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UREMIC TOXINS : A CONCEPTUAL STUDY

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Abstract : The growth of toxic substances in the body-fluid partitions during the course of developing chronic kidney disease (CKD) is liable for many of the clinical outcomes of the condition known as uremia (precisely, ‘‘urine in the blood’’). A practical and broadly gained categorization is built on molecular weight and plasma protein-binding properties[1]. In this strategy, uremic toxins are differentiated into four non-overlapping categories. European Uremic Toxin Work Group (EuTox) identified 92 organic compounds reportedly associated with uremia, 45 with a molecular weight <500 Da (23 of which were protein-bound), 25 compounds with a molecular weight >500 Da and <12,000 Da, and 22 with a molecular weight >12,000 Da[1]. All body organs and systems are influenced by the toxicity of uremic compounds retained in the course of renal failure, including the cardiovascular system, central nervous system, hematological and coagulation disorders, immune system, endocrine system, bone disease, skin, gastro-intestinal system and respiratory system. Primarily, children have physiological particularities that may influence the inflation pattern of uremic toxins. For instance, children have commensurately larger body water volumes and lower circulating proteins than adults. Secondly, the effect of toxicity on maturational and developmental processes of nearly all organ systems, which represents a central aspect of the pediatric uremic syndrome, can by explanation not be concluded from adults in whom maturation has come to an end. Growth and puberty, which are special pediatric features, are frequently affected in the pediatric uremic syndrome. The estimation of uremic toxins can be evaluated via,. Analytical Techniques and From Biological Evaluations and the Methods to reduce the concentration of uremic toxins are Dietary Modification, Reducing absorption from the gut, Reducing generation in the gut, Preservation of kidney function and Dialysis.

Keywords : Chronic kidney disease, Uremic toxins, Toxicity, Body organs, Children.

1. INTRODUCTION :

THE GROWTH OF TOXIC substances in the body-fluid partitions during the course of developing, chronic kidney disease (CKD) is liable for many of the clinical outcomes of the condition known as uremia (precisely, ‘‘urine in the blood’’). These ‘‘uremic toxins’’ show a wide arrangement of physicochemical characteristics, mechanisms of generation, and patho-biological actions at the cellular and molecular levels. An accurate understanding of these features of uremic toxins would be very useful in the pattern of strategies for their removal (via, dialysis) and in the prevention or inhibition of their unacceptable effects on tissues and organs. Owing to the heterogeneity in the structure and actions of uremic toxins, it is helpful to possess a broad classification, based on fundamental chemical and biological principles[1].

1.1 Definitions and Leading Principles

To acknowledge uremic toxins, it is inevitable to have a definition of uremia itself. (Bergstrom and Furst) issued a very succinct definition of uremia: ‘‘a toxic syndrome caused by severe glomerular deficiency associated with disturbances in tubular and endocrine functions of the kidney. It is characterized by the retention of toxic metabolites, associated with changes in the volume and composition of the body fluids and an excess or deficiency or various hormones’’[2]. This definition holds uremia as a syndrome derive from the accumulation of toxic substances in body fluids consequential to a non-fulfillment of renal excretion, as well as from hormonal surfeits and deficiencies. It does not fully holds the concept that immoderate endogenous construction or the impaired degradation of non-hormonal toxic metabolites can also engage in the production of the uremic milieu, but it does include the feasibility that express of deficiency are behind for the elements of uremic syndrome. Uremic toxins cannot be explain simply as substances present in the body fluids of individuals enduring from uremic syndrome. A relationship between the toxic substance and one or more of the patho-biological or clinical features of the uremic syndrome must be strongly indicated. To show this relationship requires the enactment of a form of Koch’s postulates, as modified by Massry in 1977[3]. The Massry/Koch requirements for the recognition of an ‘‘authentic’’ uremic toxin are:

1. The toxin must be chemically identified and characterized.
2. Quantitative analysis of the toxin in biological fluids should be possible.
3. The level of the toxin in biological fluids must be elevated in uremia.
4. A relationship between the level of the toxin in biological fluids and one or more of the manifestations of uremia must be present.
5. A reduction in the level of the toxin in biological fluids must result in the amelioration of the uremic manifestation.
6. Administration of the toxin to achieve levels similar to those observed in uremia must reproduce the uremic manifestation in otherwise normal animals or man (invitro demonstration of cellular toxicity alone is insufficient to fulfill this criterion).

In addition to these six criteria a seventh should be add-up, i.e., a plausible patho-biological mechanism should be demonstrated to explain the linkage between the toxin and the uremic manifestation.

1.2 Physicochemical Characteristics

The physicochemical characteristics of uremic toxins feasibly classified in accordance to their chemical nature (inorganic or organic), molecular mass/volume (small, ‘‘middle,’’ or large), or their distribution in body fluids (hydrophilic [water-soluble], lipophilic, or bound to plasma proteins[1]. A practical and broadly gained categorization is build on molecular weight and plasma protein-binding properties[1]. In this strategy, uremic toxins are differentiated into four non-overlapping categories, i.e.,

1. Water-soluble, low molecular weight (<500 Da), and nonprotein-bound;
2. Water-soluble, low molecular weight (<500 Da), and proteinbound;
3. Middle molecular weight (>500 Da and <12,000 Da); and
4. High molecular weight (>12,000 Da).

In accordance with the above elucidations, inorganic substances accomplished as uremic toxins would include H_2O, Na+, K+, H+, Mg++, PO_4---, Ca++, SO_4 , and trace metals such as Al, Cr, Si, and Pb. The organic compounds related to uremia are countless and diverse. Beyond 92 separate organic chemical units have been reported in coalition with uremia, but moderately a small number have fulfilled all of the Massry/ Koch postulates. In a comprehensive review of the literature from 1966 to 2002, Vanholder et al. and the European Uremic Toxin Work Group (EuTox) identified 92 organic compounds reportedly associated with uremia, 45 with a molecular weight

<500 Da (23 of which were protein bound), 25 compounds with a molecular weight >500 Da and <12,000 Da, and 22 with a molecular weight >12,000 Da[1]. The plasma concentrations of above compounds found in uremia differ from a few nanograms to grams per liter.

Even though numerous of these potential uremic toxins have increased plasma concentrations because of impaired renal excretion, many are related with elevated synthesis or impaired degradation compared with normal subjects. The high molecular weight potential uremic toxins (>12,000 Da), of which about 22 were identified in the survey of Vanholder et al.,[1] are less well-characterized and include cytokines and chemokines (interleukin6 and tumor necrosis factor), immunoglobulin light chains, leptin, complement factors, carbamylated proteins or lipoproteins, advanced glycation or oxidation products (AGEP and AOP), and inhibitor proteins (granulocyte-inhibitor protein, chemotaxis-inhibiting peptide, and degranulating-inhibitor protein). The categorization of these uremic toxins in biological fluids, based on their physicochemical characteristics, creates special requirements and unique kinetic behaviors when their removal by extracorporeal (hemodialysis and hemofiltration) or intracorporeal (peritoneal dialysis) means are under consideration.

Table 1. Free water-soluble low-molecular-weight solutes (N= 45)

Solute	Molecular Weight	Group
1-methyladenosine lg/L[4]	281	Ribonucleosides
1-methylguanosine lg/L[4]	297	Ribonucleosides
1-methylinosine lg/L[4]	282	Ribonucleosides
ADMA mg/L[5,6]	202	Guanidines
Alpha-keto--guanidinovaleric acid lg/L[7]	151	Guanidines
Alpha-N-acetylarginine lg/L[8,9]	216	Guanidines
Arab(in)itol mg/L[10,11]	152	Polyols
Argininic acid lg/L[7,8]	175	Guanidines
Benzylalcohol mg/L[12]	108	
Beta-guanidinopropionic acid lg/L[13]	131	Guanidines
Beta-lipotropin ng/L[14]	461	Peptides
Creatine mg/L[13]	131	Guanidines
Creatinine mg/L[15,16]	113	Guanidines
Cytidine lg/L[17]	234	Purines
Dimethylglycine lg/L[18]	103	
Erythritol mg/L[10,11]	122	Polyols
Gamma-guanidinobutyric acid lg/L[19,9]	145	Guanidines
Guanidine lg/L[8,9]	59	Guanidines
Guanidinoacetic acid lg/L[13]	117	Guanidines
Guanidonosuccinic acid mg/L[8,9]	175	Guanidines
Hypoxanthine mg/L[20,21]	136	Purines
Malondialdehyde lg/L[22]	71	
Mannitol mg/L[10,11]	182	Polyols
Methylguanidine lg/L[13,9]	73	Guanidines
Myoinositol mg/L[10]	180	Polyols
N2 ,N2 -dimethylguanosine lg/L[4]	311	Ribonucleosides
N4 -acetylcytidine lg/L[4]	285	Ribonucleosides
N6 -methyladenosine lg/L[4]	281	Ribonucleosides

N6 -threonylcarbamoyladenosine lg/L[4]	378	Ribonucleosides
Orotic acid mg/L[23]	174	Pyrimidines
Orotidine mg/L[23]	288	Pyrimidines
Oxalate mg/L[24]	90	
Phenylacetylglutamine mg/L[25]	264	
Pseudouridine mg/L[17,23]	244	Ribonucleosides
SDMA lg/L[7]	202	Guanidines
Sorbitol mg/L[10,11]	182	Polyols
Taurocyamine lg/L[9]	174	Guanidines
Threitol lg/L[10,11]	122	Polyols
Thymine mg/L[23]	126	Pyrimidines
Uracil lg/L[17]	112	Purines
Urea g/L[16]	60	
Uric acid mg/L[17]	168	Purines
Uridine mg/L[23]	244	Pyrimidines
Xanthine mg/L[20,21]	152	Purines
Xanthosine lg/L[4]	284	Ribonucleosides

Abbreviations are: ADMA, asymmetrical dimethylarginine; SDMA, symmetrical dimethylarginine.

Table 2. Protein-bound solutes (N =25)

Solute	**Molecular Weight**	**Group**
2-methoxyresorcinol lg/L[12]	140	Phenols
3-deoxyglucosone mg/L[26]	162	AGE
CMPF mg/L[27]	240	
Fructoselysine mg/L[28]	308	AGE
Glyoxal lg/L[29]	58	AGE
Hippuric acid mg/L[30]	179	Hippurates
Homocysteine mg/L[31-33]	135	
Hydroquinone lg/L[12]	110	Phenols
Indole-3-acetic acid lg/L[34,35]	175	Indoles
Indoxyl sulfate mg/L[27]	251	Indoles
Kinurenine lg/L[36]	208	Indoles
Kynurenic acid mg/L[37]	189	Indoles
Leptin lg/L[38,39]	16000	Peptides
Melatonin ng/L[40]	126	Indoles
Methylglyoxal lg/L[29]	72	AGE

Nε –(carboxymethyl)lysine mg/L[47]	204	AGE
p-cresol mg/L[41]	108	Phenols
Pentosidine lg/L[42]	342	AGE
Phenol mg/L[41]	94	Phenols
P-OHhippuric axid mg/L[43]	195	Hippurates
Putrescine lg/L[44]	88	Polyamines
Quinolinic acid mg/L[45]	167	Indoles
Retinol-binding protein mg/L[46]	21200	Peptides
Spermidine lg/L[44]	145	Polyamines
Spermine lg/L[44]	202	Polyamines

Abbreviations are: CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid; AGE, advanced glycation end products.

Table 3. Middle molecules (N= 22)

Solute	**Molecular Weight**	**Group**
Adrenomedullin ng/L[48]	5729	Peptides
Atrial natriuretic peptide ng/L[49]	3080	Peptides
$Beta_2$-microglobulin mg/L[46,50]	11818	Peptides
Beta-endorphin ng/L[14]	3465	Peptides
Cholecystokinin ng/L[51]	3866	Peptides
Clara cell protein (CC16) mg/L[46]	15800	Peptides
Complement factor D mg/L[52]	23750	
Cystatin C mg/L[46]	13300	Peptides
Degranulation inhibiting protein I^c lg/L[53]	14100	Peptides
Delta-sleep inducing peptide lg/L[54]	848	Peptides
Endothelin ng/L[49]	4283	Peptides
Hyaluronic acid lg/L[55]	25000	Peptides
Interleukin-1 beta ng/L[56]	32000	Cytokines
Interleukin-6 ng/L[57]	24500	Cytokines
kappa-Ig light chain mg/L[58]	25000	Peptides
lamda-Ig light chain mg/L[58]	25000	Peptides
Leptin lg/L[38,39]	16000	Peptides
Methionine-enkephalin ng/L[14]	555	Peptides
Neuropeptide Y ng/L[51]	4272	Peptides
Parathyroid hormone lg/L[59]	9225	Peptides
Retinol-binding protein mg/L[46]	21200	Peptides
Tumor necrosis factor-alpha ng/L[58,60]	26000	Cytokines

2. MECHANISM OF UREMIC TOXINS :

The uremic toxins introduced above can accumulate in body fluids between a number of categories or types of mechanisms.

- **Type I** represents 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** involves a surfeit of toxic substances in body fluids as a result of 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, often combined with continued dietary consumption (e.g., aluminum).
- **A special type of pathobiology (type IV)** is a deficiency or reduced activity of substances normally produced endogenously as a result of decreased synthesis, enhanced degradation, or biological inhibition.

Merger of more than one patho-biological process is possible. For example, urea is a uremic toxin which arises because of a **combination of type I and type III processes**: excessive accumulation because of impaired renal excretion, and continued production owing to exogenous (dietary) consumption of protein as a precursor of urea.

3. UREMIC TOXINS AND THEIR EFFECTS ON MULTIPLE ORGANS

3.1 An Absolute Parameters to Evaluate the Toxicity of Retained Compounds :

In health, the renal glomerular filter purifies the body of molecules with weights up to 58 kDa. All substances retained in the body as an outcome of renal dysfunction are inherent uremic toxins. A retained compound to be categorized as uremic toxin should encounter the following criteria [61,62,63,64,65] :

(1) The chemical structure and composition should be identifiable and the substance should be quantifiable in biological fluids using a recognized methodology.
(2) Concentrations in the biological fluids or tissues of patients with renal dysfunction should significantly exceed those in nonuremic subjects.
(3) Increases in the concentration in the blood or tissue should correlate with the clinical manifestations.
(4) The association between the biological activity and the clinical manifestations should be demonstrable in in vivo, ex vivo and in vitro test systems. The following two sections outline areas in need of elucidation through further studies.

Toxicity evaluation is an intricate process owing to not just one but several retained compounds might be concurrently entangled in the same biological and metabolic processes. Closely all body organs and systems are influenced by the toxicity of uremic compounds retained in the course of renal failure, including the

- Cardiovascular system (atheromatosis, arteriosclerosis, decreased diastolic compliance, hyper/hypotension, pericarditis)
- Central nervous system (concentration disorder, cramps, dementia, depression, fatigue, headache, motor weakness, polyneuritis, reduced sociability, restless legs, sleep disorders, stupor)
- Hematological and coagulation disorders (anemia, bleeding disorders, overcoagulation)

- Immune system (inadequate antibody formation, inflammation stimulation, susceptibility to cancer, susceptibility to infections)
- Endocrine system (dyslipidemia, glucose intolerance, stunted growth, hyperparathyroidism, hypogonadism, erectile dysfunction, decreased libido)
- Bone disease (adynamic bone disease, impaired calcitriol metabolism, osteitis fibrosa, osteomalacia, osteoporosis)
- Skin (melanosis, pruritus), gastro-intestinal system (anorexia, dyspepsia, gastrointestinal ulceration, hiccup, nausea, vomiting, pancreatitis) and
- Respiratory system (pleuritis, emphysema, sleep apnea syndrome).

Table 4. Links between retained uremic compounds and early kidney damage and impaired function of other organs

Damaged organ(s)	Clinical manifestation	Involvement of uremic toxins in the injury
Kidney[79, 80, 66, 81, 67]	AKI CKD	Sudden renal tubular and endothelial injury Progression of renal failure
Kidney-heart axis[61, 82, 63, 83, 84, 85, 86, 87]	Cardiorenal syndrome – 5 types of different interactions between chronic dysfunctions of the heart or kidneys which can induce acute or chronic dysfunction of other organs	Possible link between kidney function and cardiovascular risk
Kidney-intestinal mucosal barrier axis[68, 89, 90, 71, 72, 74]	Impaired function of key proteins of the intestinal epithelial tight junction in uremia	Translated into circulation bacteria and their products affect the activation of the innate immune system
Kidney-liver axis[75,76]	Type 1 hepatorenal syndrome Type 2 hepatorenal syndrome	Possible involvement of uremic toxins in increased splanchnic vasodilatation and renal vasoconstriction
Kidney-brain axis[77]	Cognitive disorders and dementia Uremic encephalopathy	Direct neuronal injury
Kidney-lung axis[91]	Increased lung vascular permeability in AKI	Mediators of AKI-induced lung changes

3.2 Retained Uremic Compounds as Markers of Organ Damage :

Table 4. Introduce the information regarding the role of collected uremic toxins in the onset and progression of acute and chronic renal dysfunction, and the connection between kidney disease and the dysfunction of other organs. . It has been recommended that uremic toxins encourage advancement of renal failure by damaging tubular cells and their overload accelerates the loss of kidney function, glomerulosclerosis and tubulointerstitial injury [66,67]. Pathogen overgrowth (dysbiosis) with supplemental eradication of creatinine through the intestinal wall is usual in the course of CKD. Impaired function of the intestinal mucosal barrier might describe the durability of systemic inflammation in the course of CKD [68,69, 70, 71–74]. The liver and kidneys jointly comprise an organ system liable for the removal of toxic compounds from the body. Renal function loss in patients with cirrhosis has been correlated with a worse prognosis [75, 76]. Accumulation of uremic toxins might cause cerebral endothelial dysfunction and contribute to

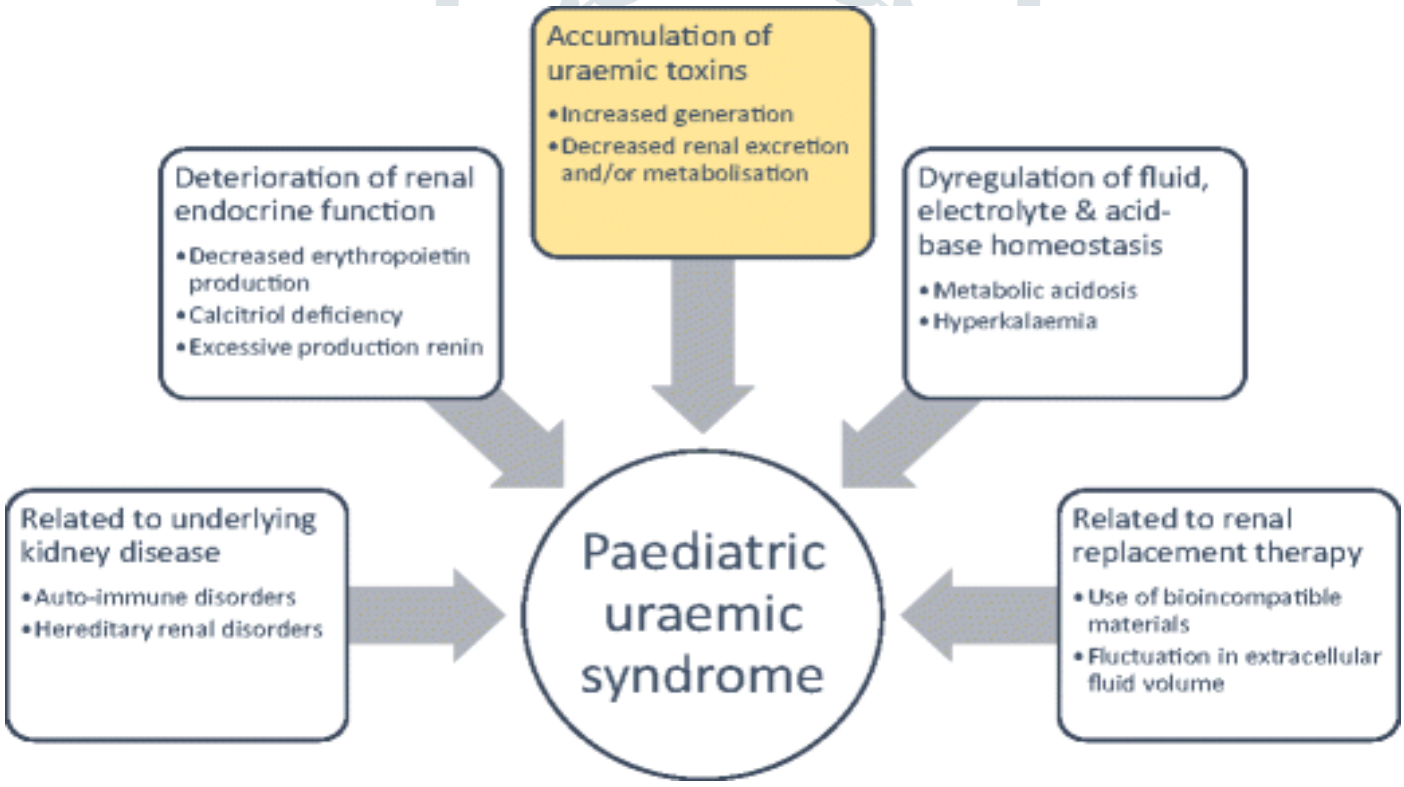
cognitive disorders in CKD [77]. Uremic toxins in AKI may modulate lung dysfunction, susceptibility to lung injury, or both [78].

4. AN INVOCATION FOR SUPPLEMENTAL UREMIC TOXIN RESEARCH IN CHILDRENS WITH CKD

Gradual loss of renal function in childhood is corresponded by the growing of a complex clinical picture, also referred to as the **Pediatric Uremic Syndrome.** This syndrome, caused by chronic kidney disease or acute renal injury, is touching nearly all organ systems (Table-5), and consequently, outcomes in a significantly diminished quality of life and rised in mortality during, and also beyond, childhood [92–94]. The convolution of the uremic syndrome is also related to its multifactorial character : due to

(1) The deterioration of the renal endocrine function (e.g., erythropoietin and calcitriol deficiency),
(2) The dysregulation of fluid and electrolyte homeostasis,
(3) The development of specific symptoms related to kidney disease (hypertension, fluid overload) and its causes (e.g., diabetes, autoimmune disorders) or
(4) Treatment (e.g., reactions to biocompatible dialysis materials), and
(5) The accumulation of toxic organic metabolites (i.e., Buremic toxins) due to decreased renal excretion and/or accompanied by increased toxin generation (Fig. 1) [95, 96].

Fig. 1 Presentation of the multifactorial origin of the pediatric uremic syndrome



Just about all the clinical studies on uremic solute retention were carried out in adult chronic kidney disease (CKD) patients, and reportedly, studies looking into the crash of uremic toxins on the developing child are effectively non-existent. Nonetheless, children, and the uremic syndrome they are experiencing from, have peculiar properties that hamper the full translation of adult experience and understanding in uremic toxicity into childhood (Fig. 2).

Primarily, children have physiological particularities that may influence the inflation pattern of uremic toxins. For instance, children have commensurately larger body water volumes and lower circulating proteins than adults. Consequently, it is improbable that the distribution, the inter-compartmental clearance, the removal pattern during dialysis, and the retention profile of uremic toxins would be uniform to those in adults [97]. Besides, the diet of children also varies on several aspects from adults, e.g., comparatively higher protein and caloric needs per kilogram body weight. As diet is one of the leading determinants of intestinal microbiota, it is therefore to be expected that the accumulation pattern of uremic toxins arising from microbial metabolism might be impacted, regardless of renal function [98,99].

Table 5: Symptoms, characteristics, and complications of the pediatric uremic syndrome. The symptoms, characteristics, and complications highlighted in bold with mark of (*) al features unique for the pediatric uremic syndrome

Fluid and electrolyte balance: polyuria, polydipsia, fluid overload, hypertension, oligo-anuria, metabolic acidosis, hyperkalemia, hyperphosphatemia, hypocalcemia
Endocrine and hormonal system: growth hormone resistance*, insulin resistance, thyroid dysfunction, hyperaldosteronism, adipokine dysbalance, pubertal delay*, anorexigenic hormones increase
Bone and soft tissue: disordered bone turnover and mineralization, bone pain, fractures, growth retardation*, vascular and soft tissue calcifications, rickets*, active vitamin D deficiency, hyperparathyroidism, FGF-23 excess, Klotho deficiency
Hematological system: anemia, erythrocyte fragility, susceptibility to infection, low response to vaccination, inflammation, hypercoagulability, bleeding tendency, bone marrow inhibition.
Gastrointestinal system: anorexia, nausea, vomiting, gastropareses, slow gastrointestinal motility, altered taste
Neurological system: polyneuropathy, coordination disturbances, tremor, cognitive dysfunctions, decreased attention span, coma, lethargy, disturbed sleep pattern
Skin and mucosa: skin atrophy, pruritus, calciphylaxis, periodontitis, stomatitis
Cardiac system: left ventricle hypertrophy, cardiomyopathy, pericarditis, coronary calcifications
Psychosocial factors: school absenteeism*, low quality of life, parental stress and burn out*
Others: malnutrition, muscle weakness, changes in drug protein binding

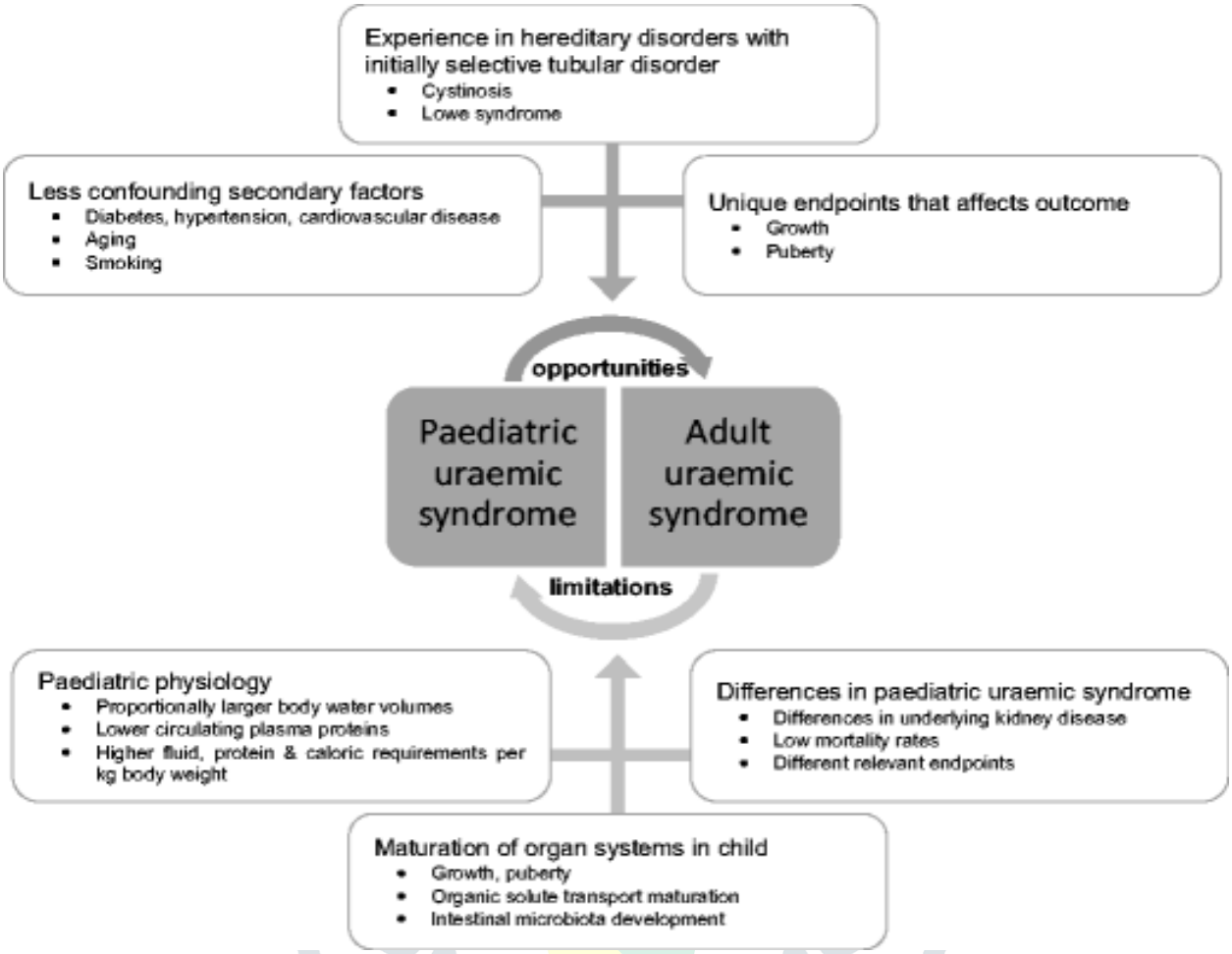
Abbreviation : FGF-23 fibroblast growth factor-23

Secondly, the effect of toxicity on maturational and developmental processes of nearly all organ systems, which represents a central aspect of the pediatric uremic syndrome, can by explanation not be concluded from adults in whom maturation has come to an end (Fig. 2). Growth and puberty, which are special pediatric features, are frequently affected in the pediatric uremic syndrome. The Annual Report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) in 2011 demonstrated that still 32.8% of children initiated with dialysis between 2002 and 2011 had significant growth failure [111]. As growth failure in children with CKD affects quality of life and is correlated with an elevated risk of hospitalization and death, it is contemplated as a relevant marker of the pediatric uremic syndrome [112, 113].

Multiple factors (e.g., nutritional, metabolic, and endocrine abnormalities) are identified in the pathophysiology of growth failure within the pediatric uremic syndrome. However unexplored yet, it is very probable that uremic toxins directly influence growth since a few studies demonstrated that enhanced removal, by applying intensified and daily hemodialysis, improved growth velocity in contrast to conventional hemodialysis [97, 100–103]. Although these learning were observational and uncontrolled, the gain-on growth achieved in these populations is striking, as standard treatment with adequate nutrition in children on maintenance hemodialysis remains associated with a mean loss in height SDS of − 0.4 to − 0.8 [104]. Alongside growth, several other maturational processes occur in childhood. There is a maturational increment in organic solute transport in the proximal tubule up to the first 2 years of life [105, 106].In consideration of gut-derived, protein-bound uremic toxins, which are inadequately removed by current dialysis techniques, based on these active transporters at the side of the tubules for their elimination; dissimilarities in their accumulation pattern and toxicity versus adulthood are very probable [107,108]. Beside the maturational changes in excretion by organic solute transport, the accumulation pattern of gut-derived uremic toxins can also be affected by the ongoing intestinal microbiota development which goes on until the first 2–3 years of life [99]. Finally, a few elements of the pediatric uremic syndrome are different from its adult counterpart. Whereas the pediatric uremic syndrome is mainly secondary to congenital anomalies of kidney and urinary tract (CAKUT) and hereditary renal diseases, the uremic syndrome in adulthood is predominantly caused by glomerulopathies (e.g., diabetic nephropathy, hypertension) and autosomal dominant polycystic kidney disease [109].

Furthermore, the dissimilarities in survival are striking. While the 5-year survival probability is 89% for children initiating renal replacement therapy, adults have an expected survival of 10% after 10 years on dialysis [110]. These low-mortality rates in childhood make the use of mortality as primary endpoint in pediatric studies less relevant or at least insufficient. Consequently, clinical outcome studies in the pediatric uremic syndrome nearly inevitably turn on consideration of other patient relevant outcomes, which may be both short term, e.g., growth, pubertal development, bone metabolism, cardiovascular risk factors, and schooling, as well as long term such as premature cardiovascular disease. In Addition, school absenteeism, education level, and parental stress and burnout are significant and unique endpoints in the pediatric uremic syndrome [101]. Several of these parameters are patient-centered and relevant to social life (growth, pubertal development, school absenteeism, familial stress), which will allow to highlight novel and up to now often neglected aspects of uremia. The obstacles explained above with respect to translation of adult knowledge on uremic toxicity to childhood may turn into an advantage, as research in the pediatric population might come-up with several opportunities to improve our understanding of uremic toxicity within both the adult and pediatric uremic syndrome (Fig. 2).

Fig. 2 Limitations and opportunities affecting respectively the translation and back translation of adult experience and knowledge to childhood uremic toxicity



For example, the majority of adult CKD patients have confounding factors (e.g., diabetes, hypertension, smoking, and aging) that, like uremic toxins, impact the cardiovascular, inflammatory, and fibrogenic system. As these factors are less prevalent or even absent in the pediatric population, clinical outcome studies in the pediatric CKD population will probably be more suitable to elucidate the cardiovascular toxicity of uremic toxins per se in comparison to those in the adult CKD population. In addition the specialty for children is the early presentation of hereditary renal diseases with initially a selective tubular defect (e.g., cystinosis). Examining these renal diseases may upgrade our understanding of the role of tubular cells and their organic solute transporters in the clearance of uremic toxins, which are hardly removed with current dialysis therapies. At long last, the pediatric uremic syndrome has unique additional endpoints, e.g., growth, that may be supportive in the clinical study of the uremic toxicity subsequently it can be evaluated in a relative short-term.

5. EVALUATION OF UREMIC TOXICITY

The assessment of uremic toxicity begins with identifying and quantifying the solutes that exist in uremic biological fluids in abnormal concentrations.

The estimation of uremic toxins can be evaluated via,.

1. Analytical Techniques and
2. From Biological Evaluations.

5.1 Analytical Techniques :

Isolated uremic retention solutes are estimated using colorimetric, fluorescence and high-performance liquid chromatographic (HPLC) methods. HPLC is also used to study groups of solutes sharing physical characteristics. Instantly '-omic' techniques, inspecting total profiles of uremic retention solutes, became accessible; they were introduced into research on uremic toxicity [114,115–120]. In the circumstance of uremia, proteomics and metabolomics have been the central '-omic' applications [114, 115, 116, 118–122]. Proteomics is suited for the study of peptides and proteins (middle molecules) [123], while metabolomics concentrates on small molecules. '-Omic' strategies are supportive and particularly beneficial as gain on for identifying pathways that are disturbed in a given pathology [124, 125].

Freshly, proteomics has been applied in biomarker discovery, and a new proteome classifier estimating CKD and its prognosis has been suggested [126]. This analysis illustrated that, However a high urinary protein excretion invariably found in renal failure progression, a low urinary protein excretion did not preclude death or dialysis. Even in patients without proteinuria, a low CKD273 score predicted renal failure progression within a follow-up period of 3.6 years [126]. This analysis would require to be evaluated in separate cohorts before implementing into clinical practice [127].

When the concentrations of uremic retention solutes applied in assays to validate their biological effects exceed those experienced in uremia, conclusions on the solutes' toxicity might have relatively little clinical relevance [128]. Consequently, quantification of the confidently identified metabolites of interest should be carried out by targeted methods before testing of the biological activity of uremic retention solutes becomes possible (Table 6). Assessment of the pathophysiologic role of these newly detected metabolites will qualify novel key culprits for the uremic syndrome to be pointed out as the initial step to pursue their specific removal.

Table 6 - Key uremic retention solutes

Uraemic retention solutes	Normal concentration, mean (SD or range)	Uraemic concentration, mean (SD or range)
Small water-soluble		
Urea (g/L)	<0.4	2.3(1.1)
ADMA (µg/L)	<60.6	878.7(38.4)
SDMA (µg/L)	76.1(21.0)	646.4(606.0)
Middle molecules		
β2m (mg/L)	1.9(1.6)	43.1(18)
IL-6 (ng/L)	4.0	8.6(3.7)
TNF-α (ng/L)	7.0	57.8(10.8)
Protein-bound		
pCS (mg/L)	1.9(1.3)	41(13.3)
IS (mg/L)	0.53(0.29)	44.5(15.3)
IAA (mg/L)	0.5(0.3)	2.4(2.2)
HA (mg/L)	3.0(2.0)	87.2(61.7)
p-OHHA (mg/L)	NA	18.3(6.6)

Extracted from [128, 194].

Abbreviations : NA, not available; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; β2m, beta 2 microglobulin; IL-6, interleukin-6; TNF-α, tumour necrosis factor-alpha; pCS, para-cresyl sulfate; IS, indoxyl sulfate; IAA, indole acetic acid; HA, hippuric acid; p-OHHA, para-hydroxyhippuric acid.

5.2 Biological Evaluations

5.2.1 Small water-soluble Compounds :

Urea was the primary uremic retention solute to be examined and is amongst all uremic retention solutes the only with the elevated concentrations in the blood of uremic patients. It demonstrates protein intake in the stable patient and has been utilized to validate nutrition and dialysis efficacy in renal patients. Urea was found to give rise the generation of Reactive oxygen species (ROS) and insulin resistance *in vitro* and in mice [129]. In an *in vitro* study, Vaziri *et al*. showed that urea induced disruption of the intestinal epithelial barrier function by reducing the expression of the tight junction proteins [Zona Occludens-1 (ZO-1), Claudin-1 and Occludin] [130]. Trecherel *et al*. explored regulatory proteins of apoptosis and showed an upregulation of Bcl2-associated death promoter (BAD), a pro-apoptotic protein [131].

Guanidines have been contemplated as uremic toxins since the 1970s [132]. Guanidines are neurotoxins [133, 134]. They might also have cardiovascular toxicity since several guanidines are, depending on leukocyte activation, pro-inflammatory at concentrations found in uremia [135, 136]. Water-soluble guanidines are also responsible for the generation of other uremic toxins like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), two middle molecules [135, 137]. The guanidines, asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA), are released from proteins that have been post-translationally methylated and subsequently hydrolysed. ADMA has for a long time been recognized as an inhibitor of nitric oxide synthase (NOS) causing endothelial dysfunction and vascular damage [138], a propensity that influences both the general and the uremic population [139–141]. Infusion of ADMA in healthy volunteers, achieving a concentration as in uremia, resulted in a decrease in cardiac output and a rise in vascular resistance [142]. SDMA, a structural analogue of ADMA, has long been considered inert [138, 143]. Its biologic activity was at primary suggested by Bode-Boger *et al.* [144], exhibiting a dose-dependent inhibition of NO synthesis centrally attributed to inhibiting the L-arginine supply to endothelial NOS. SDMA plays a role in leukocyte activation by enhancing generation of ROS, which is attributed to increased calcium influx via store-operated Ca^{2+} channels [145] and activation of nuclear factor (NF) κB resulting in cytokine production [137]. Limiting of NF-κB activation by *N*-acetylcysteine (NAC) and ROS production with SKF96365 and captopril prevented leukocyte activation [137, 145]. Freshly, Speer *et al.* [146] demonstrated that SDMA accumulates in high-density lipoprotein (HDL) particles from patients with CKD. This complex of HDL and SDMA is recognized by endothelial Toll-like receptor-2, leading to enhanced nicotinamide adenine dinucleotide phosphate-oxidase-dependent ROS production and thereby reducing endothelial NO bioavailability *in vitro* and increasing arterial blood pressure *in vivo*. Therefore, SDMA may be involved directly or indirectly in the pathogenesis of CVD via accumulation in HDL and seems neither to be inert nor to be a simple marker of renal function or CVD. Although, the individual elevation of SDMA by exogenous infusion in otherwise healthy mice affected neither renal function nor blood pressure or cardiac function [147].

5.2.2 Middle molecules

As above stated, the progressive elevation of cytokines in CKD is, in additional to the decreased renal clearance, partly attributed to an elevated generation in response to uremic toxins [148, 149]. In clinical studies in CKD, pro-inflammatory cytokines are used as a hallmark of micro-inflammation [150]. The pathophysiological role of cytokines at concentrations as occurring in CKD is often omitted. It was freshly examined that, among a few pro-inflammatory cytokines, TNF-α alone was pro-oxidative but only at high-range uremic concentrations. The increase in ROS production could be blocked by adalimumab, however blocking had no effect on the oxidative stress in whole blood from HD patients, suggesting that other uremic toxins than TNF-α are more crucial in this process [151].

5.2.3 Protein-bound compounds

Protein binding in CKD has been considered for some time, e.g. in the context of competition for drug binding [152]. It recently obtained new interest as new dialysis techniques might have the potential to improve clearance of protein-bound toxins [153].

The biological effects of the prototype protein-bound solute, indoxyl sulfate (IS), have been studied the most. A recent systematic review [154] including 27 studies demonstrating pathophysiological effects of IS and/or p-cresyl sulfate (pCS) described their interference with few central metabolic processes intricate in the uremic syndrome.

These included inflammation, oxidative stress, endothelial dysfunction, epithelial-to-mesenchymal transition, cardiac cell proliferation and renal tubular cell senescence. Subsequently, additional reports holds up the above evidence were published, covering elevated crosstalk between leukocytes and endothelium, glycocalyx degradation and vascular leakage [155]; apoptosis of osteoblasts [156]; inhibition of drug metabolism [157]; induction of tubular endothelial growth factor receptor leading to tissue remodeling [158] and inhibition of breakdown of angiotensin II [159].

Alike effects were also reported for other protein-bound toxins [160]. Indole acetic acid (IAA) appeared to limit endothelial progenitor cell production opposing their useful effect on vessel repair and neovascularization [161]. IAA brings about endothelial inflammation and oxidative stress and activates an inflammatory AhR/p38 MAPK/NF-κB pathway [162]. Recently, the ability of IAA to induce tissue factor production was associated with increased pro-coagulant activity [163, 164]. The induction of tissue factor occurred via the aryl hydrocarbon receptor pathway [164].

Recent metabolome studies frequently indicate increased levels of hippurates. Boelaert *et al*. exhibited an increase, already from CKD Stage 3 on, of the known hippuric acid (HA) and 2-,3-,4-hydroxyhippuric acid. They also identified increased levels of an unknown amino hydroxyhippuric acid and of the sulfate and glucuronide conjugates of hydroxyhippuric acid [114]. Satoh *et al*. demonstrated that subtotally nephrectomized rats given HA in their drinking water showed a decrease in inulin clearance, pointing to glomerular dysfunction. This was held up by the significant increase in the whole kidney sclerosis index. In addition, *N-acetyl-glucosaminidase* (NAG) excretion rate, an indicator of proximal tubular injury, was higher in the uraemic toxin-overloaded rats compared with the control rats [165]. Anew, HA was shown to limit the transport of two significant efflux pumps expressed on human tubular cells [166]. Next to hippurate, hydroxyhippurates were increased in plasma from CKD patients. p-Hydroxyhippuric acid (p-OHHA) limits Ca^{2+} ATPases, needed for restoring intracellular Ca^{2+} homeostasis after cell activation. Elevated intracellular Ca^{2+} modulates various polymorphonuclear leukocyte (PMNL) functions such as oxidative burst and degranulation as well as apoptosis as indicated by Cohen by the reduce in caspase activity in PMNL in the existence of p-OHHA [167].

6. METHODS TO REDUCE THE CONCENTRATIONS/PREVENTIVE MEASURES IN THE ACCUMULATION OF UREMIC TOXINS

6.1 Dietary Modification

In anuric patients, fluid consumption is generally driven by the need to dilute dietary salt. One liter is needed for every 8 g of sodium chloride ingested [168]. Dietary sodium restriction would help avoid salt and water overload and/or the need for UF. Likewise, restrictions in dietary potassium and phosphate are often recommended.

A very low-protein diet plus ketoacids (VLPD) has been utilized to decrease urea generation and might delay or reduce the need for dialysis [169]. VLPD has also been shown to reduce the generation rate of IS, a known uremic toxin [170].

6.2 Reducing absorption from the gut

Agents that hold together phosphate or exchange phosphate for other solutes are utilized to prevent phosphate accumulation in the majority of dialysis patients. Likewise, ion-exchange resins for potassium are occasionally used. Patiromer, an oral but non adsorbed potassium binder, is effective in clinical trials [171].

Oral active charcoal, a nonspecific binder of organic toxins, is routinely used to treat poisoning. It has also been utilized successfully to control uremia in patients who have refused dialysis [172] and to improve the abnormalities in gut barrier function in uremia [173].

6.3 Reducing generation in the gut

A considerable part of the uremic solutes is brought about in the intestine as explained via,. several studies, comparing the metabolome of germ-free mice versus mice with normal microbiota [174] and from HD patients with or without intact colon [175]. More recently, Holler *et al*. demonstrated the effect of prophylactic antibiotics on urinary

IS in stem cell transplant recipients [176]. In spite of its importance, the intestinal microbiota is rarely taken into account in the context of uraemic toxicity and/or in the development/optimization of therapies. Therefore, based on very few targeted studies, significant differences in the microbial composition in patients treated with HD [177] and PD [178] when compared with healthy controls have been reported. A recent untargeted study confirmed that uraemia alters the composition of the gut microbiome [179].

6.4 Preservation of kidney function

Even a severely damaged kidney may be capable of producing sufficient urine volume to limit salt and water overload and neglect the need for UF. The urine volume might be elevated, if required, by high-dose loop diuretics.

Residual renal function helps to control phosphate, beta2-microglobulin (β2m) [180] and potassium [181]. In HD patients, the removal of protein-bound toxins might be completely dependent on residual renal function. Survival is significantly associated with residual renal function in dialysis patients [182]. Multiple interventions can help preserve residual renal function. These include controlling blood sugar and blood pressure, avoiding nephrotoxic drugs and avoiding dehydration.

Influencing renal tubular handling of uraemic toxins may be another alternative and novel therapeutic approach to reduce their serum concentrations [183]. Transport of uremic toxins across the tubular cell membrane is facilitated by specific influx and efflux transporters. Changes in expression and/or function of influx transporters could decrease local toxicity to renal tubular cells [184, 185] and may also affect circulating concentrations if combined with effective efflux transport. Several uremic toxins like indole-3-lactate, kynurenine and phenyl sulfate are substrate to these transporters [174]. Drugs interfering with the function of these transporters, e.g. probenecid, limit the influx of uraemic toxins like IS, increasing viability of proximal tubular cells [186]. However, inhibition of these influx transporters will eventually contribute to further accumulation of uremic toxins. Additionally, expression of the organic anion transporters (OAT) 1, OAT3 and OAT polypeptide 4C1 (SCH4C1) appears to be decreased in CKD [187, 188]. Interestingly, Toyohara *et al.* demonstrated that the transcription of SLCO4C1 can be upregulated by statins, which leads to a higher expression on the cell membrane resulting in a decreased uraemic toxin concentration [188]. Mutsaers *et al.* recently reported that uraemic toxins inhibit substrate-specific uptake by both multidrug-resistance-associated protein (MRP4) and breast cancer-resistance protein (BCRP), two important renal efflux pumps [166].

6.5 Dialysis

Using understanding of the principles of diffusion, clearance of any solute by any artificial dialysis system can be predicted [189, 190]. Present dialysis systems, or their possible enhancements, could be optimized to achieve target clearance for any uremic toxin or group of toxins.

Low-molecular-weight toxins are easily cleared by HD. Levels of toxins similar to that exist in patients with normal renal function could be achieved by daily 8-h sessions of high-efficiency dialysis.

Higher-molecular-weight toxins can also be cleansed effectively by dialysis, as long as they are not bound to protein and the molecules are small enough to pass through the dialyser membrane's pores. Membranes that have a pore radius just smaller than that of albumin are present. Due to the lower rate of diffusion of these larger toxins, efficient clearance rates require larger membrane surface area and are helped by convection or fluid flow across the membrane. Hemodiafiltration, in which up to 100 mL/min of plasma water is filtered across the membrane, could reduce the levels of larger solutes to close to normal levels with daily 8-h treatments.

For protein-bound toxins, only the unbound fraction can be removed by HD or filtration. Clearance of bound toxins needs removal and replacement of the plasma-binding protein (generally albumin), using a membrane that is porous to albumin [191]. The plasma protein can be stripped of the bound toxin by contact with a competitive binding agent, before re-infusion of the plasma proteins into the patient. Systems capable of removing bound toxins are currently available but expensive. Current dialyser membranes bind certain toxins (e.g. β2m). Dialysers could be modified to include a matrix that would adsorb specific uraemic toxins. Since the matrix would be in direct contact with plasma proteins, these could adsorb bound toxins. A carbon-based matrix has been shown to reduce the levels of protein-bound toxins IS and pCS *in vitro* [192, 193].

CONCLUSION :

In light of the increasing numbers of patients with diagnosed CKD, there is an emergent requirement to find or research for modern or new biological markers of higher diagnostic specificity to lead treatments to limit in the course of renal failure. Many studies have been issued recently which demonstrate the toxicity of uremic compounds yet are still unable to explain the accurate mechanism of their connection with clinical symptoms of organ malfunction. They mentioned numerous problems connected to the chemical identification of these compounds and the explanation of their biological activity, but at the same time pose a number of questions which, when answered, would induce our current knowledge of the physiology and pathology of metabolic processes. The present review demonstrates that as yet only a fraction of these questions has been answered. These data can be of use as a guideline for future in vivo and in vitro experiments. Owing to Uremic retention appears to be a complex kinetic and multifactorial problem concerning a larger amount of solutes.

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