Laboratorio itinerante di dialisi peritoneale del gruppo di progetto di dialisi peritoneale della Società Italiana di Nefrologia

Le soluzioni dialitiche di oggi e di domani: quali e come usarle

Vincenzo Terlizzi

ASST – Spedali Civili di Brescia

Laboratorio
DP - Brescia

GdP Dialisi Peritonale

sin reni

- ▶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.***

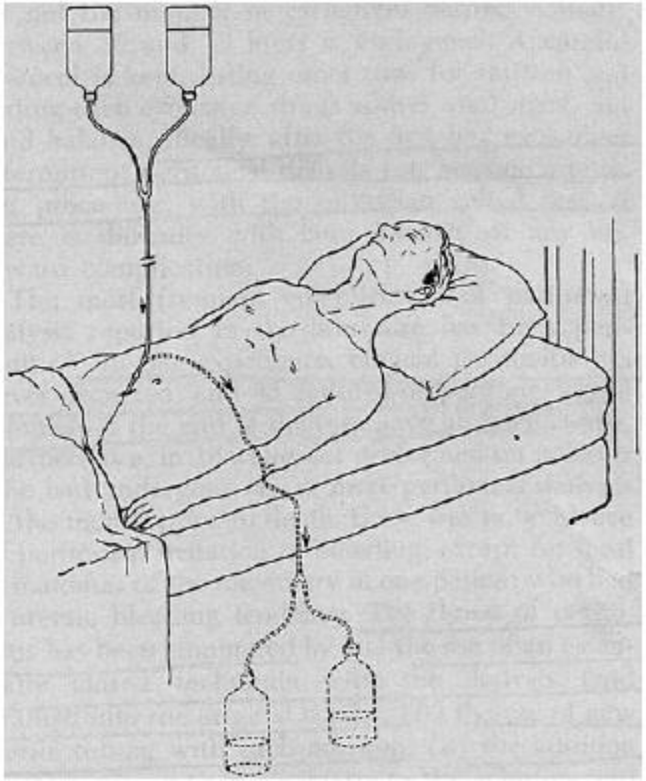


Fig. 1.3 Maxwell's paired bottle technique (From JAMA 1959, with permissior

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.

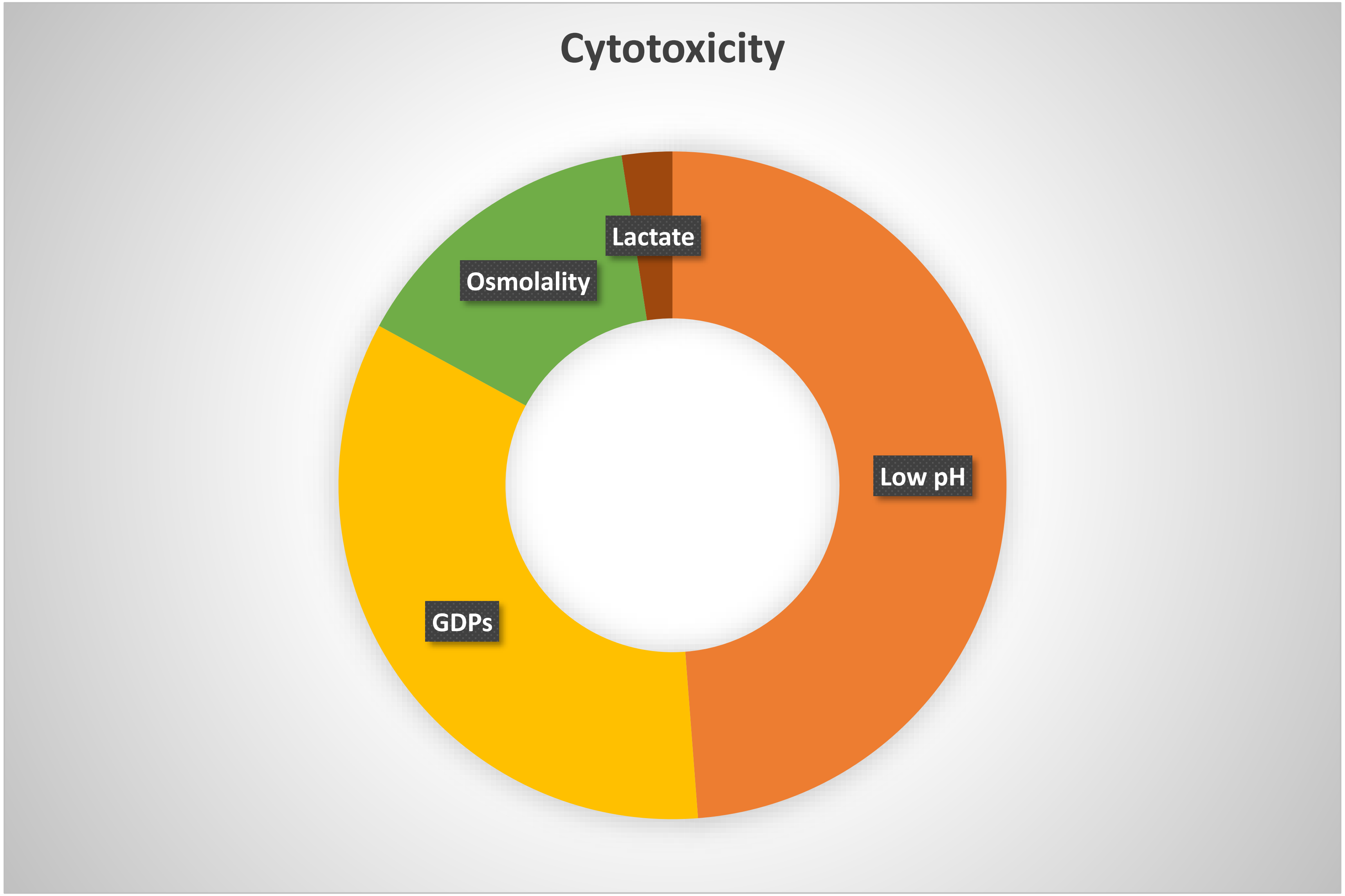
Standard peritoneal dialysis solution

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



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

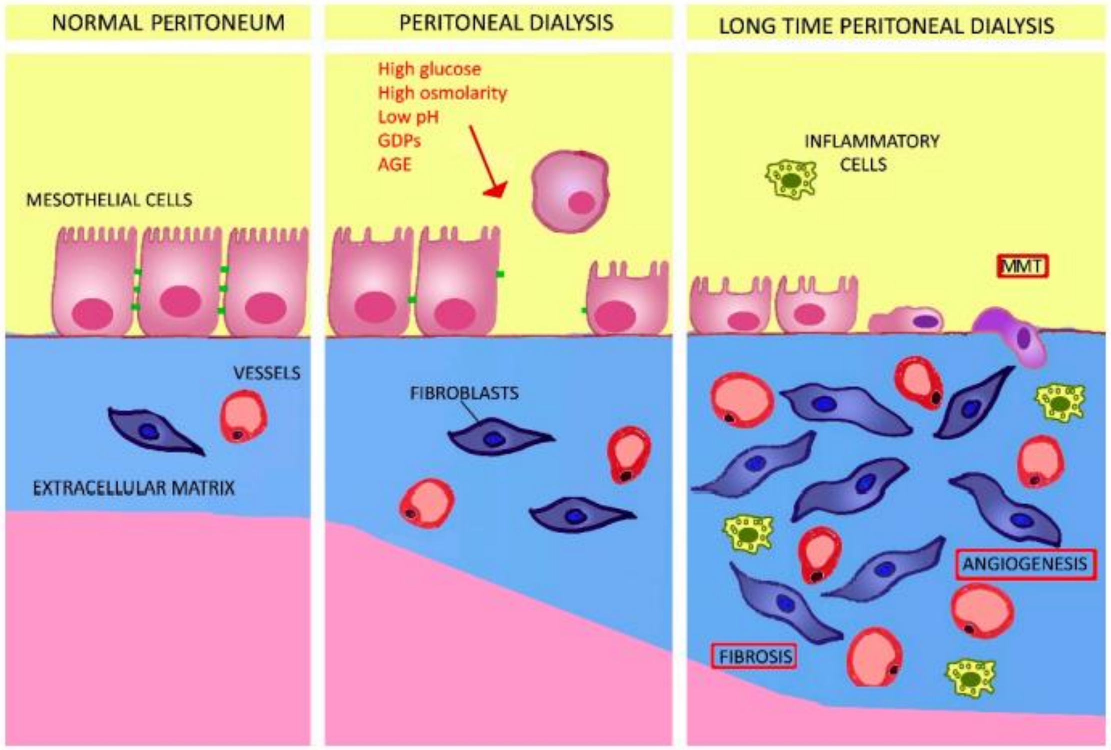
Wieslander A, et al. PDI 2001;21(suppl. 3):119-124

Proinflammatory cytokines

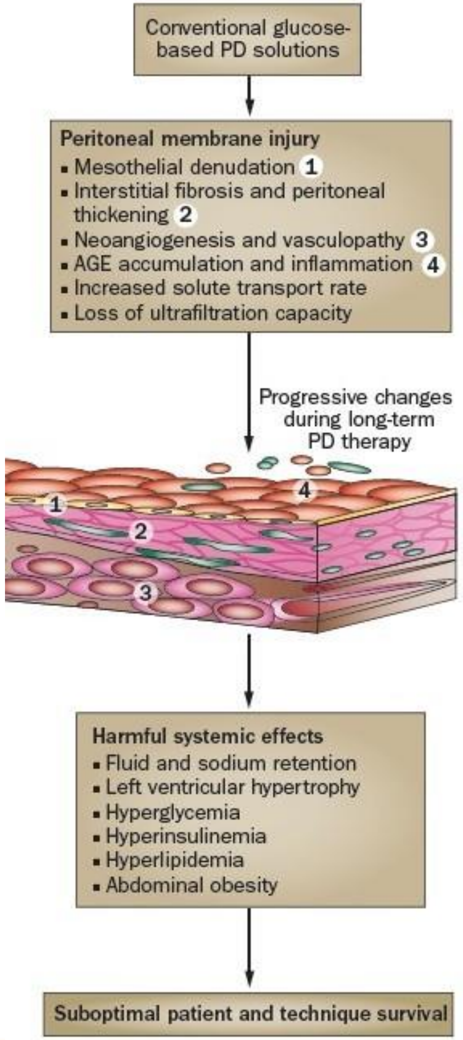
HIF-1a

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)

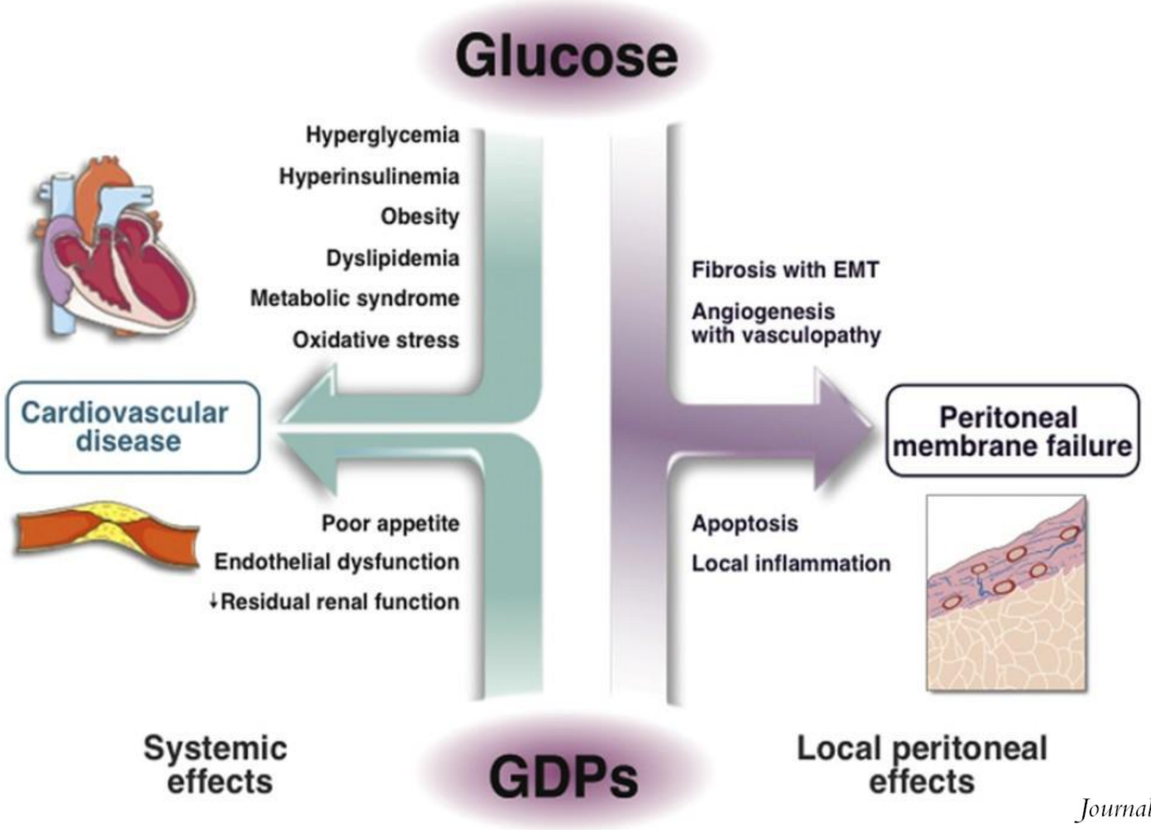
partial loss of peritoneal ultrafiltration capacity fluid retention left ventricular hypertrophy, heart failure increased risk of cardiovascular morbidity

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

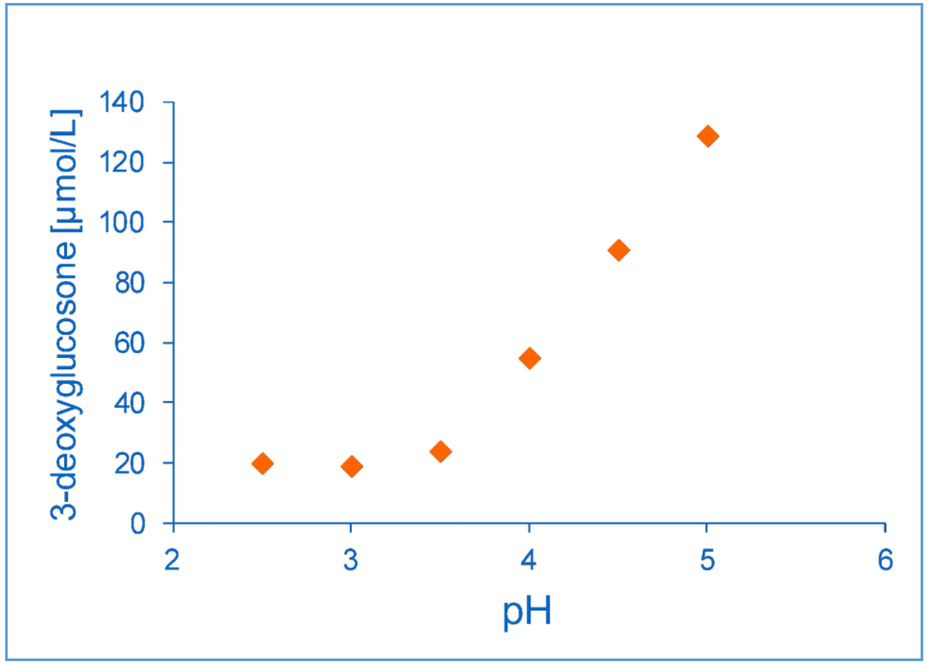
Systemic and Local Impact of Glucose and Glucose Degradation Products in Peritoneal Dialysis Solution

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



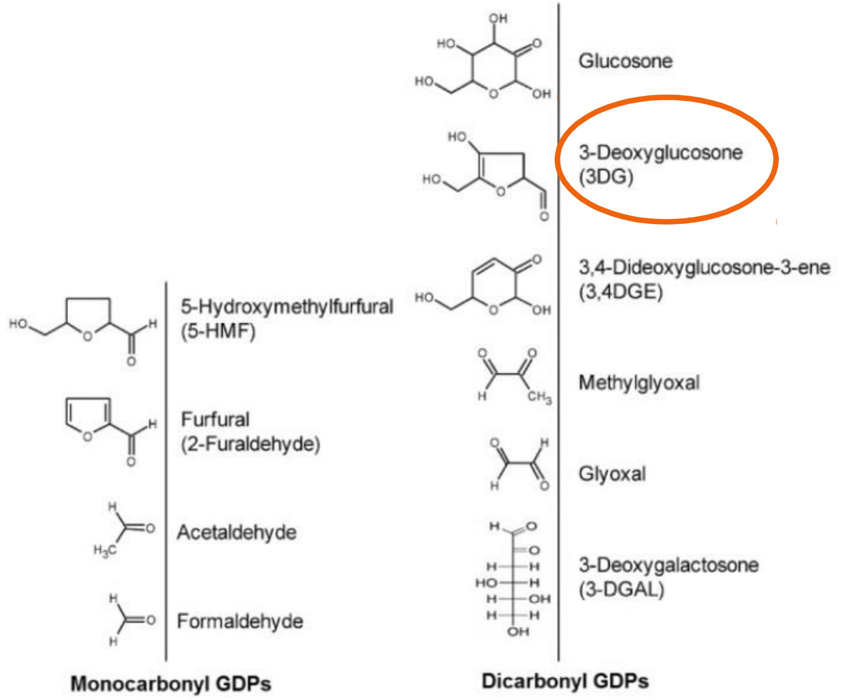
Journal of Renal Nutrition, Vol 23, No 3 (May), 2013: pp 218-222

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



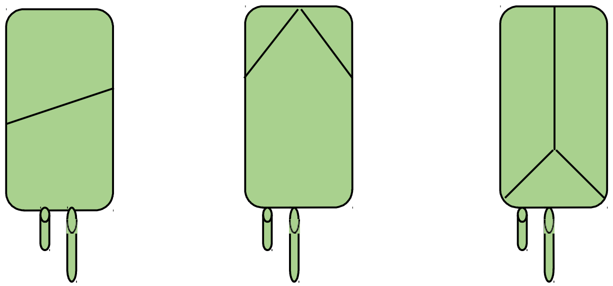
GDPs

AGEs



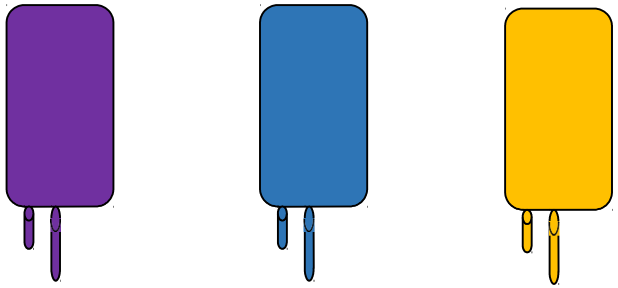
A "New" Generation of PD Solutions

Glucose based solutions



pH 7.0-7.4	pH 6.3	pH 7.0-7.4
Low GDPs	Low GDPs	Low GDPs
HCO3/Lactate	Lactate	HCO3

Alternative osmotic agents



Icodextrin	Amino Acids	Others
pH 5.6	pH 6.6	
Low GDPs	No GDPs	
Iso-osmolar	Glucose free	

Multicompartment bag system

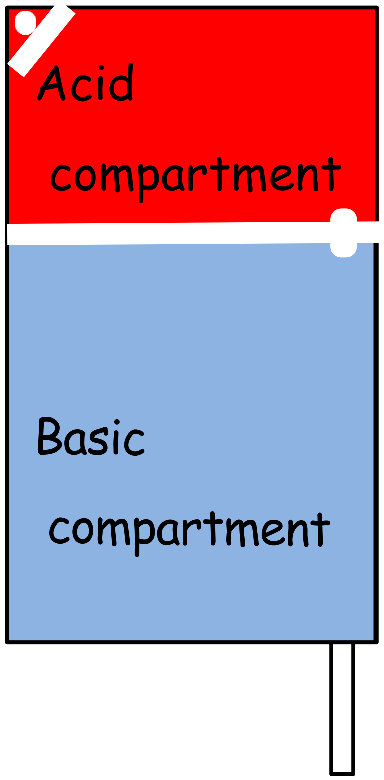
pH=2.5- 4

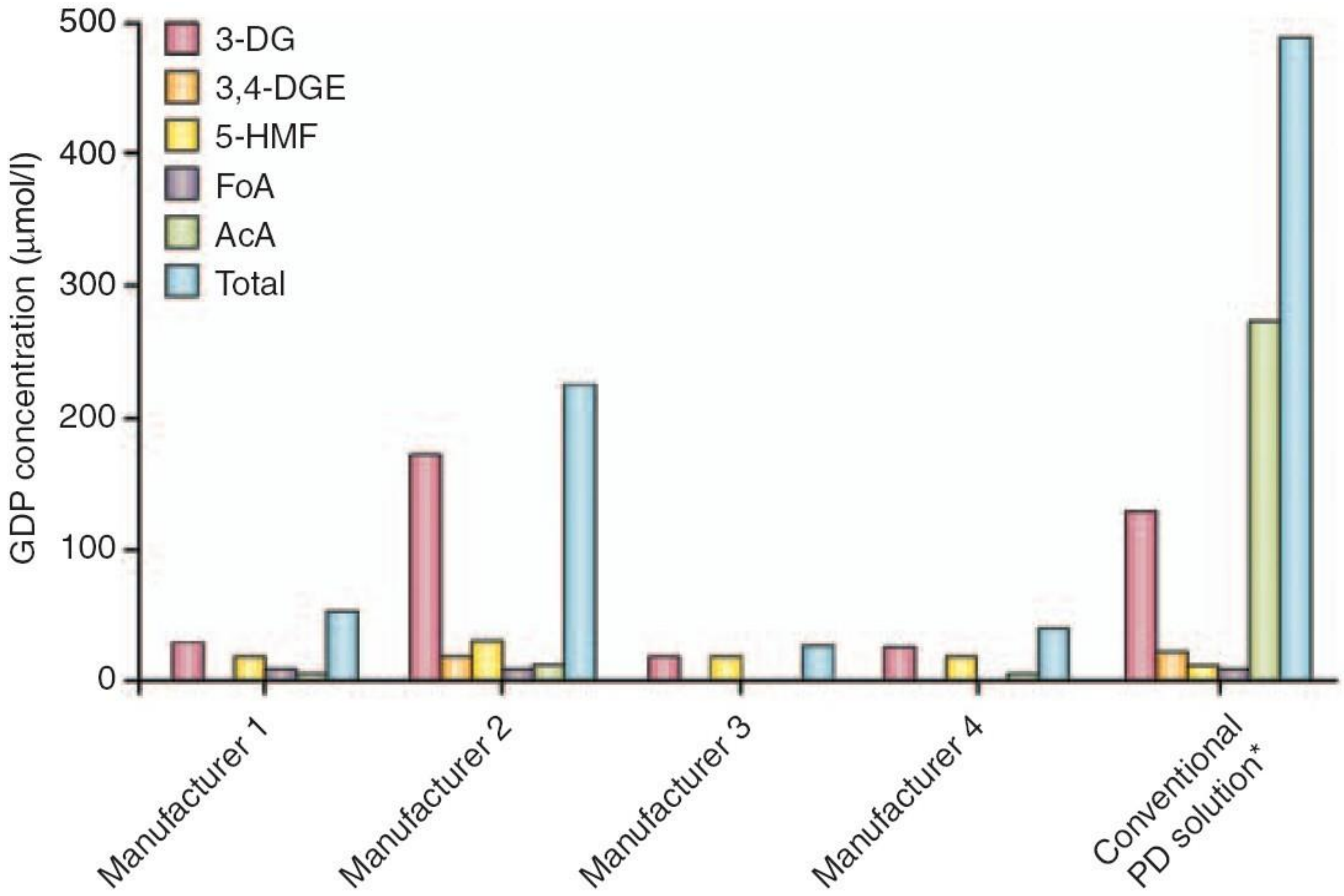
Calcium
Magnesium
Glucose

PARTITION WALL

pH= 6.3 -7.8

Bicarbonate
Bic/lactate
Lactate





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**

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

GdP Dialisi Peritoneale

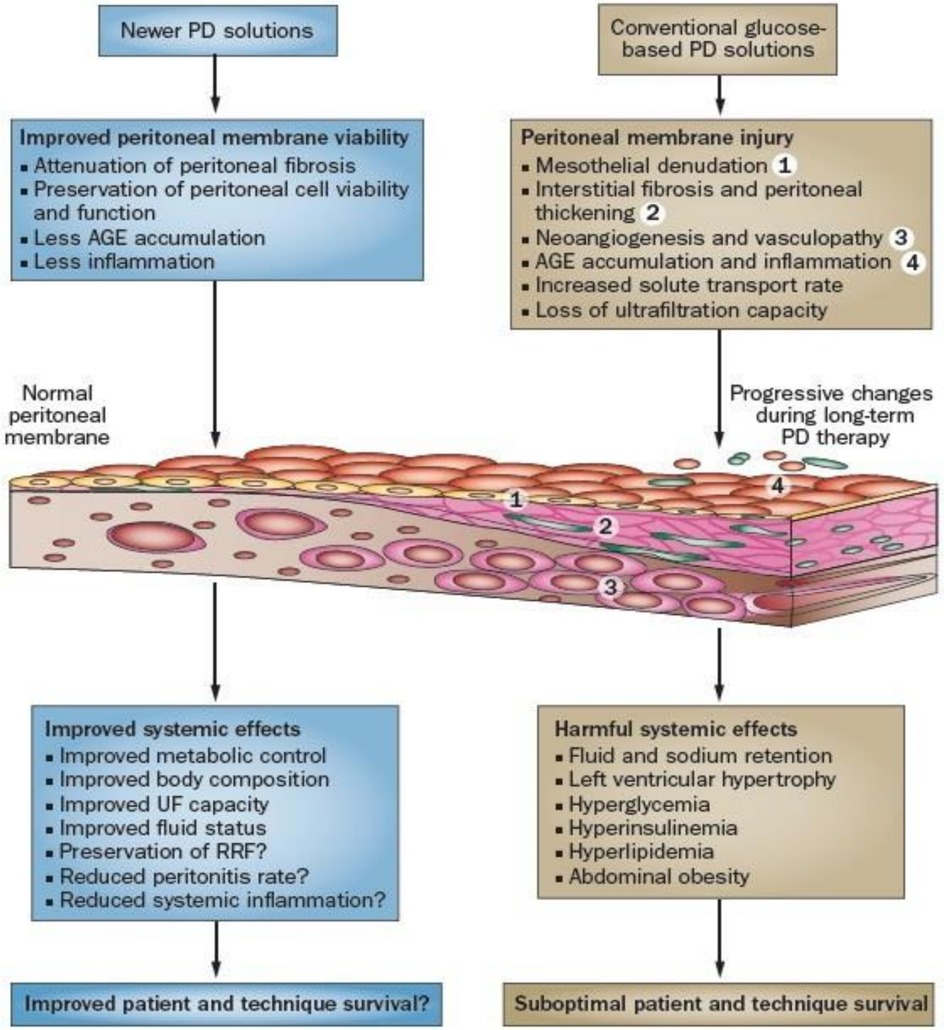


Figure 1 | A schematic presentation of the potential beneficial effects of newer peritoneal dialysis solutions. Abbreviations: AGE, advanced glycation end product; PD, peritoneal dialysis; RRF, residual renal function; UF, ultrafiltration.

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

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

RRF

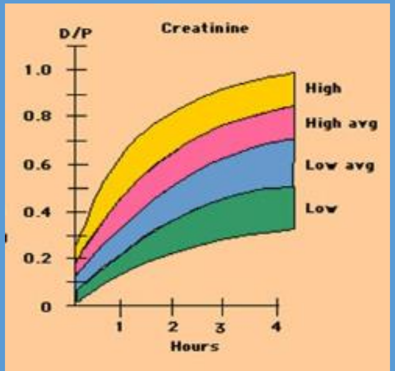
once follow-up reached 12 to 24 months

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/gfp313. 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

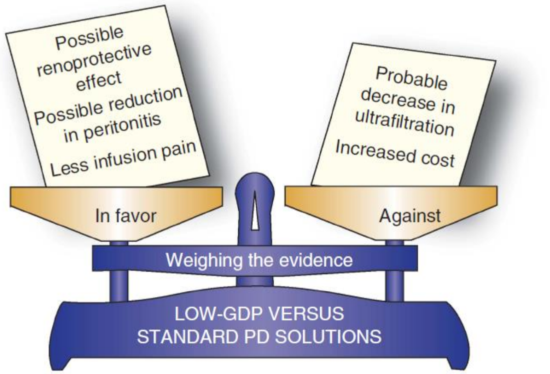


Figure 1 | Weighing the evidence on biocompatible peritoneal dialysis solutions. GDP, glucose degradation product; PD, peritoneal dialysis.

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%

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 neutral pH low-GDP fluids

lacking is a control group of children treated with conventional solutions

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

Submesothelial inflammation leukocytes, macrophages

EMT cells

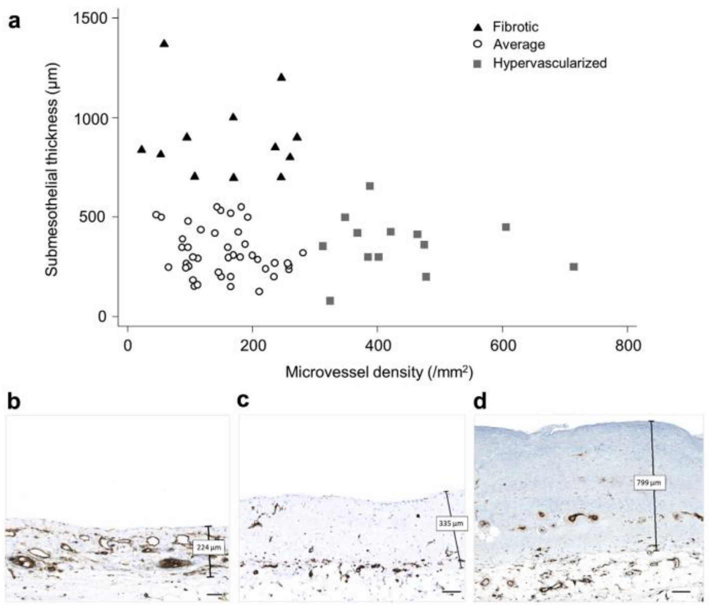


Figure 2 | Cluster analysis of patients treated with low–glucose degradation product peritoneal dialysis (PD) based on submesothelial thickness and microvessel density. Fibrotic type had increased submesothelial thickness with average microvessel density. (**a**) Hypervascularized peritoneum had increased 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.

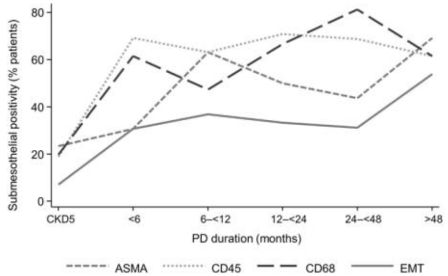


Figure 3 | Low–glucose degradation product (GDP) peritoneal dialysis (PD)–induced cellular alterations. Cellular infiltration of the parietal peritoneum with alpha smooth muscle actin (ASMA)–positive activated fibroblasts, CD45-positive leukocytes, CD68-positive macrophages, and epithelial-to-mesenchymal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

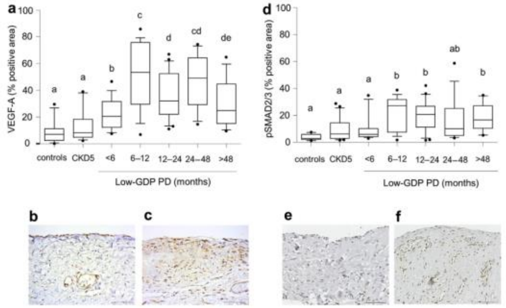


Figure 4 | Peritoneal vascular endothelial growth factor (VEGF) and tumor growth factor ß (TGF-ß) effector pSMAD abundance during low–glucose degradation product (GDP) peritoneal dialysis (PD). (**a**) Parietal peritoneal cross-sectional VEGF positivity relative to the total submesothelial area was analyzed. 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.

Laboratorio DP - Brescia

Kidney International (2018) 94, 419–429

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

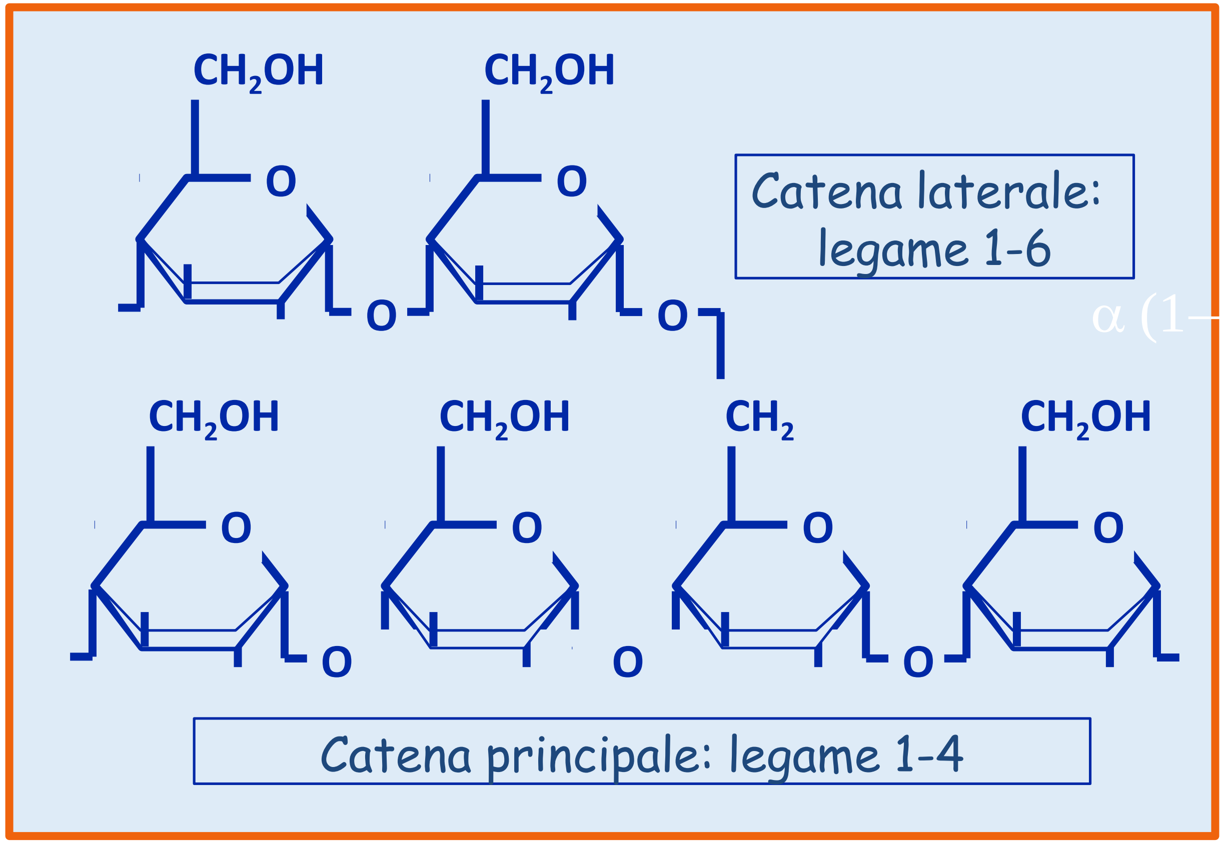
Is the peritoneal dialysis biocompatibility hypothesis dead?

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."

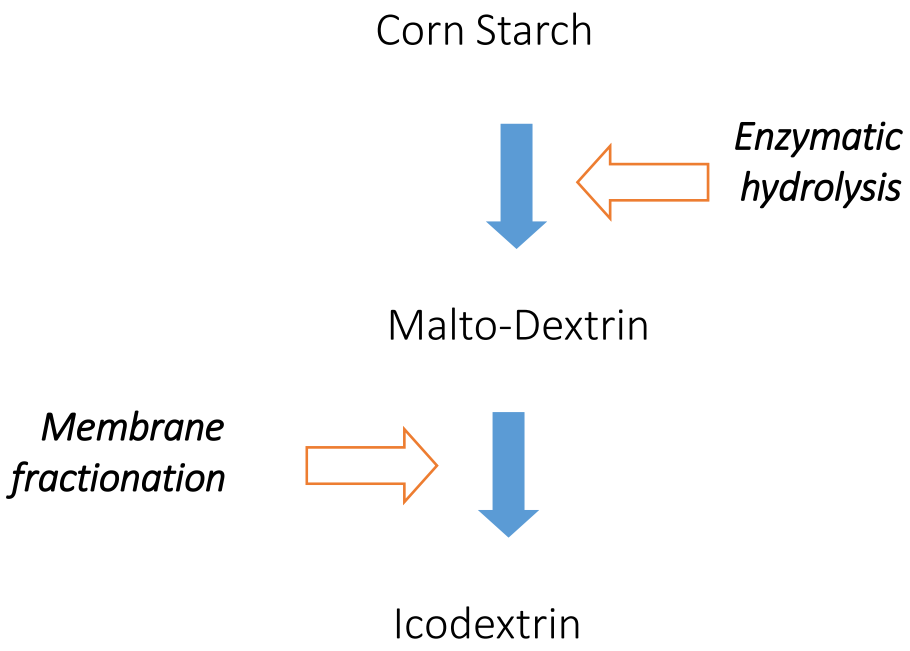
ICODEXTRIN



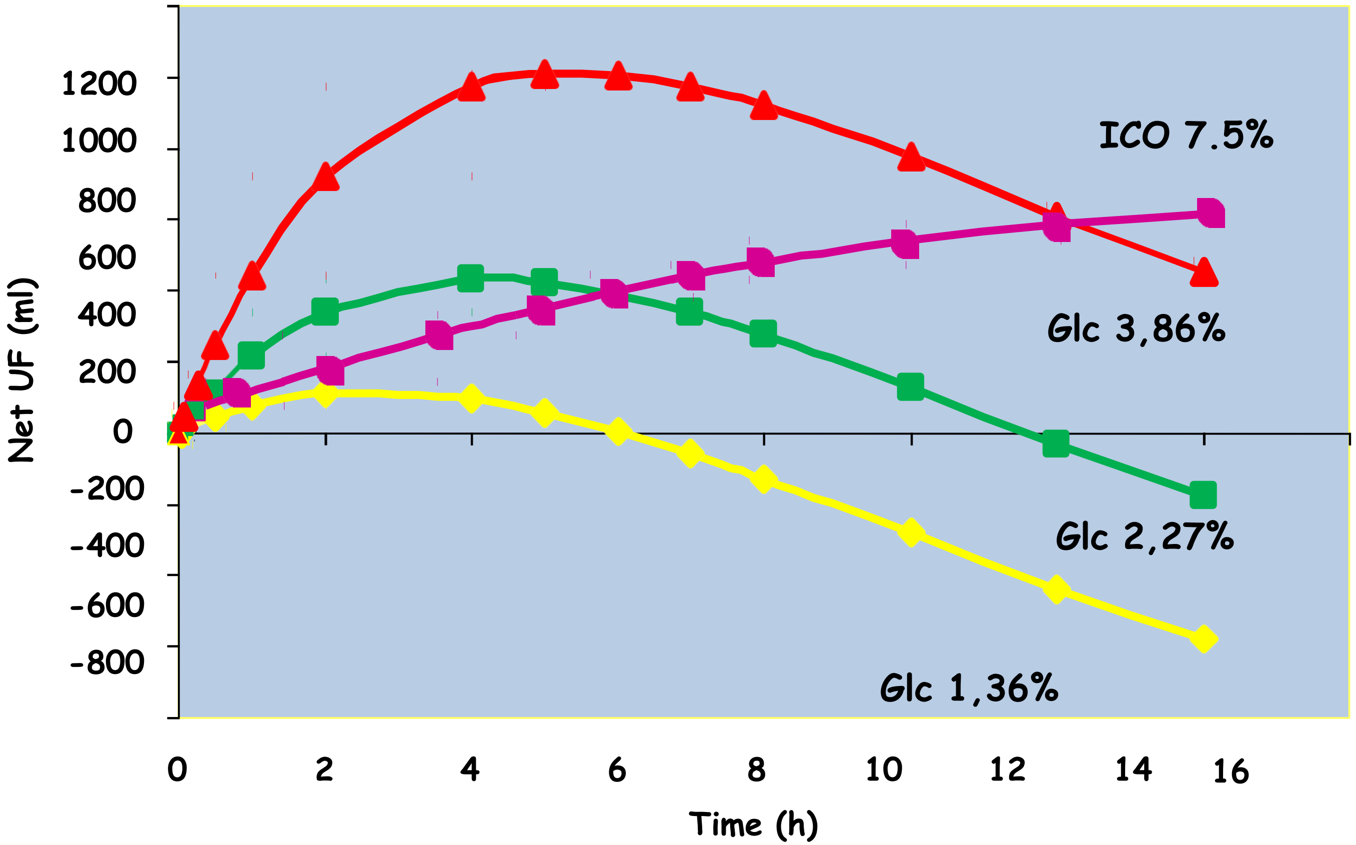
CH$_2$OH
CH$_2$OH
Catena laterale: legame 1-6
O
O
O
O
CH$_2$OH
CH$_2$OH
CH$_2$
CH$_2$OH
O
O
O
O
O
O
O
Catena principale: legame 1-4

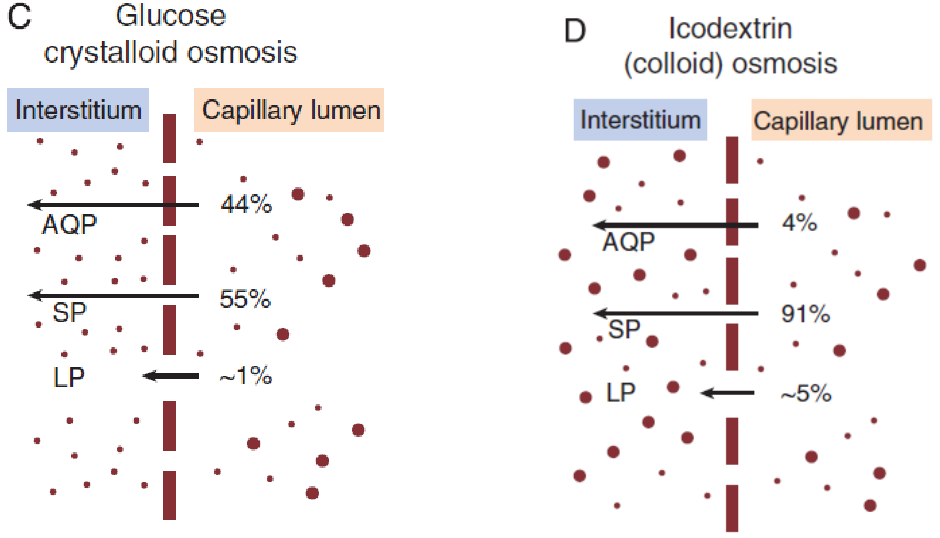
FEATURES OF ICODEXTRIN

- 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).



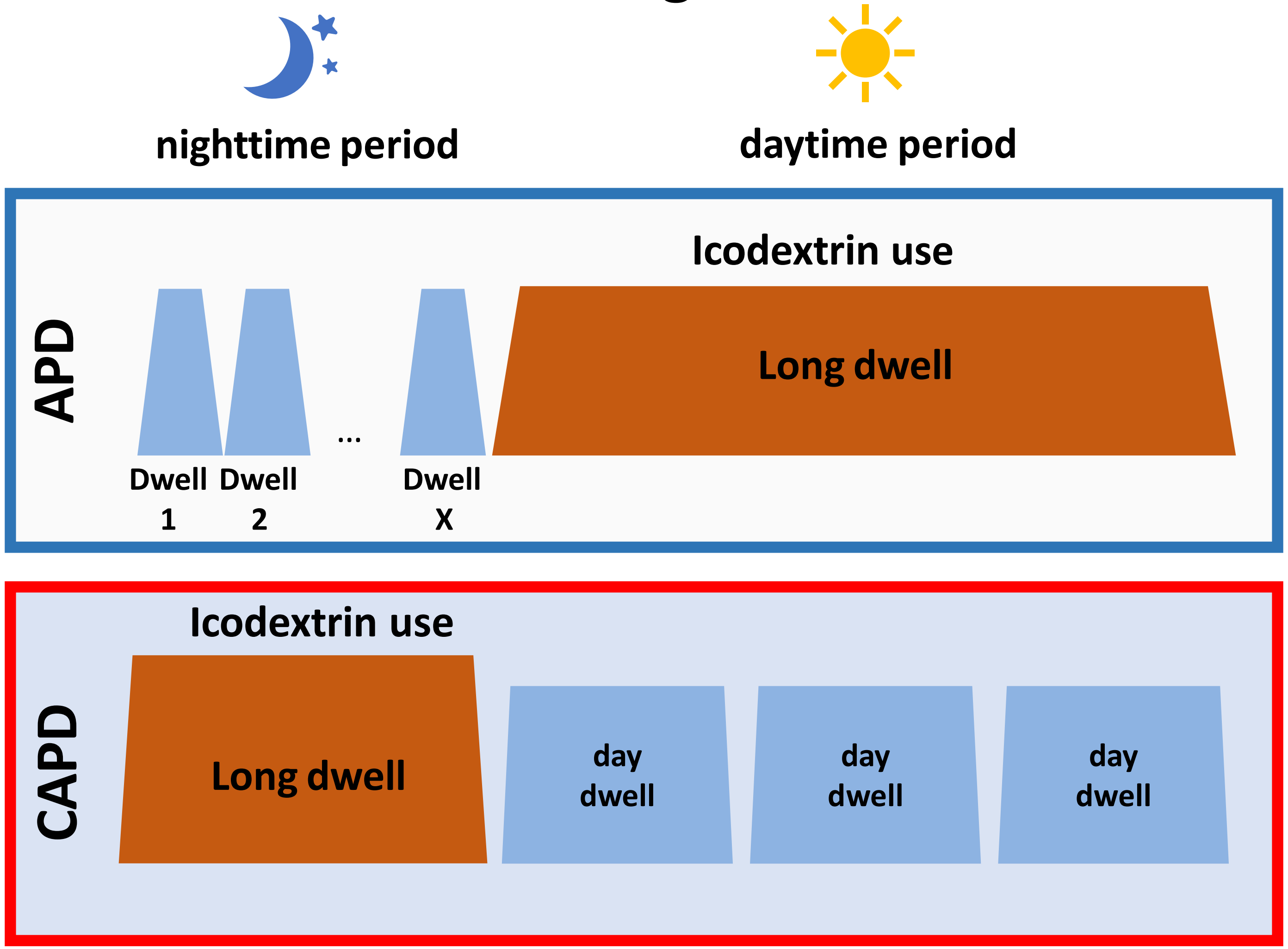
UF PROFILE: GLUCOSE vs ICODEXTRIN





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.

ndt
Nephrology Dialysis Transplantation

Original Article

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

11 trials that enrolled 1222 participants

No significant differences in

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

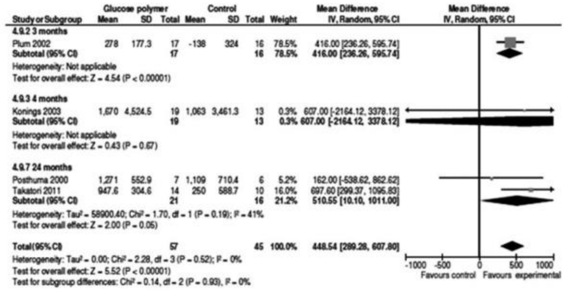


FIGURE 3: Effect of glucose polymer PD solution (icodextrin) use on daily peritoneal ultrafiltration (mL/day).

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

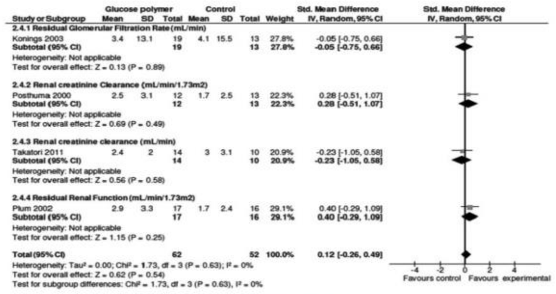


FIGURE 5: Effect of glucose polymer PD solution (icodextrin) on RRF.

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

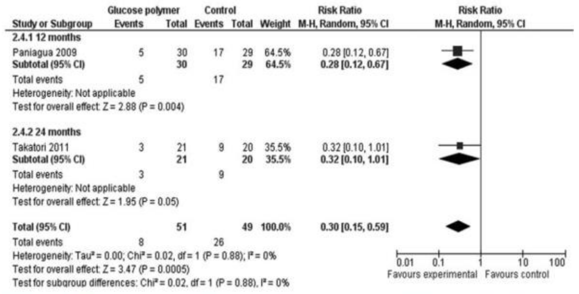


FIGURE 4: Effect of glucose polymer PD solution (icodextrin) use on uncontrolled fluid overload episodes.

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

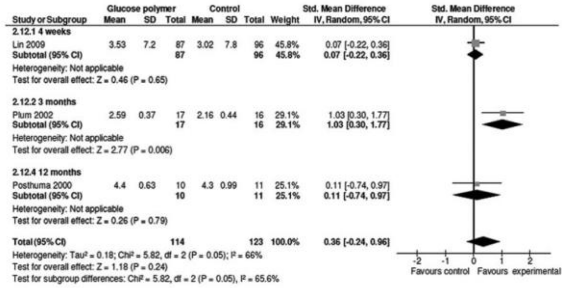


FIGURE 6: Effect of glucose polymer PD solution (icodextrin) on peritoneal creatinine clearance.

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

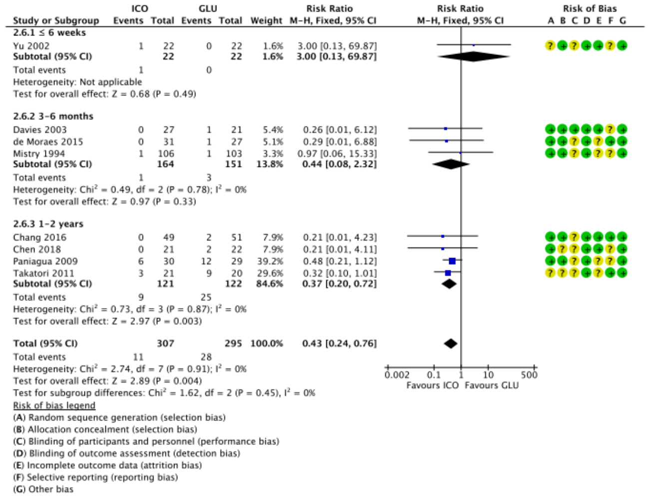


Figure 5. Uncontrolled fluid overload. Results with random-effects modeling are: risk ratio (RR; ≤6 weeks, 3.00 [0.13-69.87]; 3-6 months, 0.45 [0.08-2.58];1-2 years, 0.39 [0.21-0.75];total, 0.43 [0.24-0.78]. Risk-of-bias legend: (A) random sequence generation (selection bias), (B) allocation concealment (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.

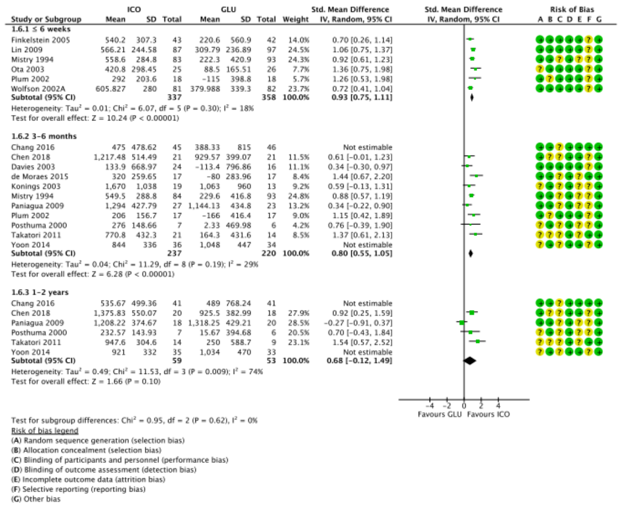


Figure 4. Ultrafiltration (any measure); (A) by duration of treatment; (B) by transport category including high/high-average (H/HA), low-average (LA), and low (L) transporters. Risk of bias legend: (A) random sequence generation (selection bias), (B) allocation concealment (selection bias), (C) blinding 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

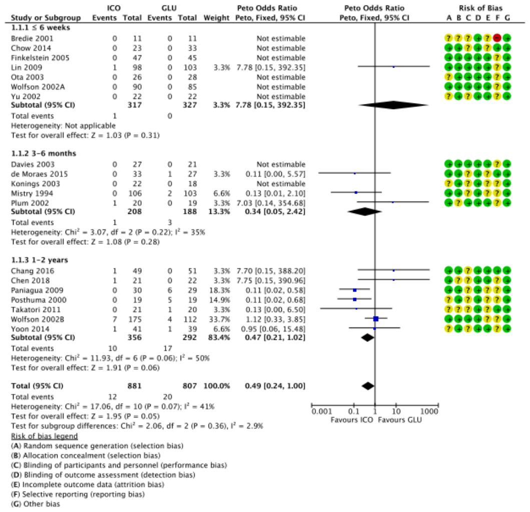
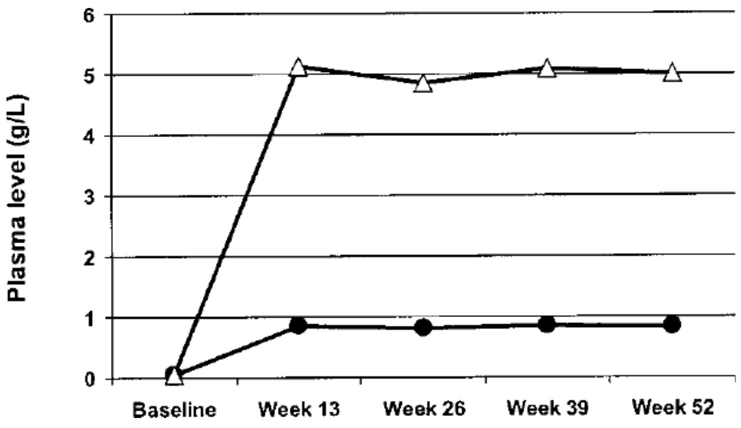
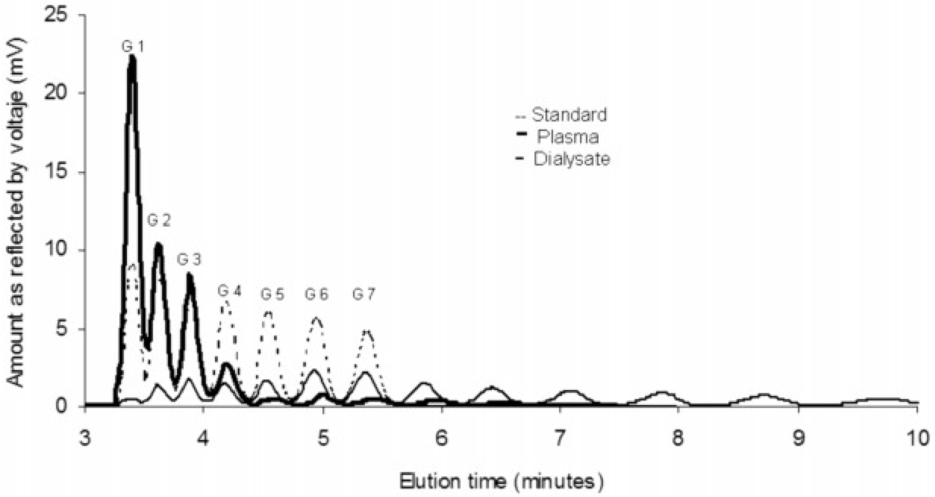


Figure 3. Mortality events; short term after 6 or more weeks, medium term after 3 to 6 months, and long term after 1 to 2 years. Risk of bias legend: (A) Random sequence generation (selection bias), (B) allocation concealment (selection bias), (C) blinding of participants and personnel (performance bias), (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





eal Dialysis Internationa

Peritoneal Dialysis International, Vol.18, pp 603-609

08968608/98 $300 + 00

…glucose dehydrogenase enzymatic reaction

A PREVIOUSLY UNDESCRIBED SIDE EFFECT OF ICODEXTRIN:

OVERESTIMATION OF GLYCEMI A BY GLUCOSE ANALYZER

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

Henri Germanos,1 Max Dratwa 1

Laboratorio
DP - Brescia

GdP Dialisi Peritonale

Soluzioni Aminoacidi (1.1%)

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

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

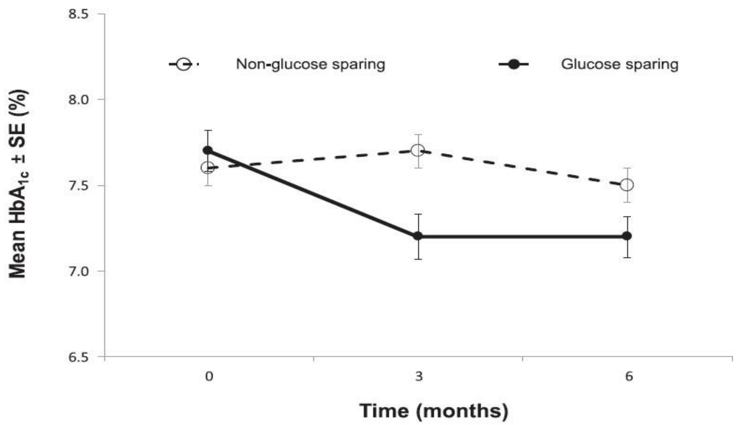
Study	Study type	Population	Interventions	Follow-up	Result
Bruno *et al.* (1989)[125]	Crossover	6	One exchange of a 1.1% amino acid-based solution	6 months	↑ nitrogen balance and MAMC; ↓ serum bicarbonate
Arfeen *et al.* (1990)[126]	Case series	7	Two exchanges of a 1.1% amino acid-based solution	2 months	↑ 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 <30.0 g/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



Subjects	0	3	6
Non-glucose sparing	125	107	118
Glucose sparing	119	86	99

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)

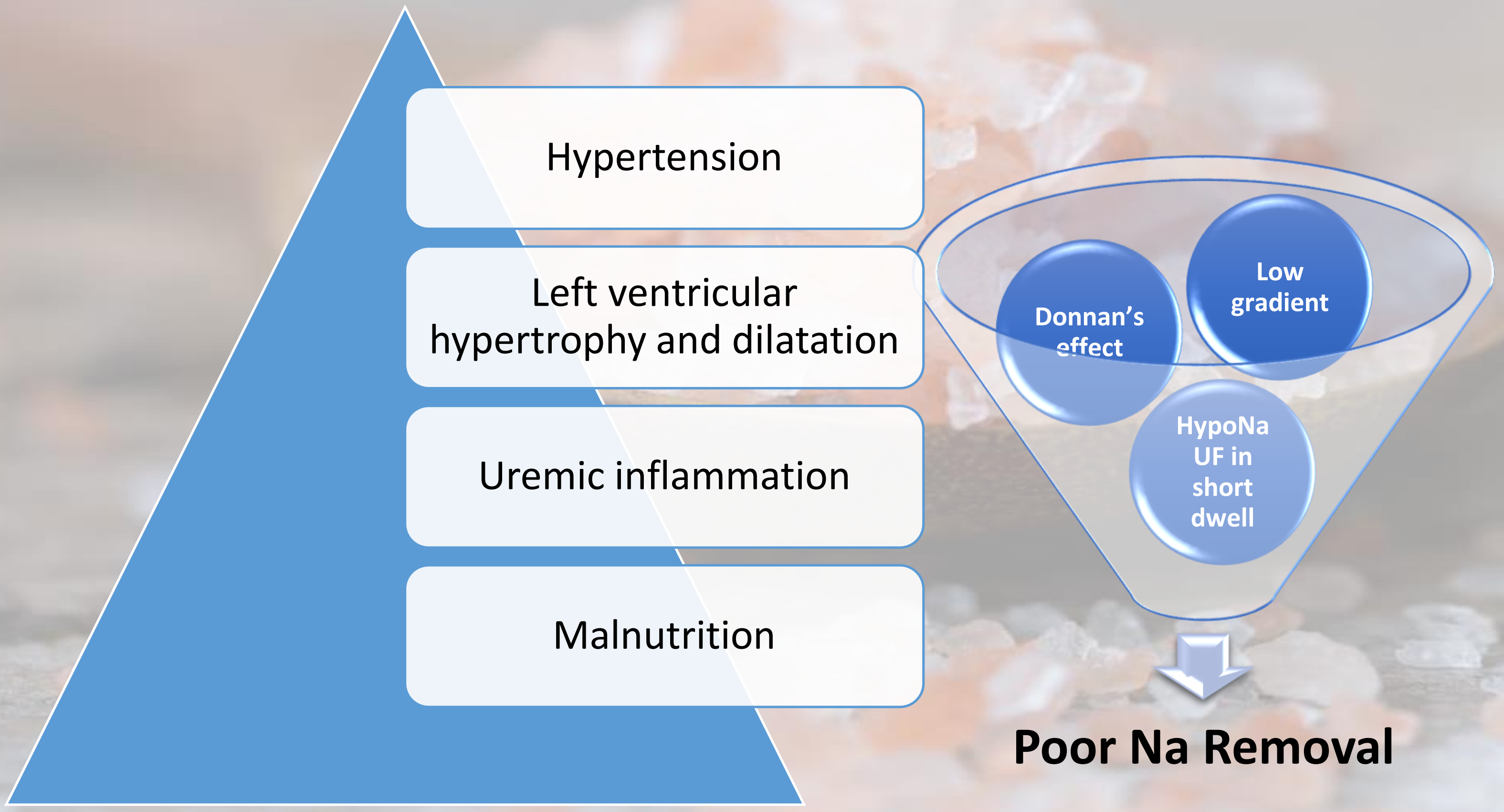
Serious adverse events (ECFV expansion)

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.

Laboratorio DP - Brescia

Dialisi Peritoneale

SODIUM



	APD	CAPD	P
NaR PD (mEq/die)	87±86	195±80	0.0001
NaR Ur (mEq/die)	53.6±57	53.0±74	0.97
UF PD (mL/die)	1047±640	1538±689	0.18
PAS (mmHg)	133.5±18.6	122.4±11.3	0.015
PAD (mmHg)	79.8±12.4	77.8±9.5	0.52
Antipertensivi (%)	70	26	0.0015

Ortega O et al Am J Nephrol 2001 (modif.)

Uncompensated

- Low Na
- Low Osm
- Less UF

Compensated

- Low Na
- High Gluc
- High Osm
- Undesired metabolic consequences?

Concern about hypoNa,
volume depletion,
hypotension

AJKD
Editorial

Sodium Levels in Peritoneal Dialysis Solution: How Low Should We Go?

Related Article, p. 753

different: ultrafiltration is driven by osmotic pressure, and if dialysate sodium concentration is reduced

Table 1. Comparison of Low-Sodium PD Solutions and Outcomes From Recent Studies

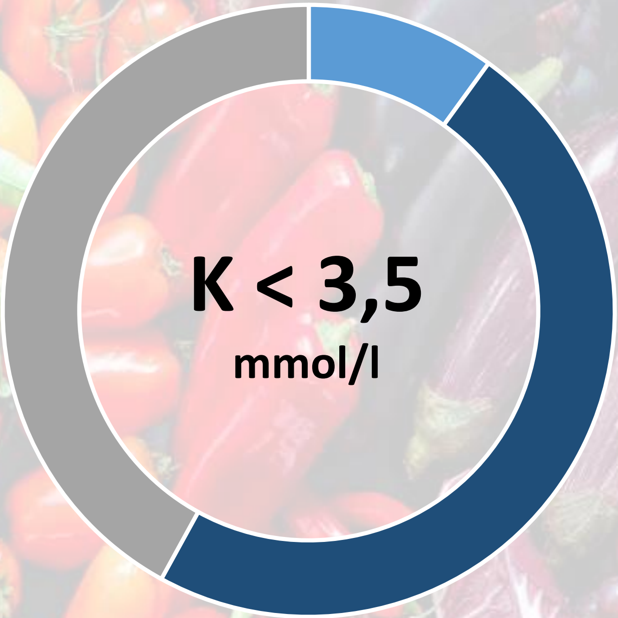
	Davies et al[14] (2009)			
	Group A	Group B	Freida et al[18] (2009)	Rutkowski et al[12,a] (2015)
Dialysate sodium, mEq/L	115	102	121	125
Compensated	Yes	No	Yes	No
No. treated	10	15	10	40
Trial design	Nonrandomized	Nonrandomized	Nonrandomized	Randomized
Daily regimen	1 dwell	1 dwell	1 dwell	All 4 dwells
Study duration, wk	8	8	16	25
UF/d	No change	Down 30%[b]	Up 48%[b]	Down 23%[b]
Dialysate sodium removal/d	Up 55%[b]	Up 35%[b]	Up 70%[b]	Up 55%[b]
SBP/DBP, mm Hg	Down 11/6[b]	No change	No change	Down 9/5[b]
ECF volume[c]	Down[b]	No change	Not measured	Not measured
Urine, volume/d	No change	No change	No change	Down 20%[b]
Serum sodium, mEq/L	No change	No change	No change	Down 2[b]
Thirst	Down[b]	Down[b]	Not measured	Down[d]

Abbreviations and definitions: ECF, extracellular fluid; PD, peritoneal dialysis; SBP/DBP, change in systolic and diastolic blood pressure; UF, ultrafiltration.
[a]More complete 12-week outcomes are used in comparisons.
[b]$P < 0.05$.
[c]As measured by bioimpedance.
[d]$P = 0.07$.

POTASSIUM

A typical 8 l/day CAPD regimen eliminate approximately 40 mEq/day.

The combination of hypokalemia and malnutrition may result in a greater incidence of Enterobacteriaceae peritonitis, by causing impairment in gut mobility, leading to small bowel overgrowth with colonic flora.



10-58% DP pts

Nolph KD et zl.. 1980

Clinical and Experimental Nephrology (2019) 23:1315–1322
https://doi.org/10.1007/s10157-019-01773-y

ORIGINAL ARTICLE

Check for updates

Acute effect of a peritoneal dialysis exchange on electrolyte concentration and QT interval in uraemic patients

Simonetta Genovesi[1,2] · Elisa Nava[1] · Chiara Bartolucci[3] · Stefano Severi[3] · Antonio Vincenti[4] · Gina Contaldo[1] · Giada Bigatti[5] · Daniele Ciurlino[5] · Silvio Volmer Bertoli[5]

Table 3 Effect of the dialytic exchange on plasma electrolyte concentration

	Baseline (SD)	T1 (SD)	T2 (SD)	T3 (SD)	T4 (SD)	ANOVA
pH	7.39 (0.03)	7.40 (0.03)	7.41* (0.03)	7.41** (0.03)	7.42** (0.04)	< 0.0001
HCO_3^- (mmol/L)	25.05 (2.17)	25.61* (2.22)	26.06** (2.19)	26.08** (1.93)	26.64**(2.34)	< 0.0001
K^+ (mmol/L)	3.96 (0.63)	3.92 (0.69)	3.92 (0.65)	3.84** (0.65)	3.88 (0.64)	0.042
Na^+ (mmol/L)	137.0 (4.5)	136.4 (4.2)	135.7** (3.6)	135.8** (3.5)	136.2* (3.8)	< 0.0001
Ca^{++} 1.25 (mmol/L)#	1.15 (0.10)	1.15 (0.10)	1.16 (0.10)	1.15 (0.10)	1.16 (0.10)	NS
Ca^{++} 1.75 (mmol/L)#	1.14 (0.10)	1.14 (0.10)	1.15 (0.10)	1.16* (0.10)	1.14 (0.10)	0.009

*$p < 0.05$ vs baseline, **$p < 0.01$ vs baseline, #$n = 15$
SD standard deviation

HR (b/min)	67 (9)	66 (9)	65* (9)	65* (10)	64** (10)	< 0.0001
QTc (msec)	433 (25)	435 (26)	435 (27)	436 (28)	437 (28)	NS
QTc (msec) Ca^{++} 1.25#	434 (23)	436 (24)	435 (23)	437* (23)	438* (24)	0.046
QTc (msec) Ca^{++} 1.75#	434 (28)	434 (28)	434 (32)	435 (32)	436 (33)	NS

15 patients,
2 manual PD 4-h exchanges with two isotonic solutions with different calcium concentration (Ca++ 1.25 vs 1.75 mmol/L).

- plasma Ca++ slightly increased only when using the Ca 1.75++ mmol/L solution
- not induce modifications of clinical relevance in the QT interval
- **even small decreases of K+ were consistently paralleled by small QT prolongations**

CALCIUM

80% of prevalent PD patients are complicated with vascular calcification, and more than one third have heart valve calcification.

RESEARCH ARTICLE

Long-term effects on PTH and mineral metabolism of 1.25 versus 1.75 mmol/L dialysate calcium in peritoneal dialysis patients: a meta-analysis

Liqin Jin*, Jingjing Zhou, Feng Shao and Fan Yang

Ca 2+ 1,75

Ca 2+ 1,75	Ca 2+ 1,25
Lower iPTH	Lower Ca tot
Similar P	Lower Ca 2+
Similar Peritonitis	Similar P
	Similar Peritonitis

Ca 2+ 1,25

	Icodestrina
Glucosio	0
Poliglucosio (g/dL)	7.5
Sodio (mEq/L)	132
Cloruro (mEq/L)	96
Calcio (mmol/L)	1,75
Magnesio (mEq/L)	0.5
Lattato (mEq/L)	40
Bicarbonato (mEq/L)	0
Osmolalità (mOsm/kg)	284
pH	5.2

CAPD e CCPD1 spesso bilancio pos Ca

TABLE 1
Potential Benefits and Risks Associated with the Use of Low-Calcium and Standard- or High-Calcium Dialysate in Peritoneal Dialysis Patients

	Ca^{++} content of dialysate: Low (1.25 mmol/L or 2.5 mEq/L)	Standard or high (1.75 mmol/L or 3 mEq/L)
Calcium balance	Neutral or slightly negative	Positive
Serum calcium	↓	More hypercalcemia
Serum phosphate	Variable	Variable
Intact PTH	Short-term ↑	↓
Arterial properties	Reduces arterial stiffening	Increases arterial stiffening
Vascular calcification	?	?
Bone mass and histology	?	?
Mortality and CVEs	?	?

PTH = parathyroid hormone; CVEs = cardiovascular events.

Restrict the dose of calcium-based phosphate binders in CKD patients

QUALE CONCENTRAZIONE DEI SOLUTI

QUALI AGENTI OSMOTICI

QUALE SOSTENIBILITA'

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	
Amino acids	**Bimodal solutions**
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

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

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

2-Deoxy-glucose ameliorates the peritoneal mesothelial and endothelial barrier function perturbation occurring due to Peritoneal Dialysis fluids exposure

Eleanna Pitaraki [a], Rajesh M. Jagirdar [a], Erasmia Rouka [b], Maria Bartosova [c], Sotirios I. Sinis [a,d], Konstantinos I. Gourgoulianis [d], Theodoros Eleftheriadis [e], Ioannis Stefanidis [e], Vassilios Liakopoulos [f], Chrissi Hatzoglou [a], Claus Peter Schmitt [c], Sotirios G. Zarogiannis [a,*]

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[b] Department of Nursing, School of Health Sciences, University of Thessaly, GAIOPOLIS, 41500, Larissa, Greece
[c] Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, University of Heidelberg, 69120, Heidelberg, Germany
[d] Department of Respiratory Medicine, Faculty of Medicine, School of Health Sciences, University of Thessaly, BIOPOLIS, 41500, Larissa, Greece
[e] Department of Nephrology, Faculty of Medicine, School of Health Sciences, University of Thessaly, BIOPOLIS, 41500, Larissa, Greece
[f] 2nd Department of Nephrology, AHEPA Hospital, Aristotle University of Thessaloniki, 54636, Thessaloniki, Greece

Biochemical and Biophysical Research Communications Volume 693, 22 January 2024,

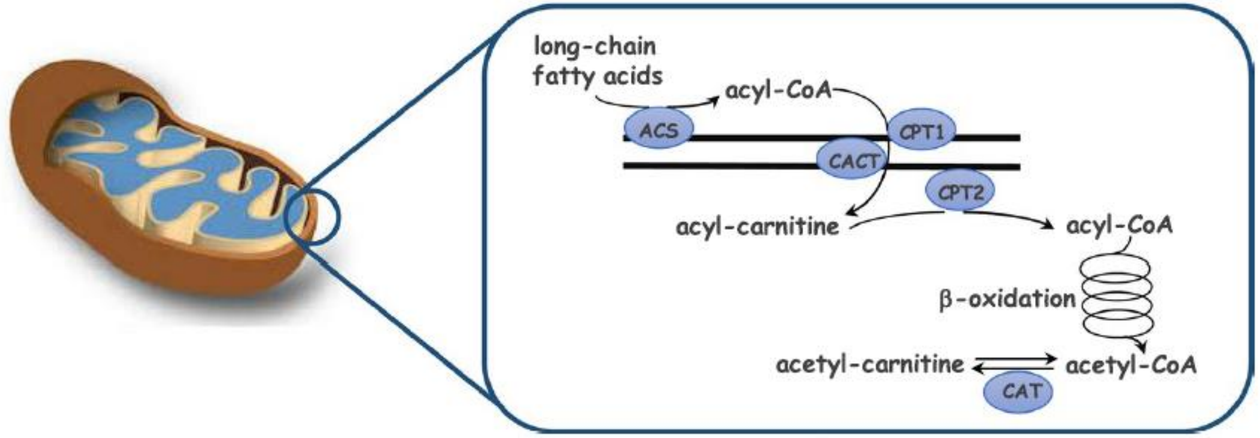
The “Osmo-Metabolic” approach to PD solutions

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



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

- 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**

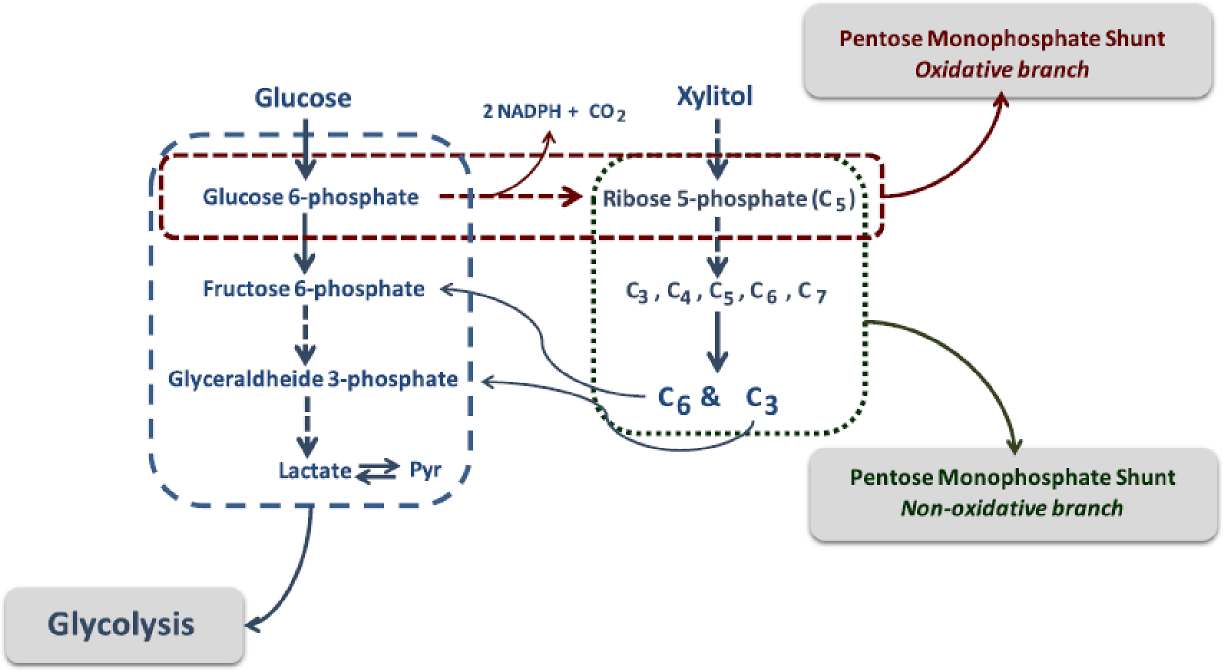
✓ **pyruvate carboxylation (PC), a pivotal enzyme in gluconeogenesis**

✓ **promotion of autophagy**

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**

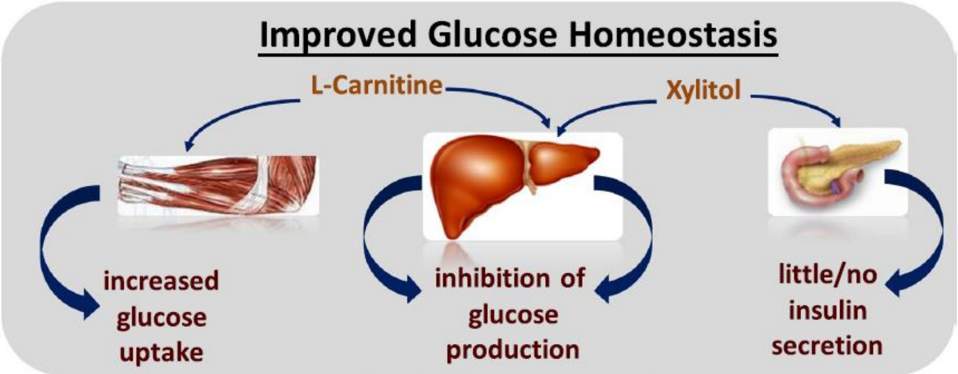
Bonomini et al. Journal of Nephrology (2021) 34:503–519

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



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,*]

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]

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

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

The effectiveness of locally-prepared peritoneal dialysate in the management of children with acute kidney injury in a south-east Nigerian tertiary hospital

Ngozi R Mbanefo, Samuel N Uwaezuoke, Ugo N Chikani, Ada I Bisi-Onyemaechi,
Uzoamaka V Muoneke, Odutola I Odetunde, Henrietta U Okafor

Department of Paediatrics, University of Nigeria Teaching Hospital Ituku-Ozalla, Enugu, Nigeria.

The fluid was composed of **440 mls of 5% D/W**, **60 mls of intravenous 8.4% sodium bicarbonate**, and **1000 mls of normal saline** to make up 1500 mls of the dialysate and comprising 1.5% dextrose strength solution. To each 1.5 L of the reconstituted fluid, 250 IU – 750 IU of **heparin** was added; a lower dose was used in cases of thrombocytopenia and/or increased international normalized ratio (INR).

A hypertonic dextrose solution of 2.5% was prepared by substituting 10% D/W for 5% D/W for those with anasarca**. Addition of 20mls of 50% dextrose to each litter of 1.5% or 2.5% increases the strength by 0.5%.**

Intravenous ceftazidime (Fortum) at 125mg/l (187.5mg in 1500mls) and vancomycin at 20mg/l (30mg in 1500mls) were added as prophylaxis against the development of peritonitis.

Afri Health Sci. 2022;22(4). 679-685

Conclusions

Glucose is effective for UF but it's a devil

More and more elderly, frail, diabetic patients

Personalize therapy

Cost considerations

Le soluzioni dialitiche di oggi e di domani: quali e come usarle

Vincenzo Terlizzi

ASST – Spedali Civili di Brescia