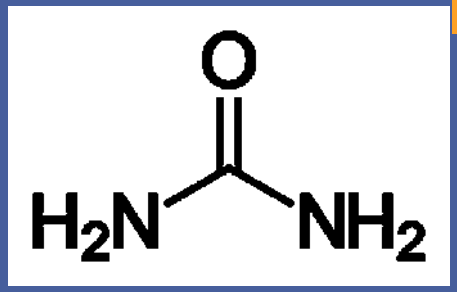
# UREMIC TOXINS

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MRCP, medicine board & teaching staff of Benghazi medical university , Head of nephro.unite /

NHC.Benghazi

28-12-2021

# AGEND

*What is uremic toxin*

*NEW CLASSIFICATION*

*UREMIC SYNDROME*

*UREMIC TOXIN CLEARANCE*

*CONCLUSION*

# definition,

Uremic toxins can be identified only in patients with kidney failure.

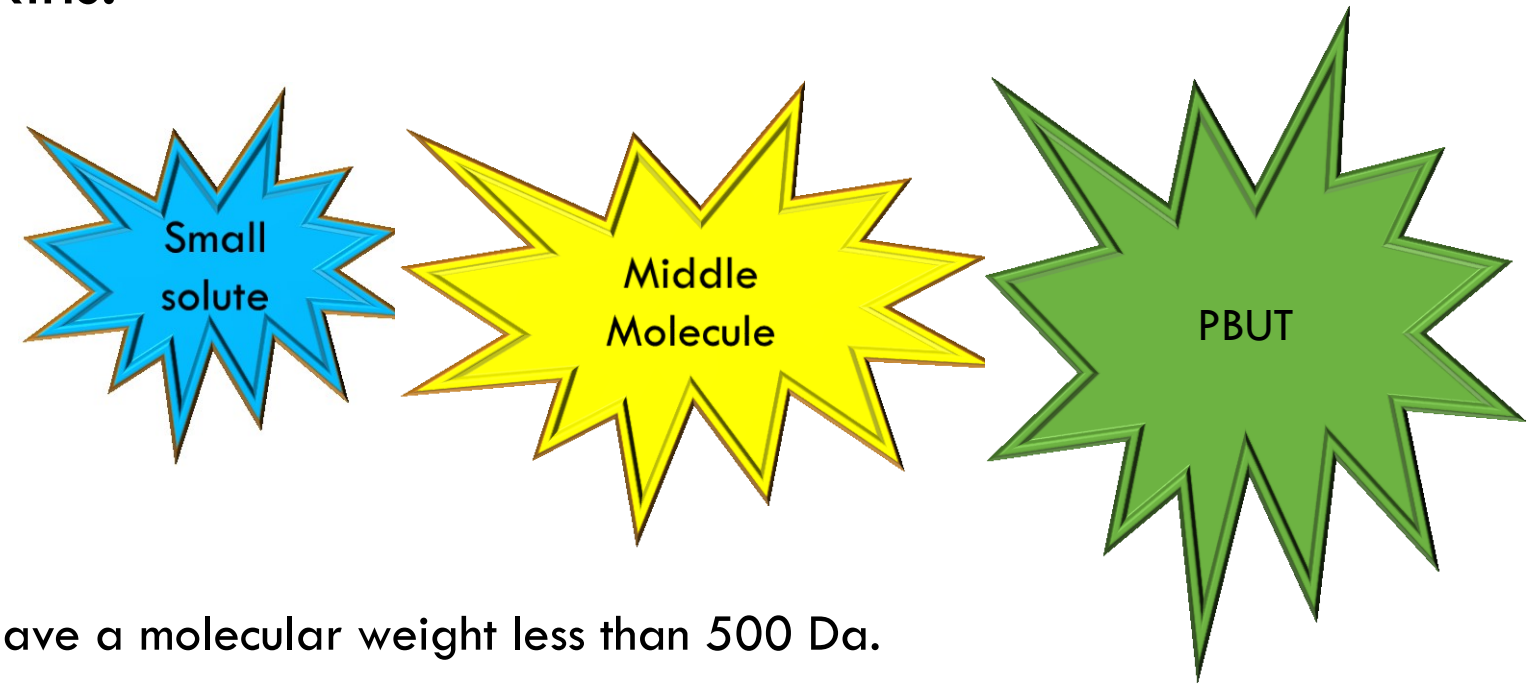
Although same substances found in healthy people can also be found in kidney patients ,they would not be recognized as uremic toxins were it not for their accumulation and toxic  effects in patients with kidney failure.

# UREAMIC TOXINS FROM *past TO up date* CLASSIFICATIOM

- European uremic toxin work group

# CLASSIFICATION OF UREMIC RETENTION COMPOUNDS

- has listed 100 compounds considered to be uremic toxins.

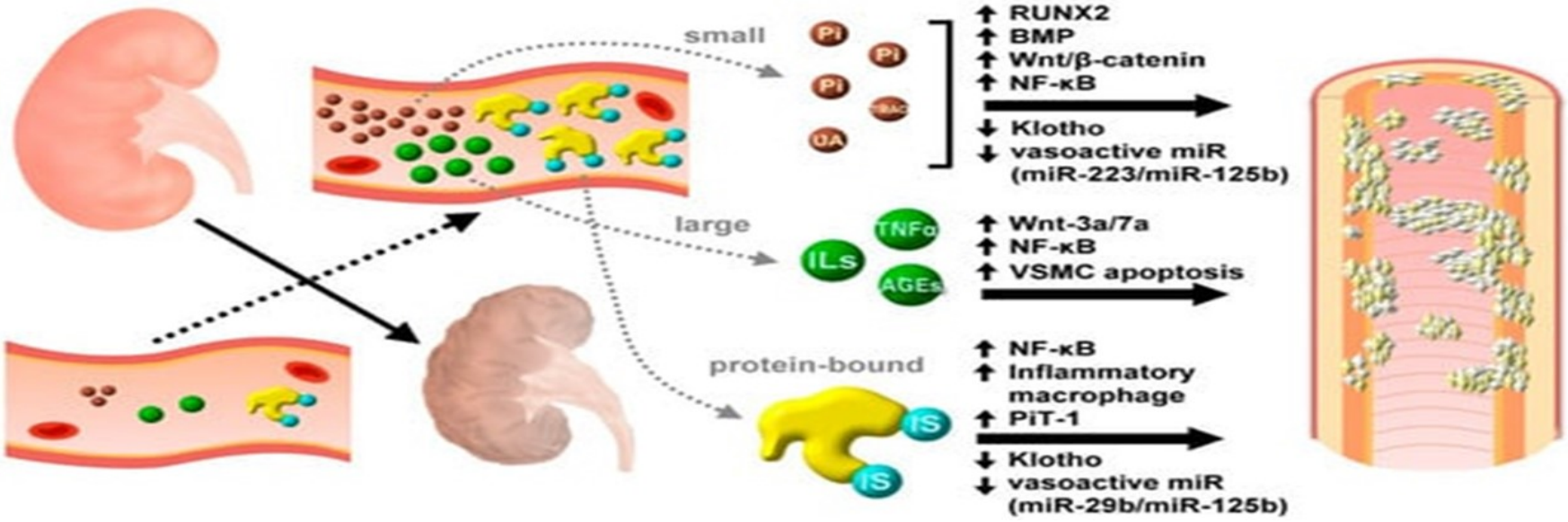


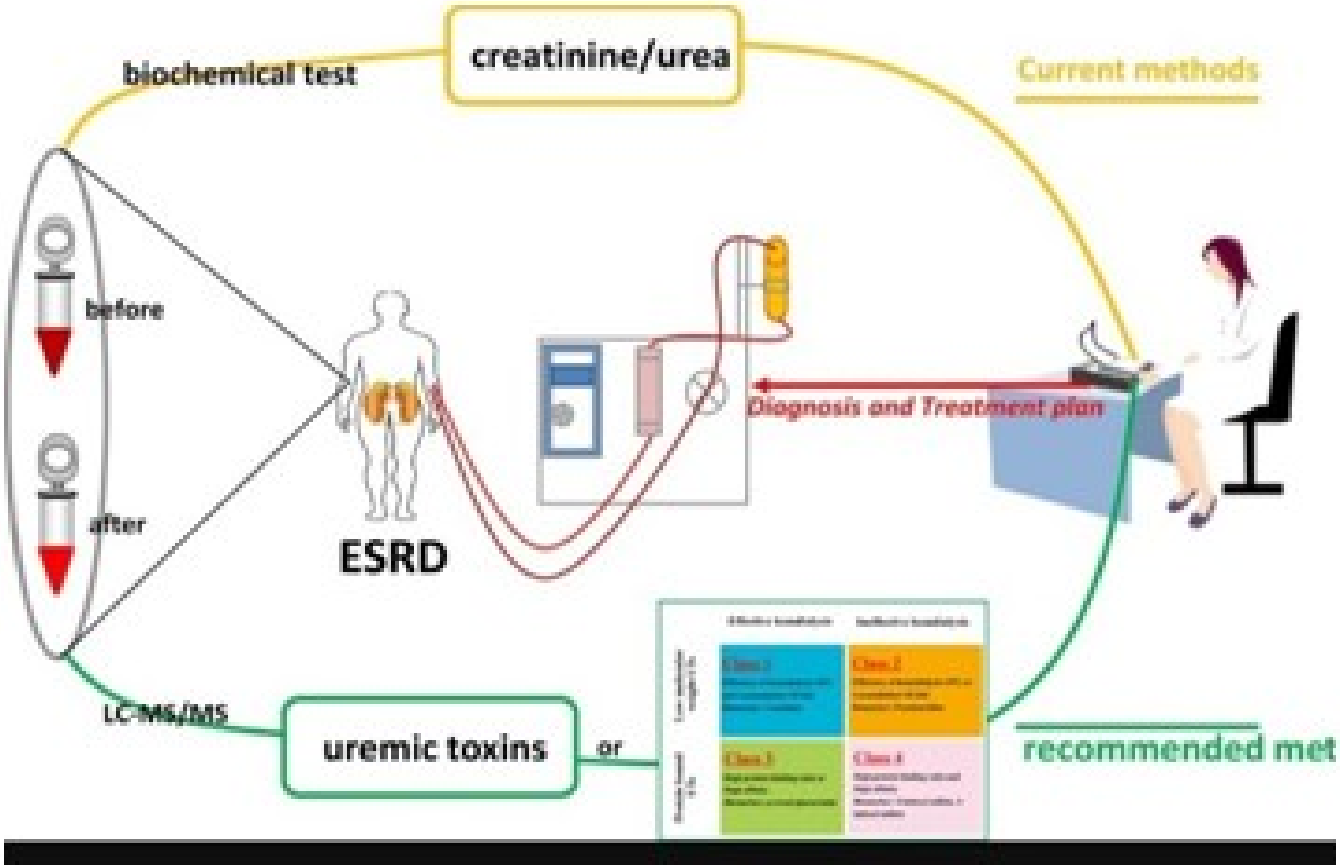

68% have a molecular weight less than 500 Da.

10% have a molecular weight between 500 and 12,000 Da.

(28%) are protein bound

| Small Water-Soluble Compounds (<500 Da) | Middle Molecule (≥500 Da) | Protein Bound Compounds (Mostly < 500 Da) |
|---|---|---|
| ADMA | ANP | AGEs |
| Carbamylated compounds | $\beta_2$-microglobulin | Homocysteine |
| Creatinine | Endothelin | Indoxyl sulfate |
| SDMA | FGF23 | Indole acetic acid |
| TMAO | Ghrelin | Kynurenines |
| Urea | Immunoglobulin light chains | *p*-cresylsulfate |
| Uric acid | Interleukin-6 | Phenyl acetic acid |
| | Interleukin-8 | |
| | Interleukin-18 | |
| | Lipids and lipoproteins | |
| | Neuropeptide Y | |
| | PTH | |
| | Retinol binding protein | |
| | TNF-α | |




creatinine/urea
biochemical test
Current methods
before
after
ESRD
Diagnosis and Treatment plan
LC-MS/MS
uremic toxins
or
recommended met

# TYPES OF DIFFERENT PATHOBIOLOGICAL WAYS

**Type I** accumulation in body fluids of toxic substances normally produced endogenously by metabolic processes, largely as a result of reduced renal excretory capacity (e.g., urea).

**Type II** excess endogenous production or impaired degradation (or both), but not because of reduced renal excretory capacity (e.g., parathyroid hormone of ADMA).

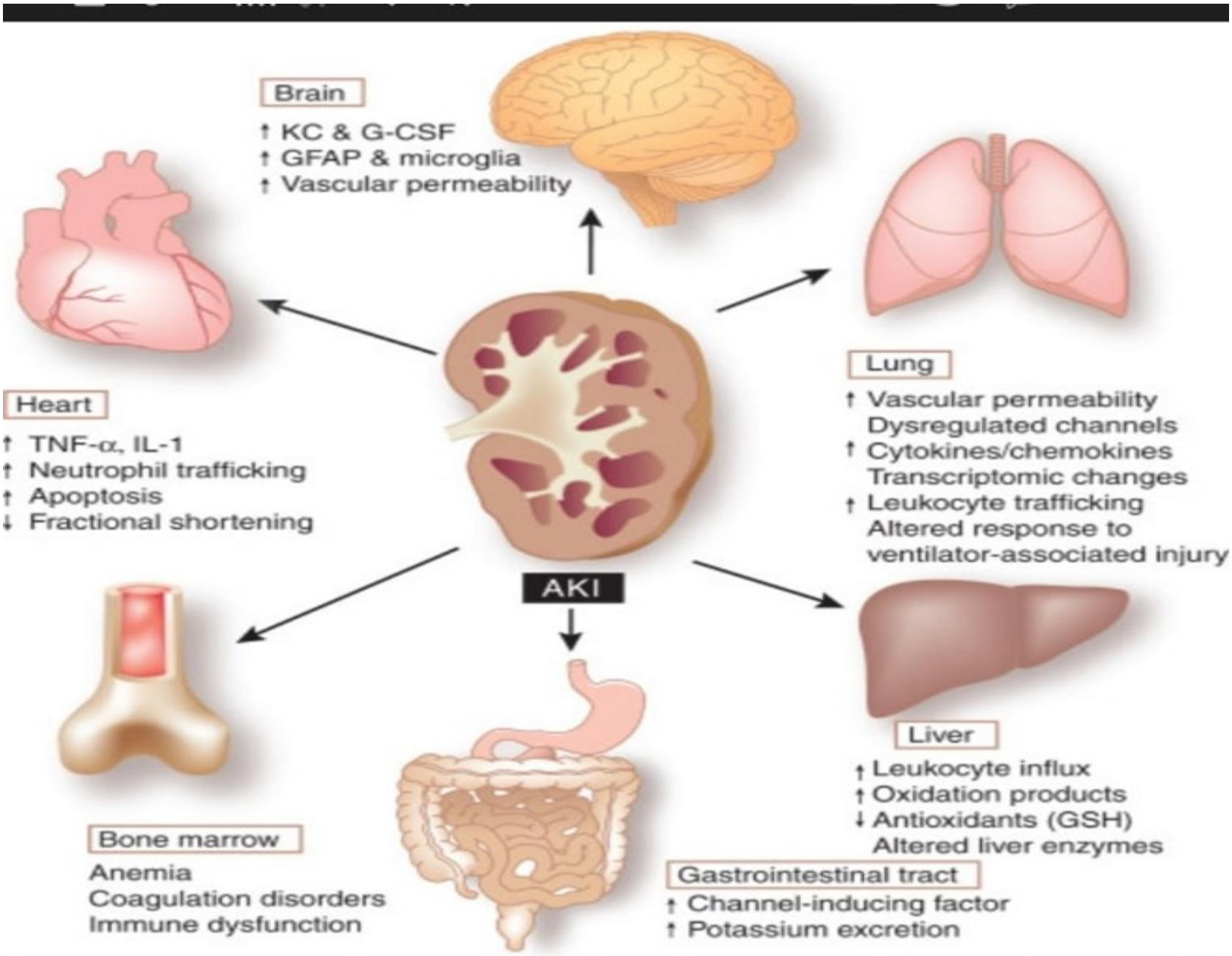
**Type III** involves the accumulation of toxic substances in biological fluids from exogenous sources by virtue of reduced renal excretory capacity,

**Type IV** is a deficiency or reduced activity of substances normally produced endogenously as a result of decreased synthesis, enhanced degradation, or biological inhibition.

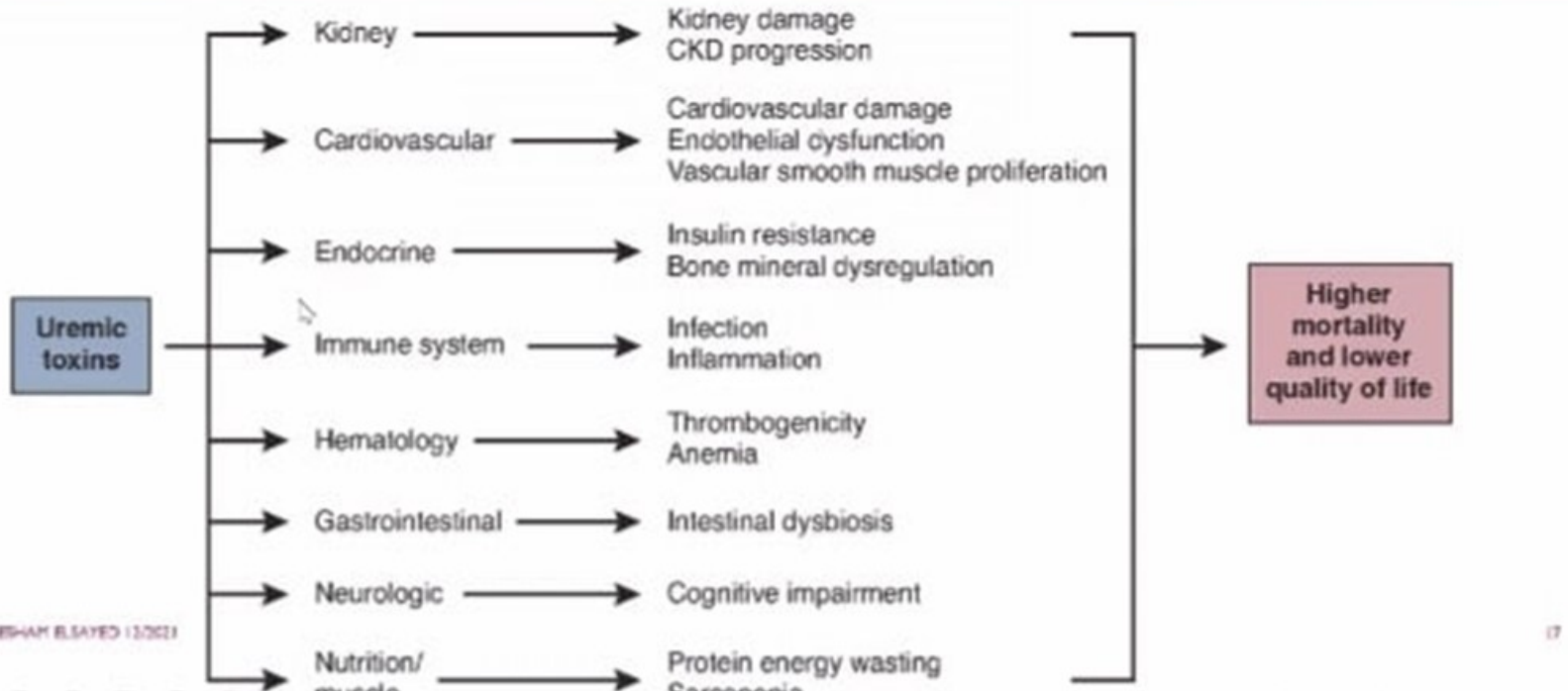
# Potential uremic toxins

- Toxin Effect
- ***Urea*** at high concentrations [>300 mg/dL(>50 mmol/L)]: headaches, vomiting, fatigue, carbamylation of proteins
- **Creatinine** Possibly affects glucose tolerance and erythrocyte survival
- 
- **Cyanate** Drowsiness and hyperglycemia, carbamylation of proteins
- **Polyols** (e.g., myoinositol) Peripheral neuropathy
- 

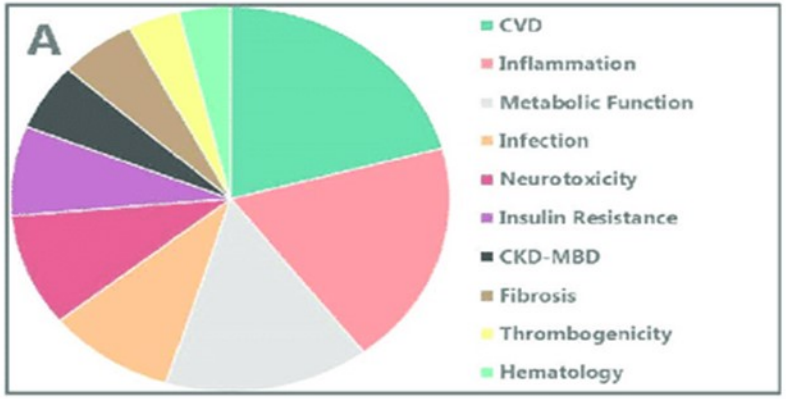
- **Phenols** Can be highly toxic as they are lipid-soluble and therefore can cross cell membranes easily
- 
- **"Middle molecules"**[note] Peritoneal dialysis patients clear middle molecules more efficiently than hemodialysis patients.
- They show fewer signs of neuropathy than hemodialysis patients
- 
- **β2-Microglobulin** Renal amyloid
- 
- **Indoxyl sulfate** Induces renal dysfunction and cardiovascular dysfunction; associated with chronic kidney disease and cardiovascular disease
- **p-cresyl sulfate** Accumulates in and predicts chronic kidney disease

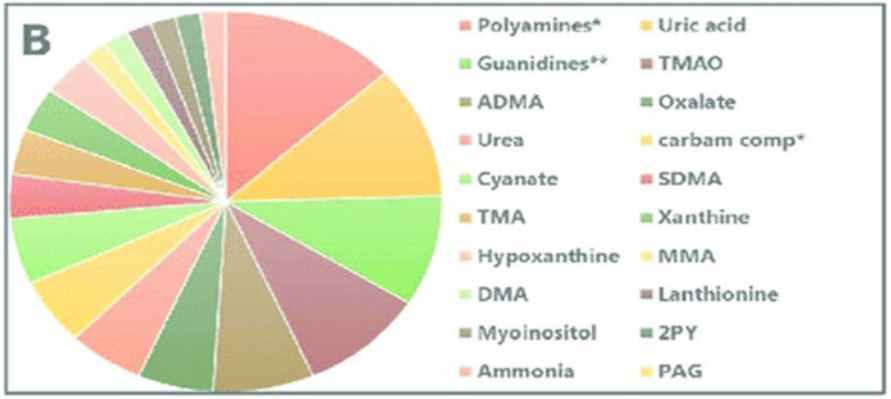

Brain
↑ KC & G-CSF
↑ GFAP & microglia
↑ Vascular permeability
Heart
↑ TNF-α, IL-1
↑ Neutrophil trafficking
↑ Apoptosis
↓ Fractional shortening
Lung
↑ Vascular permeability
Dysregulated channels
↑ Cytokines/chemokines
Transcriptomic changes
↑ Leukocyte trafficking
Altered response to
ventilator-associated injury
AKI
Bone marrow
Anemia
Coagulation disorders
Immune dysfunction
Gastrointestinal tract
↑ Channel-inducing factor
↑ Potassium excretion
Liver
↑ Leukocyte influx
↑ Oxidation products
↓ Antioxidants (GSH)
Altered liver enzymes

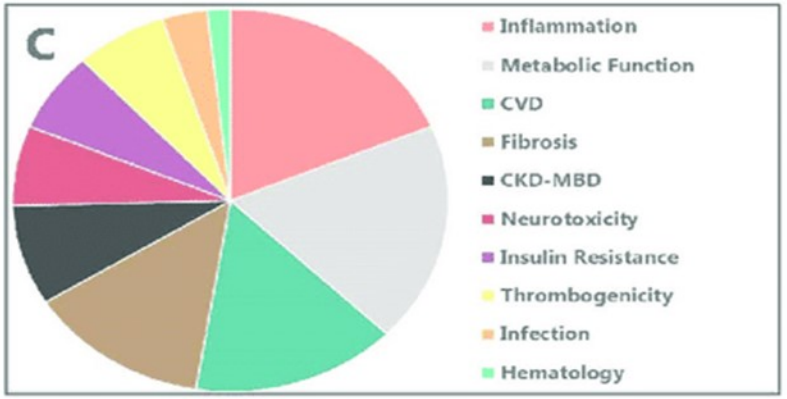
## UREMIC TOXINS AND RELATED SYSTEMIC DISORDERS. THE PATHOPHYSIOLOGIC EFFECT OF UREMIC TOXINS ON ORGAN SYSTEMS AND ASSOCIATED DISORDERS LINKED WITH OUTCOMES.

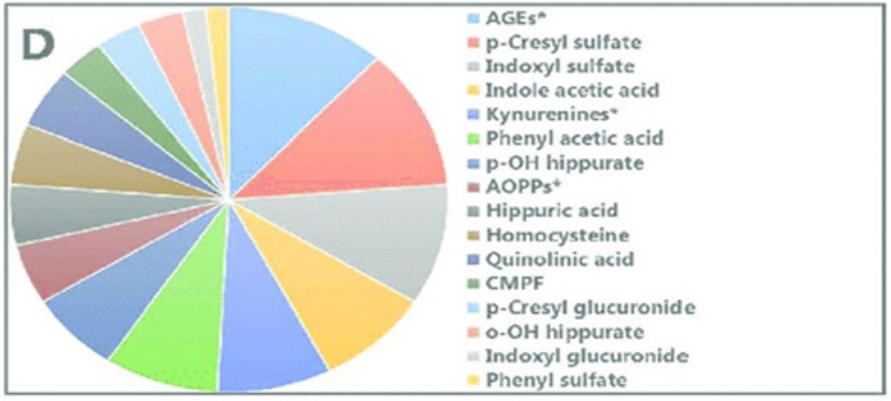


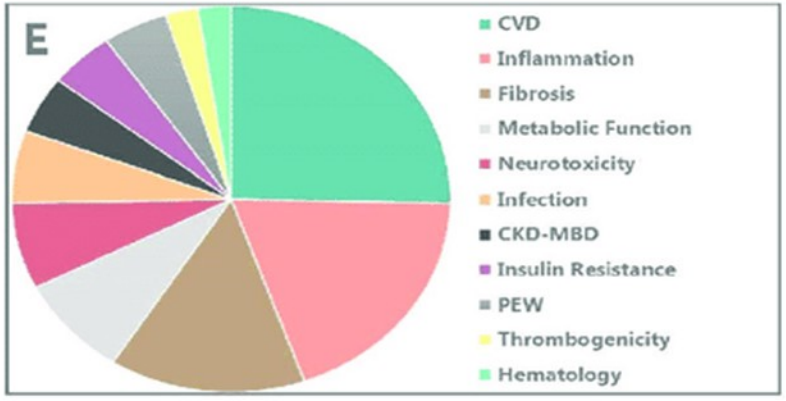

Mitchell H. Rosner , etail CJASN October 2021

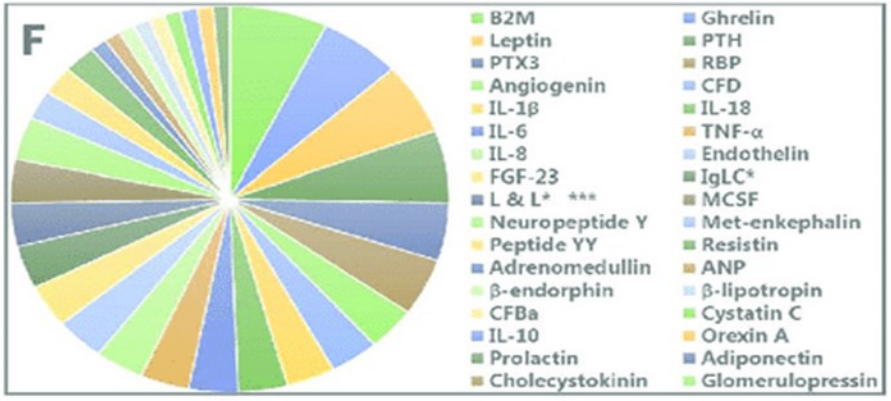

A
CVD
Inflammation
Metabolic Function
Infection
Neurotoxicity
Insulin Resistance
CKD-MBD
Fibrosis
Thrombogenicity
Hematology

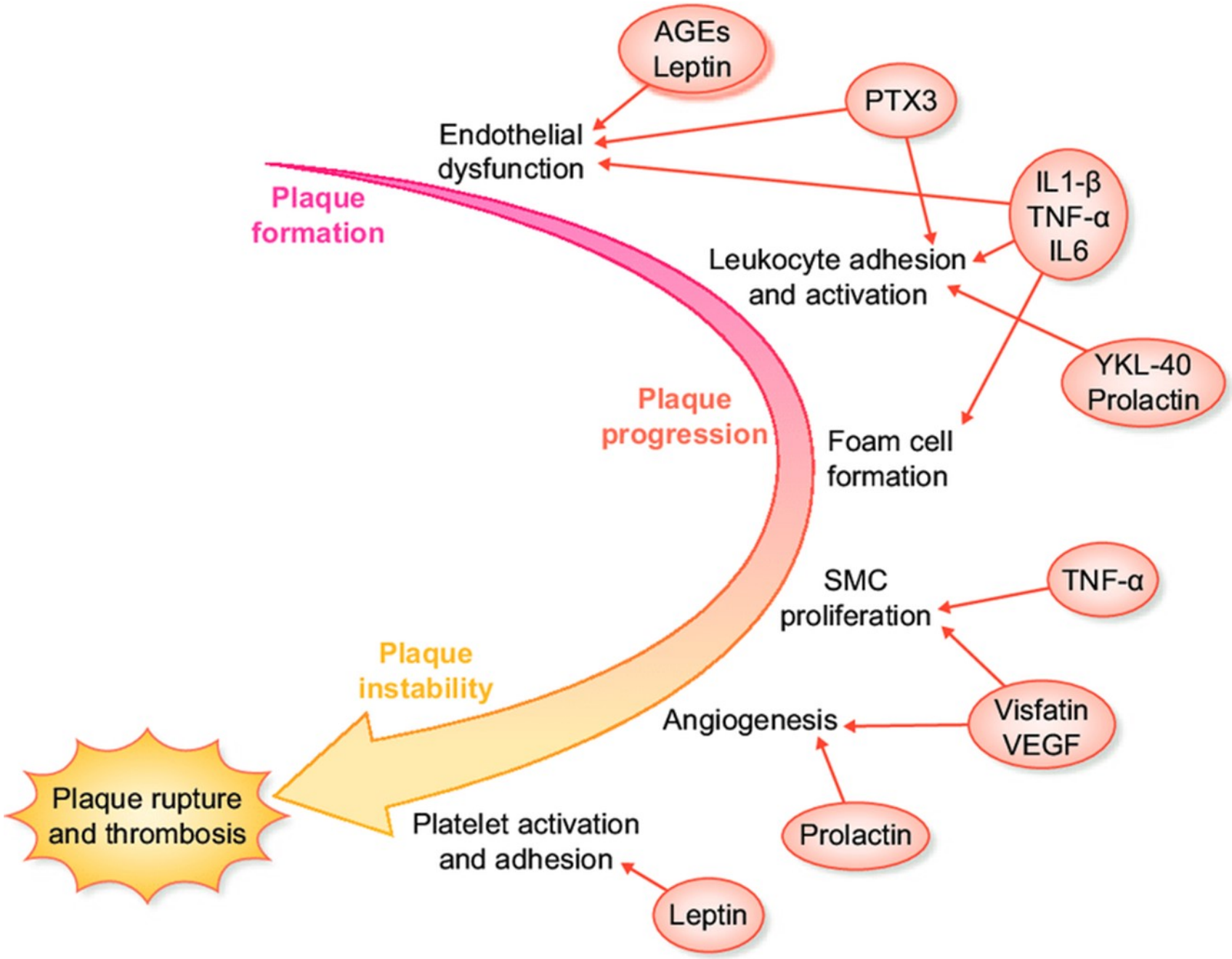

B
Polyamines*
Uric acid
Guanidines**
TMAO
ADMA
Oxalate
Urea
carbam comp*
Cyanate
SDMA
TMA
Xanthine
Hypoxanthine
MMA
DMA
Lanthionine
Myoinositol
2PY
Ammonia
PAG


C
Inflammation
Metabolic Function
CVD
Fibrosis
CKD-MBD
Neurotoxicity
Insulin Resistance
Thrombogenicity
Infection
Hematology

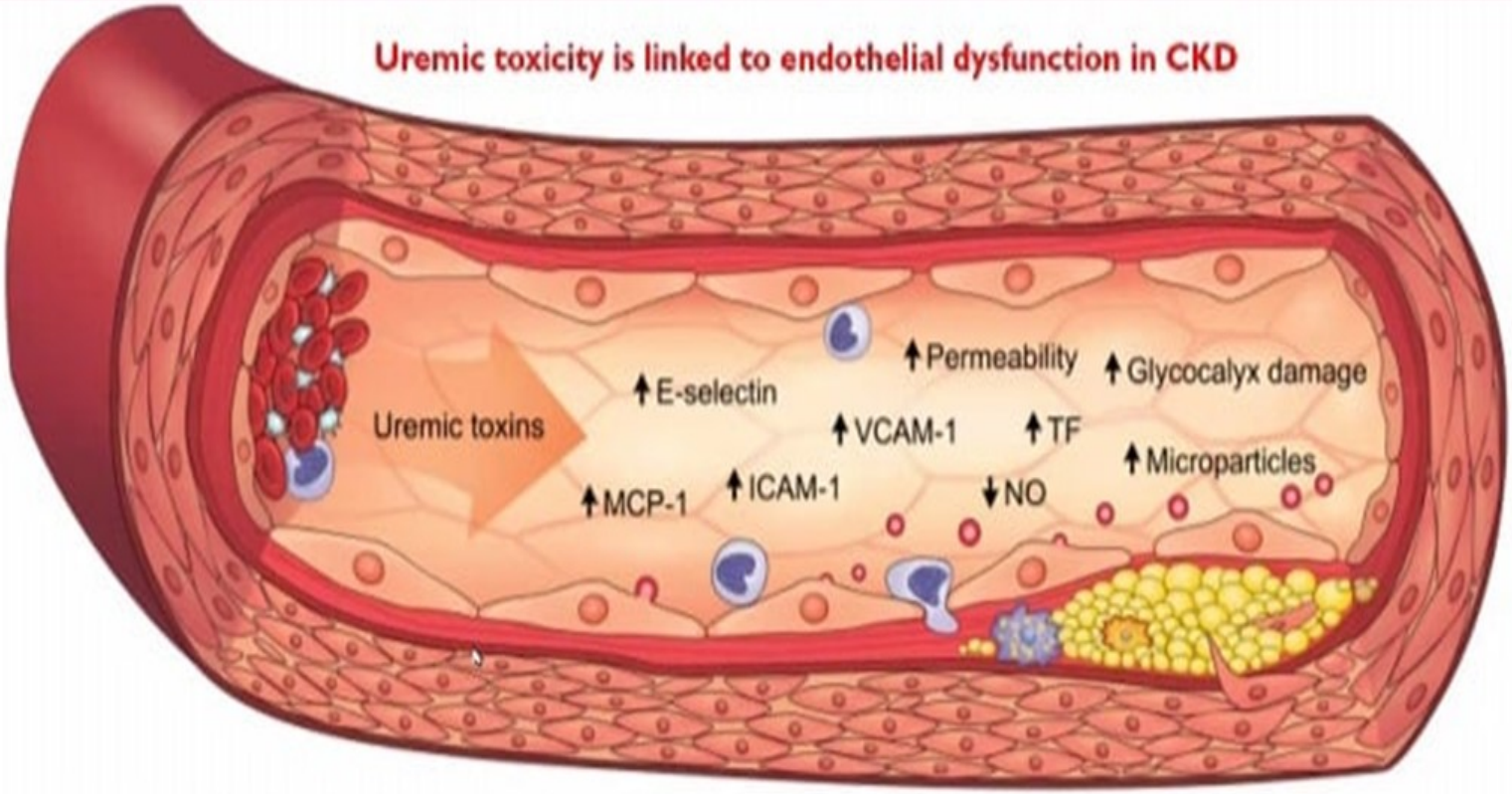

D
AGEs*
p-Cresyl sulfate
Indoxyl sulfate
Indole acetic acid
Kynurenines*
Phenyl acetic acid
p-OH hippurate
AOPPs*
Hippuric acid
Homocysteine
Quinolinic acid
CMPF
p-Cresyl glucuronide
o-OH hippurate
Indoxyl glucuronide
Phenyl sulfate


E
CVD
Inflammation
Fibrosis
Metabolic Function
Neurotoxicity
Infection
CKD-MBD
Insulin Resistance
PEW
Thrombogenicity
Hematology


F
B2M
Ghrelin
Leptin
PTH
PTX3
RBP
Angiogenin
CFD
IL-1β
IL-18
IL-6
TNF-α
IL-8
Endothelin
FGF-23
IgLC*
L & L* ***
MCSF
Neuropeptide Y
Met-enkephalin
Peptide YY
Resistin
Adrenomedullin
ANP
β-endorphin
β-lipotropin
CFBa
Cystatin C
IL-10
Orexin A
Prolactin
Adiponectin
Cholecystokinin
Glomerulopressin


AGEs
Leptin
PTX3
Endothelial
dysfunction
Plaque
formation
IL1-β
TNF-α
IL6
Leukocyte adhesion
and activation
YKL-40
Prolactin
Plaque
progression
Foam cell
formation
SMC
proliferation
TNF-α
Plaque
instability
Angiogenesis
Visfatin
VEGF
Plaque rupture
and thrombosis
Platelet activation
and adhesion
Prolactin
Leptin

## Uremic toxicity is linked to endothelial dysfunction in CKD




Induce the expression of proinflammatory factors (e.g., MCP-1, E-selectin, ICAM-1, and VCAM-1), prothrombotic factors (e.g., TF), the increase in permeability, the **reduction of NO bioavailability and the formation of endothelial microparticles**

# DIALYSIS-RELATED AMYLOID OSTEOPATHY DRAO

AJKD Official Journal of the National Kidney Foundation

B2m

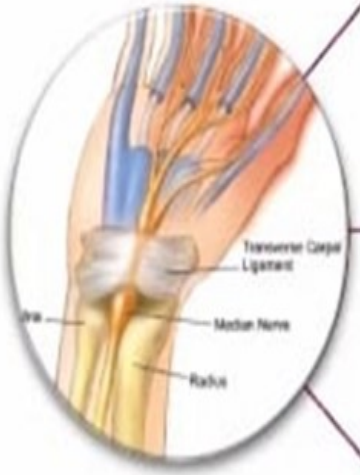
- Abnormality in structure

Local

- abnormal microenvironment
- modification of precursor proteins by inflammatory cells

co-deposition

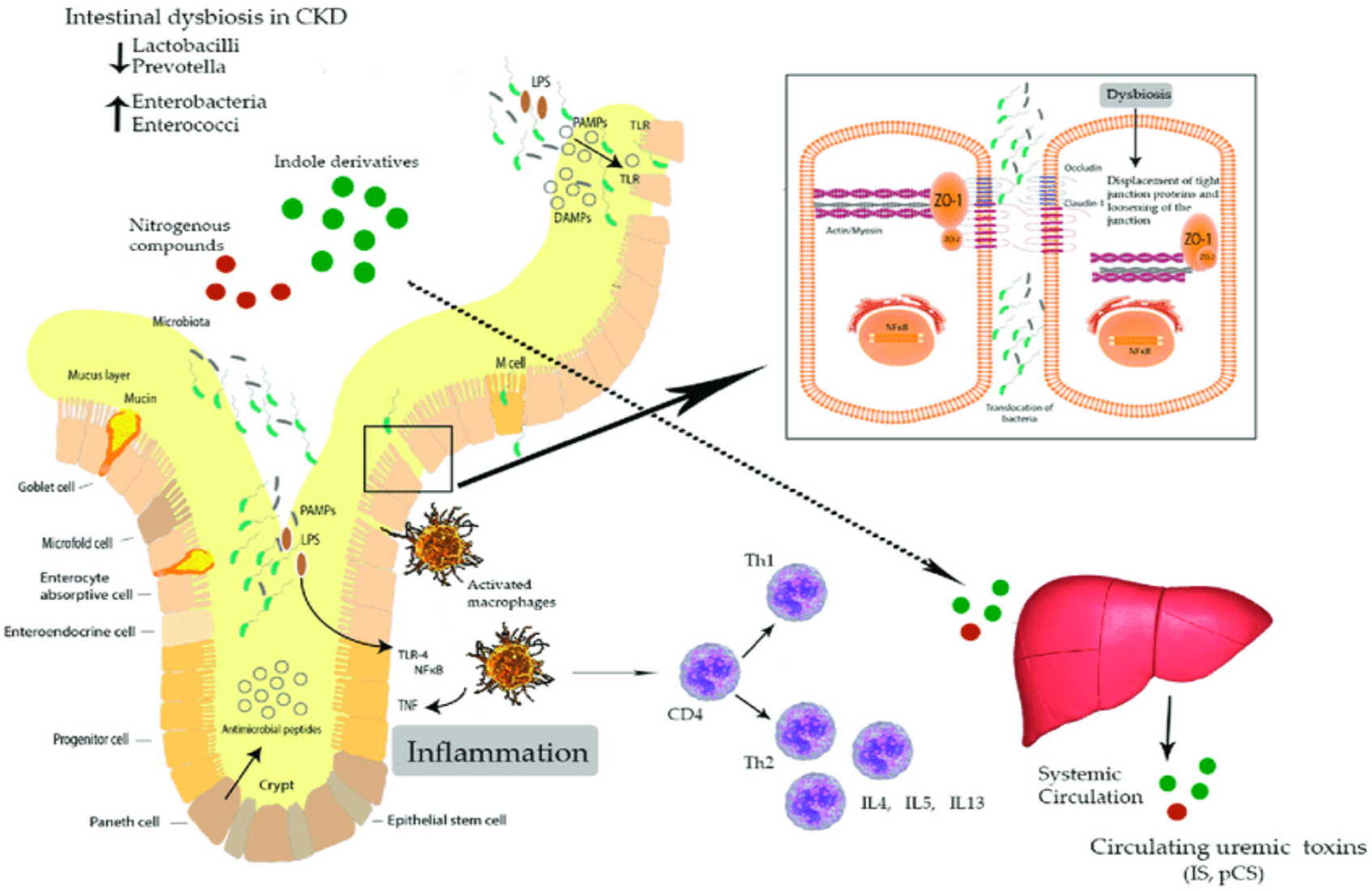
- Apolipoprotein E
- AGE



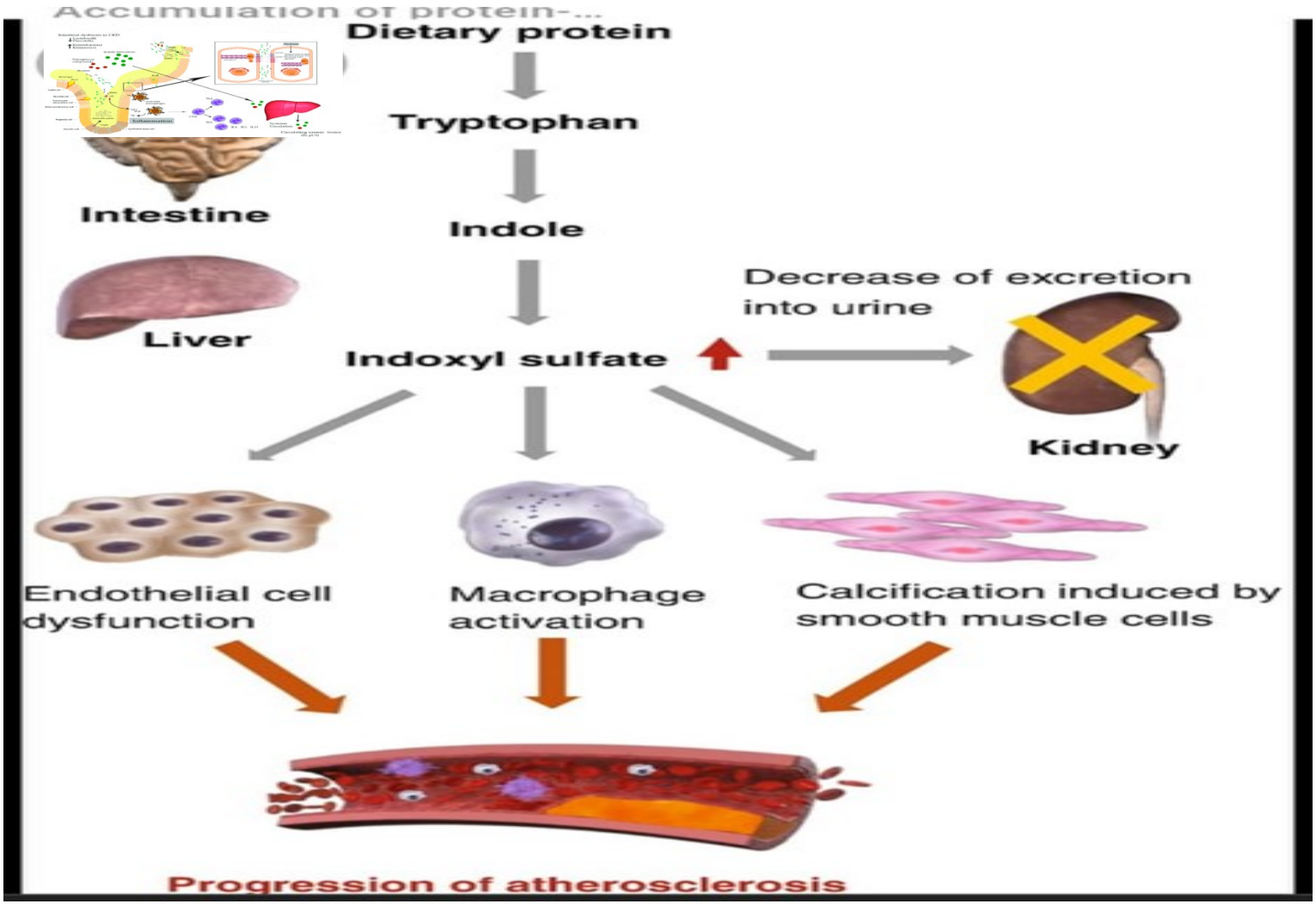

Inflammatory cells infiltrating the synovial tissue

promote inflammatory osteolysis

inflammatory cytokines induce receptor activator of nuclear factor-κB


Intestinal dysbiosis in CKD
Lactobacilli
Prevotella
Enterobacteria
Enterococci
Indole derivatives
Nitrogenous compounds
Microbiota
LPS
PAMPs
TLR
TLR
DAMPs
Mucus layer
Mucin
M cell
Goblet cell
Microfold cell
Enterocyte absorptive cell
Enteroendocrine cell
PAMPs
LPS
Activated macrophages
TLR-4
NFκB
TNF
Antimicrobial peptides
Progenitor cell
Crypt
Paneth cell
Epithelial stem cell
Inflammation
Th1
CD4
Th2
IL4, IL5, IL13
Dysbiosis
Occludin
Claudin-1
Actin/Myosin
ZO-1
ZO-2
Displacement of tight junction proteins and loosening of the junction
Translocation of bacteria
NFκB
Systemic Circulation
Circulating uremic toxins
(IS, pCS)

# Accumulation of PUT



# Residual syndrome

- People on dialysis acquire what is known as "residual syndrome“
- *Residual syndrome is a non-life-threatening disease which is displayed as toxic effects causing many of the same signs and symptoms that uremia displays*.
  There are several hypotheses why residual syndrome is present.
- They are: the accumulation of large molecular weight solutes that are poorly dialyzed (e.g. β2-microglobulin);
- the accumulation of protein-bound small molecular weight solutes that are poorly dialyzed (e.g. p-cresyl sulfate and indoxyl sulfate);

- the accumulation of dialyzable solutes that are incompletely removed (e.g. sequestered solutes like phosphate in cells or insufficient elimination of other more toxic solutes);

- indirect phenomena such as carbamylation of proteins, tissue calcification, or a toxic effect of hormone imbalance (e.g. parathyroid hormone)

- and; the toxic effects of dialysis itself (e.g. removal of unknown important vitamins or minerals).

- Dialysis increases life span but patients may have more limited function. They suffer physical limitations which include impairment of balance, walking speed, and sensory functions.

- They also suffer cognitive impairments such as impairment in attention, memory, and performance of higher-order tasks.
- Patients have been maintained longer than three decades on dialysis, but average mortality rates and hospitalizations are high. Also,
- patient rehabilitation and quality of life is poor.

# *Clinical Manifestations of the "Residual" Syndrome*

- Prolonged recovery from infection, illness
- • Impaired inflammatory and cellular immune response
- • Delayed wound healing
- • Inhibition of leukocyte phagocytosis
- • Resistance to insulin, erythropoietin, parathyroid,
- • Infertility
- • Hypothermia
- • Hypertension
- • Hyper phosphatemia
- • Intermittent vomiting
- • Frequent congestive heart failure, cardiovascular disease
- • Restless Legs

# Cont……

- .Poor stamina
- • Post dialysis lethargy, poor tolerance of hemodialysis
- • Poor appetite
- • Intermittent nausea, feeling sick
- • Insomnia, sleep disturbance
- • Impaired sexual function
- • Reduced capacity for mental concentration
- • Impaired cognitive function
- • Depression

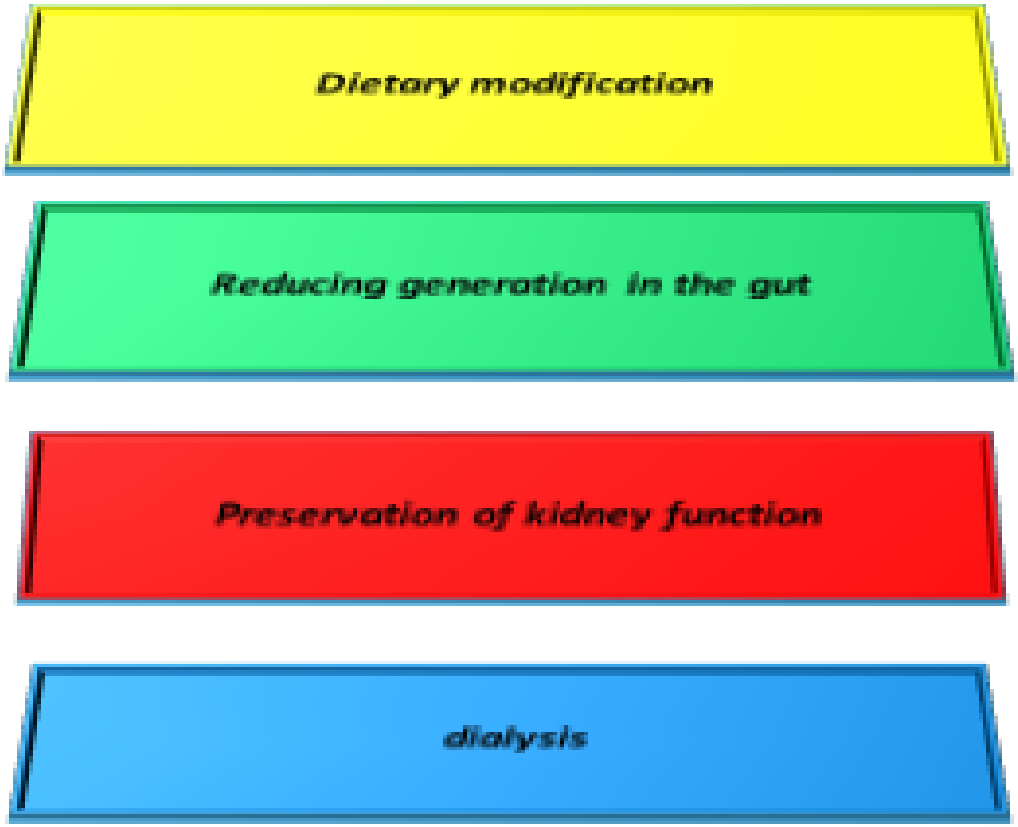
# Treatment

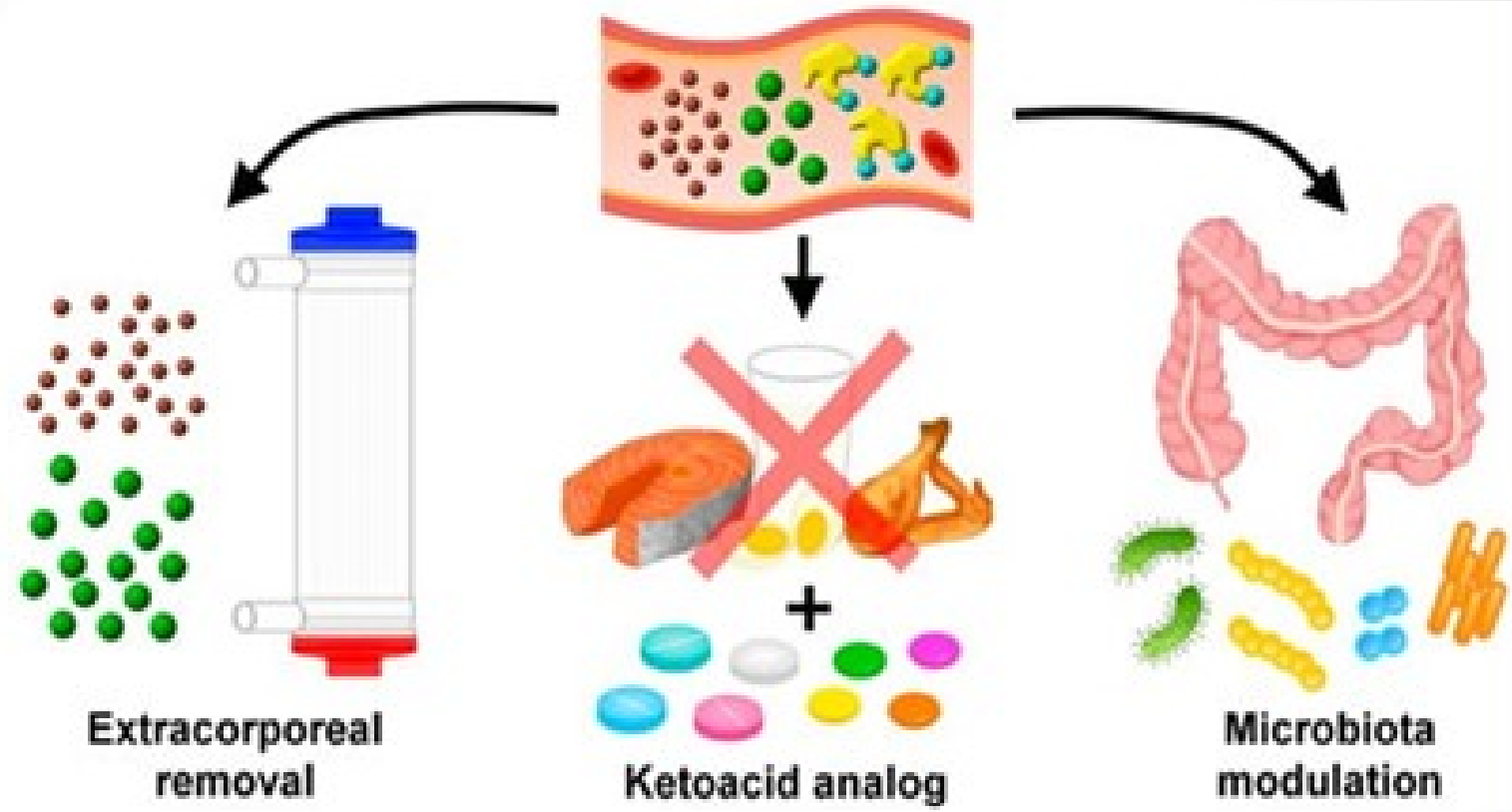
- Dialysis removes many soluble waste products that accumulate in renal failure and helps improve some conditions associated with uremia.

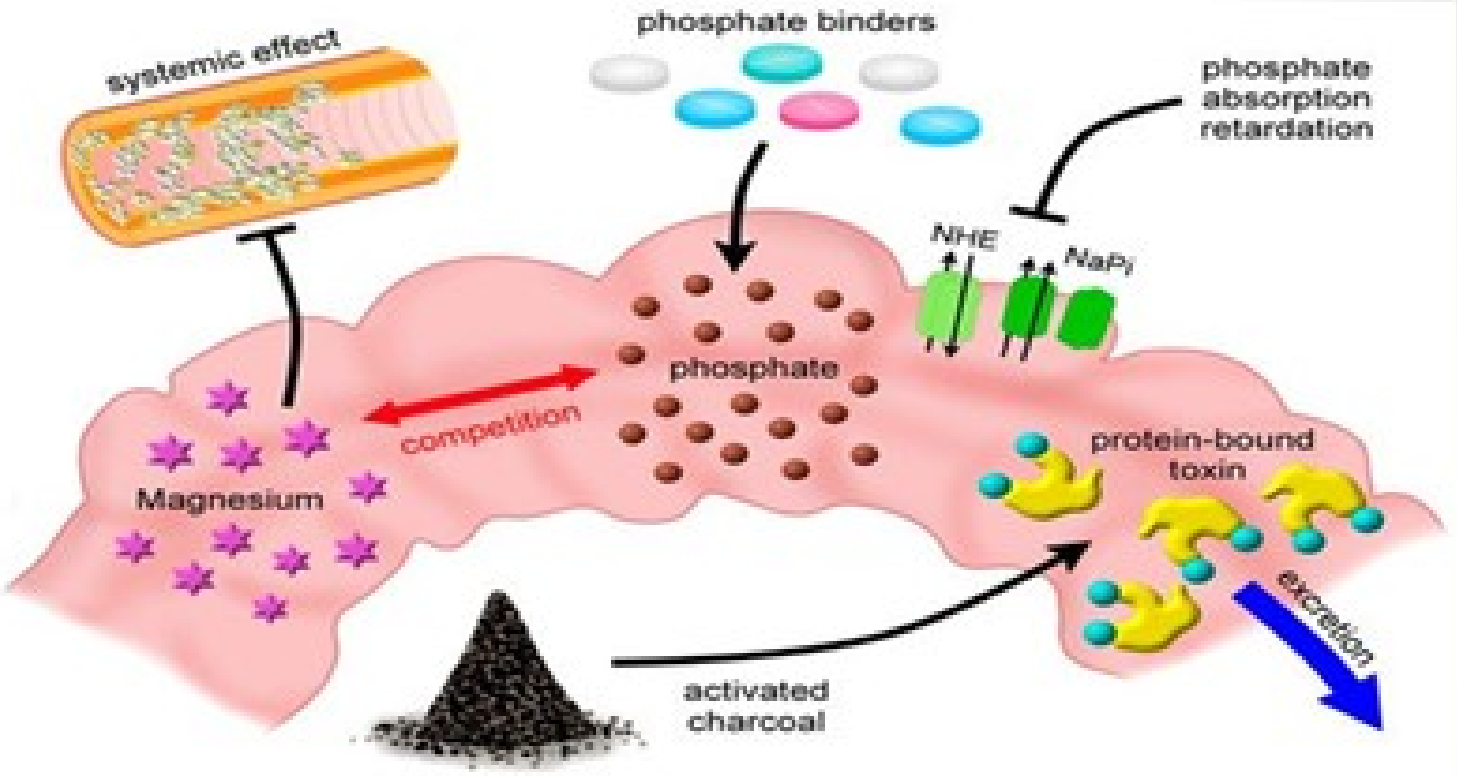
- Other uremic conditions can be alleviated with a protein-restricted diet, careful management of acid-base balance, and calcium and folate supplementation

# UREMIC TOXIN CLEARANCE

*How to decrease concentration / prevent retention of uremic toxins*



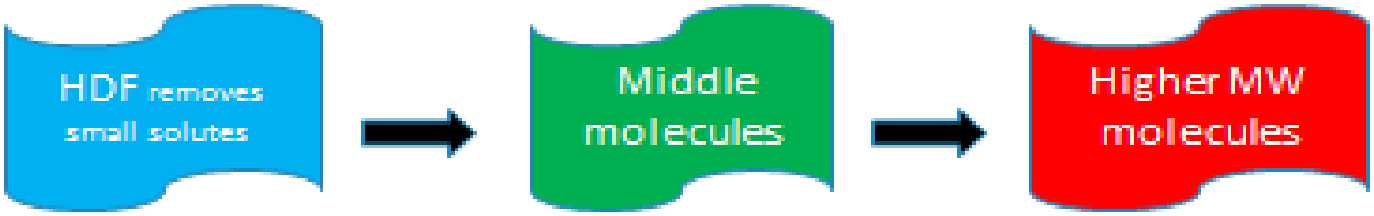

Extracorporeal removal
Ketoacid analog
Microbiota modulation


systemic effect
phosphate binders
phosphate absorption retardation
NHE
NaPi
phosphate
competition
Magnesium
protein-bound toxin
excretion
activated charcoal

# Hemodialysis strategies to remove uremic toxins

- Current techniques to overcome the retention of uremic solutes(MM &LMW proteins)

# HDF


HDF removes small solutes
Middle molecules
Higher MW molecules

# CHD (conventional hemodialysis

1. Non-physiological short – duration / inter mittentency
2. PPUT ont removed
3. Most toxins have multi compartmental distribution with high rebound
4. High Flux membranes not equal in SC

- HDF

1. Post – dilution HDF

- 2-pre – dilution HDF
- 3.Mid – dilution HDF
- 4-mixed – dilution HDF

- UF followed by infusion of replacement fluid
- Infusion of replacement fluid followed by UF
- Infusion of replacement fluid at the mid point of UF (post – dilution followed by pre- dilution )
- Infusion of replacement fluid before and after UF (pre- dilution followed by post – dilution )

Consideration in choosing specific HDF modality

- *Successful post – dilution HDF depended on*

.high extracorporeal blood flow rates (typically >350ml/min ), are liable vascular access ( ideally an AVF with a flow rate >600ml/min ).

- An ability to achieve adequate anticoagulation throughout the procedure and th absence of any condition that increase blood viscosity (high haematocrit , cryoglobulinemia and gammopathies)
- *Pre- dilution*

- In patients with no anticoagulation , or who experience high clotting during HDF
- .also in malnourished as albumin loss in minimal with the pre-dilution HDF


CJASN
CJASN September 2021, 16 (9)
Clinical Journal of the American Society of Nephrology
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Reappraisal of Hemodiafiltration for Managing Uremic Complications
Article
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In this issue of CJASN, Kang et al. report on a study comparing the effects of high-flux hemodialysis (HD) with online hemodiafiltration on neuropathy (1). Although two prior small studies found an improvement of nerve function in patients who switched to hemodiafiltration, this randomized
In this issue
CJASN

Review | Published: 01 September 2016

# Why choose high volume online post-dilution hemodiafiltration?

Carlo Basile, Andrew Davenport & Peter J. Blankestijn

*Journal of Nephrology* **30**, 181–186 (2017) | Cite this article



four large prospective randomized controlled trials (RCTs) have been conducted in different European countries to compare survival outcomes in prevalent patients receiving conventional hemodialysis with online post-dilution HDF (OL HDF).

our large meta-analyses on convective therapies have been published in the last 2 years. Taken together, these studies support the conclusion that high volume post-dilution OL HDF is associated with improved overall survival.

meta-analysis from four randomized controlled trials comparing haemodialysis (HD) with post-dilution online-haemodiafiltration (ol-HDF).

NEPHROLOGY DIALYSIS TRANSPLANTATION

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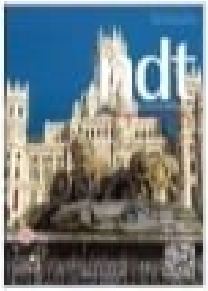

Volume 32, Issue 3
March 2017

Article Contents

Abstract

# Mortality reduction by post-dilution online-haemodiafiltration: a cause-specific analysis

Menso J. Nubé, Sanne A.E. Peters, Peter J. Blankestijn, Bernard Canaud, Andrew Davenport, Muriel P.C. Grooteman, Gulay Asci, Francesco Locatelli, Francisco Maduell, Marion Morena ... Show more

*Nephrology Dialysis Transplantation*, Volume 32, Issue 3, March 2017, Pages 548–555, https://doi.org/10.1093/ndt/gfw381
**Published:** 26 December 2016 **Article history**

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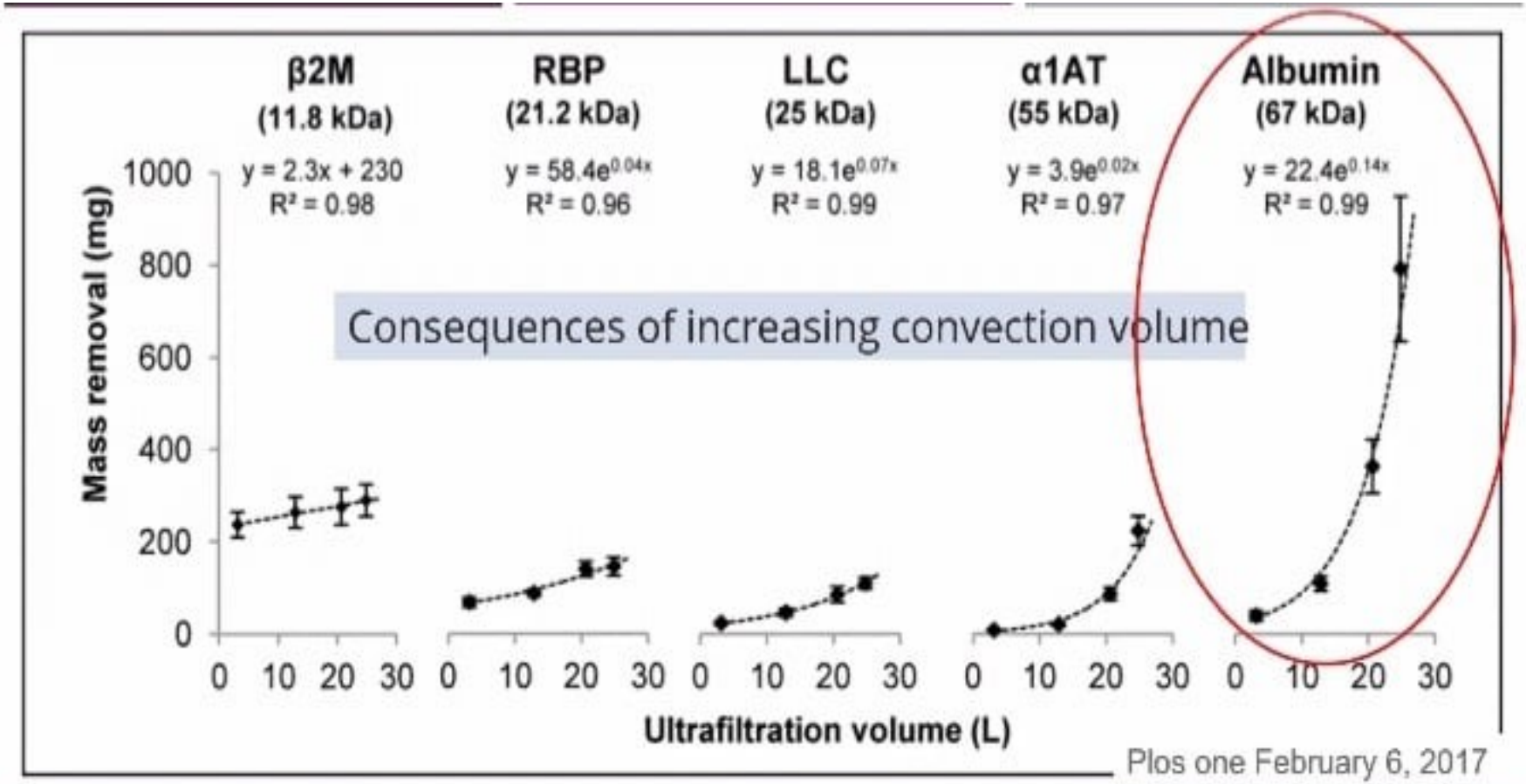
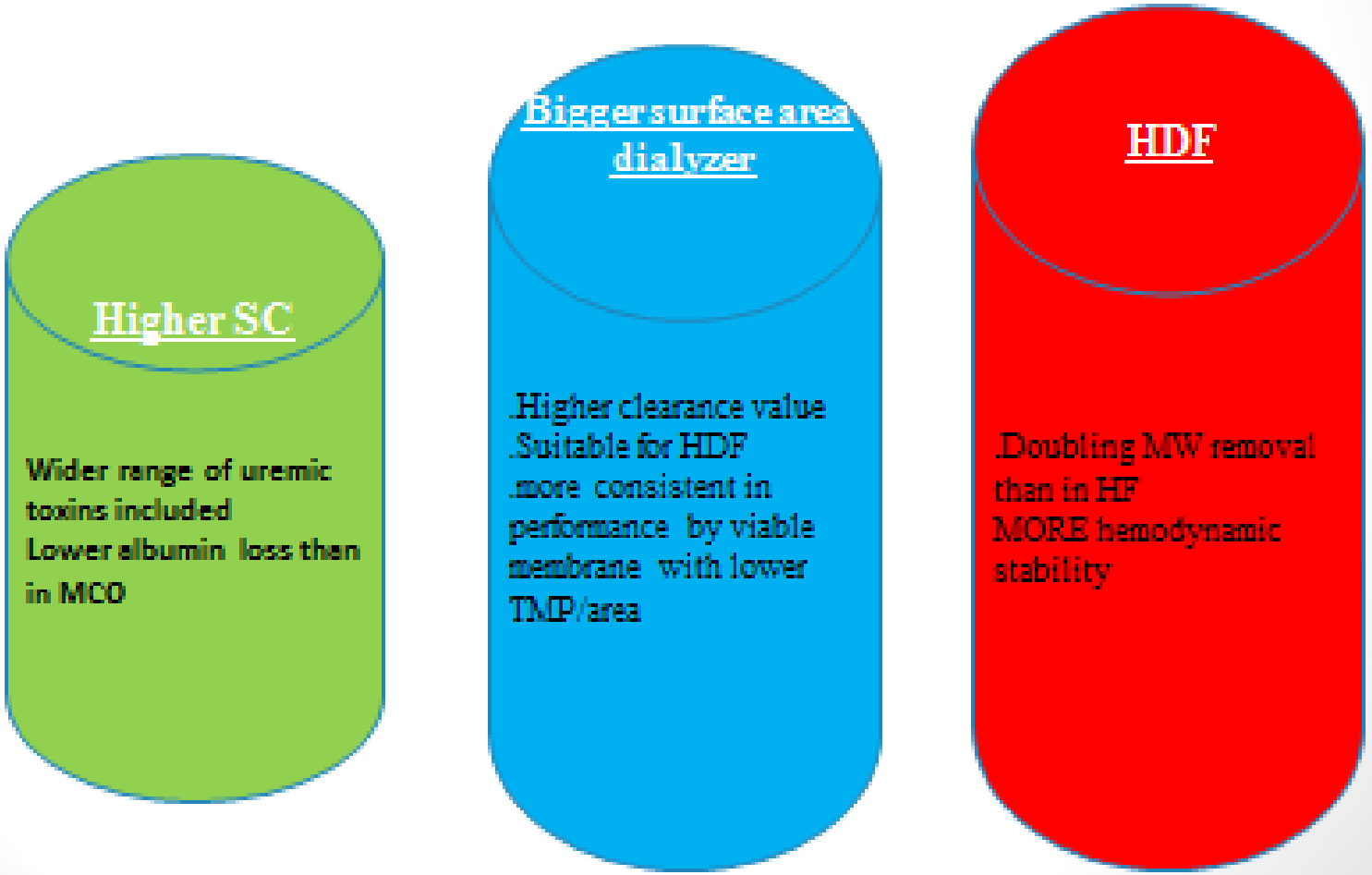

β2M
(11.8 kDa)
y = 2.3x + 230
R² = 0.98
RBP
(21.2 kDa)
y = 58.4e^0.04x
R² = 0.96
LLC
(25 kDa)
y = 18.1e^0.07x
R² = 0.99
α1AT
(55 kDa)
y = 3.9e^0.02x
R² = 0.97
Albumin
(67 kDa)
y = 22.4e^0.14x
R² = 0.99
Consequences of increasing convection volume
Mass removal (mg)
1000
800
600
400
200
0
0 10 20 30
Ultrafiltration volume (L)
Plos one February 6, 2017

*Potential benefits of using bigger surface area and wider sc dialysis membrane*

- Using a bigger and wider Sc dialyzers



## *Bigger surface area dialyzer in HDF*

- Increase convection volume
  - High blood flow rate
  - Long treatment time
  - High filtration fraction
  - Larger dialyzer surface area and KUF
  - Biocompatible dialyser
  - High UF CO- efficient
- Decrease convection volume
  - Lower dialyzer surface area and KUF
  - Poor vascular access
  - High HCT
  - Frequent TMP alarm

# CONCLUSION

- The RRT strategies should be pointed toward individualized therapy with an optimum removal of the uremic toxin
- Don't depended only on high flux dialyzer to remove uremic toxin
- HDF especially post – dilution is more effective of middle and large toxin compare to other
- Uremic toxin still need work up to improve quality of life in dialysis patient and decrease MR

# THANKS