NHS Great Ormond Street Hospital for Children Learning Academy

Advances in Paediatric Dialysis

UNIVERSITEIT GENT

UREMIC TOXINS: WHAT THEY DO AND HOW TO CLEAR THEM

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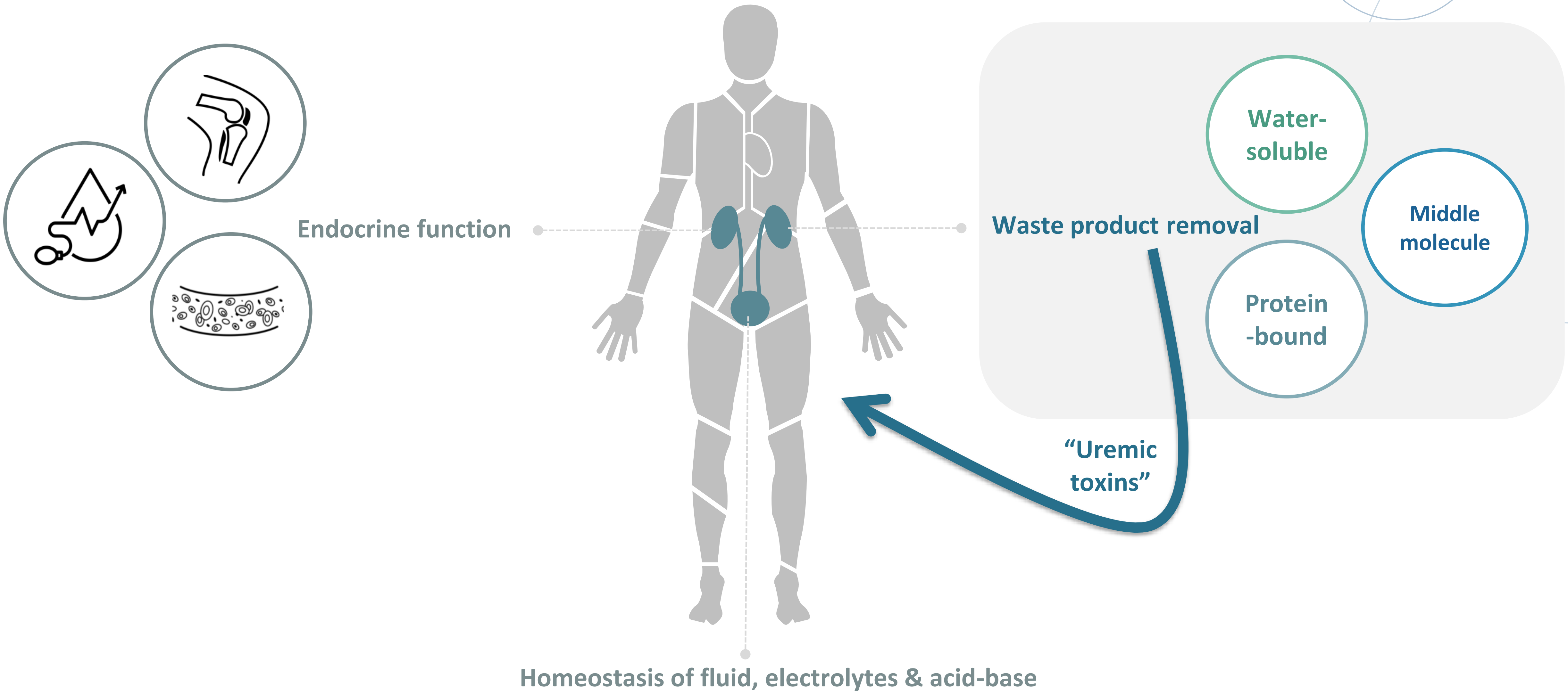
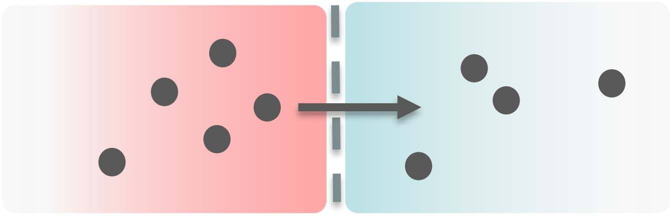
fwo UToPaed UNIVERSITEIT GENT HDF, hearts & height study

Introduction



Introduction

Water-soluble



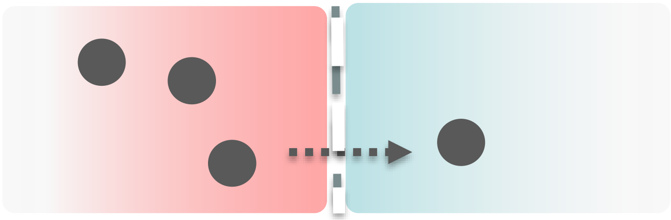
MW < 500 Da

Diffusion

Concentration gradient

Urea

Middle molecule



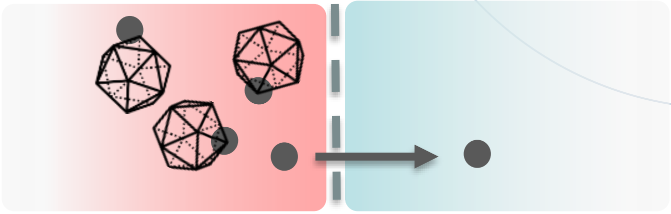
MW > 500 Da

Convection

Pressure gradient

B2-microglobulin

Protein-bound



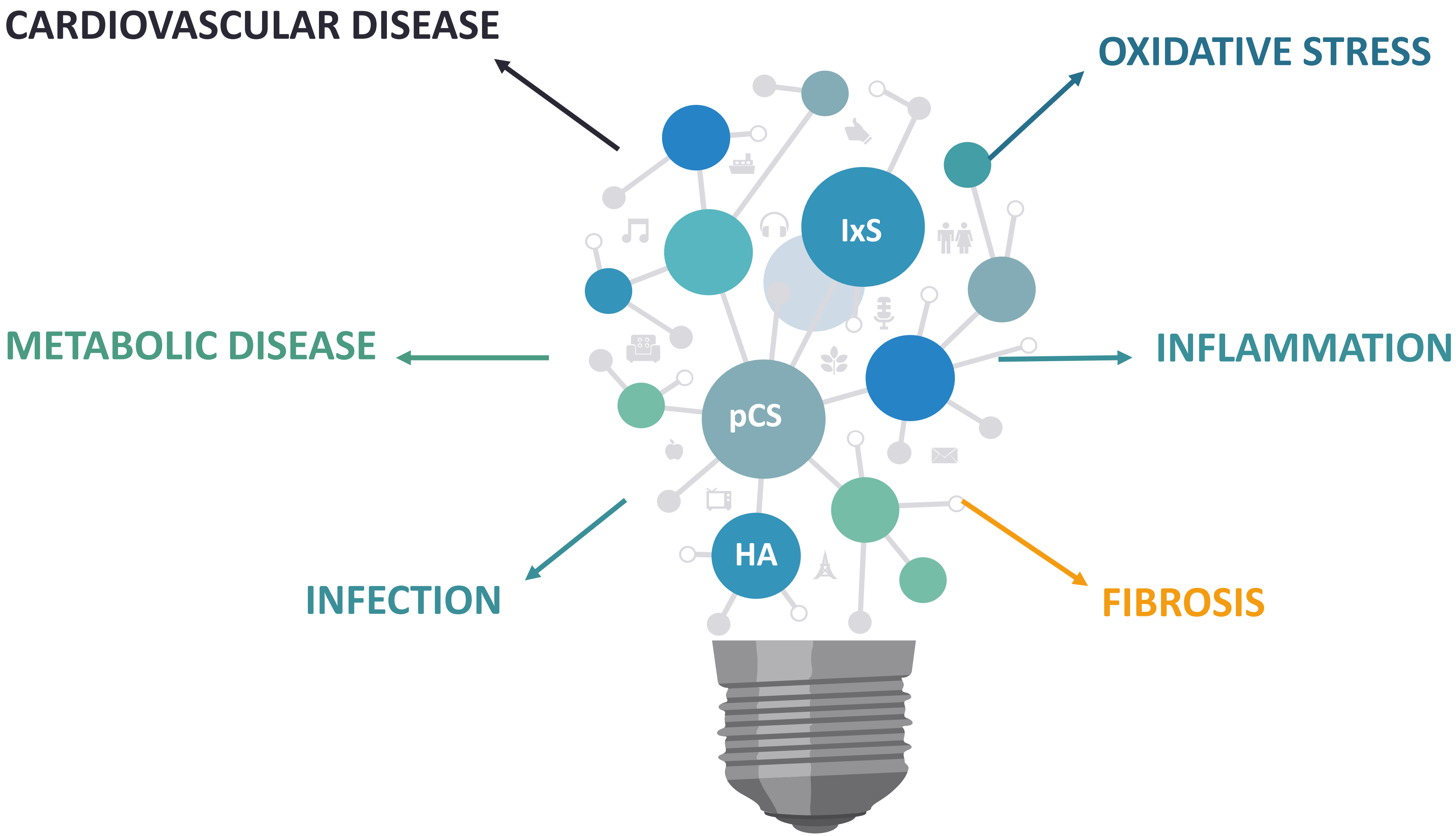
< 500 Da, protein-bound

Diffusion, convection, adsorption

Indoxyl sulfate, p-cresylsulfate

Uremic toxins, what they do?

Pathophysiology



Which uremic toxins are making our patient sick?

- Confounding factors (pre-existing CV disease)
- Large inter-patient variability
- Inability to decrease a single compound
- Complex and multifactorial interplay between different key elements, present for longer time

Which uremic toxins are making our patient sick?

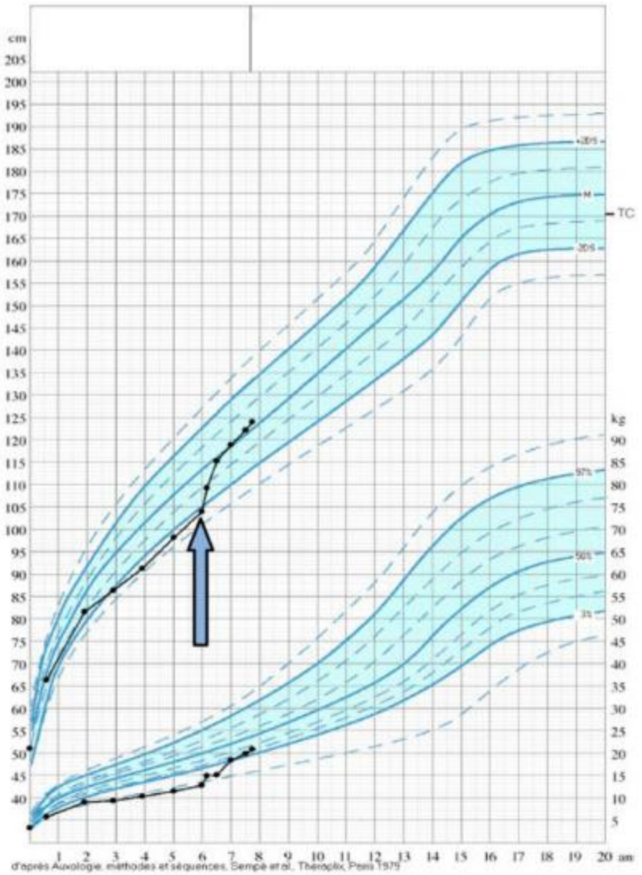
No confounding factors
or co-morbidities

Isolated kidney disease

Growth

Opportunities in
pediatric population

Enhancing uremic solute removal improves growth



Nephrol Dial Transplant (2010) 25: 867–873
doi: 10.1093/ndt/gfp565
Advance Access publication 4 November 2009

Daily online haemodiafiltration promotes catch-up growth in children on chronic dialysis

Michel Fischbach, Joelle Terzic, Soraya Menouer, Céline Dheu, Laure Seuge and Ariane Zalosczic

Nephrology Dialysis Transplantation Children's Unit, University Hospital Hautepierre, Avenue Molière, 67098 Strasbourg, France

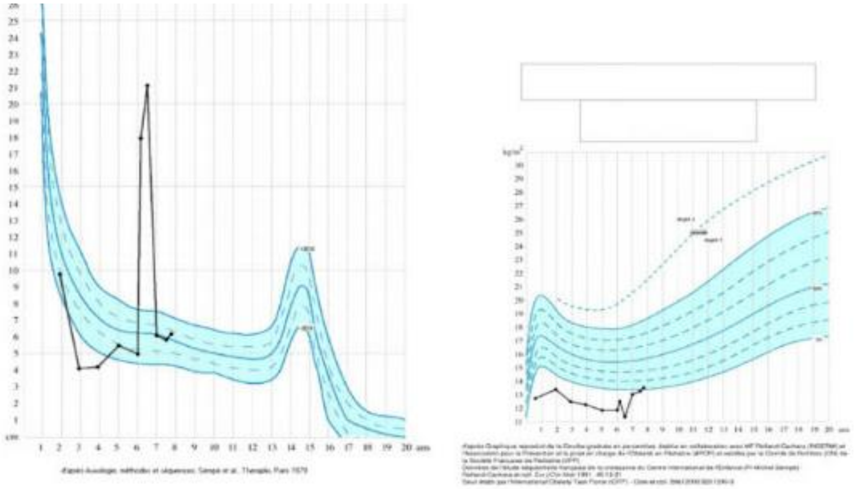


Figure 2 Daily intensive online hemodiafiltration (↑) promotes catch-up growth (from reference 12).

In pediatrics?

Pediatric Nephrology (2018) 33:921–924
https://doi.org/10.1007/s00467-018-3920-8

EDITORIAL COMMENTARY

CrossMark

A plea for more uremic toxin research in children with chronic kidney disease

Evelien Snauwaert[1] • Wim Van Biesen[2] • Ann Raes[3] • Griet Glorieux[2] • Raymond Vanholder[2] • Johan Vande Walle[3] • Sunny Eloot[2]

Received: 30 January 2018 / Revised: 9 February 2018 / Accepted: 9 February 2018 / Published online: 2 March 2018

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UToPaed study: uremic toxins in pediatric CKD

more advanced and appropriate tools to improve management of children with CKD

Great Ormond Street Hospital Charity

UZA Kennis / Ervaring / Zorg

Cliniques universitaires SAINT-LUC UCL BRUXELLES

UZ

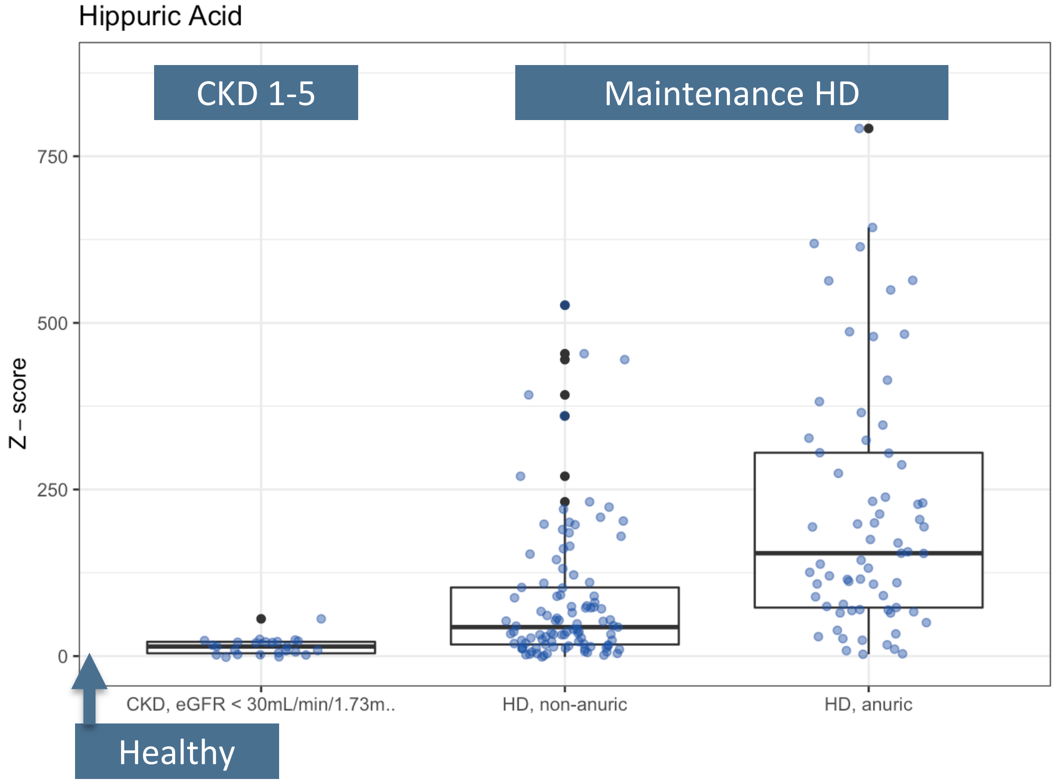
UZ LEUVEN

CHU de Liège

Hôpital Universitaire des Enfants Reine Fabiola

Universitair Kinderziekenhuis Koningin Fabiola

Pediatric reference frame



50 healthy children
65 children CKD stage 1-5 (not on dialysis)
170 children hemodialysis

6 protein-bound uremic toxins
4 small water-soluble uremic toxins
2 middle molecules

Ensure use of biologically relevant uremic toxin levels in experimental studies

Allow proper design of studies

Snauwaert et al. 2018 (NDT), Snauwaert et al. 2018 (Ped Nephrol), Snauwaert et al. 2019 (Toxins)

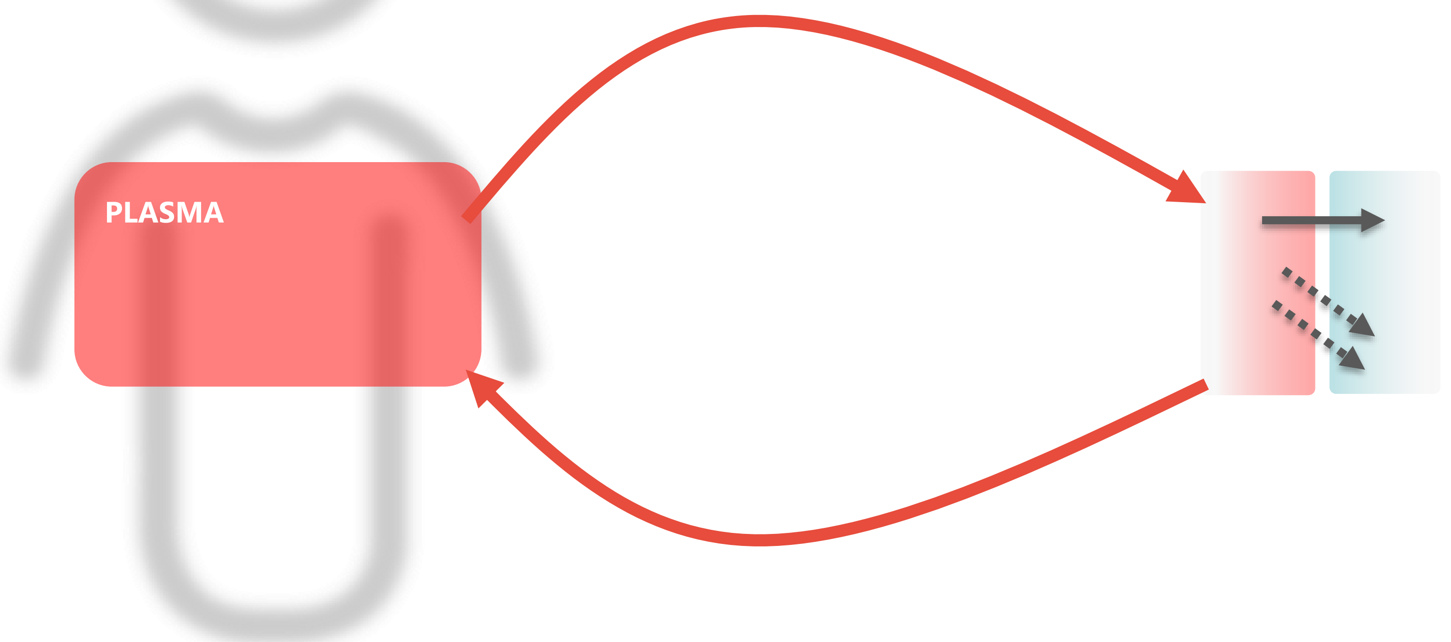
Results from observational study to be announced soon

Uremic toxins, how to clear them?

How to clear uremic toxins?

2 SOLUTE TRANSPORT IN THE PATIENT

1 SOLUTE REMOVAL AT THE DIALYZER

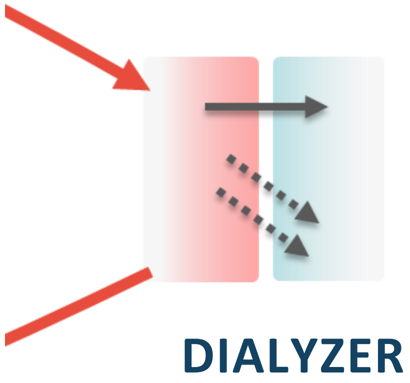


Kinetics
Total solute removal (mass)

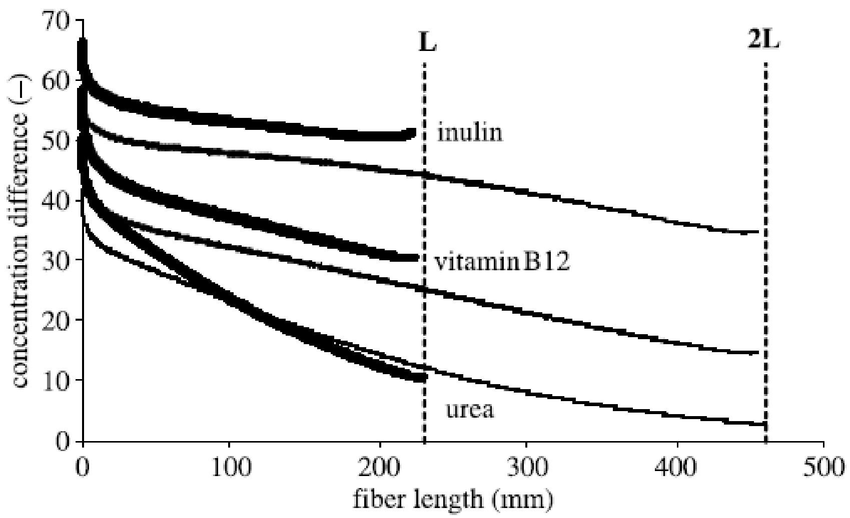
↔

Clearance &
extraction ratio

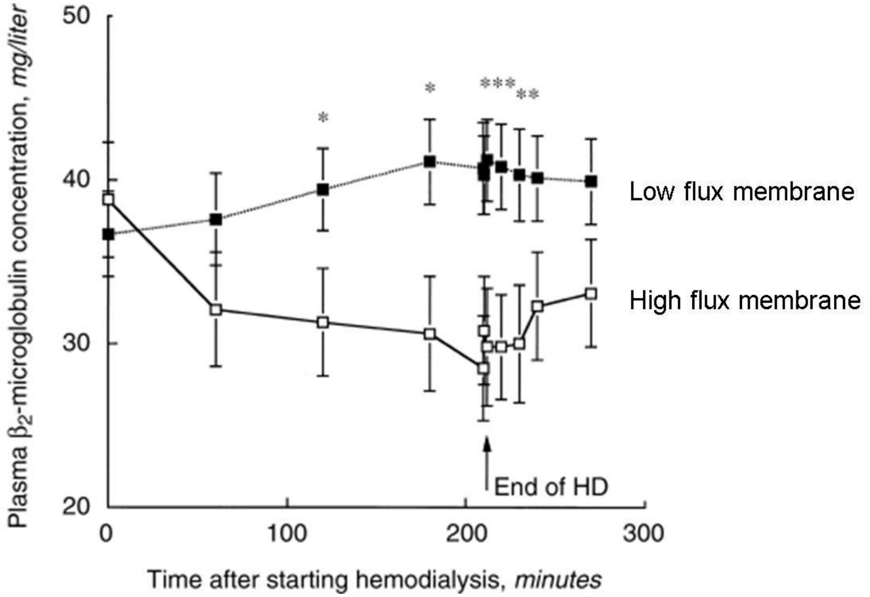
Solute transport in the dialyzer



Clearance and extraction ratio ≈ blood flow + membrane + dialysate flow



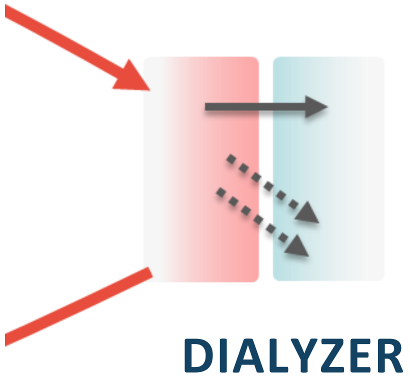
Dialyzer fiber length, diameter and permeability

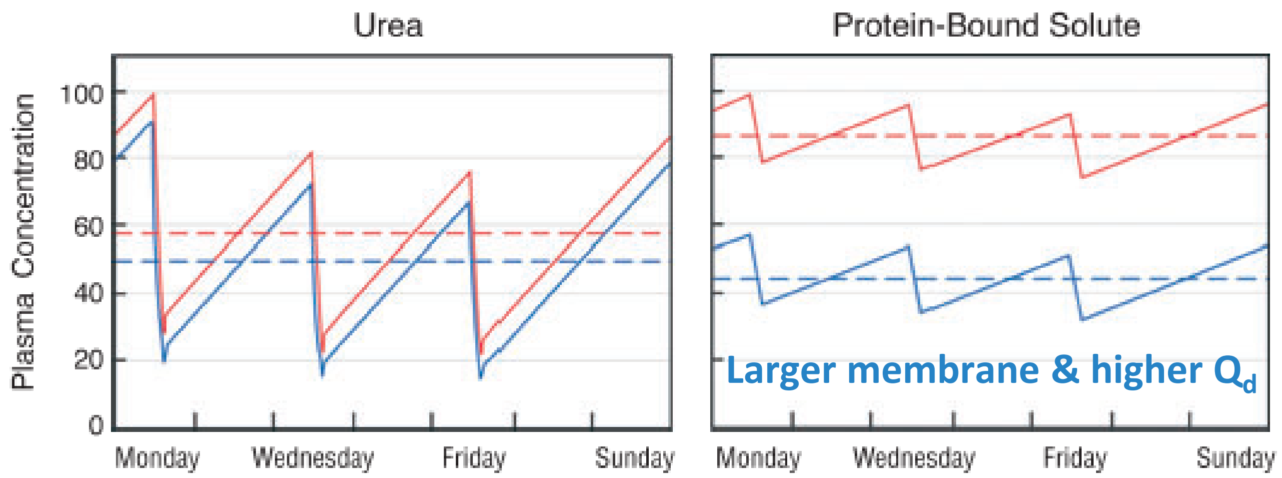


Adding convection to diffusion

Eloot et al., Comp Meth Biomech Biomed Eng 2006; Leypoldt et al., Kidney Int, 1999

Solute transport in the dialyzer





TAC_{urea} decreases by 15%

TAC_{solute} decreases by 50%

Table 2. Instantaneous clearance (mL/min) at 60 min

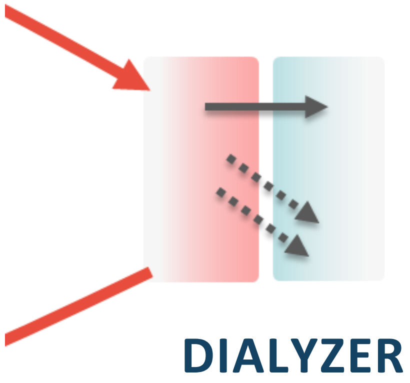
	Post-HDF	Pre-HDF	Pre-HF
Urea	243.0 ± 18.7	230.1 ± 10.5*	150.7 ± 15.0°°,§§
Creatinine	179.4 ± 48.3	148.9 ± 22.3*	103.7 ± 19.9°°,§§
Uric acid	166.4 ± 14.1	153.4 ± 9.8*	104.8 ± 8.9°°,§§
β_2M	82.8 ± 16.1	67.2 ± 18.5*	87.5 ± 9.6§
Hippuric acid	131.2 ± 15.6	121.4 ± 13.1*	68.7 ± 23.9°,§
Indole acetic acid	66.6 ± 8.6	67.5 ± 9.3	38.8 ± 5.4°°,§§
Indoxylsulfate	33.4 ± 7.4	34.7 ± 9.9	18.7 ± 6.6°°,§§
p-Cresylsulfate	23.5 ± 4.6	24.6 ± 6.4	12.9 ± 2.5°°,§§
CMPF			

Pre-HDF versus post-HDF: **P* < 0.017, ***P* < 0.001; pre-HF versus post-HDF: °*P* < 0.017, °°*P* < 0.001; pre-HF versus pre-HDF: §*P* < 0.017, §§*P* < 0.001.

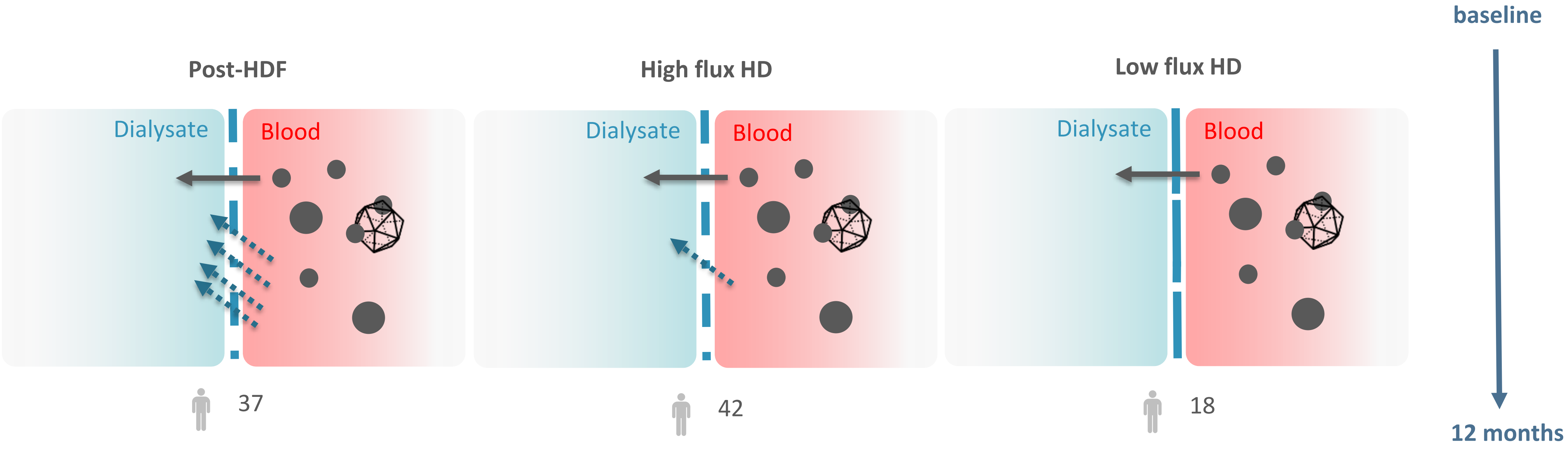
Diffusion = well established removal strategy of free fraction protein-bound uremic toxins

Meyer et al., Seminars in dialysis 2011; Sirich et al., NDT, 2012; Meert et al., NDT, 2009

Solute transport in the dialyzer

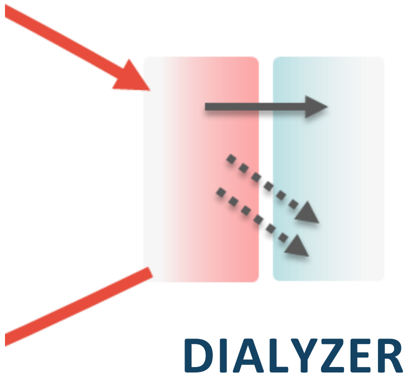


Research question: does post-HDF decrease levels of protein-bound uremic toxins ?

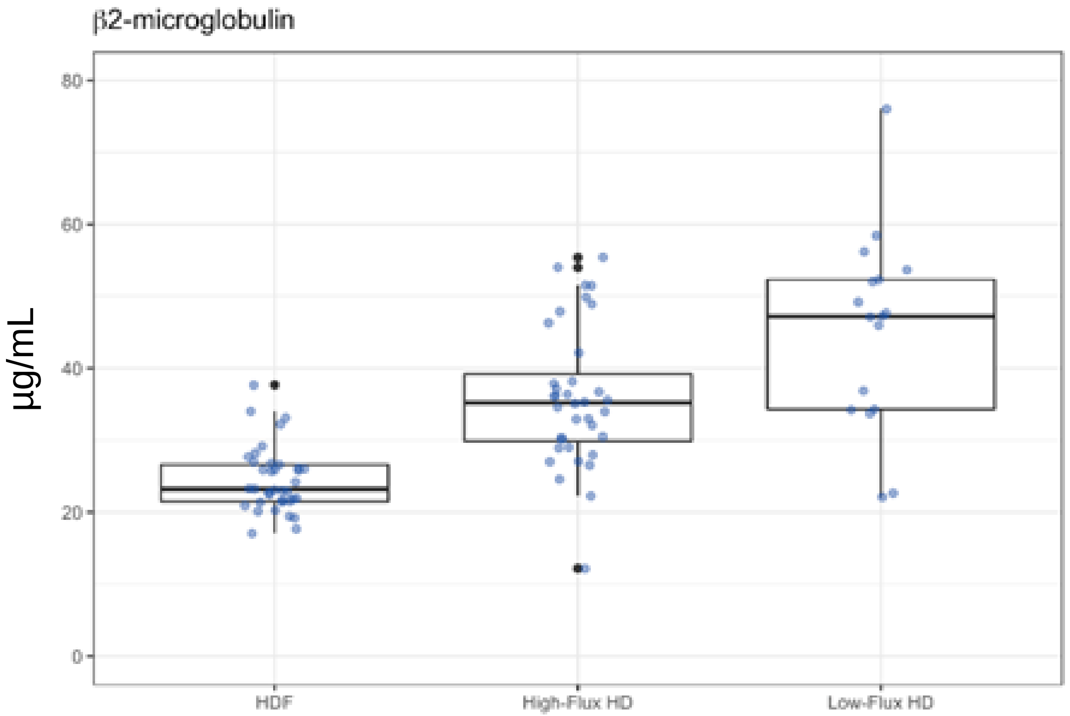


Snauwaert et al., NDT, 2020 Apr 1;35(4):648-656.

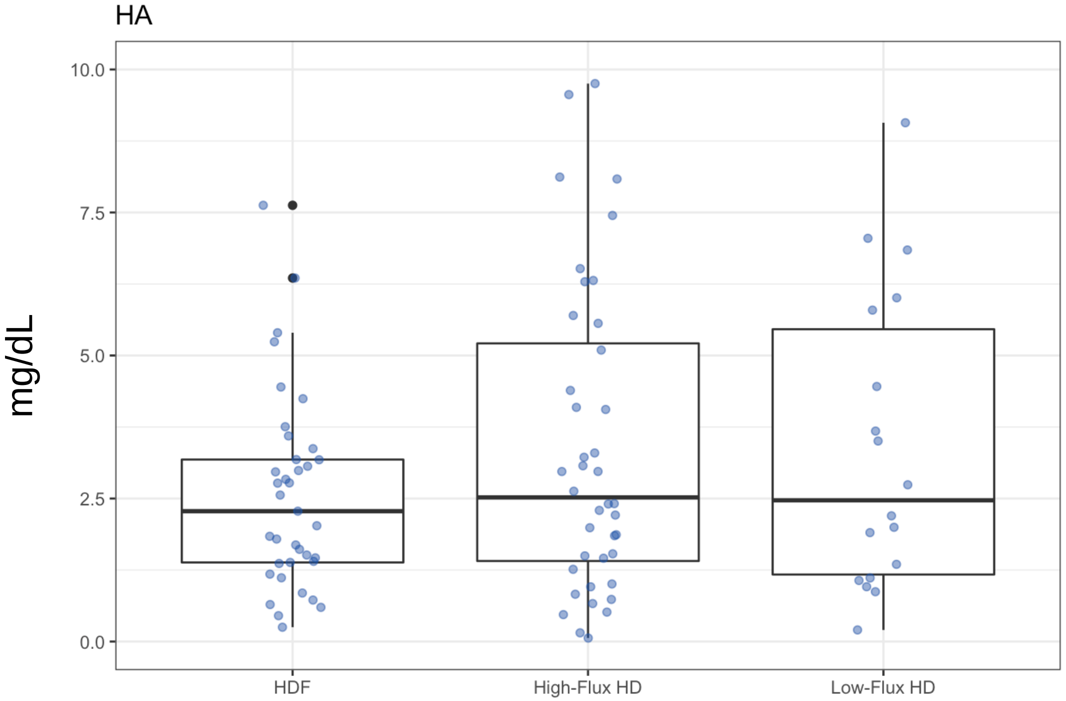
Solute transport at the dialyzer



MIDDLE MOLECULES

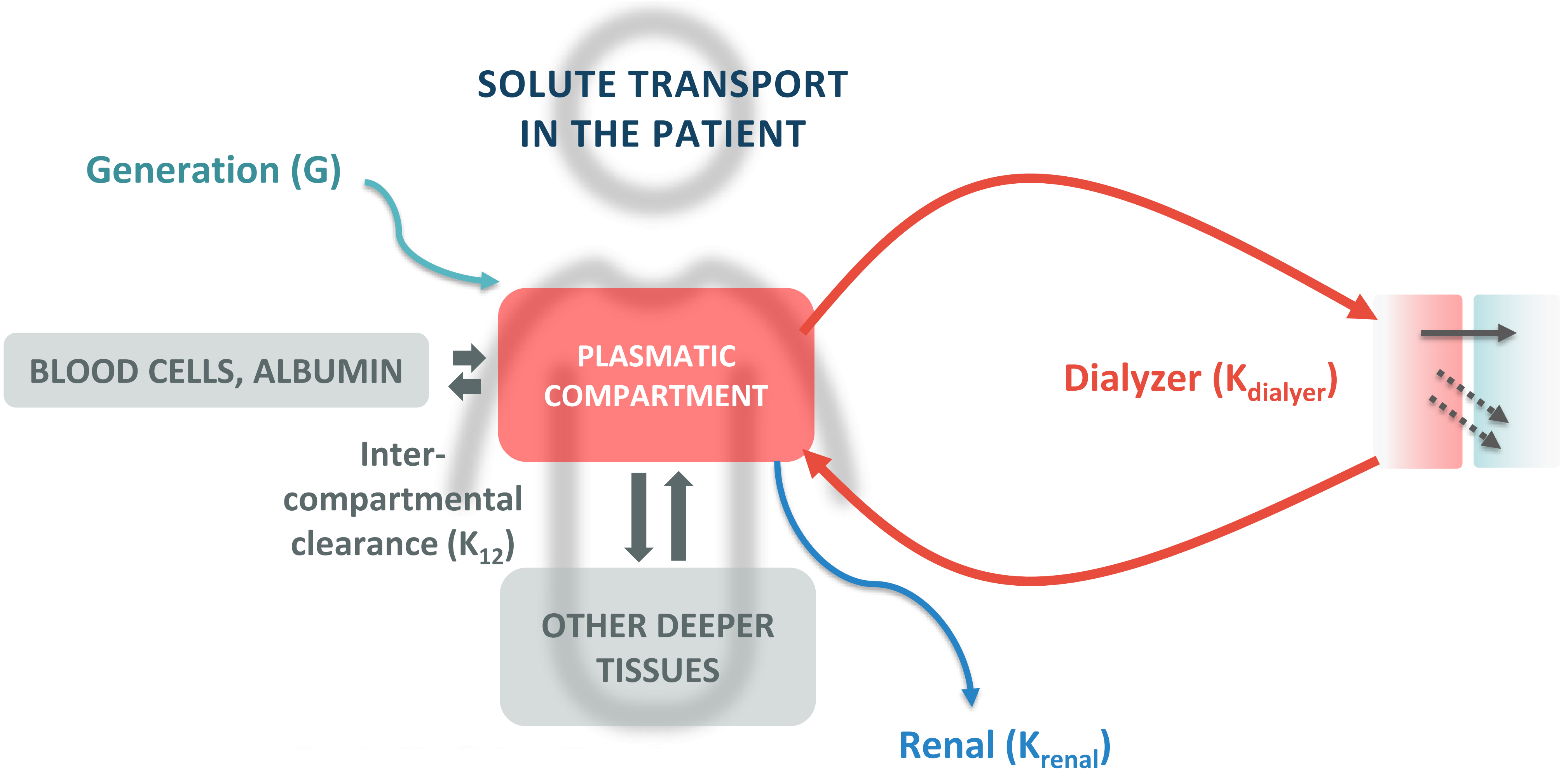


PROTEIN-BOUND UREMIC TOXINS



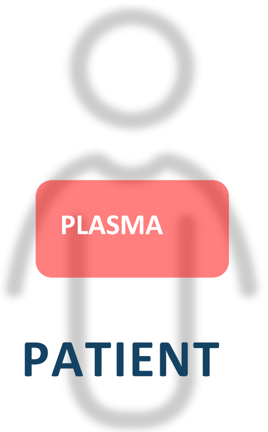
Snauwaert et al., NDT, 2020 Apr 1;35(4):648-656.

Solute transport in the patient

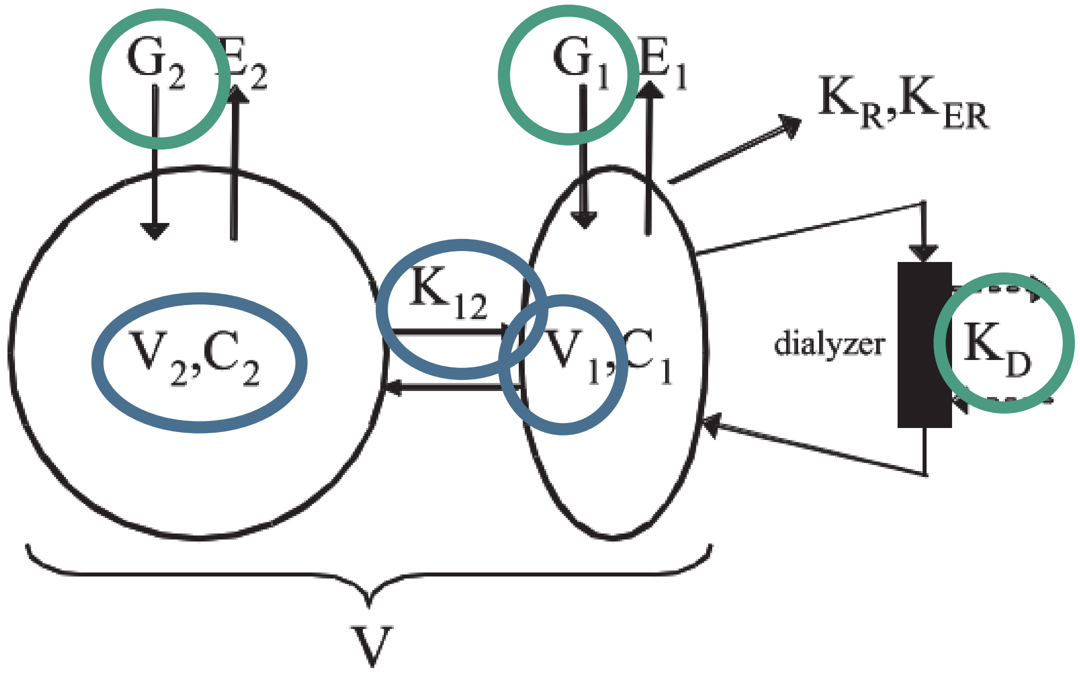


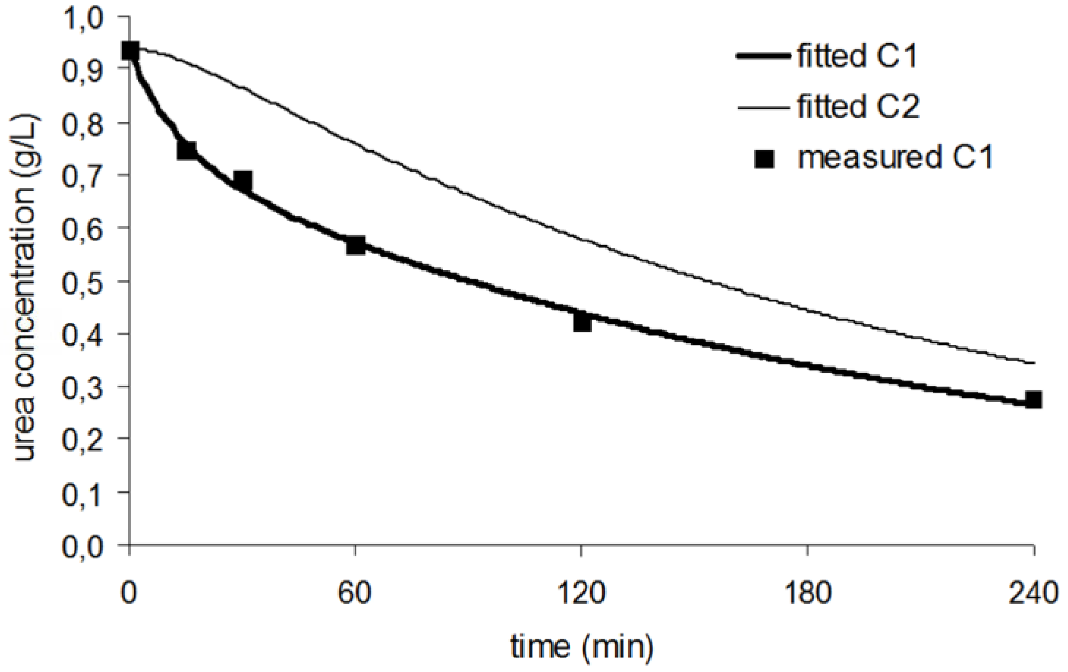
Eloot et al., Seminars in Dialysis, 2012

Solute transport in the patient



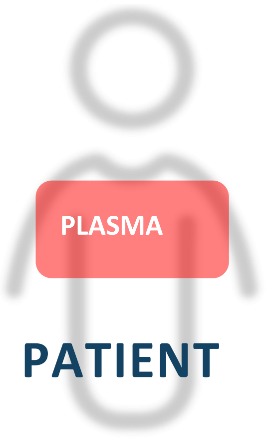
Two-compartiment kinetic model

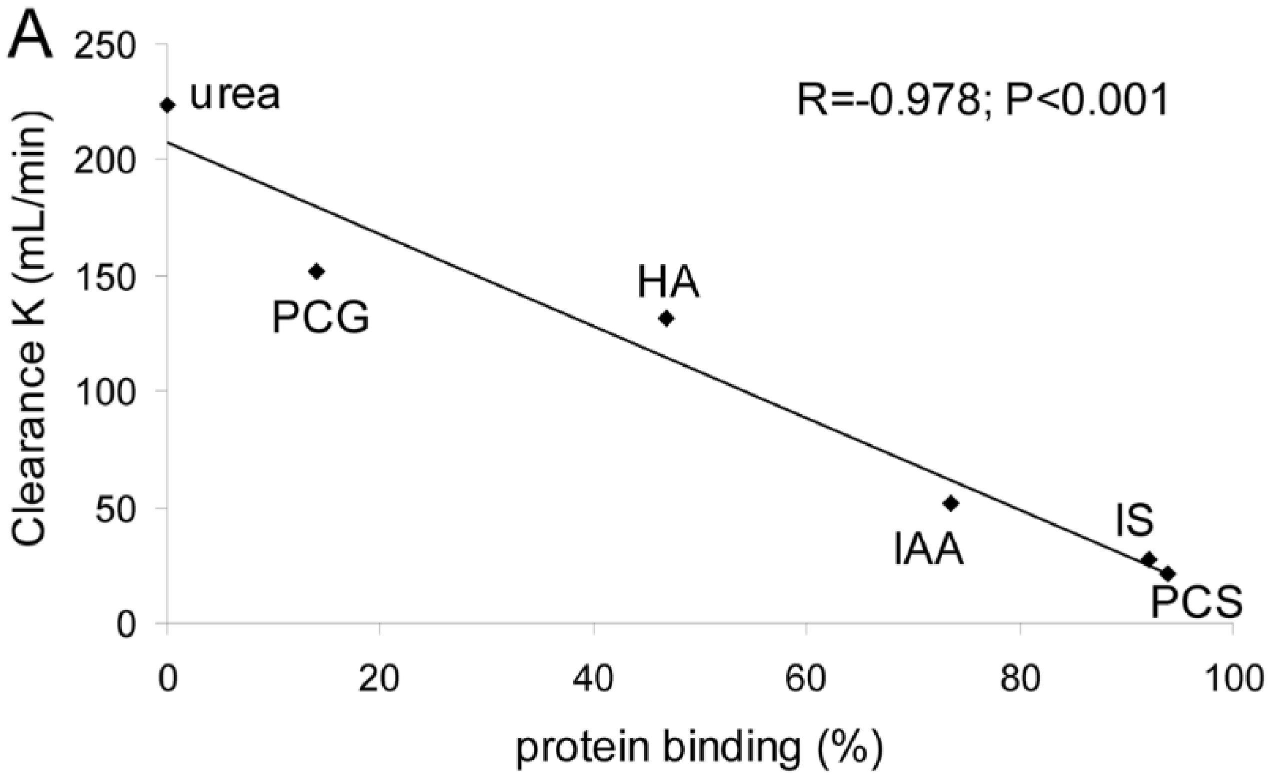




Eloot et al., Seminars in Dialysis, 2012; Eloot et al., PLOS one, 2016

Solute transport in the patient



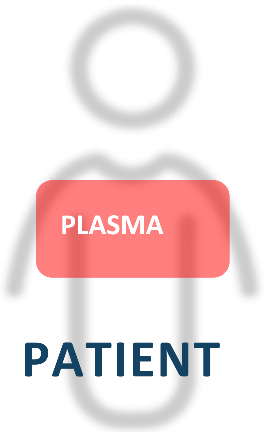


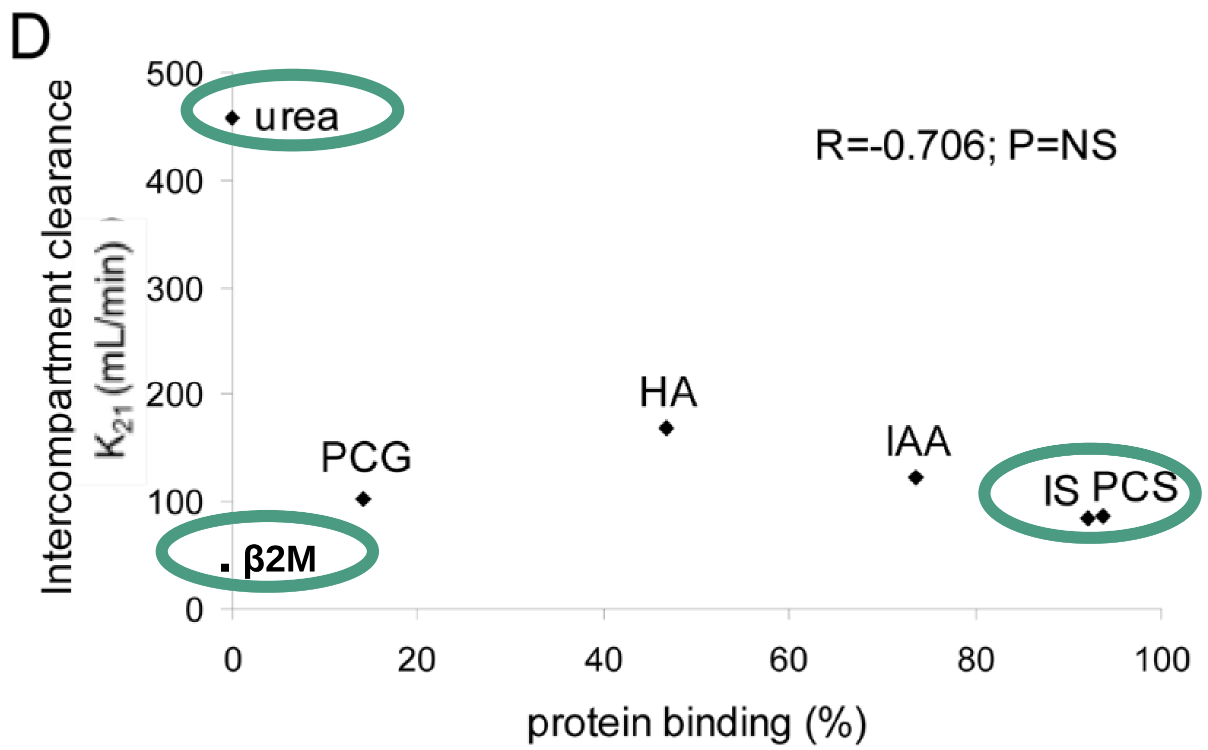
Dialyzer clearance shows an inverse relation with % protein-binding

Only free fraction can be removed!

Eloot et al., PLOS one, 2016

Solute transport in the patient





Multicompartimental distribution + slow intercompartimental clearance (K12)

= slow transport into the plasma

Eloot et al., PLOS one, 2016

Solute transport at the dialyzer

Haemodiafiltration does not lower protein-bound uraemic toxin levels compared with haemodialysis in a paediatric population

Evelien Snauwaert[1], Wim Van Biesen[1], Ann Raes[1], Griet Glorieux[1], Johan Vande Walle[1], Sanne Roels[2], Raymond Vanholder[1], Varvara Askiti[3], Karolis Azukaitis[4], Aysun Bayazit[5], Nur Canpolat[6], Michel Fischbach[7], Krid Saoussen[8], Mieczyslaw Litwin[9], Lukasz Obrycki[9], Fabio Paglialonga[10], Bruno Ranchin[11], Charlotte Samaille[12], Franz Schaefer[13], Claus Peter Schmitt[13], Brankica Spasojevic[14,15], Constantinos J. Stefanidis[3], Rukshana Shroff[16,*] and Sunny Eloot[1,*]

Snauwaert et al., NDT, 2020 Apr 1;35(4):648-656.

Seminars in Dialysis

A Sad but Forgotten Truth: The Story of Slow-Moving Solutes in Fast Hemodialysis

Sunny Eloot, Wim Van Biesen, and Raymond Vanholder
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Does the Adequacy Parameter Kt/V_{urea} Reflect Uremic Toxin Concentrations in Hemodialysis Patients?

Sunny Eloot*, Wim Van Biesen, Griet Glorieux, Nathalie Neirynck, Annemieke Dhondt, Raymond Vanholder

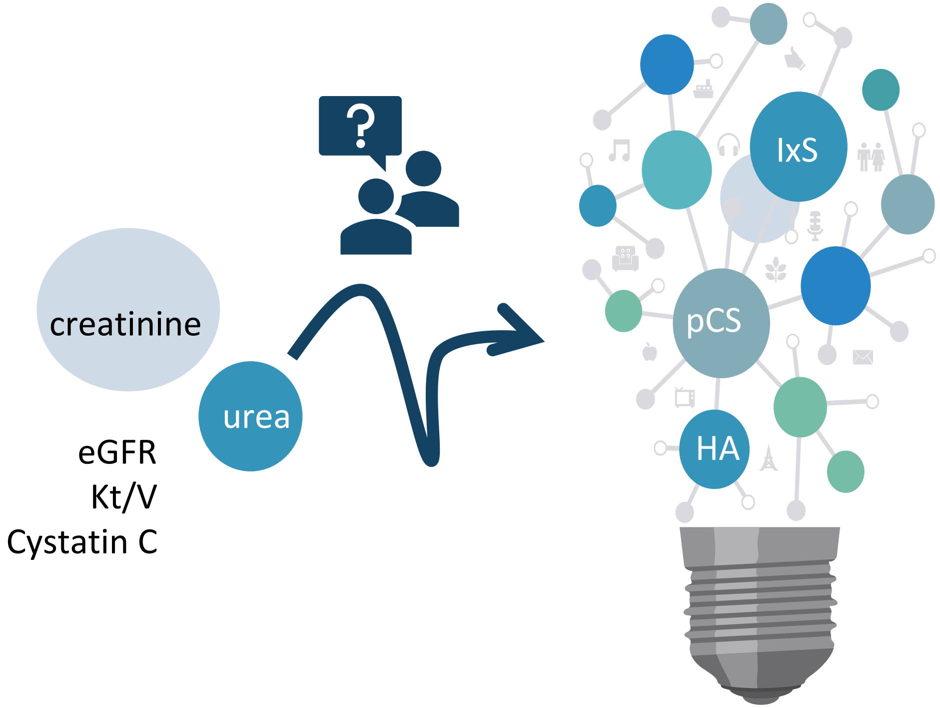
Nephrology Section, Department of Internal Medicine, Ghent University Hospital, Gent, Belgium

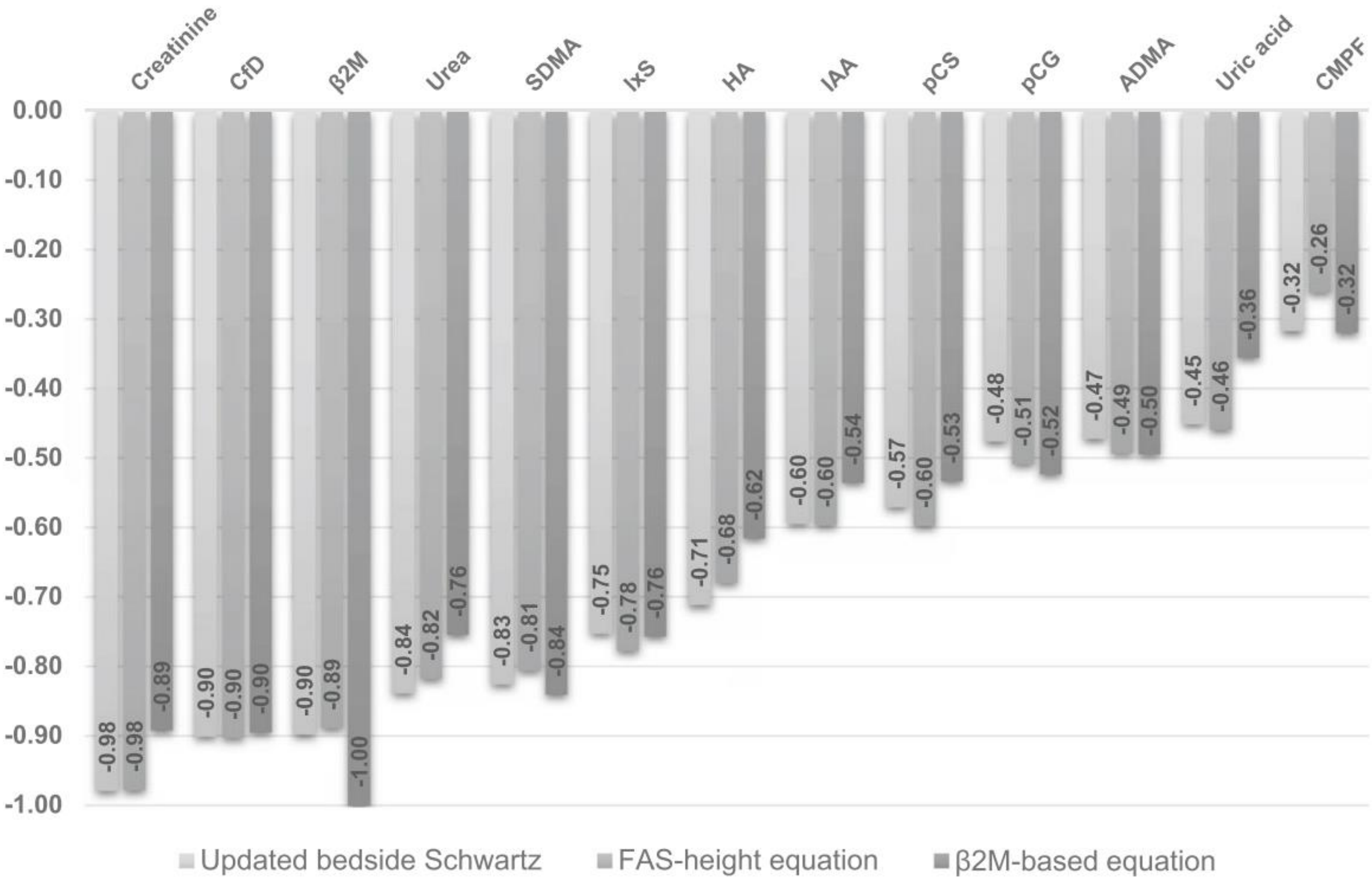
PLOS | ONE

Abstract

Hemodialysis aims at removing uremic toxins thus decreasing their concentrations. The present study investigated whether Kt/V_{urea}, used as marker of dialysis adequacy, is correlated with these concentrations. Predialysis blood samples were taken before a midweek session in 71 chronic HD patients. Samples were analyzed by colorimetry, HPLC, or ELISA for a broad range of uremic solutes. Solute concentrations were divided into four groups according to quartiles of Kt/V_{urea}, and also of different other parameters with potential impact, such as age, body weight (BW), Protein equivalent of Nitrogen Appearance (PNA), Residual Renal Function (RRF), and dialysis vintage. Dichotomic concentration comparisons were performed for gender and Diabetes Mellitus (DM). Analysis of Variance in quartiles of Kt/V_{urea} did not show significant differences for any of the solute concentrations. For PNA, however, concentrations showed significant differences for urea ($P<0.001$), uric acid (UA), p-cresylsulfate (PCS), and free PCS (all $P<0.01$), and for creatinine (Crea) and hippuric acid (HA) (both $P<0.05$). For RRF, concentrations varied for β_2-microglobulin ($P<0.001$), HA, free HA, free indoxyl sulfate, and free indole acetic acid (all $P<0.01$), and for p-cresylglucuronide (PCG), 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid (CMPF), free PCS, and free PCG (all $P<0.05$). Gender and body weight only showed differences for Crea and UA, while age, vintage, and diabetes mellitus only showed differences for one solute concentration (UA, UA, and free PCS, respectively). Multifactor analyses indicated a predominant association of concentration with protein intake and residual renal function. In conclusion, predialysis concentrations of uremic toxins seem to be dependent on protein equivalent of nitrogen appearance and residual renal function, and not on dialysis adequacy as assessed by Kt/V_{urea}. Efforts to control intestinal load of uremic toxin precursors by dietary or other interventions, and preserving RRF seem important approaches to decrease uremic solute concentration and by extension their toxicity.

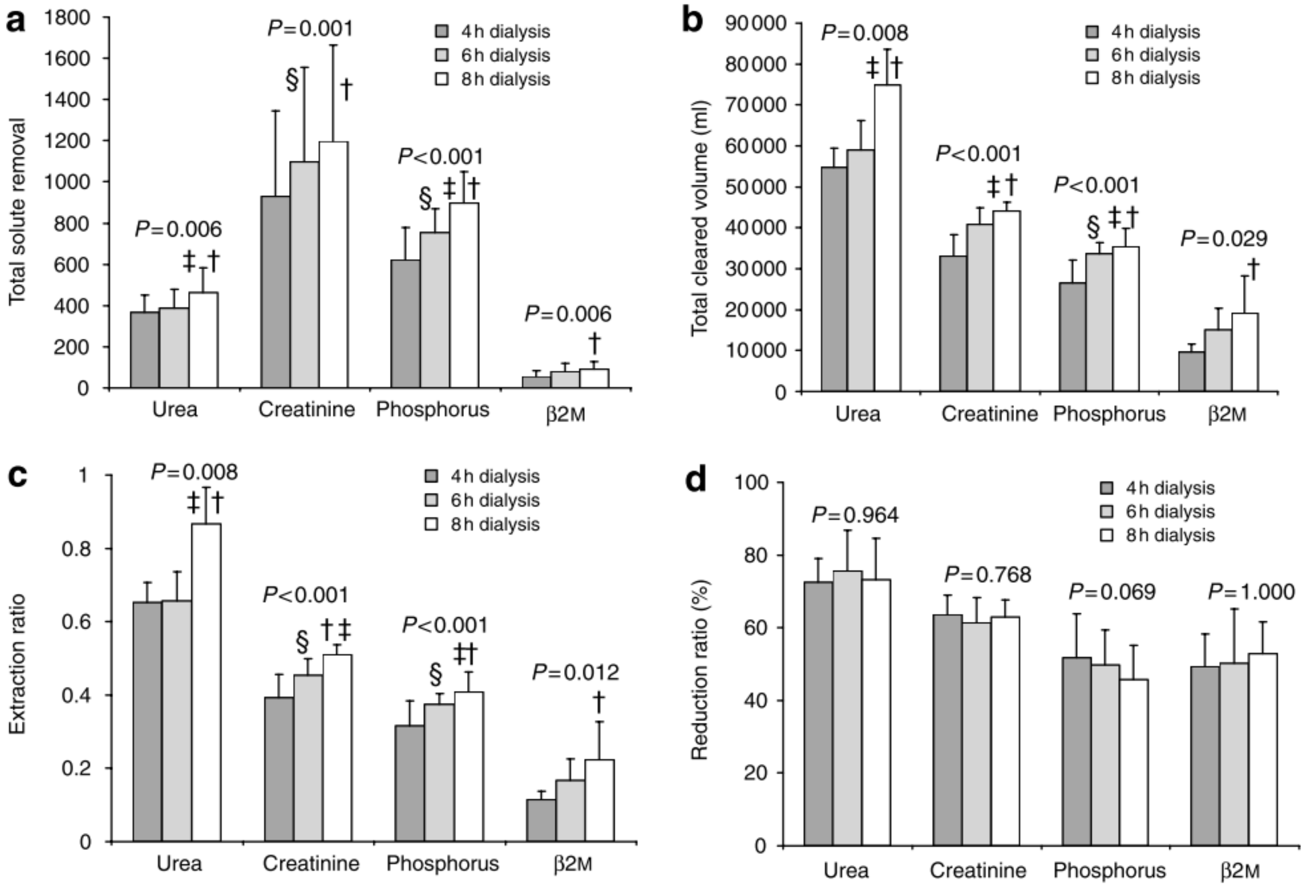
Current markers are poor predictors of overall uremic toxin accumulation

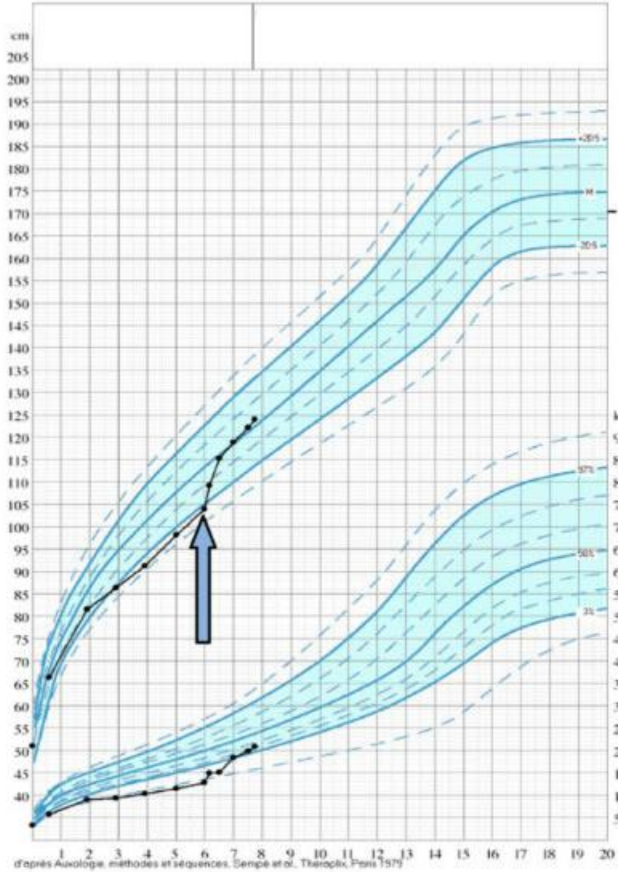




Snauwaert et al. 2018 (Ped Nephrol)

Alternative strategies to decrease uremic toxicity?





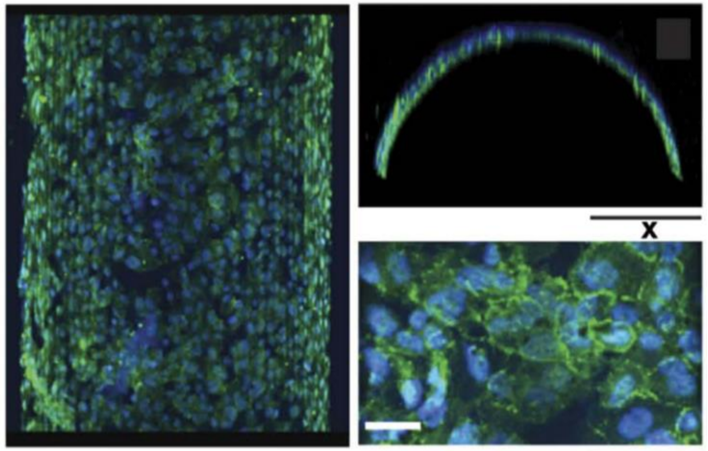
time...

Extended hemodialysis strategies

Figure 2 | Removal parameters. (**a**) Total solute removal (mg, except for urea in 0.1 g), (**b**) total cleared volume (ml), (**c**) dialyzer extraction ratio, (**d**) and reduction ratio (%) of urea, creatinine, phosphorus, and β2-microglobulin for the 4, 6, and 8 h dialysis session.

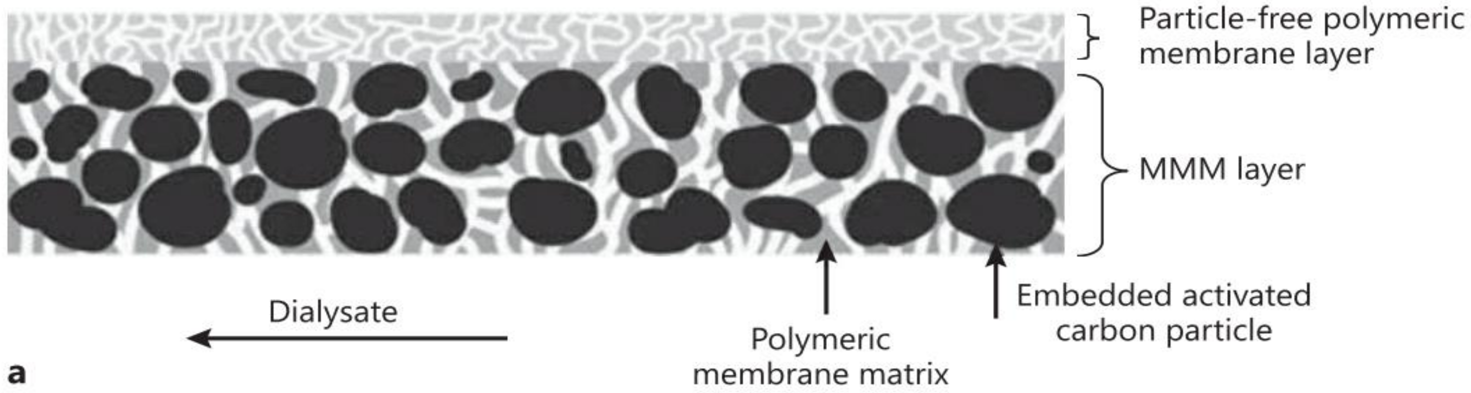
Eloot et al., Kidney Int, 2016

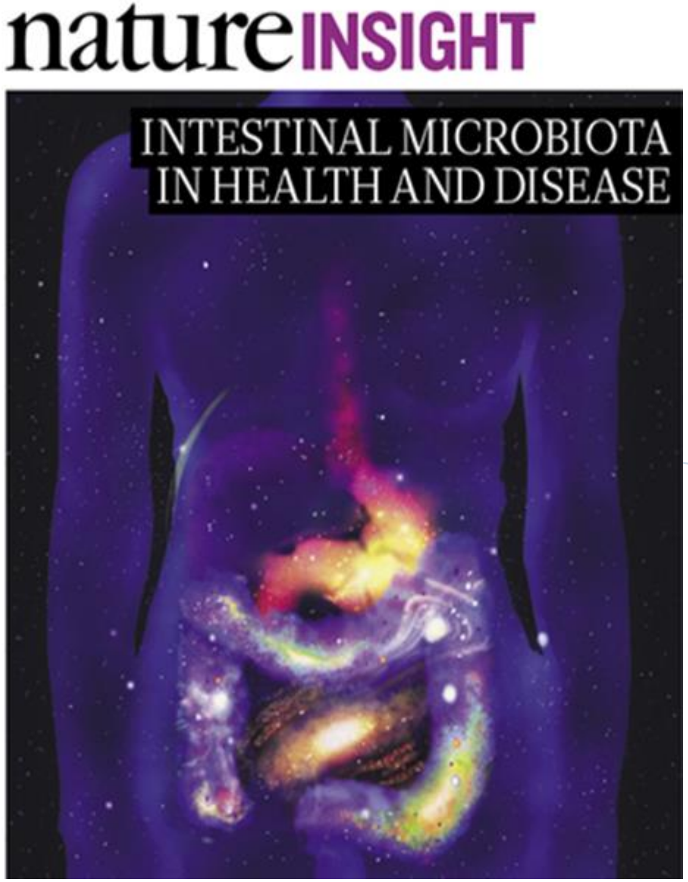
Alternative strategies to decrease uremic toxicity?



PRESERVATION OF RESIDUAL KIDNEY FUNCTION

MEMBRANES WITH ADSORPTIVE CAPACITY





DIETARY FIBER, PRE-, PRO, and SYNBIOTICS

Jansens et al. 2016; Tijink et al. 2014

Take-home messages

Question 1: Which statement is true?

A. Solute transport at the dialyzer is solely dependent on Q_d and Q_b

B. Solute removal at the dialyzer is the only determinant of uremic solute removal

C. With even the most recent advances, it seems that small solute removal in the dialyzer is close to its optimum.

D. The main removal strategy of protein-bound uremic toxins is convection

Answers Question 1: Which statement is true?

A. Solute transport at the dialyzer is solely dependent on Q_d and Q_b **+ membrane**

B. Solute removal at the dialyzer is the only determinant of uremic solute removal **FALSE + Patient kinetics**

C. **With even the most recent advances, it seems that small solute removal in the dialyzer is close to its optimum.**

D. The main removal strategy of protein-bound uremic toxins is convection **FALSE = Diffusion of free fraction**

Question 2: Which statement is true?

A. eGFR is a good predictor of overall uremic toxin accumulation

B. Kt/V is a good marker of dialysis adequacy as it reflects overall uremic toxin removal

C. Solute transport in the patient limits the increase of performance with the traditional dialytic approaches.

D. Intercompartiment clearance (K_{12}) of urea and β2-microglobuline are similar, e.g. 800mL/min

Answers Question 2: Which statement is true?

A. eGFR is a good predictor of overall uremic toxin accumulation **Only partially!**

B. Kt/V is a good marker of dialysis adequacy as it reflects overall uremic toxin removal **FALSE**

C. **Solute transport in the patient limits the increase of performance with the traditional dialytic approaches.**

D. Intercompartiment clearance (K_{12}) of urea and β2-microglobuline are similar, e.g. 800mL/min **β2M = 50mL/min, only 6% of K_{12} of urea**

TEAMWORK DIVIDES THE TASK & DOUBLE THE SUCCESS

Mentors & Promotors
Sunny Eloot
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Wim Van Biesen
Ann Raes
Griet Glorieux
Raymond Vanholder
Rukshana Shroff

Lab & data
Sophie Lobbestael
Tom Mertens
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Sofie Vermeiren
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Sanne Roels
An Desloovere
Elke De Bruyne
Charlotte Vanherzeele
Christel Beerens
Nathalie Polfliet
Katty Van Cauwenberghe
Katya Degroote
Karlien Dhondt
Members of advisory board

Collaborators
Elena Levtchenko
Nathalie Godefroid
Koen Van Hoeck
Laure Collard
Chiodini Benedetta
Rukshana Shroff

& their local team

All patients and families participating


UF-Totaal
0
Eff. Bloedflow
71
Cum.Bloedvol.
10.8
Systeem Parameters
Dialyse Presentatie

THANK YOU!