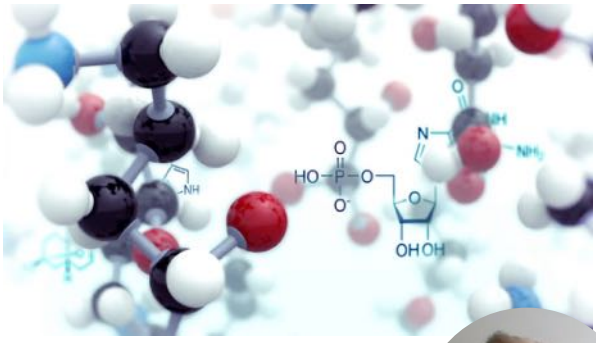
UNE NOUVELLE DÉFINITION DE LA TOXICITÉ URÉMIQUE

R Vanholder, University Hospital, Ghent, Belgium



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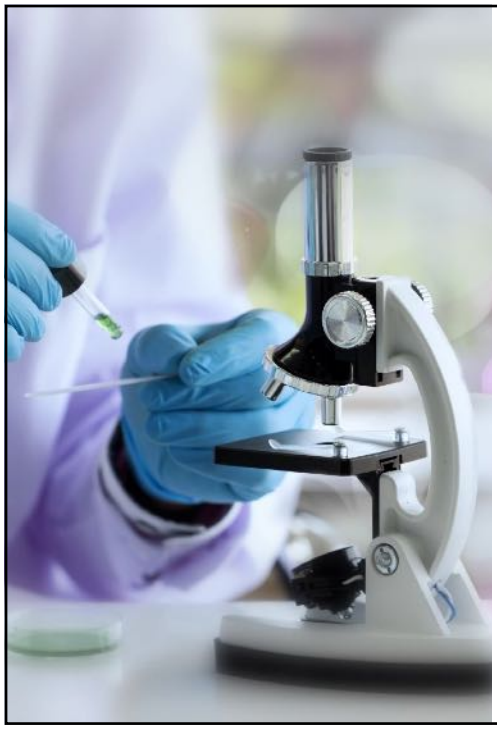
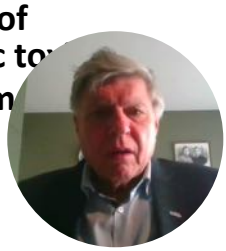


SUMMARY

- **What are uremic toxins?**
- **Current (old) vs. new classification**
- **Prototype molecules and their toxicity**
- **Classification according to evidence of toxicity**
- **What is the dialysis strategy of preference to remove uremic to**
- **Can we solve everything by m dialysis more adequate?**



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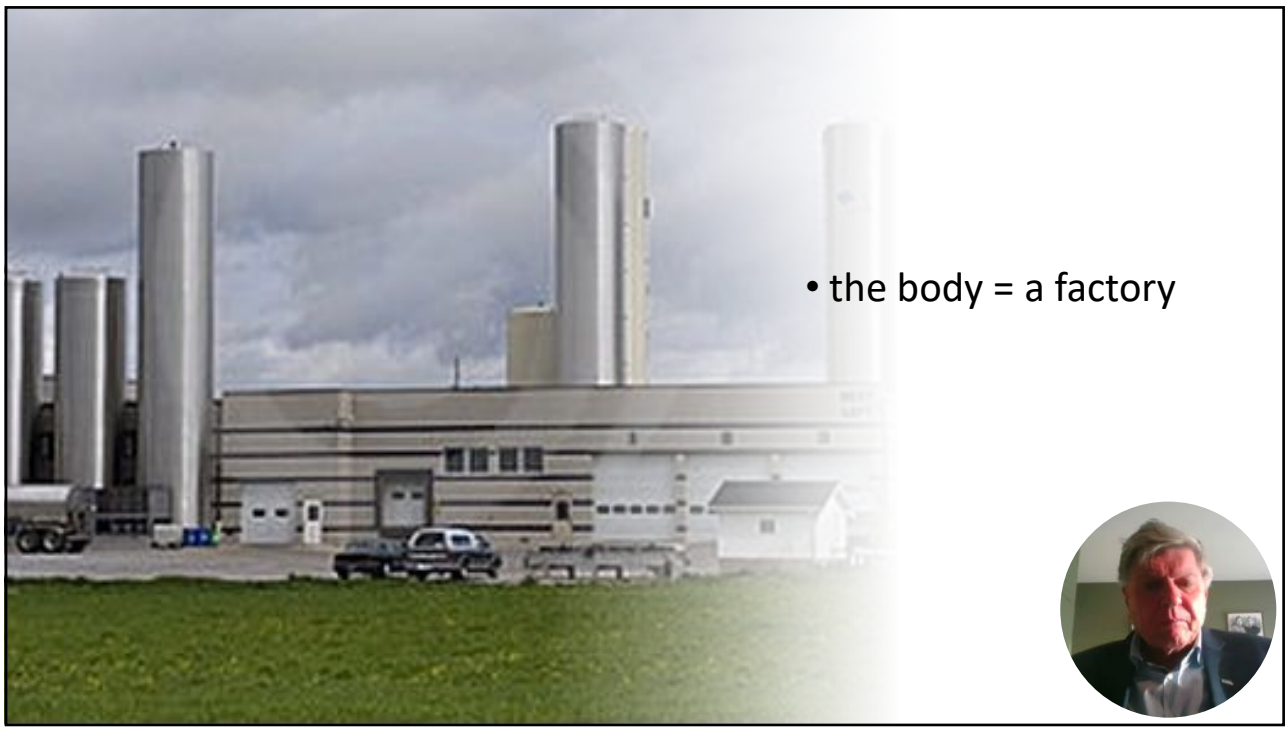
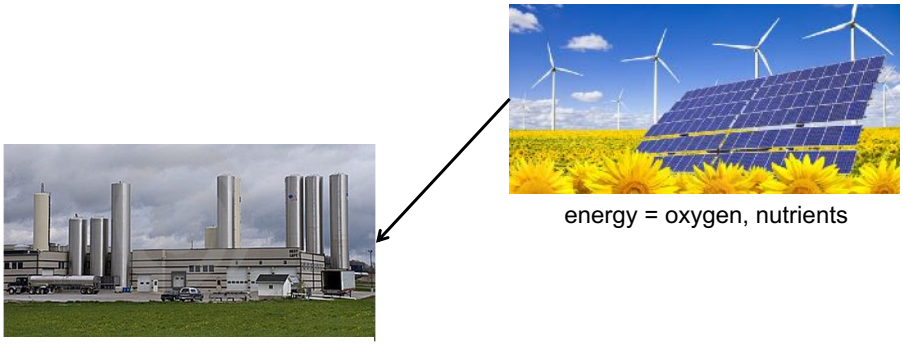

• the body = a factory

3

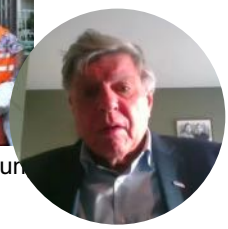

energy = oxygen, nutrients
the body = a factory

4

the body = a factory

energy = oxygen, nutrients

garbage collection = kidneys, liver, lun



5

URINE

6

Kidney International, Vol. 63 (2003), pp. 1934–1943

Review on uremic toxins: Classification, concentration, and interindividual variability

RAYMOND VANHOLDER, RITA DE SMET, GRIET GLORIEUX, ANGEL ARGILÉS, ULRICH BAURMEISTER, PHILIPPE BRUNET, WILLIAM CLARK, GERALD COHEN, PETER PAUL DE DEYN, REINHOLD DEPPISCH, BEATRICE DESCAMPS-LATSCHA, THOMAS HENLE, ACHIM JÖRRES, HORST DIETER LEMKE, ZIAD A. MASSY, JUTTA PASSLICK-DEETJEN, MARIANO RODRIGUEZ, BERND STEGMAYR, PETER STENVINKEL, CIRO TETTA, CHRISTOPH WANNER, and WALTER ZIDEK, For the EUROPEAN UREMIC TOXIN WORK GROUP (EUTox)

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Solute	CN	CU	CMAX	MW	Ref	Group
1-methyladenosine μg/L	17.1±5.1/10	104.0±56.2/17	216.4	281	12	Ribonucleosides
1-methylguanosine μg/L	13.7±16.9/10	41.6±23.8/17	89.2	297	12	Ribonucleosides
1-methylinosine μg/L	13.5±3.9/10	620.4±203.4/14	1027.2	282	12	Ribonucleosides
ADMA mg/L	0.2±0.06/6	1.6±1.2/10	7.3[a]	202	13,14	Guanidines
α-keto-δ-guanidinovaleric acid μg/L	<30.2/66	–	140.4[a]	151	15	Guanidines
α-N-acetylarginine μg/L						

Table 3. Middle molecules (*N* = 22)

Solute	CN	CU	CMAX	MW	Ref	Group
Methionine-enkephalin ng/L	<18.3/10	32.2/22	75.5[a]	555	22	Peptides
Neuropeptide Y ng/L	<80.0	64.9±25.5/19	115.9	4272	57	Peptides
Parathyroid hormone μg/L	<0.06	1.2±0.6/10	2.4	9225	65	Peptides
Retinol-binding protein mg/L	<80	192.0±78.0/112	369.2[a]	21200	53	Peptides
Tumor necrosis factor-αng/L	13.3±3.0/28	114.0±147.0/230	408.0	26000	63,66	Cytokines

90 uremic toxins

- ***Small water soluble compounds (<500D):*** 1-Methyladenosine, 1-Methylguanosine, 1-Methylinosine, ADMA, γ-Keto-guanidinovaleric acid, α-N-acetylarginine, Arab(in)itol, Argininic acid, Benzylalcohol, ß-guanidinopropionic acid, Creatine, Creatinine, Cytidine, Dimethylglycine, Erythritol, γ- guanidinobutyric acid, Guanidine, Guanidinoacetic acid, Guanidonosuccinic acid, Hypoxanthine, Mannitol, Methylguanidine, Myoinositol, N4-acetylcytidine, N6-methyladenosine, Orotic acid, Orotidine, Oxalate, Phenylacetylglutamine, Pseudouridine, SDMA, Sorbitol, Taurocyamine, Threitol, Thymine, Uracil, Urea, Uric acid, Uridine, Xanthine, Xanthosine
- ***Protein-bound molecules:*** 2-Methoxyresorcinol, 3-deoxyglucosone, CMPF, Dimethylguanosine, Fructoselysine, Glyoxal, Hippuric acid, Homocysteine, Hydroquinone, Indole-3-acetic acid, Indoxyl sulfate, Interleukin 1ß, Interleukin 6, Kinurenine, Kynurenic acid, Leptin, Melatonin, Methylglyoxal, N-(carboxylmethyl)lysine, P-cresol, Pentosidine, Phenol, Phenylacetic acid, Phenylethylamine, P-OHhippuric acid, Putrescine, Quinolinic acid, Retinol binding protein, S-nitrosothiol, Spermidine, Spermine, Thiocyanate, Tumor Necrosis Factor α
- ***Middle molecules (>500D):*** Adrenomedullin, Atrial natriuretic peptide, ß2-microglobulin, ß-endorphin, Cholecystokinin, Clara cell protein, Complement factor D, Cystatin C, Degranulation inhibiting protein I, Delta-sleep inducing peptide, Endothelin (ng/L), Ghrelin, Hyaluronic Acid, Interleukin 1ß, Interleukin 6, Interleukin-18, κ-Ig light chain, λ-Ig light chain, Leptin, MC-SF, Methionine-enkephalin, Neuropeptide Y, Orexin A, Parathyroid hormone, Retinol binding protein, Tumor Necrosis Factor α

Vanholder et al, KI, 63:1934-1943; 2003

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CLINICAL RESEARCH www.jasn.org

Normal and Pathologic Concentrations of Uremic Toxins

Flore Duranton,* Gerald Cohen,† Rita De Smet,‡ Mariano Rodriguez,§ Joachim Jankowski,‖ Raymond Vanholder,‡ and Angel Argiles,* on behalf of the European Uremic Toxin Work Group

*RD-Néphrologie, Montpellier, France; †Medizinische Universität Wien, University Klinik für Innere Medizin III, Abteilung für Nephrologie und Dialyse, Wien, Austria; ‡Nephrology Section, University Hospital Ghent, G... Belgium; §Unidad de Investigacion, University Hospital Reina Sofia, Cordoba, Spain; and ‖Charité, Exp... Nephrology and Hypertension, Berlin, Germany

9

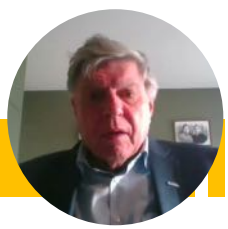
56 newly reported molecules

ABSTRACT

An updated review of the existing knowledge regarding uremic toxins facilitates the design of experimental studies. We performed a literature search and found 621 articles about uremic toxicity published after a 2003 review of this topic. Eighty-seven records provided serum or blood measurements of one or more solutes in patients with CKD. These records described 32 previously known uremic toxins and 56 newly reported solutes. The articles most frequently reported concentrations of β2-microglobulin, indoxyl sulfate, homocysteine, uric acid, and parathyroid hormone. We found most solutes (59%) in only one report. Compared with previous results, more recent articles reported higher uremic concentrations of many solutes, including carboxymethyllysine, cystatin C, and parathyroid hormone. However, five solutes had uremic concentrations less than 10% of the originally reported values. Furthermore, the uremic concentrations of four solutes did not exceed their respective normal concentrations, although they had been previously described as uremic retention solutes. In summary, this review extends the classification of uremic retention solutes and their normal and uremic concentrations, and it should aid the design of experiments to study the biologic effects of these solutes in CKD.

J Am Soc Nephrol 23: 1258–1270, 2012. doi: 10.1681/ASN.2011121175

- Duranton et al, JASN, 23: 1258-1270; 2012



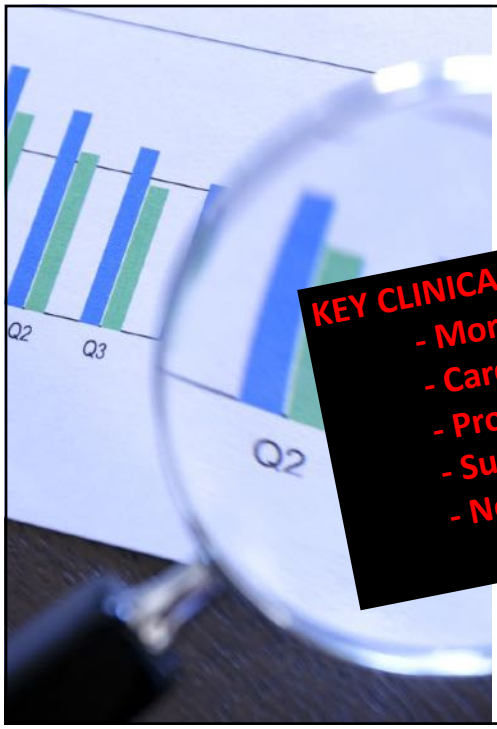
10

GFR categories (ml/min/1.73 m²)		<10 mg/g	10–29 mg/g	30–299 mg/g	≥300 mg/g
G1	≥105	0.93 (0.74–1.16)	1.33 (1.04–1.72)	2.46 (1.88–3.23)	2.89 (1.36–5.32)
	90–104	1 (reference)	1.03 (1.20–2.19)	1.82 (1.36–2.45)	4.77 (3.10–7.22)
G2	75–89	1.03 (0.85–1.24)	1.48 (1.23–1.78)	1.73 (1.29–2.32)	4.01 (2.62–6.14)
	60–74	1.09 (0.92–1.29)	1.58 (1.31–1.91)	2.18 (1.58–3.02)	4.23 (2.95–6.06)
G3a	45–59	1.52 (1.18–1.97)	2.38 (1.91–2.96)	3.13 (2.32–4.22)	4.97 (3.70–6.66)
G3b	30–44	2.40 (1.80–3.21)	3.07 (1.73–5.44)	4.12 (2.84–5.98)	6.10 (4.08–9.10)
G4	15–29	13.51 (4.89–37.35)	7.99 (1.95–32.81)	5.60 (3.66–8.57)	9.49 (4.97–18.10)
G5	<15				

…nes and risk of CVD mortality. Chronic kidney disease (CKD) in… …failure. The shaded area…

- Matsushita et al, Nat Rev Nephrol, 2022

11



RECOMMENDATIONS

KEY CLINICAL OUTCOMES
- **Mortality**
- **Cardio-vascular damage**
- **Progression of kidney disease**
- **Susceptibility to infection**
- **Neurologic manifestations**

Cognitive dysfunction

…solute
…s on solute
…mes and

…d to improve
…is of removal
… and

…sification schema must link uremic
…traditional clinical outcomes and quality of
measures, including prutitus, restless legs and
time after dialysis

Rosner et al, cJASN, doi: 10.2215/CJN.02660221

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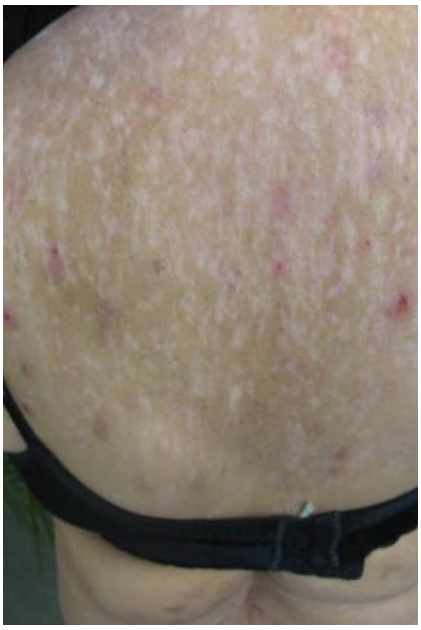
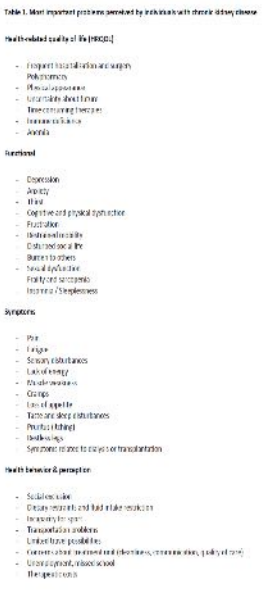
PATIENT-REPORTED OUTCOME MEASURES (PROMS)





Vanholder et al, Clin Kidney J, 14, 1719-1730, 2021

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PATIENT-REPORTED OUTCOME MEASURES (PROMS)

Vanholder et al, Clin Kidney J, 14, 1719-1730, 2021

14

CJASN ePress. Published on October 7, 2021 as doi: 10.2215/CJN.02660221

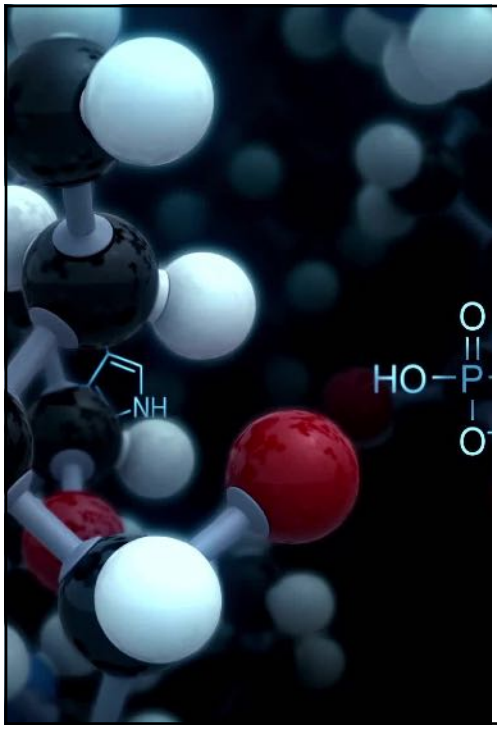
REVIEW

Classification of Uremic Toxins and Their Role in Kidney Failure

Mitchell H. Rosner,[1] Thiago Reis,[2,3] Faeq Husain-Syed,[4] Raymond Vanholder,[5] Colin Hutchison,[6,7] Peter Stenvinkel,[8] Peter J. Blankestijn,[9] Mario Cozzolino,[10] Laurent Juillard,[11,12] Kianoush Kashani,[13] Manish Kaushik,[14] Hideki Kawanishi,[15] Ziad Massy,[16,17] Tammy Lisa Sirich,[18,19] Li Zuo,[20] and Claudio Ronco,[21,22]

Rosner et al, cJASN, doi: 10.2215/CJN.02660221

15



THE CURRENT CLASSIFICATION

- **The small water soluble compounds**
  - MW: <500 Daltons
  - Easy to remove with any type of dialysis
  - Prototype: urea
- **The protein bound compounds**
  - MW: mostly <500 Daltons
  - Difficult to remove with any type of dialysis
  - Prototypes: indoles, cresols
- **The "middle molecules"**
  - MW: >500 Daltons
  - Removable only with large pore dialyzers
  - Prototype: β2-microglobulin

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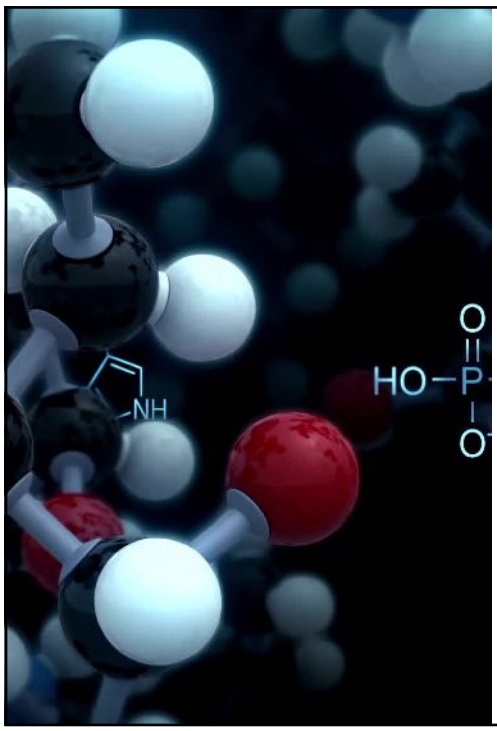

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CONTINUUM!

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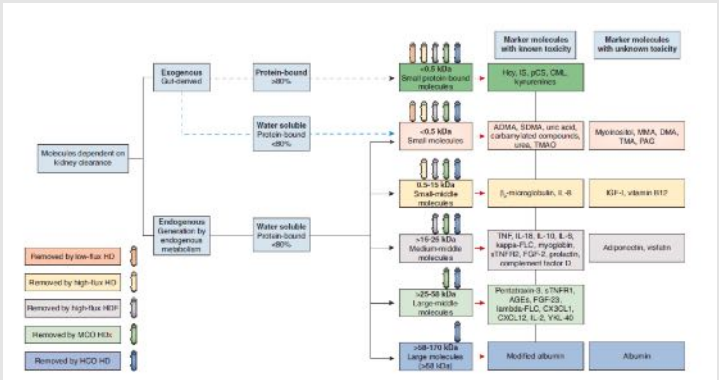
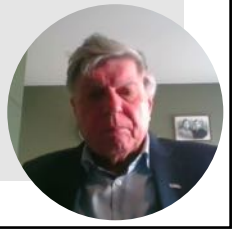
THE NEW CLASSIFICATION



- Rosner et al, cJASN, doi: 10.2215/CJN.02660221



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OLD VS. NEW CLASSIFICATION

OLD

Small water soluble molecules

Protein bound molecules

Middle molecules

NEW

- Small water soluble molecules
- Small protein bound molecules
- Small middle molecules
- Medium middle molecules
- Large middle molecules
- Large molecules

19

OLD VS. NEW CLASSIFICATION

OLD

Small water soluble molecules

Protein bound molecules

Middle molecules

NEW

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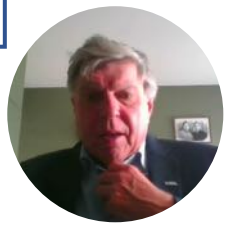
- Large molecules



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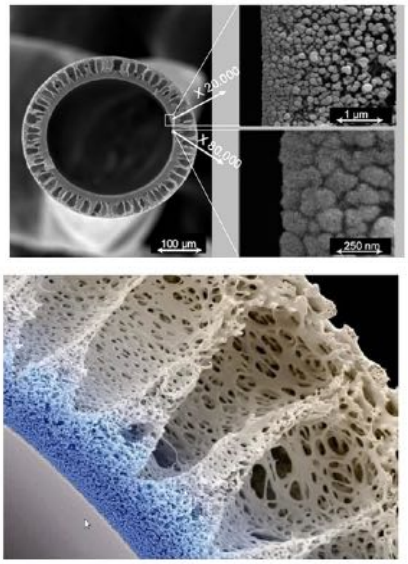
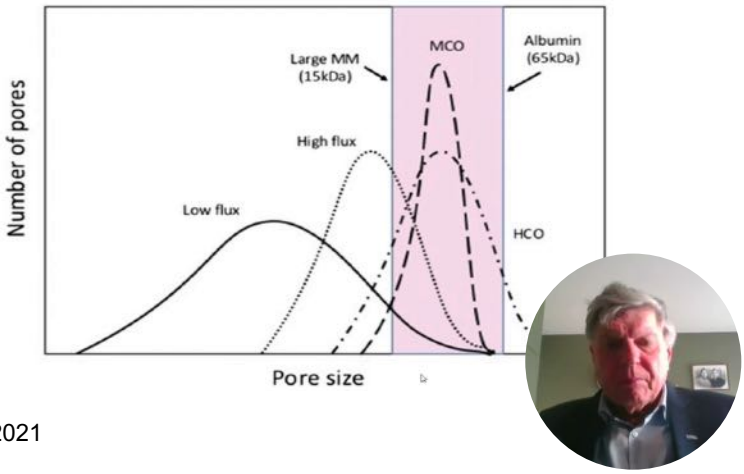
“Disruptive” medium cut-off Membranes

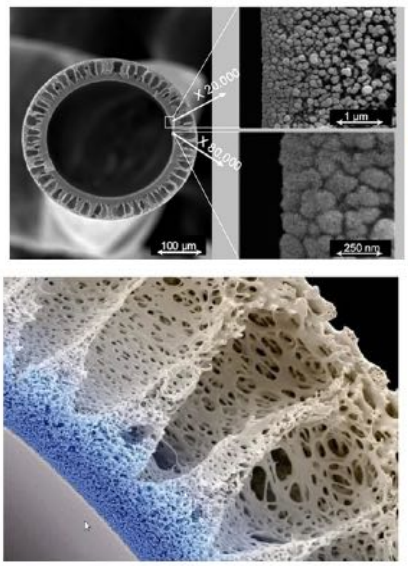


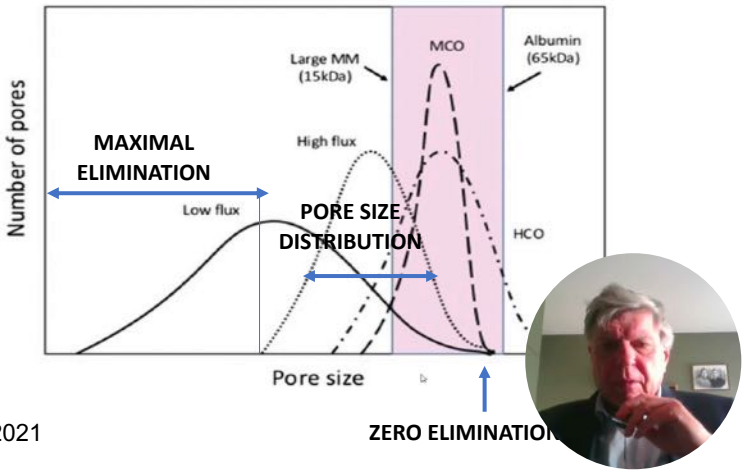


Reis et al, J Bras Nefrol, 43, 410-416, 2021

21

“Disruptive” medium cut-off Membranes





Reis et al, J Bras Nefrol, 43, 410-416, 2021

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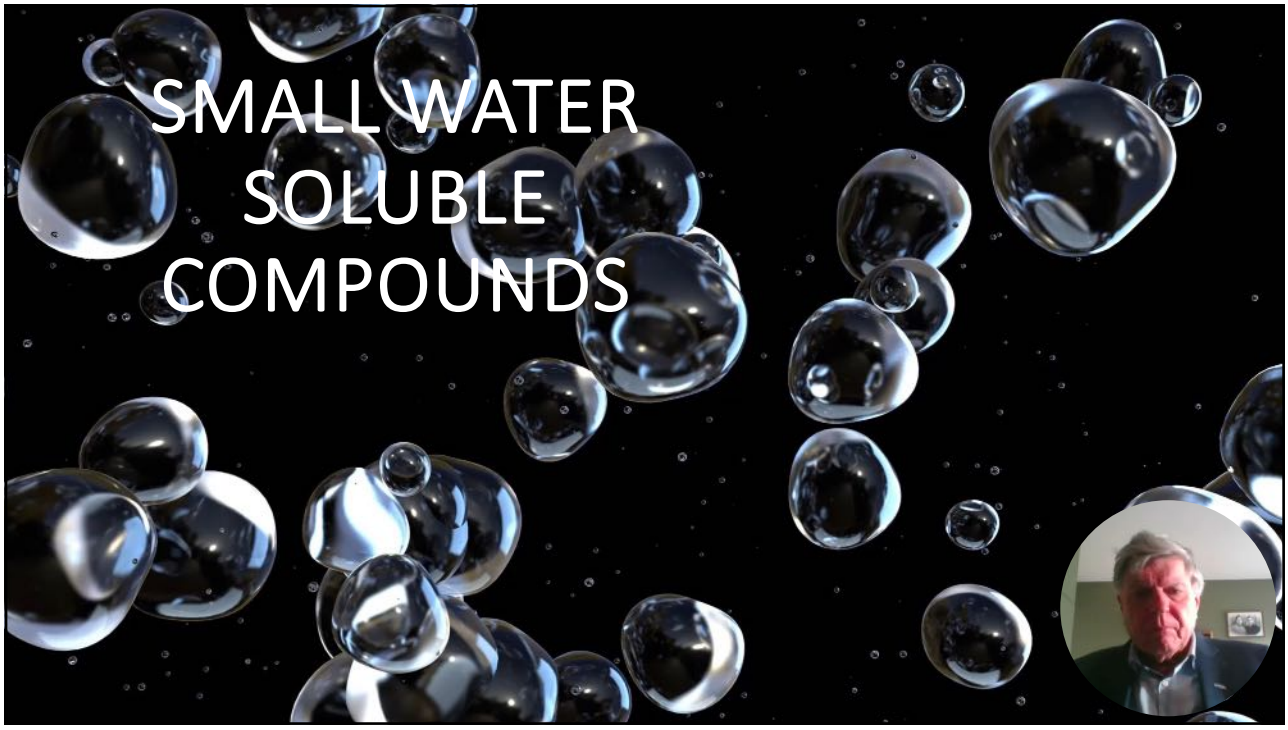
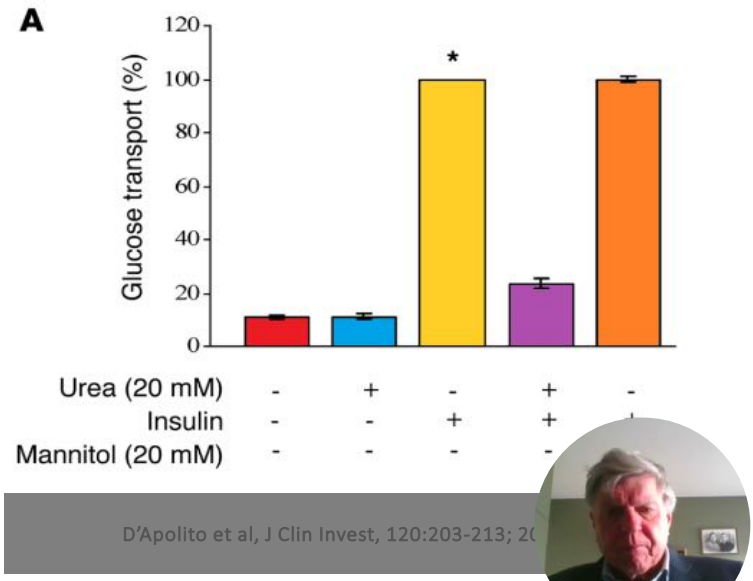
EXAMPLES
FROM
EACH
GROUP
passion
magnetism
ingenuity
NEGATIVE
POSITIVE

23


SMALL WATER
SOLUBLE
COMPOUNDS

24

UREA INDUCES INSULIN RESISTANCE



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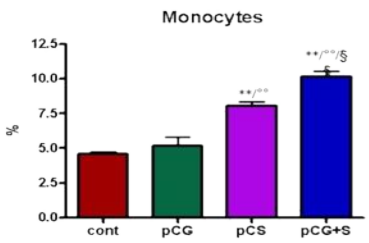
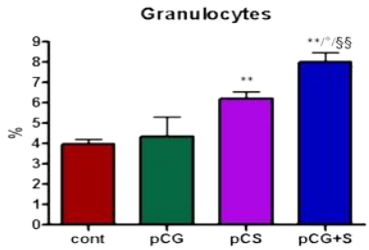
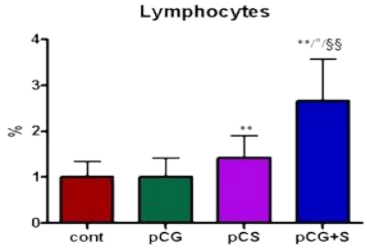
SMALL PROTEIN BOUND MOLECULES

26

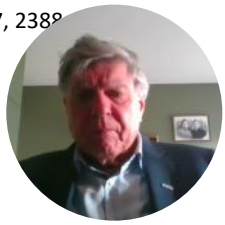
LEUKOCYTE ACTIVATION BY P-CRESYL SULFATE AND P-CRESYL GLUCURONIDE







Meert et al, NDT, 27, 2388-2396, 2012



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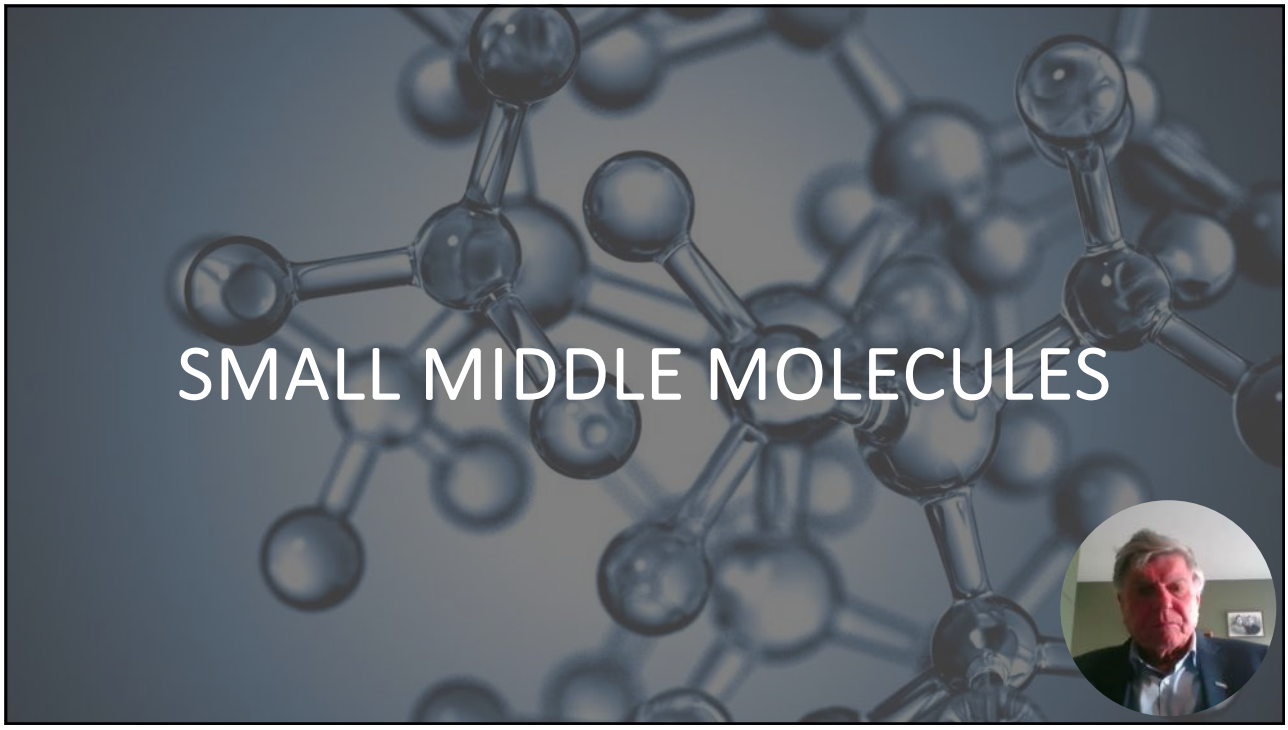

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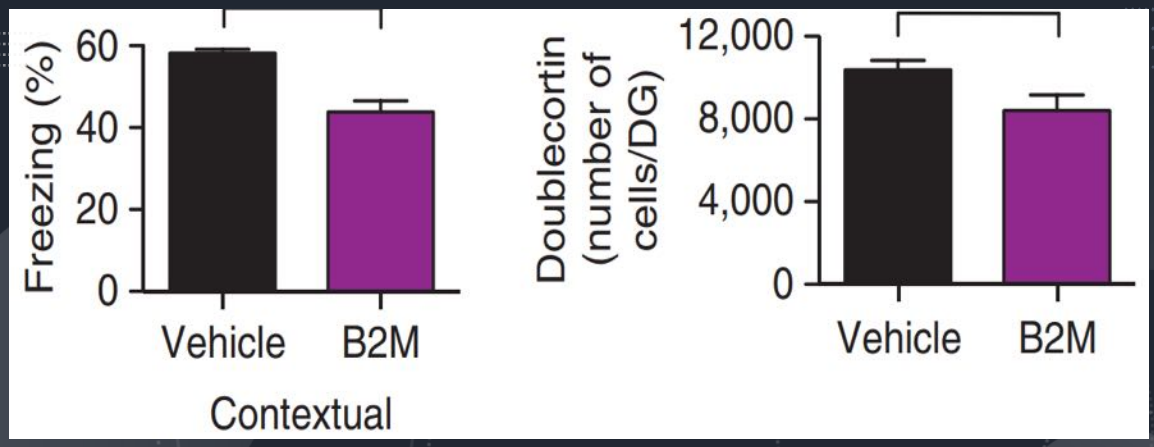

β2-MICROGLOBULIN IMPAIRS COGNITIVE FUNCTION

- Smith et al, Nat Med, 21:932-939; 2015

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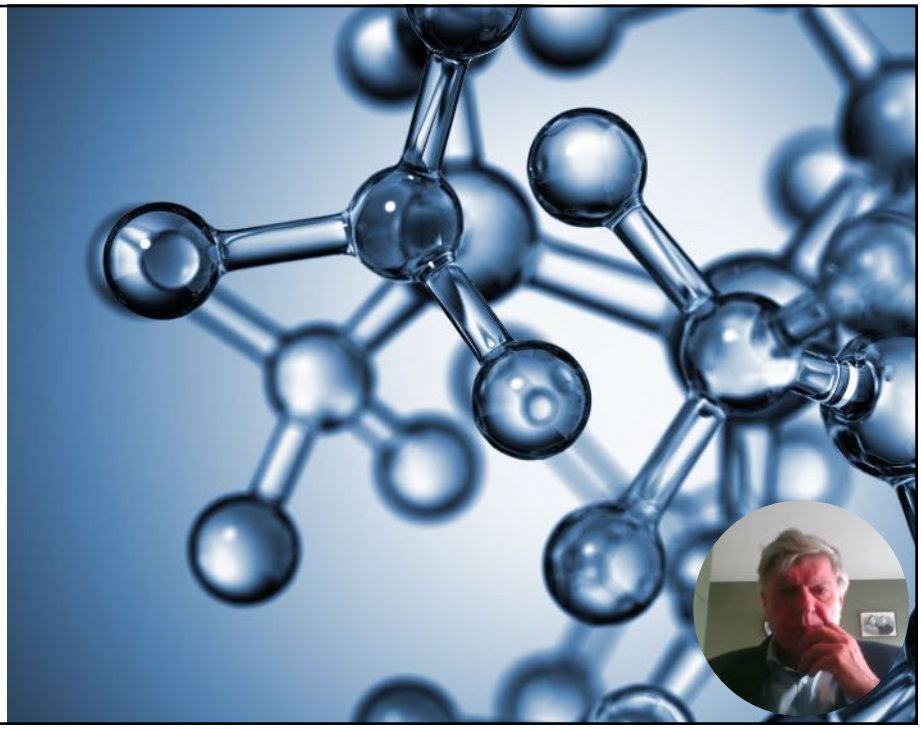
MEDIUM MIDDLE MOLECULES



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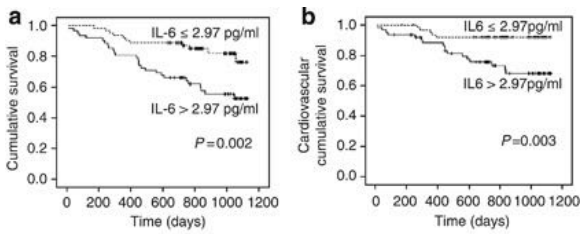

Number of patients at risk

	Days of follow-up					
	0	200	400	600	800	1000
IL-6 ≤ 2.97 pg/ml	63	62	56	56	42	23
IL-6 > 2.97 pg/ml	62	57	50	42	28	23

IL-6 AND MORTALITY IN CKD

- Barreto et al, KI, 77: 550-556; 2010

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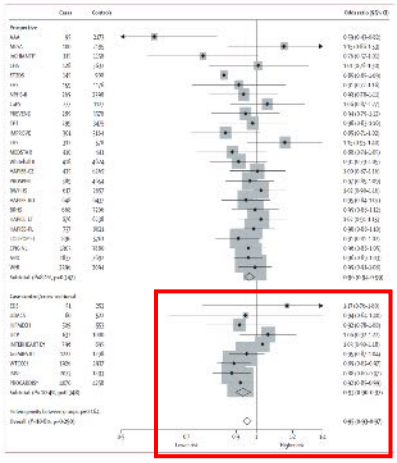
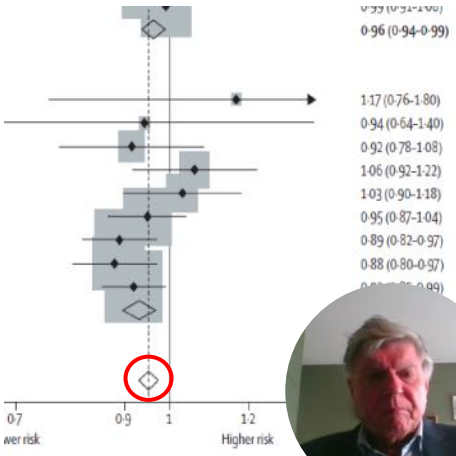
INTERLEUKIN-6 RECEPTOR BLOCKADE REDUCES CARDIOVASCULAR RISK



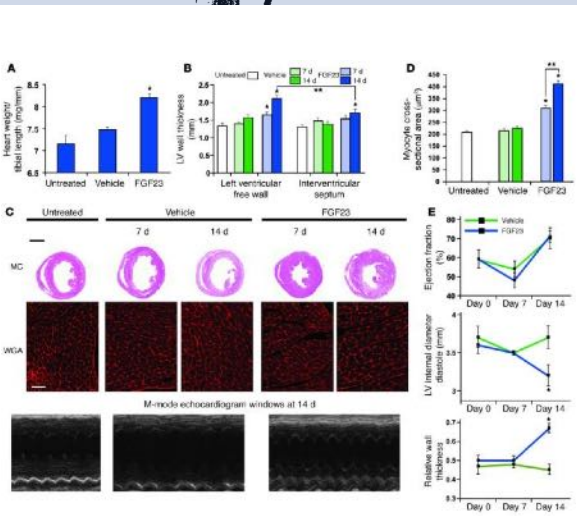


Swerdlow at al, Lancet, 379, 1214-1224, 2012

32

LARGE MIDDLE MOLECULES

33



FGF-23: MORE THAN A SIMPLE MARKER

- Faul et al, J Clin Invest, 121: 4393-4408; 2011

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GROUP	MOLECULES	EFFECT
Small water soluble compounds	Urea	Insulin resistance
Protein bound compounds	P-cresyl sulfate	Pro-inflammatory/ oxidative
Small middle molecules	Beta-2 microglobulin	Cognitive dysfunction
Medium middle molecules	Interleukin-6	Pro-inflammatory
Large middle molecules	Fibroblast growth factor-23	Cardiac hypertrophy

EXAMPLES FROM EACH GROUP

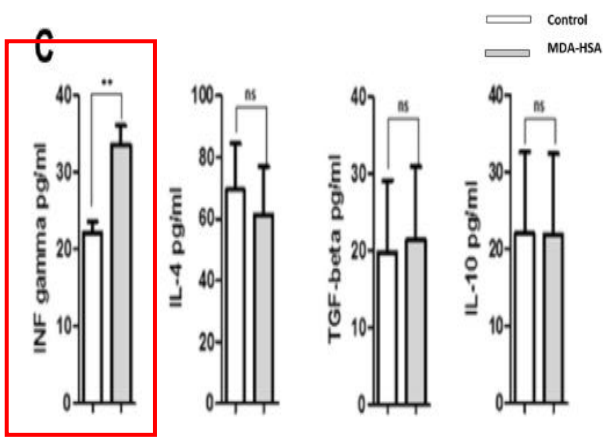
- **Molecules and effects are examples and not exhaustive**

35

LARGE MOLECULES

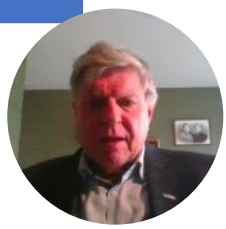
36

MDA-ALBUMIN INCREASES PRO-INFLAMMATORY CYTOKINES



Other potential ligands

- AGEs
- Guanidines
- SDMA
- Carbamoyl
- ....



Rahman, JACC Bas Translat Med, 4, 480-494, 2019

37

CLASSIFICATION BASED ON EVIDENCED TOXICITY

38

CLASSIFICATION BASED ON EVIDENCED TOXICITY

Table 8. Uremic toxins with the highest toxicity score.

Evidence Score: 4	Exp. Score	Evidence Score: 3	Exp. Score
p-Cresyl sulfate	7	AGEs	7
β_2-Microglobulin	6	Indoxyl sulfate	6
ADMA	5	Uric acid	6
Kynurenines	5	Ghrelin	5
Carbamylated compounds	3	Indole acetic acid	5
FGF-23	3	Parathyroid hormone	5
Interleukin-6	3	Phenyl acetic acid	5
TNF-α	3	TMAO	5
SDMA	2	Retinol binding protein	4
		Endothelin	3
		IgLC	3
		Interleukin-1β	3
		Interleukin-8	3
		Neuropeptide Y	3
		Lipids & lipoproteins	2

Exp.: experimental; ADMA: Asymmetric Dimethylarginine; FGF23: Fibroblast Growth Factor-23; TN
Tumor Necrosis Factor; SDMA: Symmetric Dimethylarginine; AGEs: Advanced Glycation End Products; TM
Trimethylamine-N-Oxide; IgLC: Immunoglobulin Light Chains.

Vanholder et al, Toxins, 10, 33, 2018

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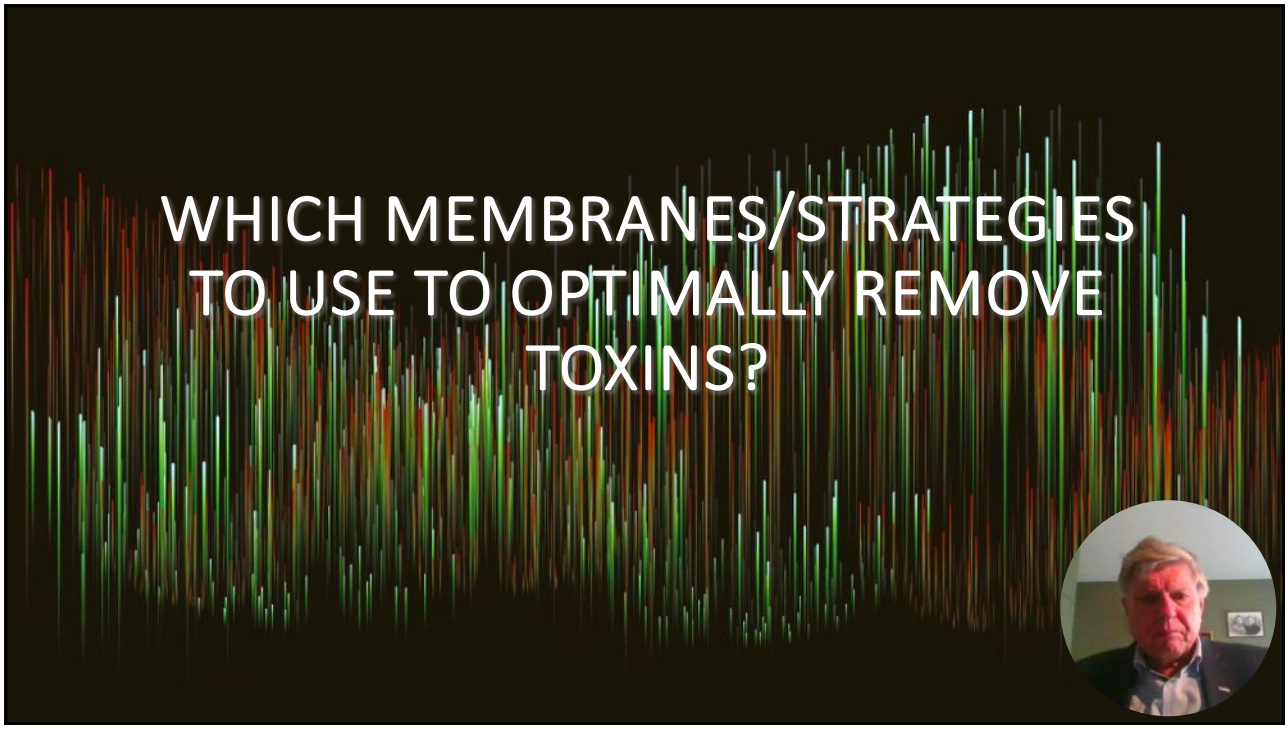
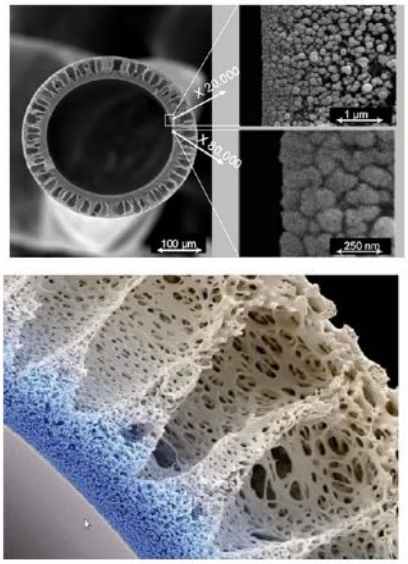
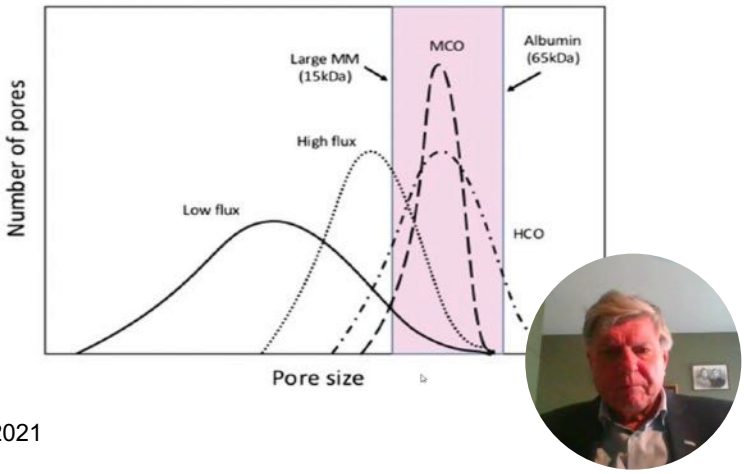


40

“Disruptive” middle cut-off Membranes

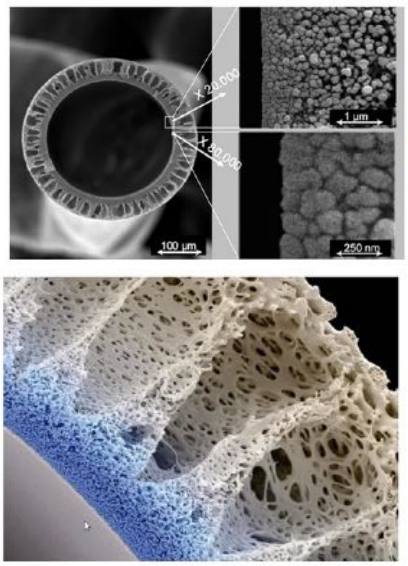




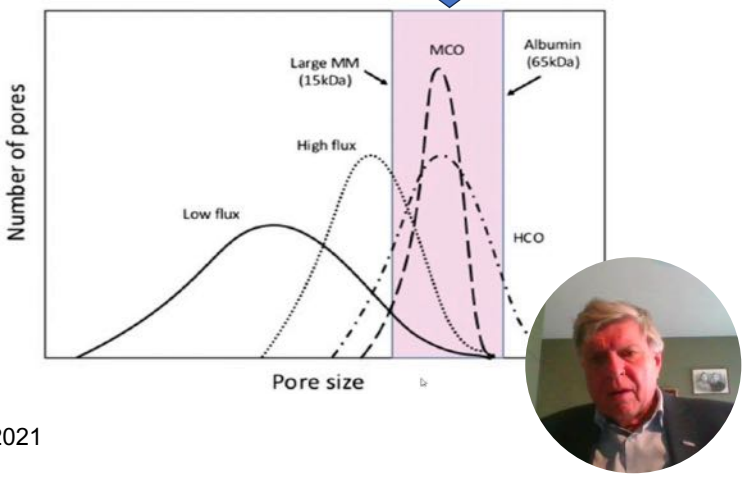
Reis et al, J Bras Nefrol, 43, 410-416, 2021

41

“Disruptive” medium cut-off Membranes



HEMODIAFILTRATION



Reis et al, J Bras Nefrol, 43, 410-416, 2021

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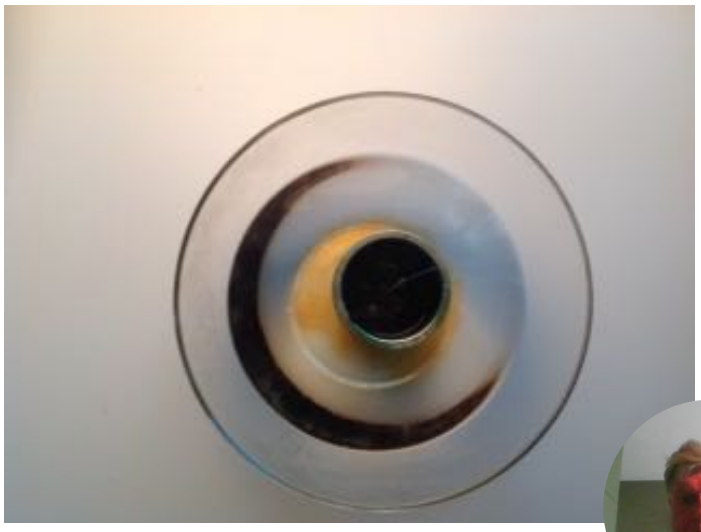
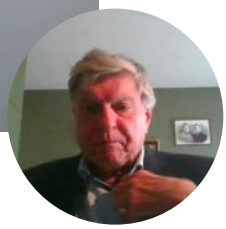
DIFFUSION





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CONVECTION

44

CLASSIFICATION BASED ON EVIDENCED TOXICITY

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TNF-α	3	TMAO	5
SDMA	2	Retinol binding protein	4
		Endothelin	3
		IgLC	3
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		Neuropeptide Y	3
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Exp.: experimental; ADMA: Asymmetric Dimethylarginine; FGF23: Fibroblast Growth Factor-23; TN
Tumor Necrosis Factor; SDMA: Symmetric Dimethylarginine; AGEs: Advanced Glycation End Products; TMA
Trimethylamine-N-Oxide; IgLC: Immunoglobulin Light Chains.

Vanholder et al, Toxins, 10, 33, 2018

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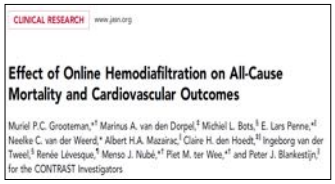
4 RCTs SHOWED NO SURVIVAL ADVANTAGE


CLINICAL RESEARCH

Hemofiltration and Hemodiafiltration Reduce Intradialytic Hypotension in ESRD


Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study

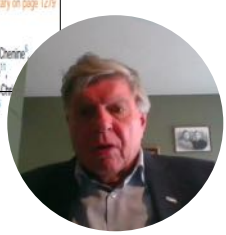

CLINICAL RESEARCH

Effect of Online Hemodiafiltration on All-Cause Mortality and Cardiovascular Outcomes


clinical trial

Treatment tolerance and patient-reported outcomes favor online hemodiafiltration compared to high-flux hemodialysis in the elderly

Locatelli et al, JASN, 21:1798-1807; 2010: the "Italian" study
Grooteman et al, JASN, 23:1087-1096; 2012: CONTRAST
Ok et al, NDT, 28:192-202; 2013: the "Turkish" study
Morena et al, KI, 91: 1495-1509; 2017: FRENCHIE



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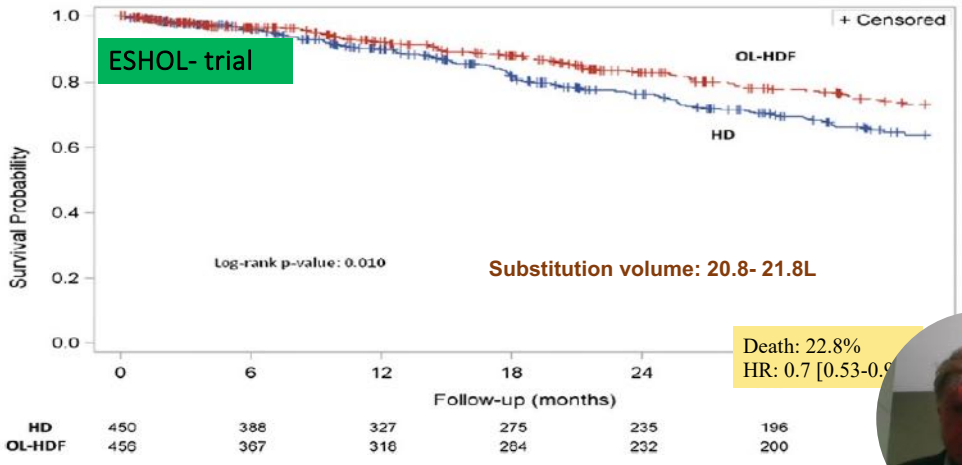
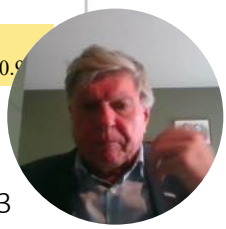
HEMODIAFILTRATION: SURVIVAL ADVANTAGE VS. HEMODIALYSIS





Maduell et al, JASN, 24: 487-497; 2013

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

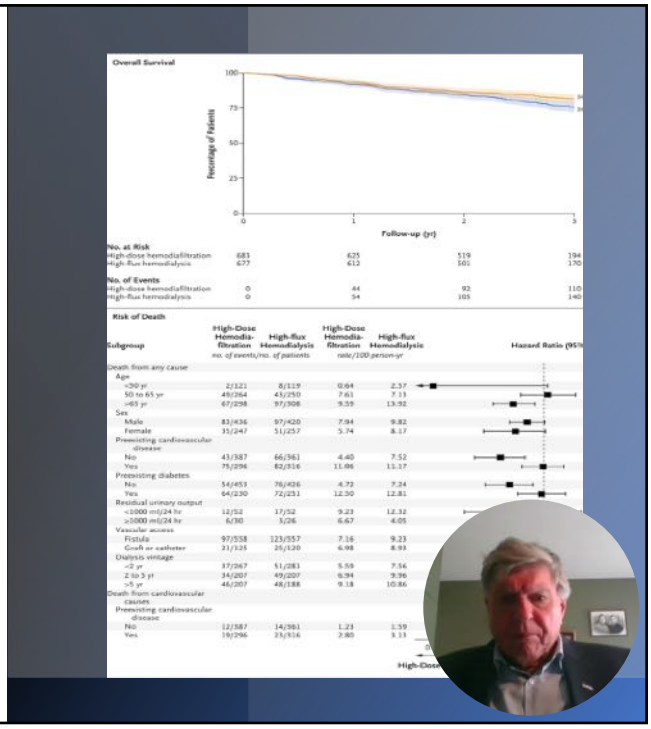
Effect of Hemodiafiltration or Hemodialysis on Mortality in Kidney Failure

Peter J. Blankestijn, M.D., Robin W.M. Vernooij, Ph.D., Carinna Hockham, Ph.D., Giovanni F.M. Strippoli, M.D., Bernard Canaud, M.D., Jörgen Hegbrant, M.D., Claudia Barth, M.D., Adrian Covic, M.D., Krister Cromm, M.Sc., Andrea Cucui, M.D., Andrew Davenport, M.D., Matthias Rose, M.D., Marietta Török, M.D., Mark Woodward, Ph.D., and Michiel L. Bots, M.D., for the CONVINCE Scientific Committee Investigators*

48

MORTALITY HF-HD VS. HIGH DOSE ON-LINE HDF

Blankestijn et al, NEJM, 389, 700-709, 2023



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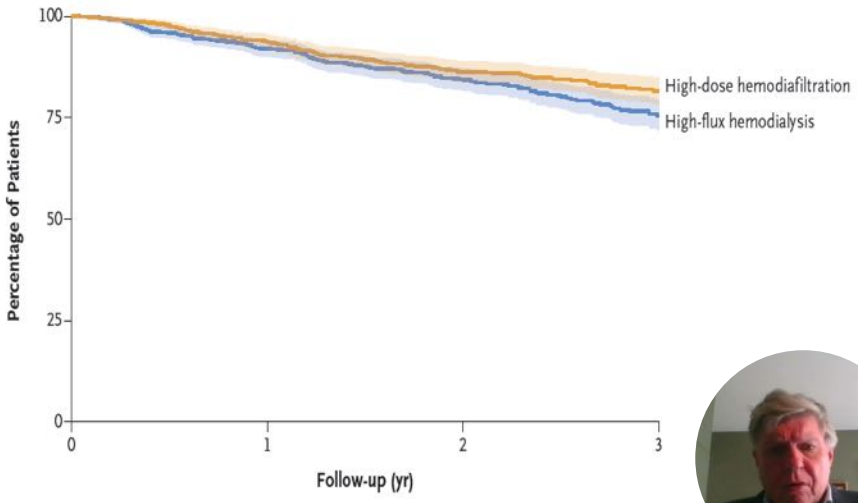
HIGH-DOSE HDF vs. HF-HD



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METHODS

We conducted a pragmatic, multinational, randomized, controlled trial involving patients with kidney failure who had received high-flux hemodialysis for at least 3 months. All the patients were deemed to be candidates for a convection volume of at least 23 liters per session (as required for high-dose hemodiafiltration) and were able to complete patient-reported outcome assessments. The patients were assigned to receive high-dose hemodiafiltration or continuation of conventional high-flux hemodialysis. The primary outcome was death from any cause. Key secondary outcomes were cause-specific death, a composite of fatal or nonfatal cardiovascular events, kidney transplantation, and recurrent all-cause or infection-related hospitalizations.

WHICH MEANS GOOD VASCULAR ACCESS

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Subgroup	Hemodialysis	Hemodialysis	Hemodialysis	Hemodialysis	Hazard Ratio (95% CI)
	no. of events/no. of patients		*rate/100 person-yr*		
Death from any cause					
Age					
<50 yr	2/121	8/119	0.64	2.57	0.25 (0.06–1.05)
50 to 65 yr	49/264	43/250	7.61	7.13	1.05 (0.75–1.49)
>65 yr	67/298	97/308	9.59	13.92	0.68 (0.53–0.89)
Sex					
Male	83/436	97/420	7.94	9.82	0.81 (0.65–1.01)
Female	35/247	51/257	5.74	8.17	0.70 (0.47–1.02)
Preexisting cardiovascular disease					
No	43/387	66/361	4.40	7.52	0.58 (0.42–0.79)
Yes	75/296	82/316	11.06	11.17	0.99 (0.76–1.28)
Preexisting diabetes					
No	54/453	76/426	4.72	7.24	0.65 (0.48–0.87)
Yes	64/230	72/251	12.50	12.81	0.97 (0.72–1.31)
Residual urinary output					
<1000 ml/24 hr	12/52	17/52	9.23	12.32	0.76 (0.37–1.59)
≥1000 ml/24 hr	6/30	3/26	6.67	4.05	1.59 (0.56–4.45)
Vascular access					
Fistula	97/558	123/557	7.16	9.23	
Graft or catheter	21/125	25/120	6.98	8.93	
Dialysis vintage					
<2 yr	37/267	51/281	5.59	7.56	
2 to 5 yr	34/207	49/207	6.94	9.96	
>5 yr	46/207	48/188	9.18	10.86	
Death from cardiovascular causes					

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Variable	(N=683)		(N=677)		(95% CI)†
	no. (%)	no. of events/ 100 patient-yr (95% CI)	no. (%)	no. of events/ 100 patient-yr (95% CI)	
Primary outcome					
Death from any cause	118 (17.3)	7.13 (5.90–8.54)	148 (21.9)	9.19 (7.77–10.79)	0.77 (0.65–0.93)
Secondary outcomes					
Death					
Cardiovascular	31 (4.5)	1.87 (1.27–2.66)	37 (5.5)	2.30 (1.62–3.17)	0.81 (0.49–1.33)
Noncardiovascular	87 (12.7)	5.26 (4.21–6.48)	111 (16.4)	6.89 (5.67–8.30)	0.76 (0.59–0.98)
Infection-related					
Including Covid-19	38 (5.6)	2.30 (1.62–3.15)	54 (8.0)	3.35 (2.52–4.37)	0.69 (0.49–0.96)
Excluding Covid-19	23 (3.4)	1.39 (0.88–2.09)	33 (4.9)	2.05 (1.41–2.88)	0.68 (0.42–1.10)
Fatal or nonfatal cardiovascular outcome‡	136 (19.9)	9.05 (7.60–10.71)	126 (18.6)	8.48 (7.07–10.10)	1.07 (0.86–1.33)
Kidney transplantation	75 (11.0)	4.80 (3.77–6.01)	71 (10.5)	4.72 (3.69–5.96)	1.0
Recurrent hospitalization — no.§					
For any nonfatal cause	998	61.34 (57.59–65.27)	895	56.36 (52.73–60.18)	
Infection-related					
Including Covid-19	234	14.32 (12.54–16.28)	219	13.92 (12.14–15.88)	
Excluding Covid-19	152	9.34 (7.92–10.95)	156	9.82 (8.34–11.49)	0.9

53

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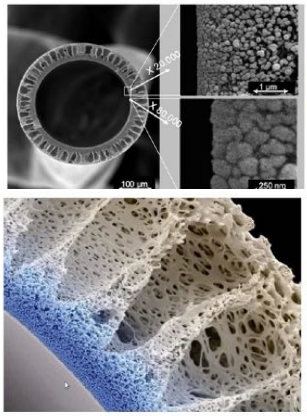
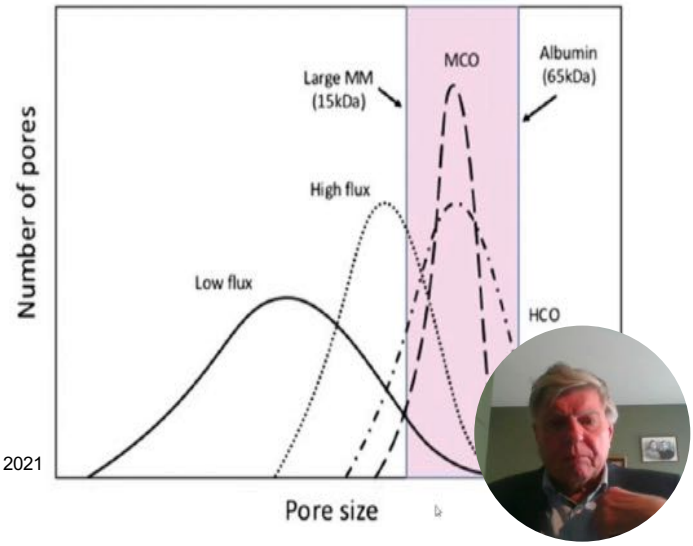
Disruptive" MEDIUM cut-off Membranes



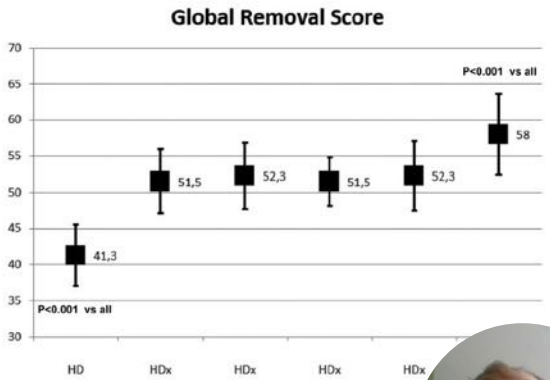
Reis et al, J Bras Nefrol, 43, 410-416, 2021



55

MIDDLE MOLECULE REMOVAL

- Maduell et al, CKJ, 2023, https://doi.org/10.1093/ckj/sfac167



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nature SCIENTIFIC REPORTS

High-performance dialyzers and mortality in maintenance hemodialysis patients

Masanori Abe[1,2✉], Ikuto Masakane[1,3], Atsushi Wada[1,4], Shigeru Nakai[1,5], Eiichiro Kanda[1,6], Kosaku Nitta[1,7] & Hidetomo Nakamoto[1,8]

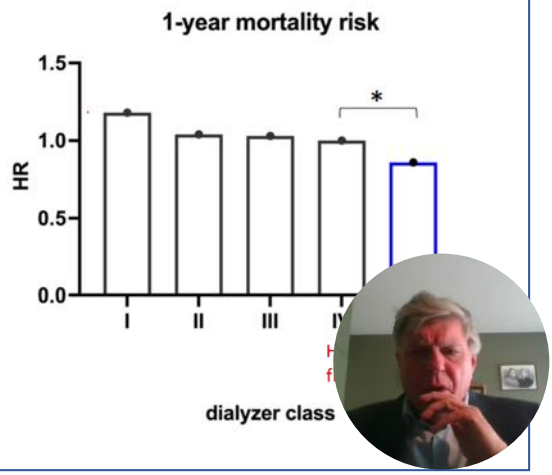
Nationwide prospective cohort study

242,467 patients

Low-flux
(< 10 mL/min clearance)

High-flux
(10–30 and 30–50 mL/min clearance)

Super high-flux
(50–70 and ≥ 70 mL/min clearance)



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ORIGINAL ARTICLE

Super high-flux membrane dialyzers improve mortality in patients on hemodialysis: a 3-year nationwide cohort study

Masanori Abe[1,2], Ikuto Masakane[1,3], Atsushi Wada[1,4], Shigeru Nakai[1,5], Kosaku Nitta[1,6] and Hidetomo Nakamoto[1,7]

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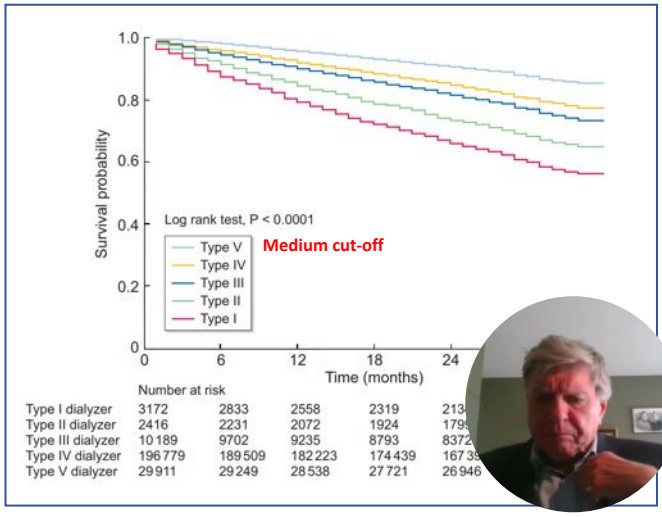

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ARE DIALYSIS STRATEGIES THE IDEAL SOLUTION TO COMBAT UREMIC TOXICITY?

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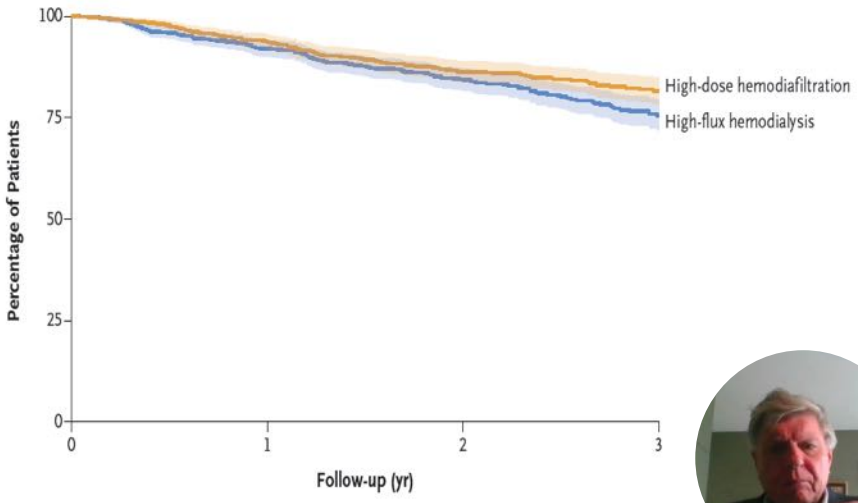
HIGH-DOSE HDF vs. HF-HD



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toxins

MDPI

Review

What If Not All Metabolites from the Uremic Toxin Generating Pathways Are Toxic? A Hypothesis

Raymond Vanholder [1,*], Sanjay K. Nigam [2], Stéphane Burtey [3] and Griet Glorieux [1]

[1] Nephrology Section, Department of Internal Medicine and Pediatrics, Ghent University Hospital, 9000 Ghent, Belgium; griet.glorieux@ugent.be
[2] Departments of Pediatrics and Medicine (Nephrology), University of California San Diego, La Jolla, CA 92093, USA; snigam@health.ucsd.edu
[3] Centre de Recherche en Cardiovasculaire et Nutrition (C2VN), Institut de la Santé et de la Recherche Médicale (INSERM), Institut National de la Recherche pour l'Agriculture, l'Alimentation et l'Environnement (INRAE), Aix Marseille University, 13005 Marseille, France; stephane.burtey@univ-amu.fr
* Correspondence: raymond.vanholder@ugent.be

Toxins **2022**, *14*, 221. https://doi.org/10.3390/toxins14030221

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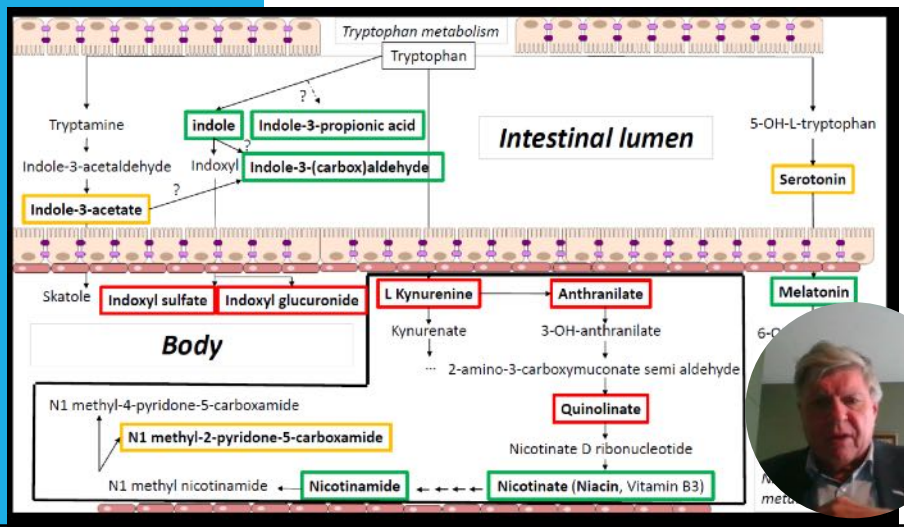
METABOLISM PRODUCES TOXINS BUT ALSO BENEFICIAL COMPOUNDS

Vanholder et al,
Toxins, 14, 221, 2022



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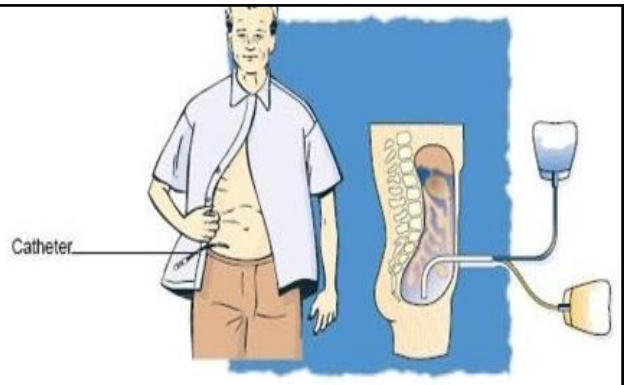
WHAT IS THE LINK WITH DIALYSIS?



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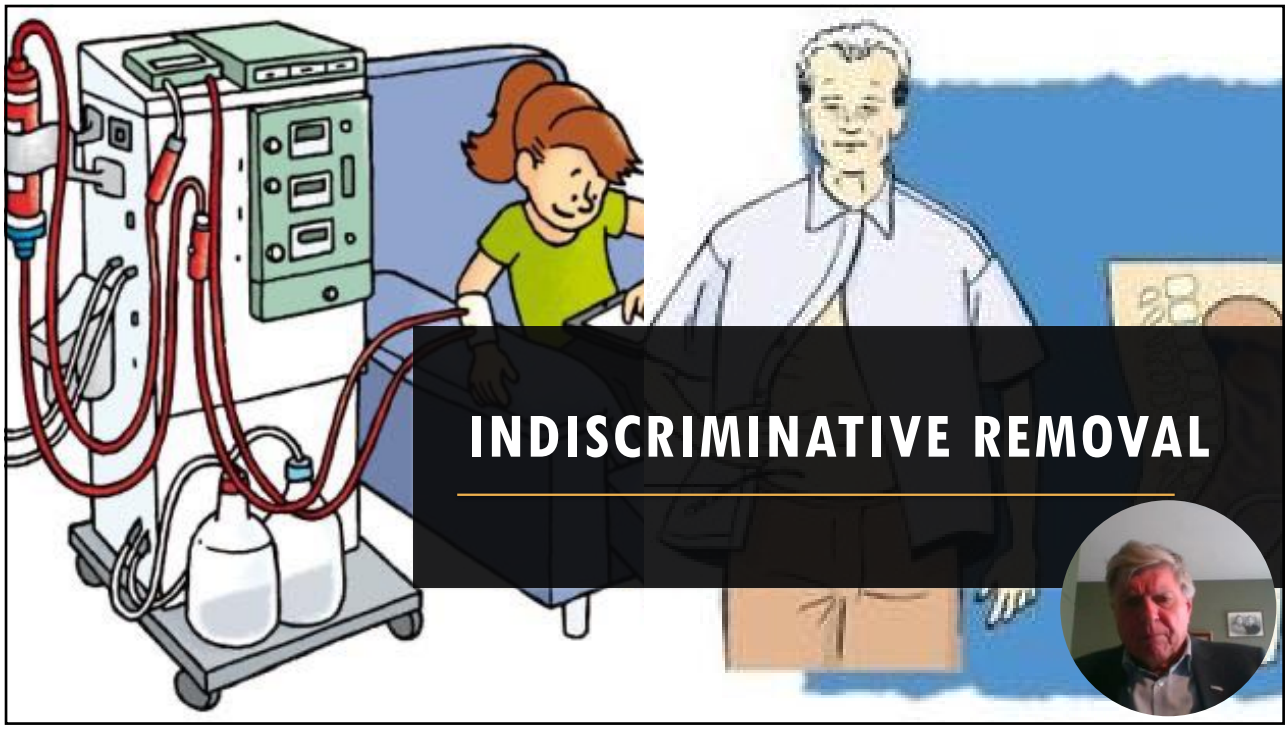

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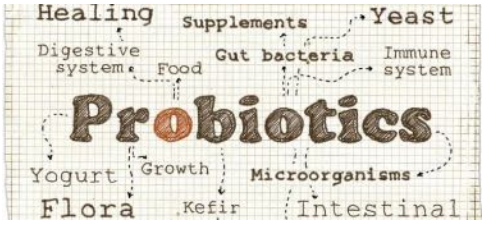
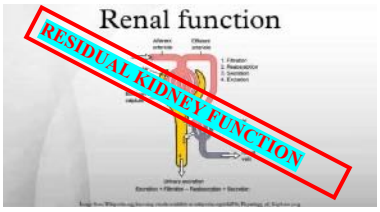
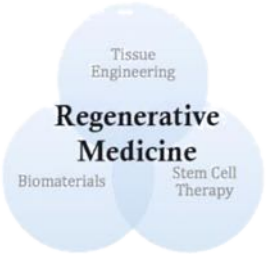
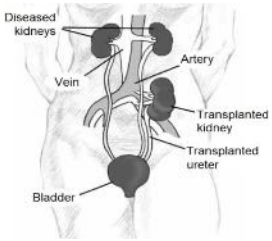
CONCLUSIONS: THERAPEUTIC IMPLICATIONS









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CONCLUSIONS

- Uremic toxicity is provoked by a large variety of waste products with variable characteristics

- Removal of those compounds became more and more efficient over the past decades

- Various types of molecules are all as important to affect body functions

- We may need a change of paradigm focusing on avoiding the loss of essenti metabolites

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BACK-UPS

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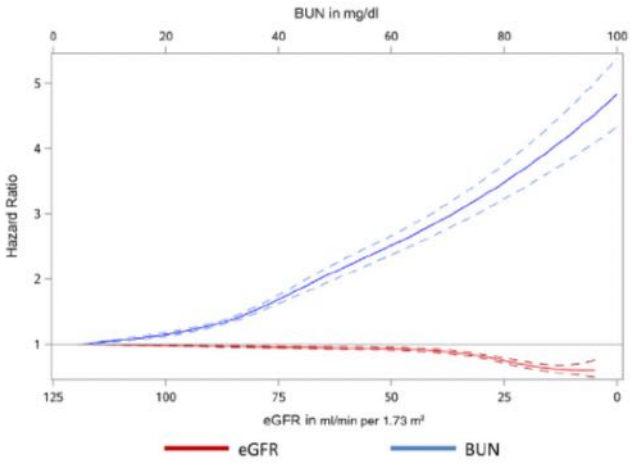
UREA IS ASSOCIATED WITH DEVELOPMENT OF DIABETES

- Xie et al, KI, 93: 741-752; 2018



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CLINICAL IMPACT OF P-CRESOL

p-Cresol and hospitalisation for infection

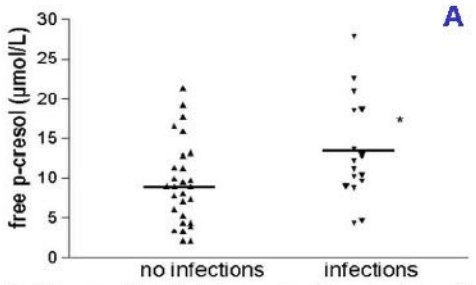
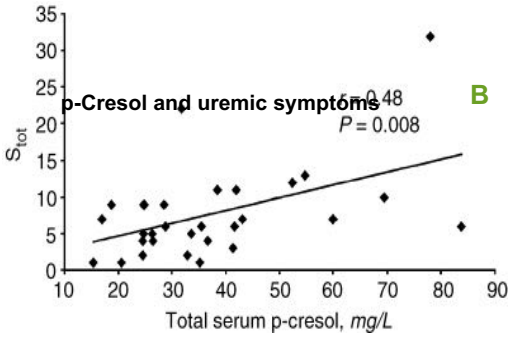


Fig. 4. Free *p*-cresol in patients who were (n = 16) or were not (n = 28) hospitalized because of infection.
*, $P < 0.05$.



C

	HR	95% CI
Comorbidity score	**1.49**	**1.19-1.86**
Malnutrition (SGA)	**4.22**	**2.15-8.29**
Free p-cresol	**2.28**	**1.12-4.64**

A: De Smet et al. Clin Chem 49: 470-478, 2003
B: Bammens et al. Kidney Int 64: 2238-2243, 2003
C: Bammens et al. Kidney Int, 69: 1081-1087, 2006

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Subgroup	filtration	Hemodialysis	filtration	Hemodialysis	Hazard Ratio (95% CI)
	no. of events/no. of patients		*rate/100 person-yr*		
Death from any cause					
Age					
<50 yr	2/121	8/119	0.64	2.57	0.25 (0.06–1.05)
50 to 65 yr	49/264	43/250	7.61	7.13	1.05 (0.75–1.49)
>65 yr	67/298	97/308	9.59	13.92	0.68 (0.53–0.89)
Sex					
Male	83/436	97/420	7.94	9.82	0.81 (0.65–1.01)
Female	35/247	51/257	5.74	8.17	0.70 (0.47–1.02)
Preexisting cardiovascular disease					
No	43/387	66/361	4.40	7.52	0.58 (0.42–0.79)
Yes	75/296	82/316	11.06	11.17	0.99 (0.76–1.28)
Preexisting diabetes					
No	54/453	76/426	4.72	7.24	0.65 (0.48–0.87)
Yes	64/230	72/251	12.50	12.81	0.97 (0.72–1.31)
Residual urinary output					
<1000 ml/24 hr	12/52	17/52	9.23	12.32	0.76 (0.37–1.59)
≥1000 ml/24 hr	6/30	3/26	6.67	4.05	1.59 (0.56–4.45)
Vascular access					
Fistula	97/558	123/557	7.16	9.23	0.77 (0.64–0.94)
Graft or catheter	21/125	25/120	6.98	8.93	0.78 (0.45–1.34)
Dialysis vintage					
<2 yr	37/267	51/281	5.59	7.56	0.73 (0.53–1.00)
2 to 5 yr	34/207	49/207	6.94	9.96	0.70 (0.46–1.06)
>5 yr	46/207	48/188	9.18	10.86	0.85 (0.64–1.15)
Death from cardiovascular causes					

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TABLE 1. Comparison of water and dialysate purity standards

	Standard water	Standard dialysate	Ultrapure water	Ultrapure dialysate	Sterile dialysate
Bacterial limits[a] (CFU/ml)	< 100–200	< 100–200	< 0.1	< 0.1	$< 10^6$
Endotoxin limits[b]	< 0.25–2.0	< 0.25	< 0.03	< 0.03	< 0.03

[a]Adequate monitoring and microbiologic techniques (e.g., ultrapure dialysis fluid, Poor Media TGEA, R2A, 17–23°, 7 days).
[b]Sensitive LAL assay, threshold detection limit < 0.03 EU/ml.

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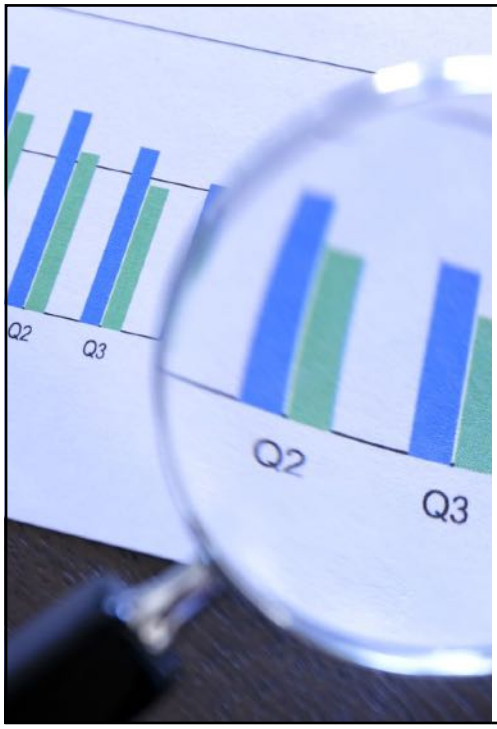

RECOMMENDATIONS

Future studies should focus on correlating solute concentrations or the effect of interventions on solute concentration with clinically relevant outcomes and outcomes important to patients.

Ideally, dialysis prescriptions would be tailored to improve these symptoms and quality of life on the basis of removal patterns of uremic solutes linked to symptoms and outcomes.

The new classification schema must link uremic symptoms to traditional clinical outcomes and quality of life measures, including pruritus, restless legs and recovery time after dialysis

Rosner et al, cJASN, doi: 10.2215/CJN.02660221

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