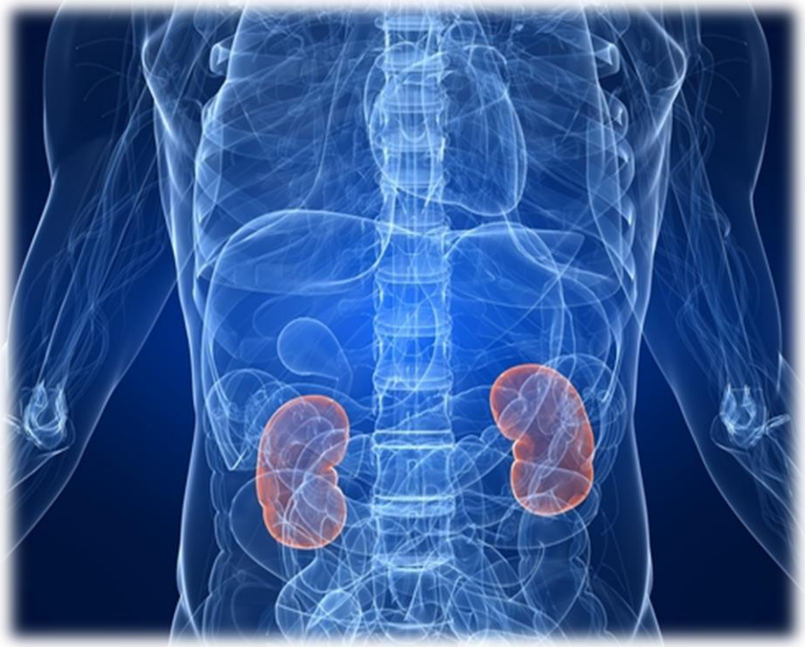
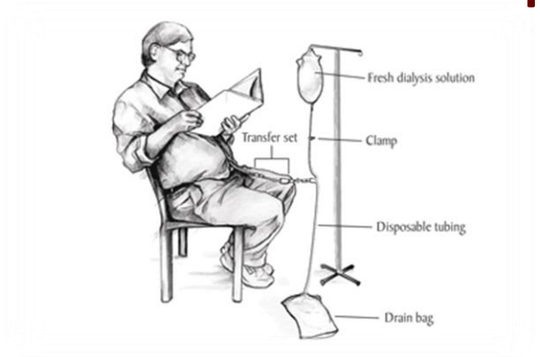
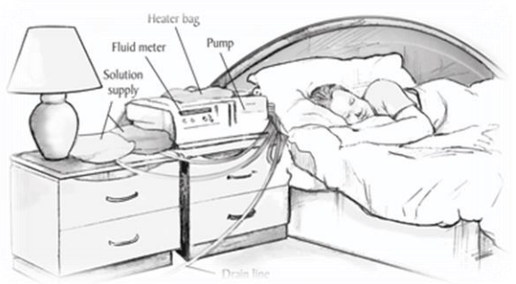
A Novel Glucose-Sparing Strategy in Formulating Peritoneal Dialysis Solutions: the Osmo-Metabolic Approach



Arduino Arduini, MD
R&D Department
CoreQuest Sagl
Switzerland

Achilles' Heel of Peritoneal Dialysis





Poorly biocompatible PD solutions

↓

Technique Failure

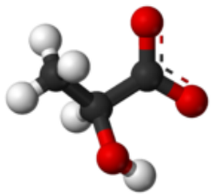
↑

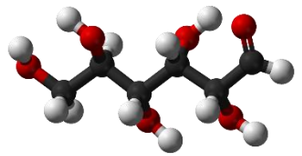
Peritonitis

The death of Achilles …

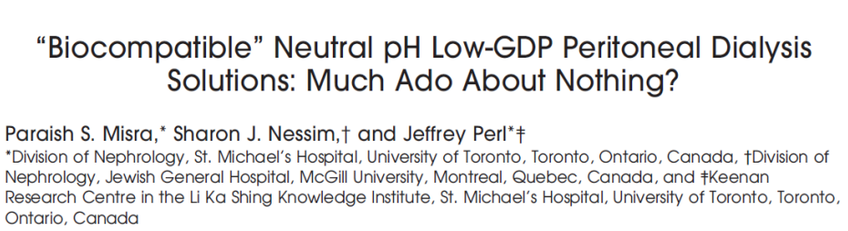
Potential factors believed to be responsible for the poor biocompatibility of PD solutions

- **Glucose degradation products (GDP)**
  - 3-deoxyglucosone;
  - 3,4-dideoxyglucosone-3-ene;
  - 5-hydroxymethyl furaldehyde;
  - acetaldehyde;
  - formaldehyde;
- **Lactate**
- **Low pH**
- **High osmolarity**
- **Glucose**





Where do we stand with the commercially available biocompatible PD solutions (low-GDP and neutral pH)?



"Biocompatible" Neutral pH Low-GDP Peritoneal Dialysis Solutions: Much Ado About Nothing?

Paraish S. Misra,* Sharon J. Nessim,† and Jeffrey Perl*‡

*Division of Nephrology, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada, †Division of Nephrology, Jewish General Hospital, McGill University, Montreal, Quebec, Canada, and ‡Keenan Research Centre in the Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada

see clinical trial on page 419

Is the peritoneal dialysis biocompatibility hypothesis dead?

Peter G. Blake[1]

- '… no convincing conclusion can be drawn about the benefits of low-GDP solution to patients …'
- '… The search for truly more biocompatible PD solutions based on osmotic agents other than glucose may be the most desirable strategy …'

Blake P.G. Kidney Int 2018; 94:246-48

Misra et al. Semin Dial 2017; 30:164-73

Outcome of Intraperitoneal Glucose Load

Local effects

⇩

Glucotoxicity

⇩

Changes to peritoneal membrane structure and function

⇩

Fluid overload

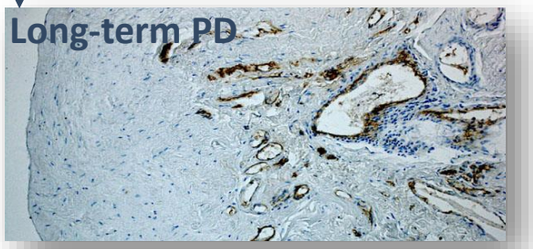
Systemic effects

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

Carbohydrate load:
- ✓ Hyperinsulinemia
- ✓ Selective Insulin Resistance

Increased Cardiovascular Risk

Decrease Technique Survival



Submesothelial fibrosis Vascular proliferation

Exogeneous or endogenous hyperinsulinemia increases cardiovascular morbidity and mortality

Mortality and Other Important Diabetes-Related Outcomes With Insulin vs Other Antihyperglycemic Therapies in Type 2 Diabetes

Craig J. Currie, Chris D. Poole, Marc Evans, John R. Peters, and Christopher Ll. Morgan

Department of Primary Care and Public Health (C.J.C., C.D.P., C.Ll.M.), School of Medicine, Cardiff University, and Department of Global Epidemiology (C.J.C., C.D.P., C.Ll.M.), Pharmatelligence, Cardiff CF14 4UJ, United Kingdom; and Department of Medicine (M.E., J.R.P.), University Hospital of Wales, Cardiff CF14 4XW, United Kingdom

J Clin Endocrinol Metab (2013) 98:668-77

Diabetologia (2004) 47:1245–1256
DOI 10.1007/s00125-004-1433-4

Diabetologia

Plasma insulin and cardiovascular mortality in non-diabetic European men and women: a meta-analysis of data from eleven prospective studies

The DECODE Insulin Study Group

Mortality in Individuals Treated With Glucose-Lowering Agents: A Large, Controlled Cohort Study

Marc Claesen,* Pieter Gillard,* Frank De Smet, Michiel Callens, Bart De Moor, and Chantal Mathieu

STADIUS Center for Dynamical Systems (M.Cl., B.D.M.), Signal Processing and Data Analytics, Department of Electrical Engineering, iMinds Medical IT, (M.Cl., B.D.M.), and Department of Public Health and Primary Care (F.D.S.), KU Leuven, B-3000 Leuven, Belgium; Department of Clinical and Experimental Medicine (P.G., C.M.), University of Leuven-KUL and University Hospitals Leuven, B-3000 Leuven, Belgium; and Department of Medical Management (F.D.S., M.Ca.), National Alliance of Christian Mutualities, B-1090 Brussels, Belgium

J Clin Endocrinol Metab (2016) 101:461-69

Ning *et al. Cardiovascular Diabetology* 2012, **11**:76
http://www.cardiab.com/content/11/1/76

CARDIO VASCULAR DIABETOLOGY

ORIGINAL INVESTIGATION Open Access

Development of coronary heart disease and ischemic stroke in relation to fasting and 2-hour plasma glucose levels in the normal range

Feng Ning[1*], Lei Zhang[1,2,3,4], Jacqueline M Dekker[5], Altan Onat[6,7], Coen DA Stehouwer[8], John S Yudkin[9], Tiina Laatikainen[2], Jaakko Tuomilehto[1,2,10,11], Kalevi Pyörälä[12] and Qing Qiao[1,2] on behalf of the DECODE Finnish and Swedish Study Investigators

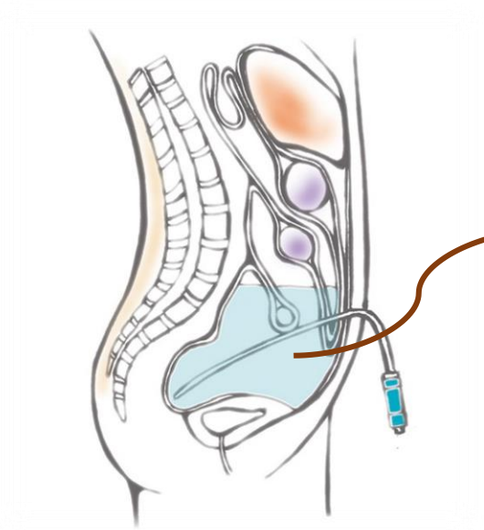
952 THE NEW ENGLAND JOURNAL OF MEDICINE April 11, 1996

HYPERINSULINEMIA AS AN INDEPENDENT RISK FACTOR FOR ISCHEMIC HEART DISEASE

JEAN-PIERRE DESPRÉS, PH.D., BENOÎT LAMARCHE, M.SC., PASCALE MAURIÈGE, PH.D., BERNARD CANTIN, M.D., GILLES R. DAGENAIS, M.D., SITAL MOORJANI, PH.D.,* AND PAUL-J. LUPIEN, M.D.

NEJM (1996) 334:952-57

Attributes of an ideal “osmo-metabolic” agent …

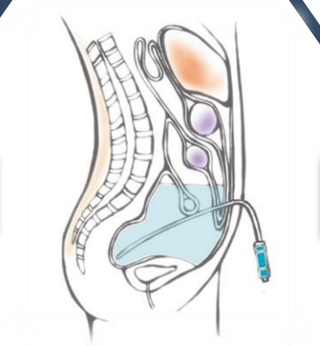


Osmo-Metabolic Agents:

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

Outcome of Intraperitoneal Glucose Load

Local effects



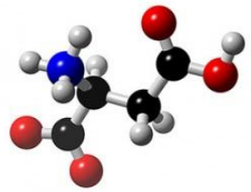
Systemic effects

Increased Cardiovascular Risk

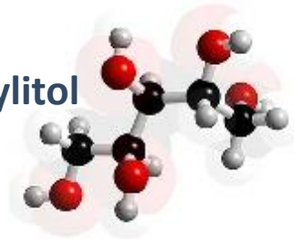
Mitigating the 'Load' in PD patients

The basic concept is to identify osmotic-agents able (a) to preserve peritoneal membrane wellfare and (b) to exert favorable metabolic effects to counteract common comorbidities like IR/diabetes in a combinatorial fashion …

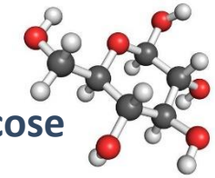
L-carnitine



D-Xylitol



D-Glucose

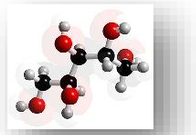


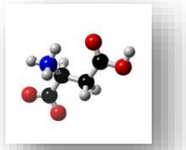
Xylitol's & Carnitine's highlights:

- Naturally occurring compounds
- Extremely stable (no degradation products when steam sterilized)
- Osmotic properties comparable to glucose
- Excellent biocompatibility profile (*in vitro*) than current osmotic agents for PD
- Excellent safety profile
- Therapeutic add on values (i.e., dysmetabolic diseases)
  - Modulation of gluconeogenesis (Carnitine & Xylitol)
  - Increase muscle insulin sensitivity (Carnitine)

Xylitol's highlights:

- 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





Previous *in vitro* and *in vivo* studies from our research team have shown that carnitine is an osmotic agent, with a biocompatibility profile better than glucose along with a favorable metabolic action in insulin resistant conditions

http://www.kidney-international.org original article

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]

Pharmacological Research 63 (2011) 157–164

Contents lists available at ScienceDirect

Pharmacological Research

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

Perspective

Pharmacological use of L-carnitine in uremic anemia: Has its full potential been exploited?☆

Mario Bonomini[a,*], Victor Zammit[b], Charles D. Pusey[c], Amedeo De Vecchi[d], Arduino Arduini[e,*]

Drug Design, Development and Therapy

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Effect of peritoneal dialysis fluid containing osmo-metabolic agents on human endothelial cells

J Nephrol
DOI 10.1007/s40620-014-0076-x

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

Pharmacology & Therapeutics 120 (2008) 149–156

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

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

Associate editor: K. Suckling

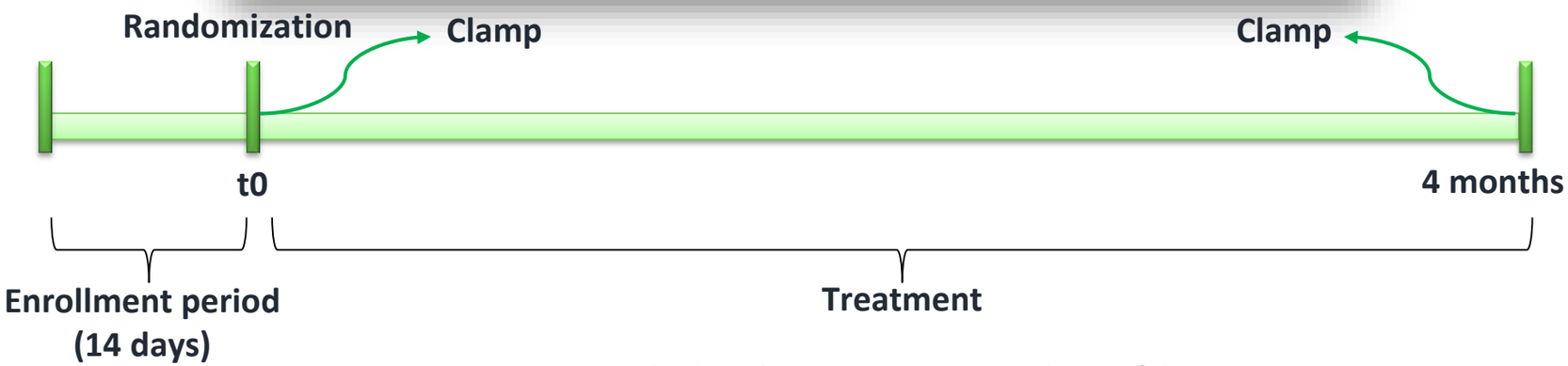
Carnitine in metabolic disease: Potential for pharmacological intervention

Arduino Arduini[a,*], Mario Bonomini[b], Vincenzo Savica[c], Antonino Amato[d], Victor Zammit[e]

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	

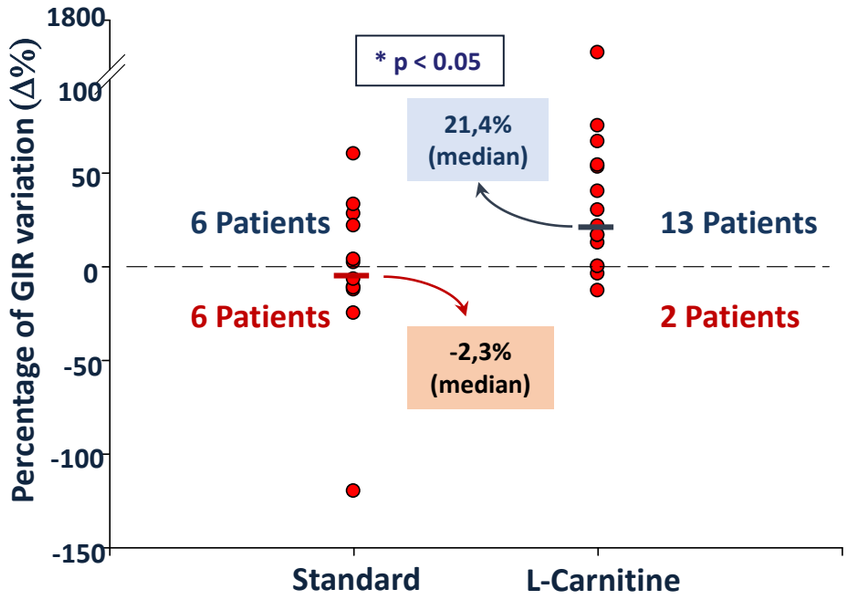
Primary end point: change in insulin sensitivity, evaluated by euglycemic hyperinsulinemic clamp

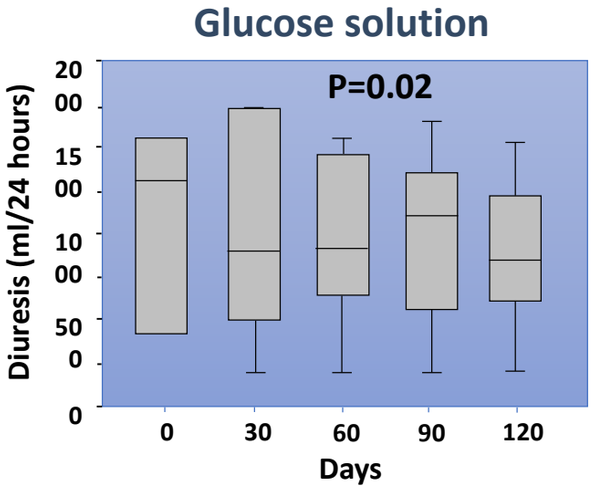
Am J Kidney Dis (2013) 62:929-38

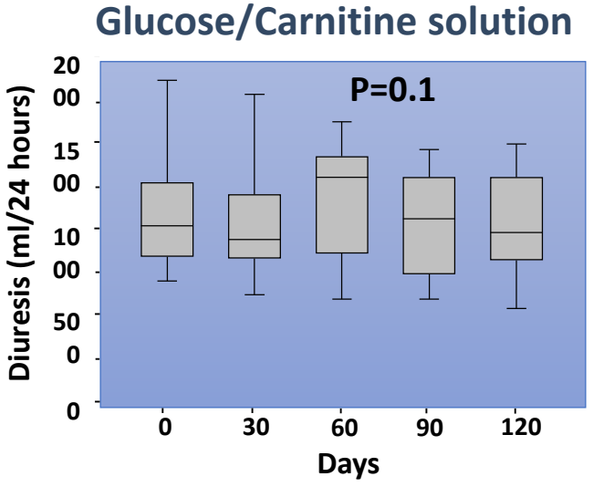
AJKD Am J Kidney Dis. 62(5):929-938. © 2013 I
Original Investigation

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]







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

- Study plan: from 5 to 11 months treatment with 4 daily exchanges of 2 L, 3 of which containing xylitol 1.5% and one with xylitol 3% (150 gr of xylitol daily load)
- Patient population: 6 PD patients with poorly controlled type I diabetes

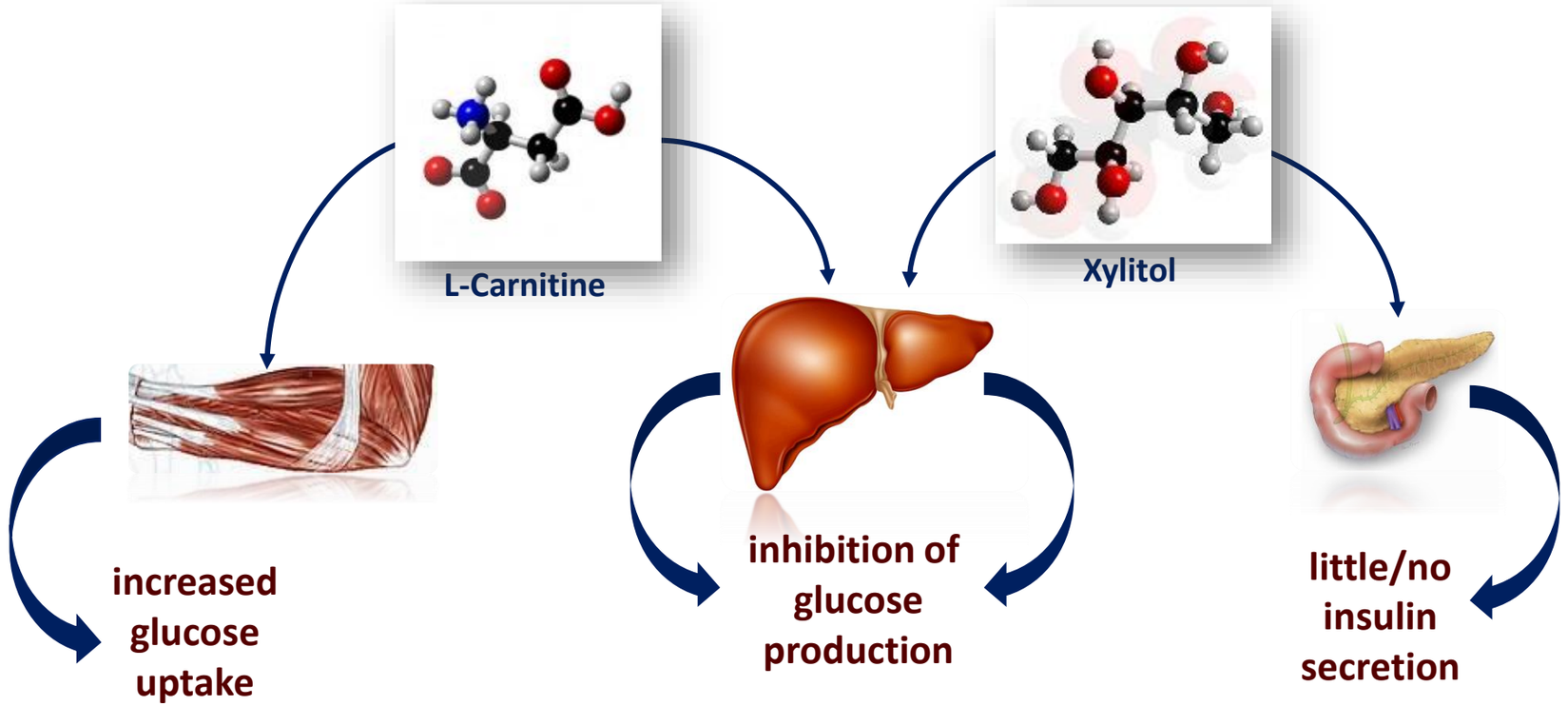
	before	after
Body weight (Kg)	58.3±12.4	56.4±11.6
MAP (mm Hg)	102±4.2	98±5.3
Peritoneal UF (ml/day)	1350	1460

Residual kidney function and ematochemical parameters (i.e., SGOT, SGPT, CPK, LDH γGT, bilirubin) were not different before and after xylitol treatment

	before	after
HbA1c (%)	12.9±0.82	10.7±1.08*
Insulin Dosage (UI)	124±16	59±14*
Uric acid (mg/dL)	5.6±0.7	9.1±1.0*
Lactic acid (mg/dL)	12.6±3.5	17.5±3.1*
Phosphorus (mg/dL)	4.3+1.1	2.8+0-7*
Triglycerides (mg/dL)	316±49	213±42*
Cholesterol	308±43	245±40*
HDL-Cholesterol	38±6.6	47±7.3*

Bazzato et al. Trans Am Soc Artif Intern Organs 1982

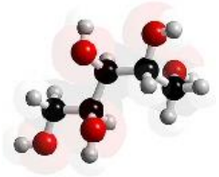
Combining xylitol & carnitine: glucose sparing along with an insulin-independent modulation of glucose disposal/production



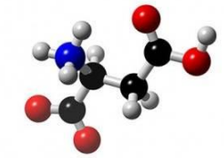
Composition of XyloCore Formulations:

Osmotic Strength	Low Strength (LS)	Medium Strength (MS)	High Strength (HS)
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 (0.02%)		
Sodium, mmol/L	132		
Calcium, mmol/L	1.3		
Magnesium mmol/L	0.5		
Chloride, mmol/L	101		
Lactate, mmol/L	35		
pH	7.2 ± 0.5		
Osmolarity mosmol/L	346.5	399.1	480.8

XyloCore® Low[a], Medium[b] and High Strength[c] correspond to Physioneal®, Fixioneal® or Dianeal® containing 1.36%[a] 2.27%[b] and 3.86%[c] (w/v) glucose and Balance®, Bicavera® or other Fresenius PD solutions with 1.5%[a], 2.3%[b] and 4.25%[c] (w/v) glucose, respectively. Differences within the same category of osmotic strength of less than 3%.



Ongoing Clinical Trial with XyloCore…



FIRST

Efficacy and SaFety Assessments of a Peritoneal DIalysis Solution Containing Glucose, Xylitol and L-CaRnitine Compared to STandard PD SoluTions in Continuous Ambulatory Peritoneal Dialysis (NCT 0400136)

- A phase II, prospective, investigational, open, multi-center study -

Primary objectives

To assess the safety and tolerability of the experimental solutions by:

- **recording the incidence and severity of adverse events;**
- **recording a subjective questionnaire on the patient's perception of well being;**
- **monitoring the changes in routine blood biochemical and hematological parameters.**

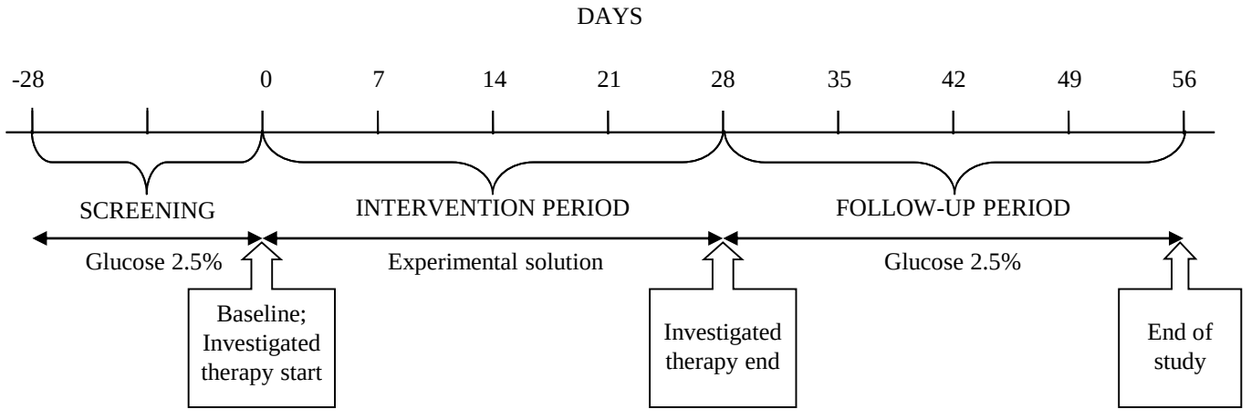
Secondary objectives

To assess the effects of experimental solutions:

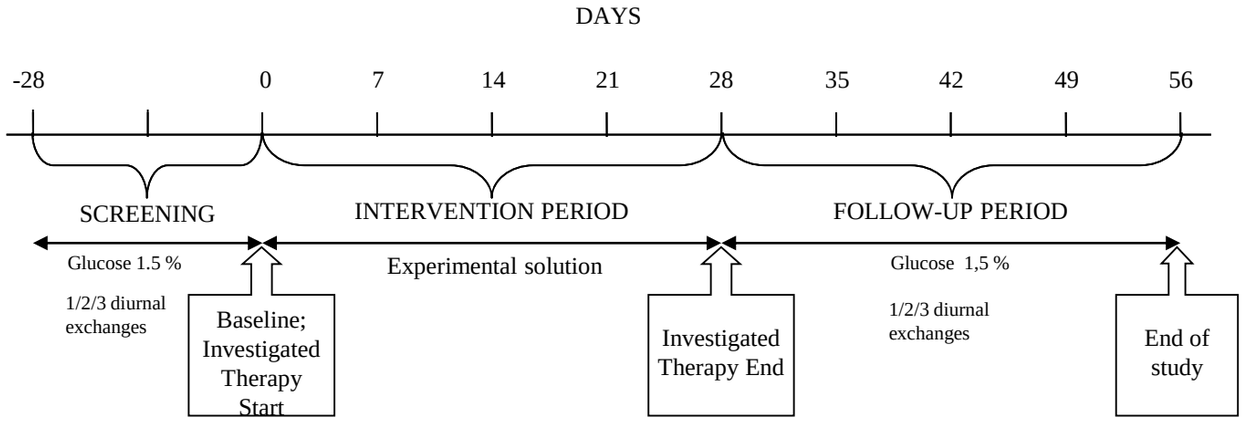
- **peritoneal clearances;**
- **peritoneal transport characteristics with respect to Day 0 and the follow-up period**

Study Design

Group A



Group B



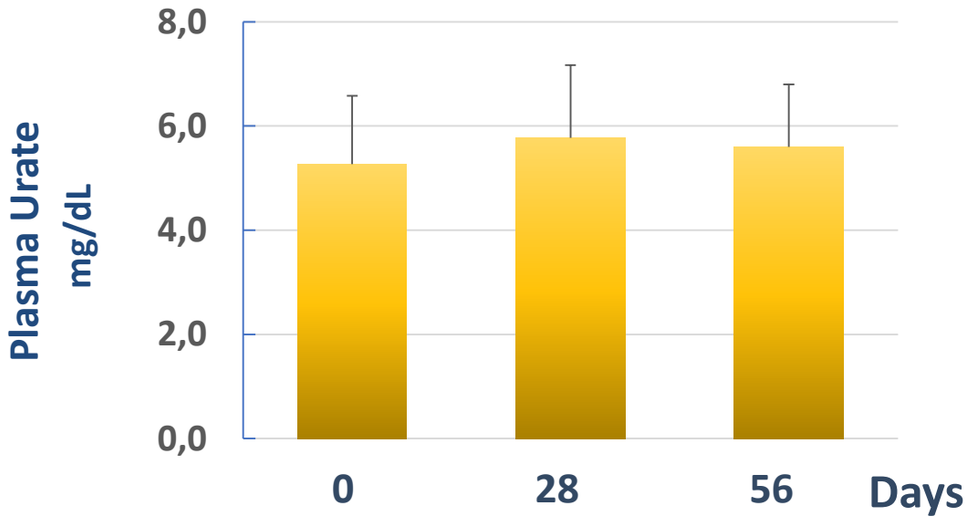
Patients recruited

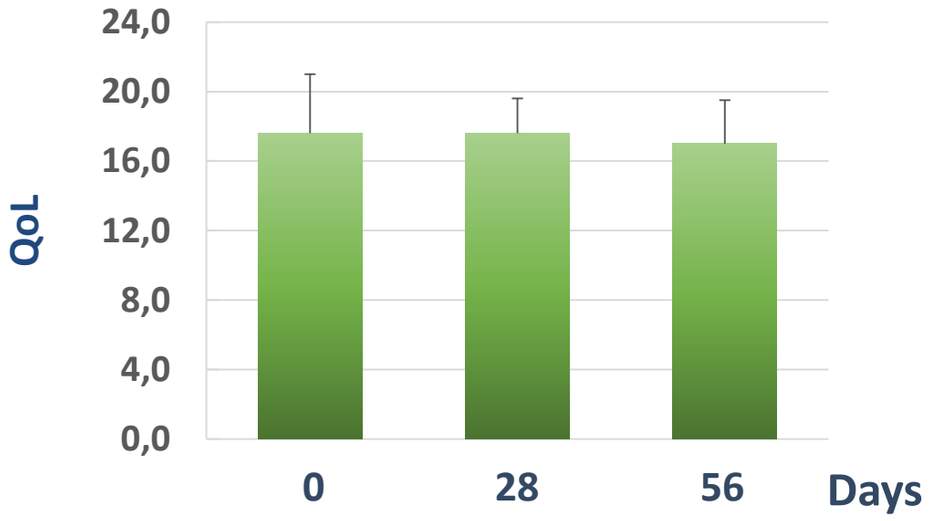
3 F, 4 M; age 70±5.8 years
dialytic age 8.9±1.9 months

4 M; age 56±12 years
dialytic age 9.5±0.6 months

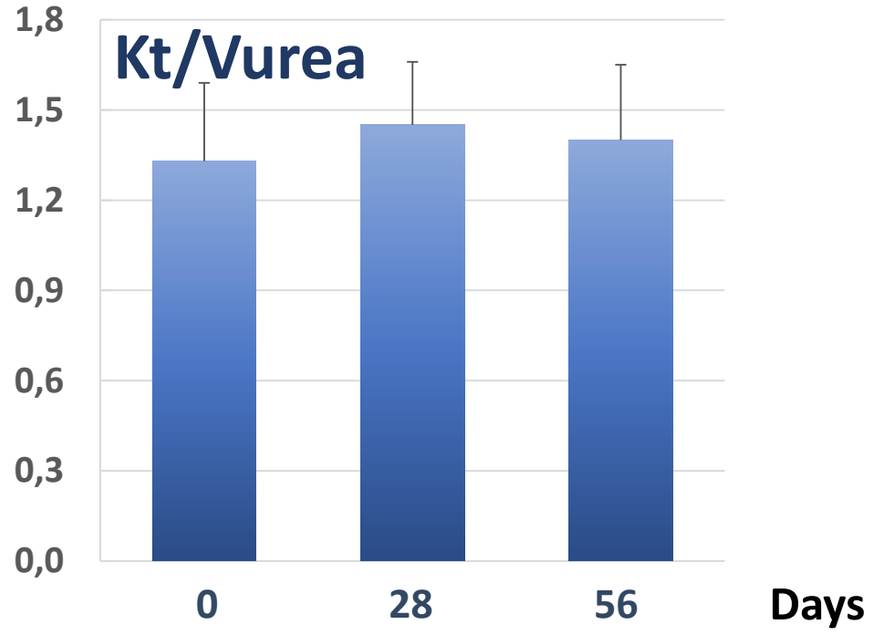
Safety and Tolerabilty Outcomes

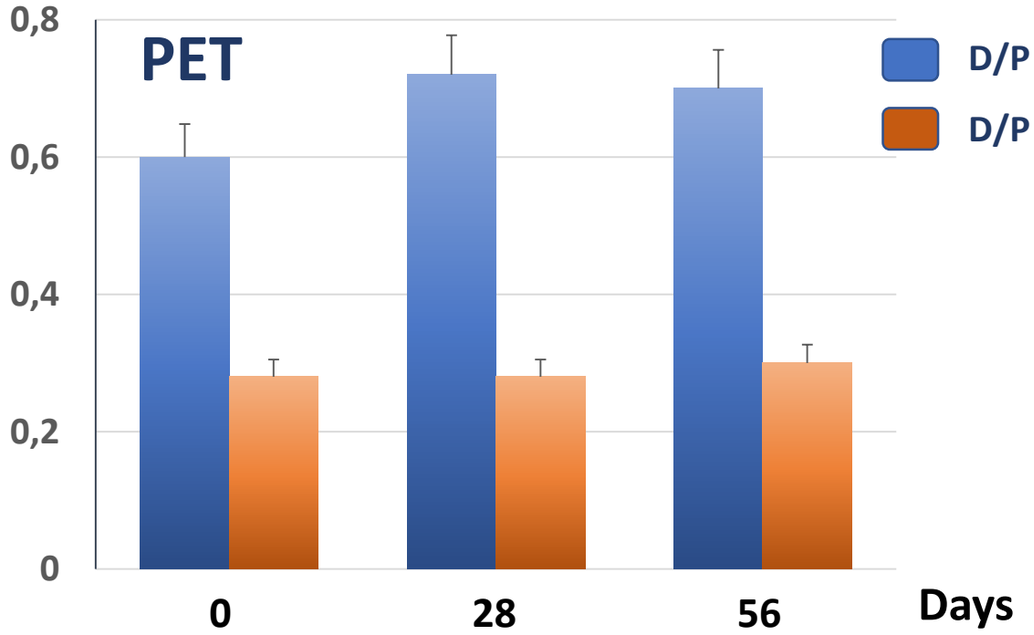
- ✓ No minor or major adverse events were recorded
- ✓ No significant differences of blood biochemical and hematological parameters were observed throughout the clinical trial

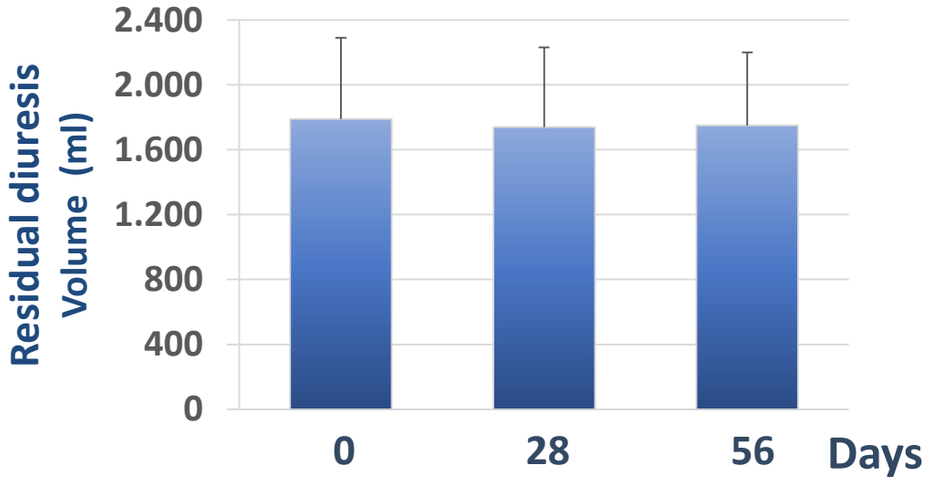


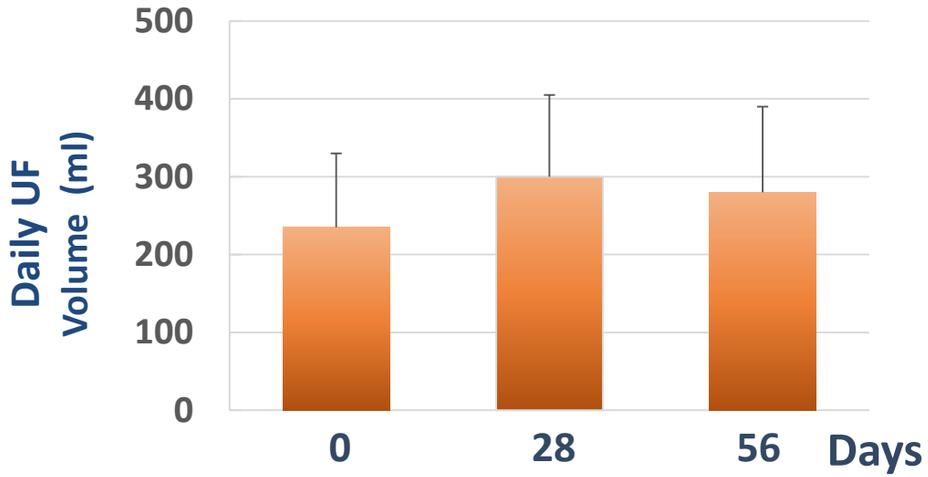


Efficacy Outcomes









Planned Clinical Trial with XyloCore …

ELIXIR

A Study to **E**va**L**uate the Eff**I**cacy and Safety of **X**yloCore, a Glucose Spar**I**ng Expe**R**imental 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:
Primary Endpoint of this study in CAPD patients is to demonstrate the non-inferiority of XyloCore compared to the Physioneal with regards to safety and efficacy. The primary outcome measure is total weekly Kt/V_{urea} after a 24-week period using the assigned PD solution, assessed using a peritoneal function test.
*Secondary Endpoints are: c*hanges in glycemic control medication use, as defined by a change in medication dose and use in diabetic CAPD patients (Type 1 and 2); Changes from the baseline value of total, LDL, HDL and LDL cholesterol, serum triglycerides, and insulin in all CAPD; Quality of Life; Hematological parameters (hemoglobin and EPO requirements).

COREQUEST

ELIXIR

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

إكسير

Investigators:	**Multi-Center (Germany, Italy, Denmark, Spain, UK, Sweden, Israel)** **Germany is the reference member state (Decentralized Procedure)**
Sample size:	Planned 170 patients.
Study Population	Male and female, adults' patients with End Stage Renal Disease (ESRD) on CAPD since at least 3 months, in clinical stable condition.

Pre-clinical and clinical data, study design and endpoints were recently discussed during a 'Scientific Advice' with the German Drug Agency (BfArM). The agency agreed that all the documentation presented supported the study design for the planned single pivotal phase III study.

- **Coordinating Investigator:**
  - **Prof. Werner Kleophas (Germany)**
- **Chairman:**
  - **Prof. Piergiorgio Messa (Italy)**
- **National Coordinators:**
  - **Prof. Simon Davies (UK)**
  - **Prof. Mario Bonomini (Italy)**
  - **Prof. Olof Heimburger (Sweden)**
  - **Prof. Johan Povlsen (Denmark)**
  - **Prof. Alberto Ortiz (Spain)**
  - **Prof. Tatiana Tanisiychuk (Israel)**

Iperboreal Pharma

Maybe XyloCore will be the right ingredient of إكسير to rescue Achilles