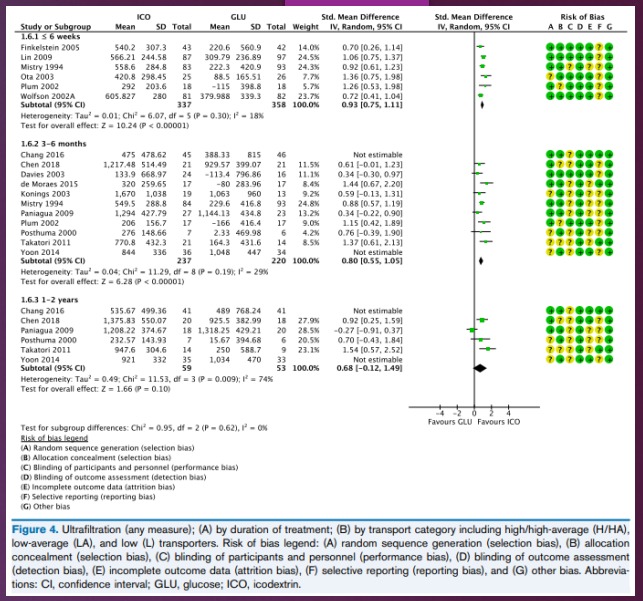


Figure 4. Ultrafiltration (any measure); (A) by duration of treatment; (B) by transport category including high/high-average (H/HA), low-average (LA), and low (L) transporters. Risk of bias legend: (A) random sequence generation (selection bias), (B) allocation concealment (selection bias), (C) blinding of participants and personnel (performance bias), (D) blinding of outcome assessment (detection bias), (E) incomplete outcome data (attrition bias), (F) selective reporting (reporting bias), and (G) other bias. Abbreviations: CI, confidence interval; GLU, glucose; ICO, icodextrin.

Ultrafiltration was improved with icodextrin (medium-term MD, 208.92 [95% CI, 99.69-318.14] mL/24 h; high certainty of evidence), reflected also by **fewer episodes of fluid overload** (RR, 0.43 [95% CI, 0.24-0.78]; high certainty).

Icodextrin-containing PD probably decreased mortality risk compared to glucose-only PD (Peto OR, 0.49 [95% CI, 0.24-1.00]; moderate certainty).

Despite evidence of lower peritoneal glucose absorption with icodextrin-containing PD (medium-term MD, −40.84 [95% CI, −48.09 to −33.59] g/ long dwell; high certainty), this **did not directly translate to changes in fasting plasma glucose** (−0.50 [95% CI, −1.19 to 0.18] mmol/L; low certainty) and **hemoglobin A1c levels** (−0.14% [95% CI, −0.34% to 0.05%]; high certainty).

Safety outcomes and residual kidney function were similar in both groups; health-related quality-of-life and pain scores were inconclusive.

19 RCTs that enrolled 1,693 participants

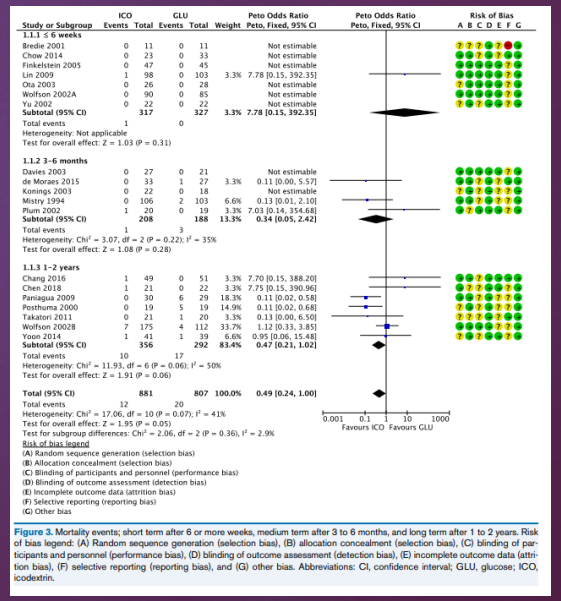
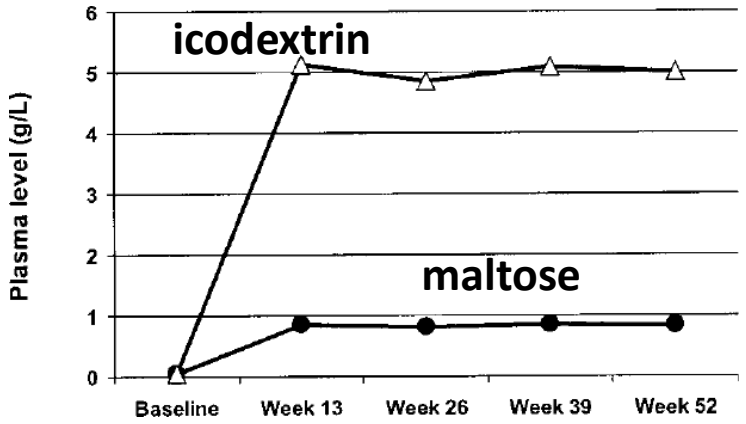
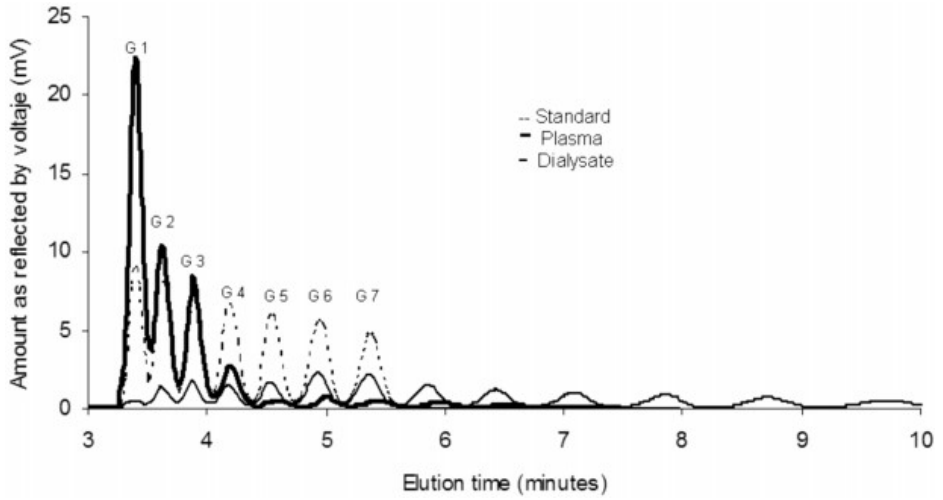


Figure 3. Mortality events; short term after 6 or more weeks, medium term after 3 to 6 months, and long term after 1 to 2 years. Risk of bias legend: (A) Random sequence generation (selection bias), (B) allocation concealment (selection bias), (C) blinding of participants and personnel (performance bias), (D) blinding of outcome assessment (detection bias), (E) incomplete outcome data (attrition bias), (F) selective reporting (reporting bias), and (G) other bias. Abbreviations: CI, confidence interval; GLU, glucose; ICO, icodextrin.

Am J Kidney Dis. 75(6):830-846; 2020





Wolfson M. Am J Kidney Dis. 2002;40:1055-1065

García-López E, Lindholm B. Perit Dial Int 2009; 29:370-376

ICODEXTRIN METABOLITES

Peritoneal Dialysis International, Vol.18, pp 603-609
Printed in Canada.

08968608/98 $300 + 00

…glucose dehydrogenase enzymatic reaction

A **PREVIOUSLY UNDESCRIBED SIDE EFFECT OF ICODEXTRIN:**

OVERESTIMATION OF GLYCEMI A BY GLUCOSE ANALYZER

www.glucosesafety.com

Robert Wens, 1 Michel Taminne,3 Jacques Devriendt,2 Frédéric Collart,1 Nilüfer Broeders,1 Fabienne Mestrez,1

Henri Germanos,1 Max Dratwa 1

Soluzioni Aminoacidi (1.1%)

Essential	Non essential
Histidine	Alanine
Isoleucine	Arginine
Leucine	Glycine
Lysine	Proline
Methionine	Serine
Phenylalanine	Tyrosine
Threonine	
Tryptophan	
Valine	
14.1g (64%)	7.9 g (36%)

glucose free

Osm. 365

pH 6.6

latt. 40

Nutrition in patients on peritoneal dialysis

Seung-Hyeok Han and Dae-Suk Han. Nat. Rev. Nephrol. 2012;8:163-175

Table 2 | Studies showing positive effects of 1.1% amino acid-based solution in patients on peritoneal dialysis

Study	Study type	Population	Interventions	Follow-up	Result
Bruno *et al.* (1989)[125]	Crossover	6	One exchange of a 1.1% amino acid-based solution	6 months	↑ nitrogen balance and MAMC; ↓ serum bicarbonate
Arfeen *et al.* (1990)[126]	Case series	7	Two exchanges of a 1.1% amino acid-based solution	2 months	↑ serum albumin; ↓ serum bicarbonate
Kopple *et al.* (1995)[127]	Case series	19	1–2 exchanges of a 1.1% amino acid-based solution	20 days	↑ nitrogen balance, BUN and transferrin; ↓ serum bicarbonate
Faller *et al.* (1995)[128]	Case series	15	One exchange of a 1.1% amino acid-based solution	3 months	↑ serum albumin, BUN and transferrin; no change in serum bicarbonate
Chertow *et al.* (1995)[129]	Observational	183	One exchange of a 1.1% amino acid-based solution	Mean 6.6 months	↑ serum albumin; no change in serum bicarbonate
Misra *et al.* (1996)[130]	Randomized crossover	18	One exchange of a 1.1% amino acid-based solution	6 months	Improved nutrition score; no change in serum albumin and transferrin; ↑ serum albumin in patients with baseline albumin <30.0g/l
Jones *et al.* (1998)[131]	Randomized controlled	134	One or two exchanges of a 1.1% amino acid-based solution ($n=71$); control ($n=63$)	3 months	↑ IGF-I, serum albumin, prealbumin, and transferrin; ↓ serum bicarbonate
Taylor *et al.* (2002)[132]	Observational	22	One exchange of a 1.1% amino acid-based solution	Mean 13.6 months	↑ serum albumin and nPCR; one episode of peritonitis per 23 treatment months; 4% annual mortality rate
Li *et al.* (2003)[133]	Randomized controlled	60	One exchange of a 1.1% amino acid-based solution ($n=30$); control ($n=30$)	36 months	↑ nPNA and DPI; no change in mortality rate and incidence of peritonitis
Park *et al.* (2006)[134]	Observational	43	One exchange of a 1.1% amino acid-based solution	12 months	↑ LBM, hand grip strength, nPNA and IGF-I; no change in serum albumin, prealbumin and DPI; ↓ serum bicarbonate

Abbreviations: BUN, blood urea nitrogen; DPI, dietary protein intake; IGF-I, insulin-like growth factor I; LBM, lean body mass; MAMC, mid-arm muscle circumference; nPNA, normalized protein nitrogen appearance; nPCR, normalized protein catabolic rate.

Randomized, Controlled Trial of Glucose-Sparing Peritoneal Dialysis in Diabetic Patients

Philip K.T. Li,* Bruce F. Culleton,† Amaury Ariza,‡ Jun-Young Do,§ David W. Johnson,‖ Mauricio Sanabria,† Ty R. Shockley,† Ken Story,† Andrey Vatazin,¶ Mauro Verrelli,** Alex W. Yu,†† and Joanne M. Bargman,‡‡ *on behalf of the IMPENDIA and EDEN Study Groups*

Primary outcome: change in HbA1c

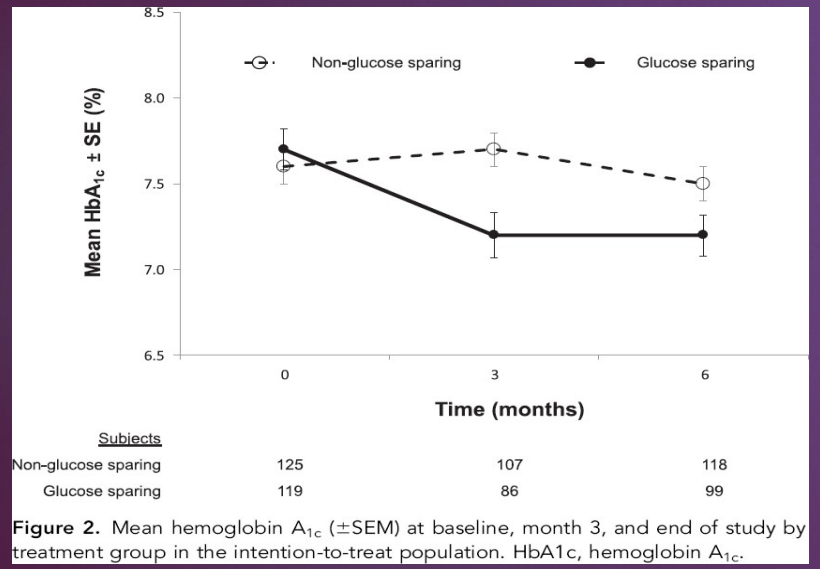


Figure 2. Mean hemoglobin A_{1c} (±SEM) at baseline, month 3, and end of study by treatment group in the intention-to-treat population. HbA1c, hemoglobin A_{1c}.

Secondary outcome

VLDL	↓
Apolipoprotein B	↓
Triglycerides	↓
Albumin	↓
Deaths (not solutions related)	↑
Serious adverse events (ECFV expansion)	↑

A low-glucose dialysis regimen improves metabolic indices in diabetic patients receiving peritoneal dialysis but may be associated with an increased risk of extracellular fluid volume expansion.

Thus, use of glucose-sparing regimens in peritoneal dialysis patients should be accompanied by close monitoring of fluid volume status.

J Am Soc Nephrol. 2013; 24:1889-1900

Guidelines

PERITONEAL DIALYSIS INTERNATIONAL

Peritoneal Dialysis International
1–10

DOI: 10.1177/0896860819895364
journals.sagepub.com/home/ptd
SAGE

International Society for Peritoneal Dialysis practice recommendations: Prescribing high-quality goal-directed peritoneal dialysis

Edwina A Brown[1], Peter G Blake[2], Neil Boudville[3], Simon Davies[4,5], Javier de Arteaga[6], Jie Dong[7], Fred Finkelstein[8], Marjorie Foo[9], Helen Hurst[10], David W Johnson[11], Mark Johnson[12], Adrian Liew[13], Thyago Moraes[14], Jeff Perl[15], Rukshana Shroff[16], Isaac Teitelbaum[17], Angela Yee-Moon Wang[18] and Bradley Warady[19]

Clinical use of recommendations

Which dialysis solution?

Peritoneal Diaysis Outcomes and Practice Patterns Study (PDOPPS) data[13] showed significant variations in the use of different strengths of hypertonic glucose PD solutions, icodextrin and neutral pH, low glucose degradation product (GDP) solutions depending on availability and reimbursement policies in different countries. Longer follow-up is needed to determine the association between the use of these solutions and patient outcomes. The ISPD cardiovascular guideline published in 2015[9] recently reviewed the evidence regarding icodextrin, neutral pH and low GDP solutions; this has been updated by a Cochrane review published in 2018.[14]

A. Once-daily icodextrin should be considered as an alternative to hypertonic glucose solutions for long dwells in people doing PD who are experiencing difficulties maintaining euvolemia due to insufficient peritoneal ultrafiltration, taking into account the individual's peritoneal transport state (**GRADE 1B**).

Poor solute removal	Blood tests Small solute clearance (Kt/V_{urea}; creatinine clearance) Nutrition assessment
Non-dialysis factors: comorbidities, frailty, protein-energy wasting	Frailty assessment Cognitive function assessment Nutrition assessment Hospitalization rate

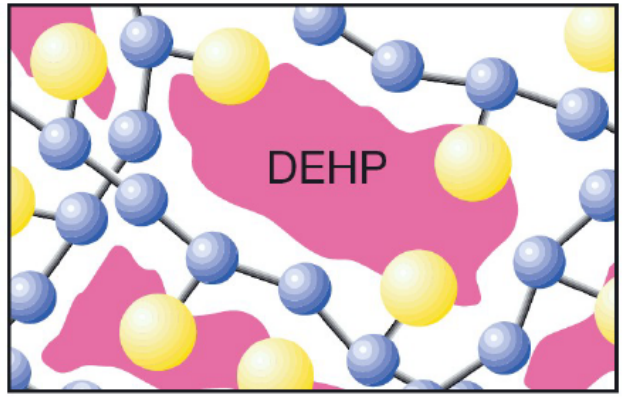
PD: peritoneal dialysis.

B. Use of neutral pH, low GDP PD solutions improves preservation of residual kidney function and urine output (**GRADE 1A**). There is low certainty evidence that use of these fluids may have little or no effect on technique survival or mortality.

Identification of individuals who are 'failing to thrive'

When prescribing person-centred high-quality PD, a challenge is to identify individuals who would benefit from an increase in dialysis prescription or change in dialysis

PVC



Polivinilcloruro

Plastificanti (ftalati)

Combustione:
acido cloridrico e suoi prodotti di reazione
…diossine

Biofine ®

Clear-flex®

NO PVC

NO Plastificanti

Combustione:
H_2O e CO_2

Review

How to Improve the Biocompatibility of Peritoneal Dialysis Solutions (without Jeopardizing the Patient's Health)

Mario Bonomini [1,*], Valentina Masola [2,3], Giuseppe Procino [4], Victor Zammit [5], José C. Divino-Filho [6], Arduino Arduini [7] and Giovanni Gambaro [2]

Table 1. Proposed strategies to improve the biocompatibility of standard peritoneal dialysis solution.

- Low/absent formation of GDP and neutral pH	
Lactate buffer	
Bicarbonate buffer	
Lactate and bicarbonate buffer	
- Replacement of glucose with other osmotic agent(s)	
Icodextrin	**Bimodal solutions**
Amino acids	
Glycerol	Increase triglycerid, gluconeogenesis
Taurine	Accumulation
Hyperbranched polyglycerol	Define metabolism?
- Addition of cytoprotective agents	
Sulodexide	SGLT2i
Heparin	
Sodium citrate	
Carnosine	
Alanyl-glutamine	
Molecular hydrogen	
- Use of osmo-metabolic agents	
L-carnitine	
Xylitol	
L-carnitine and xylitol	

Modified from Bonomini et al. Int. J. Mol. Sci. 2021, *22*(15), 7955

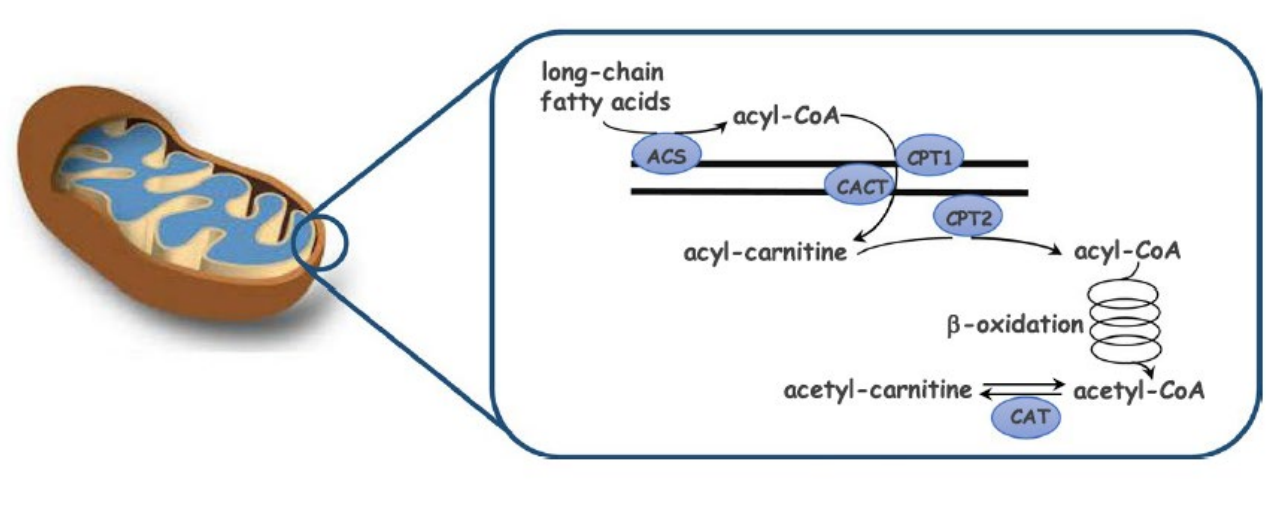
The “Osmo-Metabolic” approach to PD solutions

Osmo-metabolites are substances which exhibit both **osmotically and metabolically favorable properties**

This approach would ensure **glucose-sparing** not only by reducing intraperitoneal glucose exposure without compromising ultrafiltration, but also by the independent **mitigation of underlying systemic negative metabolic effects** caused by the glucose load, a sort of bioactive glucose sparing

Bonomini et al. Journal of Nephrology (2021) 34:503–519

Carnitine



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

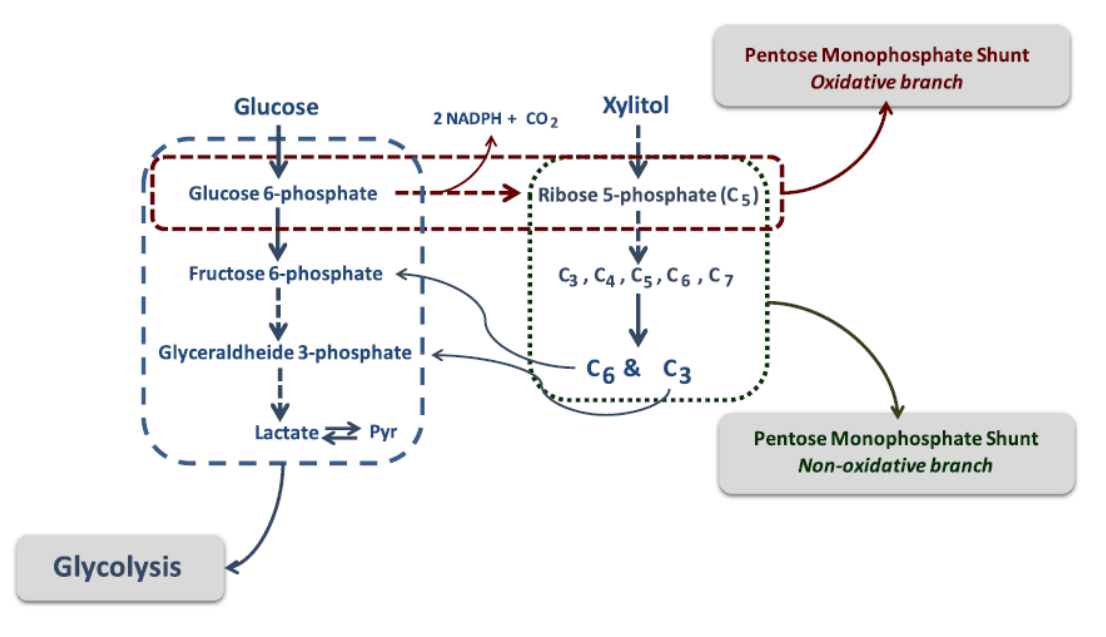
- ✓ **pyruvate dehydrogenase (PDH) kinase involved in metabolism of glucose oxidation**
- ✓ **pyruvate carboxylation (PC), a pivotal enzyme in gluconeogenesis**
- ✓ **promotion of autophagy**

L-Carnitine (molecular weight 161.2 Da) is a naturally
occurring compound known to be essential for fatty acid

The presence in mitochondria of the equilibrium enzyme
CrAT, increases **acetyl-carnitine production at the expenses of acetyl-CoA**, due to a mass-action effect driven by the increased L-carnitine concentration. Therefore, the possibility to modulate the intra-mitochondrial acetyl-CoA pool by overexposure of tissues to carnitine, may have **favourable metabolic consequences toward glucose and lipid homeostasis in insulin resistance** and diabetic patients, because acetyl-CoA plays a key role in the regulation of several important cellular functions such as gluconeogenesis, glucose oxidation, protein acetylation, and steroid and fatty acid biosynthesis.

Bonomini et al. Journal of Nephrology (2021) 34:503–519

Xylitol



Xylitol is a five-carbon sugar alcohol (pentitol, molecular weight 151.2 Da)

The potential favourable effects of exogenous xylitol administration on glucose homeostasis:
- the glycaemic index of xylitol is much lower than that of glucose
- xylitol is a very poor insulin-secretagogue
- Xy-5-P is an allosteric activator of protein phosphatase 2A, this results in a rapid increase in F 2,6-P2, activation of phosphofructokinase, thus activating glycolysis, and inhibiting gluconeogenesis

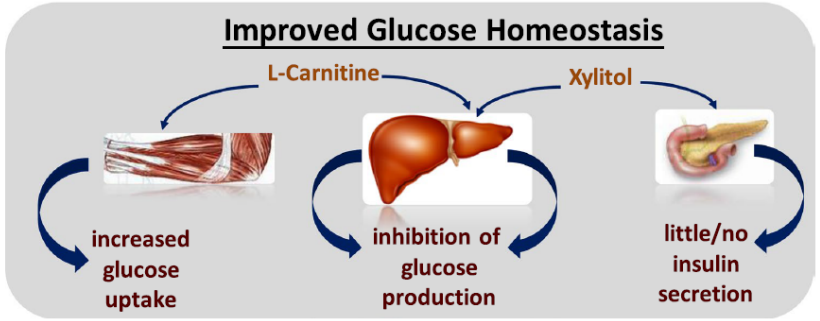
Bonomini et al. Journal of Nephrology (2021) 34:503–519

Introduce more than one osmo-metabolic agent into the dialysate with the aim of achieving a favorable synergetic action.

The L-Carnitine/Xylitol Approach in PD Fluid: a Bioactive Glucose Sparing

Reduced Glucose concentration

not altering the UF profile



Bonomini et al. Journal of Nephrology (2021) 34:503–519

nutrients

MDPI

Article

Biological Effects of XyloCore, a Glucose Sparing PD Solution, on Mesothelial Cells: Focus on Mesothelial-Mesenchymal Transition, Inflammation and Angiogenesis

Valentina Masola [1,2,*], Mario Bonomini [3], Maurizio Onisto [2], Pietro Manuel Ferraro [4,5], Arduino Arduini [6] and Giovanni Gambaro [1]

Article

A New Peritoneal Dialysis Solution Containing L-Carnitine and Xylitol for Patients on Continuous Ambulatory Peritoneal Dialysis: First Clinical Experience

Carmela Rago [1,†], Teresa Lombardi [1,†], Giorgia Di Fulvio [1], Lorenzo Di Liberato [1], Arduino Arduini [2], José C. Divino-Filho [3] and Mario Bonomini [1,*]

On going study

ELIXIR trial is a randomized, controlled, parallel groups, international multicenter study, whose primary objective is the noninferiority of the experimental solution compared to a glucose- based low-GDP PD solution with regard to safety and efficacy, CAPD over a 6-month treatment period (NCT03994471).

Study Start (Actual) ⓘ

2022-12-14

Primary Completion (Estimated) ⓘ

2024-12

Study Completion (Estimated) ⓘ

2024-12

Enrollment (Estimated) ⓘ

170

Study Type ⓘ

Interventional

Phase ⓘ

Phase 3

Conclusions

Glucose is effective for UF but it's a devil

More and more elderly, frail, diabetic patients

Importance of preserving the RRF

Cost considerations

LE SOLUZIONI PER LA DIALISI PERITONEALE

VINCENZO TERLIZZI

ASST SPEDALI CIVILI BRESCIA