

Pathophysiologic Effects of Uremic Retention Solutes

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The uremic syndrome can be defined as a deterioration of biochemical and physiologic functions, in parallel with the progression of renal failure, resulting in complex and variable symptomatology (1–3). The compounds that accumulate in the uremic blood and tissues during the development of end-stage renal disease (ESRD), directly or indirectly due to a deficient renal clearance, are called uremic retention solutes. These retention solutes may modify biochemical or physiologic functions; if they do so, they contribute to the uremic syndrome. Only a few solutes have an established role as uremic toxins. According to Bergström, apart from inorganic compounds, urea, oxalic acid, parathyroid hormone (PTH), and β_2 -microglobulin conform to the most strict definition of uremic toxins (4). However, this does not preclude a potential toxic role for various other retention solutes (5).

The following factors, which are not always considered, might affect uremic solute concentration and their impact on biologic functions. (1) In addition to classical sources of uremic solutes such as dietary protein breakdown, alternative sources such as environment, herbal medicines, or psychedelic drugs may play a role in uremic toxicity. (2) Many solutes with toxic capacity enter the body through the intestine. Changes in the composition of intestinal flora, or changes in intestinal production and absorption, might alter their serum concentration. (3) Some uremic solutes interfere with functions that directly affect the biochemical action of other solutes: the expression of PTH receptors, the response to $1,25(\text{OH})_2$ vitamin D_3 , as well as the protein binding and breakdown of several other solutes. (4) Most uremic patients are prescribed a host of drugs. Interference of drugs with protein binding and/or tubular secretion of uremic solutes will influence their biologic effect. (5) Lipophilic compounds may be responsible at least in part for functional alterations in uremia. (6) The impact of residual renal function on uremic solute retention should not be neglected. (7) The main strategy that has been used up to now to decrease uremic solute concentration is dialysis, but dialysis is nonspecific and removes essential compounds as well. (8) Uremic solutes accumulate not only in the plasma but also in the cells, where most of the biologic activity is exerted. Re-

moval of intracellular compounds during dialysis through the cell membrane may be hampered, resulting in multicompartamental kinetics and inadequate detoxification. It is of note that lower morbidity and mortality are observed in patients submitted to long dialysis sessions (6,7). Compounds may be cleared more efficiently with continuous or long-lasting low efficiency strategies, because removal is more gradual.

Our views on the uremic syndrome and several uremic solutes have changed substantially during the last decade. Therefore, it was thought timely to summarize the present state of knowledge about the biochemical, physiologic, and/or clinical impact of those compounds that have been subjected to relatively thorough evaluation during these last 10 years. Specific attention was also paid to generation and removal patterns.

Urea

In spite of the extensive number of studies to which urea has been submitted relative to its toxicity, the number of reports in which a well-defined adverse biochemical or physiologic impact has been reported is relatively low. However, in a classical study by Johnson *et al.*, it was demonstrated that dialysis against dialysate containing high urea concentrations worsens clinical symptoms (8). Several recent studies point to an important pathophysiologic impact of urea. Lim *et al.* have shown that urea inhibits NaK2Cl cotransport in human erythrocytes (9), as well as a number of cell volume-sensitive transport pathways. The NaK2Cl cotransport is a ubiquitous process that serves numerous vital functions, among which cell volume and extrarenal potassium regulation are the most important. Extracellular urea also decreases cAMP production, albeit at concentrations exceeding those observed in clinical uremia (10). The presence of urea in blood has been held responsible for a decreased affinity of oxygen for hemoglobin because of 2,3-diphosphoglycerate binding (11). Urea inhibits macrophage inducible nitric oxide synthesis at the posttranscriptional level (12).

Apart from its direct toxicity, urea is a precursor of some of the guanidines, especially guanidinosuccinic acid (see below), which by itself induces direct biochemical alterations. As the most important osmotically active solute, urea may also provoke dialysis dysequilibrium, if the decrease in plasma concentration during dialysis occurs too rapidly.

Urea is unequivocally recognized as a marker of solute retention and removal in dialyzed patients. It is one of the few solutes that have been correlated convincingly with clinical outcome of hemodialysis (13). However, it is not the peak concentration *per se*, but the low reduction ratios during dial-

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ysis and more likely the high ambient level (time average) that are related to increased mortality (14). Hence, high blood concentrations of urea do not necessarily relate to a poor outcome if removal is sufficient (*e.g.*, in continuous ambulatory peritoneal dialysis [CAPD] patients and/or in patients receiving a high protein diet) (15).

Middle Molecules/Peptides

More than a decade ago, middle molecules (molecular weight [MW] range, 300 to 12,000 D) were held responsible for the uremic syndrome, but it was difficult to identify the exact structure of the responsible molecules (1). Nevertheless, several clinical, metabolic, and/or biochemical disturbances are caused by uremic compounds that conform with the middle MW range. Chromatographic fractions with a MW between 1 and 5 kD extracted from uremic human ultrafiltrate inhibit appetite and suppress food intake in animals (16). A 500- to 2000-D subfraction of uremic serum inhibits apolipoprotein (apo) A-I secretion in a human hepatoma cell line (17), which may be related to atherogenicity. Andress *et al.* described an inhibitor of osteoblast mitogenesis originating from uremic plasma with a MW between 750 and 900 D (18).

Dialysis membranes with a capacity to remove middle molecules (high flux membranes) have been related to lower morbidity and mortality (19–22); however, at the same time these highly efficient membranes are often less complement-activating than their counterpart unmodified cellulose in many studies. Hence, the relative importance of the levels of middle molecules *versus* biocompatibility-related events is not always clear.

Some of the recently defined uremic compounds, *e.g.*, β_2 -microglobulin (β_2 M) and advanced glycosylation end products (AGE), as well as PTH, conform to the structural definition of middle molecules. Because of the large amount of information on the biochemical impact of these three compounds, they will be discussed separately in the following subsections.

β_2 -Microglobulin

β_2 M (MW approximately 12,000 D) is a component of the major histocompatibility antigen. Dialysis-related amyloid, as found in amyloid bone disease and carpal tunnel syndrome after long-term dialysis, is to a large extent composed of β_2 M. Recent data demonstrate that this amyloidosis develops earlier than previously suspected. In some patients it is observed after 1 to 2 yr of dialysis, in the setting of both hemodialysis and peritoneal dialysis (23,24).

Advanced glycosylation end products (see section below) and β_2 M are closely related. AGE-modified β_2 M has been identified in the amyloid of hemodialyzed patients (25). At least three major AGE modifications of β_2 M may play a role: pentosidine- β_2 M (26), carboxymethyllysine- β_2 M (25,27), and imidazolone- β_2 M (28). AGE-modified β_2 M enhances monocytic migration and cytokine secretion (29), suggesting that foci containing AGE- β_2 M may initiate an inflammatory response leading to bone and joint destruction. On the other hand, AGE modification is not essential for β_2 M-related tissue destruction (30).

β_2 M-related compounds might also be involved in other aspects of the uremic syndrome. One of the peptides with a granulocyte inhibitory effect described by Haag-Weber *et al.* had partial homology with β_2 M (31). Commercially available assays for concentration measurements of intact β_2 M cross-react with this peptide, resulting in an overestimation of true β_2 M concentration in uremic plasma samples.

Serum β_2 M levels are generally lower in CAPD patients when compared with hemodialysis patients (32), but this might be attributable at least in part to better conservation of endogenous residual renal function. Although the clinical expression of dialysis-related amyloidosis disappears after kidney transplantation, the underlying pathologic processes such as bone cysts and tissular β_2 M deposits remain present (33).

Because β_2 M is only removed by dialyzers with a large pore size, it may be representative in its kinetic behavior of other large molecules. Apart from its role in amyloidosis, the biologic impact of β_2 M seems to be minor.

Parathyroid Hormone

PTH, a middle molecule with a MW of ± 9000 D, is generally recognized as a major uremic toxin, although its increase in concentration during ESRD is merely attributable to enhanced glandular secretion, rather than to decreased removal by the kidneys. Excess PTH gives rise to an increase in intracellular calcium, resulting in disturbances in the function of virtually every organ system, including bone mineralization, pancreatic response, erythropoiesis, and immune, cardiac, and liver function (34–38). PTH is one of the few substances that has been causally linked to uremic neuropathy, and it plays a role in fibroblast activation. PTH is also related to a number of uremic symptoms, *e.g.*, pruritus.

Downregulation of PTH-PTHrP receptor mRNA expression is observed in liver, kidney, and heart of rats with advanced chronic renal failure (39,40). Parathyroidectomy does not entirely prevent PTH/PTHrP receptor downregulation (41), suggesting that this alteration depends on more than elevated PTH alone.

The increased PTH concentration in uremia is the result of a number of compensatory homeostatic mechanisms. Hyperparathyroidism results at least in part from phosphate retention, decreased production of calcitriol (1,25(OH)₂ vitamin D₃), and/or hypocalcemia. Therapy with calcitriol or one of its analogues lowers serum PTH levels (42). It not only suppresses PTH release, but may also restore the secretory reserve of the parathyroid gland during hypocalcemia (42).

Advanced Glycosylation End Products

Glucose and other reducing sugars react nonenzymatically with free amino groups to form reversible Schiff base adducts (in days) and stable Amadori products (in weeks), which are then converted into AGE through chemical rearrangements and dehydration reactions (43), as first described by Maillard. Several AGE compounds are peptide-linked degradation products (MW 2000 to 6000 D) (44). Among the postulated structures for AGE are imidazolone, pyrrole aldehyde, pentosidine, and N^ε-(carboxymethyl)lysine.

Schiff base formation affects the interaction of the vitamin D receptor with responsive DNA elements, such as osteocalcin, vitamin D-responsive elements (VDRE), or constructed VDRE attached to a cat reported gene in transfected cells (45). AGE cause an inflammatory reaction in monocytes by the induction of interleukin-6, tumor necrosis factor- α , and interferon- γ (46). AGE-modified β_2 M may play an important role in the formation of dialysis-associated amyloidosis (29) (see earlier section). AGE can react with and chemically inactivate nitric oxide (NO) (47), a potent endothelium-derived vasodilator, anti-aggregant, and antiproliferative factor. AGE also induce oxidative protein modification (48). Transferrin and lysozyme, after contact with AGE-modified albumin, lose their immune-enhancing properties (49).

It is of note that food contains AGE and that AGE are absorbed intestinally (26). AGE are retained not only in renal failure but also in diabetes mellitus and aging, where they are held responsible for tissue damage and functional disturbances. Specific receptors for AGE have been identified (RAGE), and their expression is already enhanced during moderate uremia (50).

Serum concentrations of AGE are higher in dialyzed ESRD patients without diabetes mellitus than in nonuremic diabetic patients; in the uremic population, they do not depend on the glycemic status (26,51). Diabetic patients with ESRD have the highest AGE levels. Increased serum concentrations in ESRD patients might be attributed to increased intake, production, and/or retention. In spite of continuous contact with glucose, CAPD patients do not have higher serum AGE levels when compared with hemodialysis patients (44). Nevertheless, protein glycation has been demonstrated in the peritoneal membrane (52).

This group of molecules highlights the growing interest of attempting to remove more of the larger molecules with dialysis that are retained in uremia, and perhaps to initiate more specific removal via adsorption columns.

Other Middle Molecules

Granulocyte inhibiting protein I (GIP I), recovered from uremic sera or ultrafiltrate, affects various functions of the polymorphonuclear cells involved in the killing of invading bacteria (53). The compound has structural analogy with the variable part of kappa light chains. Another peptide with granulocyte inhibitory effect (GIP II) has partial homology with β_2 M, and inhibits granulocyte glucose uptake and respiratory burst activity (31). It was extracted from uremic ultrafiltrate (31) and CAPD dwell fluid (54). A degranulation inhibiting protein (DIP), identical to angiogenin, was isolated from a plasma ultrafiltrate obtained from high flux membranes and from peritoneal effluent of uremic patients (55). The structure responsible for the inhibition of degranulation is different from the sites responsible for the angiogenic or ribonucleolytic activity of angiogenin. A modified variant of ubiquitin inhibits polymorphonuclear chemotaxis (56). In none of these studies are the exact concentrations in uremic sera or biologic fluids reported.

Molecules with a Molecular Weight in Excess of 12 kD

The kinetic behavior in dialysis of molecules with a molecular weight above 12 kD should be comparable to that of the somewhat smaller true middle molecules. Serum concentrations of cystatin C (13.3 kD), Clara cell protein (CC16) (15.8 kD), and retinol binding protein (RBP) (21.2 kD) are elevated in renal failure (57). Cystatin C is a cysteine-proteinase inhibitor. CC16 is an α -microprotein, playing an immunosuppressive role in the respiratory airways (58).

Leptin, a 16-kD plasma protein suppressing appetite (59) and inducing weight reduction in mice (60), is retained in renal failure (61). The increase in serum leptin is almost entirely due to a rise in the free (non-protein-bound) concentration (61), and has been suggested to play a role in the decreased appetite of uremic patients. Increased leptin is associated with low protein intake and loss of lean tissue (62). Recent data suggest an inverse correlation in uremia between leptin and indices of nutritional status such as serum albumin or lean body mass (63), and a direct correlation with C-reactive protein (64). However, leptin levels are also elevated in obese people and hence are not necessarily related to reduced appetite. Body fat and serum leptin correlate positively in uremia (64). Therefore, the biochemical role of leptin in renal failure remains inadequately defined.

Guanidines

The guanidines are a large group of structural metabolites of arginine. Among them are well-known uremic retention solutes, such as creatinine and methylguanidine. Several of the guanidino compounds modify key biologic functions. Creatinine has been held responsible for chloride channel blocking (65,66), reduces the contractility of cultured myocardial cells (67), although only at concentrations exceeding 5 times those encountered in ESRD, and is a precursor of methylguanidine (68). Guanidinosuccinic acid and guanidinopropionic acid inhibit neutrophil superoxide production (69). Guanidinosuccinic acid, γ -guanidinobutyric acid, methylguanidine, homoarginine, and creatine induce seizures after systemic and/or cerebroventricular administration in animals (65,66). A mixture of guanidino compounds suppresses the natural killer cell response to interleukin-2 (70).

Arginine, which is also a guanidino compound, markedly enhances the production of NO. Some of the other guanidines as arginine-analogues are strong competitive inhibitors of nitric oxide synthase. The inhibition of NO synthesis results in saphenous (71) and mesenteric (72) vasoconstriction, hypertension (73), ischemic glomerular injury (74), immune dysfunction (75), and neurologic changes (76). Asymmetric dimethylarginine (ADMA) is the most specific endogenous compound with inhibitory effects on NO synthesis. In the brain, ADMA causes vasoconstriction and inhibition of acetylcholine-induced vasorelaxation (77). These findings might be of relevance in view of the relatively high concentrations of the methylarginines in the brain. The concentration of ADMA is significantly increased in ESRD (78), and has been implicated in the development of hypertension (79–81). The increase in symmetric dimethylarginine (SDMA) is more pro-

nounced, but this compound is biologically less active. Methylguanidine, another endogenous guanidine, only shows a modest (1 to 5%) inhibitory activity on cytokine- and endotoxin-inducible NO synthesis, compared to synthetic compounds such as N^G -monomethyl-L-arginine (82).

In contradiction to the hypothesis of inhibition of NO synthesis in uremia, Noris *et al.* pointed to an enhanced NO production in at least some uremic patients, which was related to uremic bleeding (83).

The generation of the guanidines synthesized from arginine in the proximal convoluted tubule, such as guanidinoacetic acid and creatine, is depressed in ESRD (84). On the other hand, the synthesis of guanidinosuccinic acid, guanidine, and methylguanidine is markedly increased, which can be attributable to urea recycling.

Oxalate

Massive oxalate retention is not common in dialyzed patients, except in primary hyperoxaluria (85), where production is increased due to a genetically mediated alteration of metabolism. In ESRD patients without primary hyperoxaluria, oxalate plasma levels are increased approximately 40-fold compared with healthy control subjects (86).

Secondary oxalosis in ESRD patients without primary hyperoxaluria is characterized by deposition of calcium oxalate in the myocardium, bone, articular surfaces, skin, and blood vessels (87), although the latter location is rather infrequent. These events were reported with inefficient dialysis strategies in the early days of renal replacement therapy, but are now seen less frequently, except in the presence of excessive intake of oxalate precursors, *e.g.*, ascorbic acid, green leafy vegetables, rhubarb, tea, chocolate, or beets (88), or in the presence of inflammatory bowel disease (89).

The role of pyridoxine (vitamin B₆) in oxalate accumulation in uremia remains a matter of debate (90). In rats with chronic renal failure, pyridoxine depletion results in increased urine oxalate excretion and depressed renal function (91). However, pyridoxine supplementation up to 300 mg/d for 1 mo did not reduce plasma levels or affect generation of oxalate in CAPD patients (90). Pyridoxine at 800 mg/d on the other hand caused a decrease in oxalate concentration in hemodialysis patients (92). High doses of pyridoxine might, however, induce gastrointestinal intolerance.

Phosphorus

High levels of organic phosphates are related to pruritus and hyperparathyroidism (93). Dietary phosphate restriction reduces PTH levels over a wide range of Ca^{2+} concentrations, independent of plasma calcitriol (94). Phosphorus excess inhibits 1α -hydroxylase and hence the production of calcitriol, the active vitamin D metabolite (95). Phosphorus retention is also involved in changes of polyamine metabolism by causing a decrease in the activity of spermidine/spermine N^1 -acetyltransferase, the enzyme responsible for their degradation (96); these events result in intestinal dysfunction and the development of a proliferative state of the intestinal villi (96).

At least in animals, phosphate restriction has an attenuating

effect on the progression of renal failure. The results are less compelling in humans (97).

The blood phosphorus concentration is the result of protein catabolism and protein intake as well as the ingestion of other dietary sources (*e.g.*, Coca-Cola). Restriction of oral protein intake increases the risk of malnutrition (93), which can be avoided by the administration of oral phosphate binders (98). The effect of the latter, however, is often insufficient, especially in subjects with a high phosphorus intake.

p-Cresol

p-Cresol is a phenolic and volatile compound with a MW of only 108.1 D. Its serum concentration is elevated in renal failure (99). It is strongly toxic for hepatocytes, inducing lactate dehydrogenase leakage from rat liver slices (100), and inactivates the enzyme β -hydroxylase, which plays a role in the transformation of dopamine to norepinephrine (101). Several other functions, such as cellular oxygen uptake (102), drug protein binding (103), growth (104), and the permeability of the cell membrane (105) are affected as well. *p*-Cresol inhibits various metabolic processes related to the production of free radicals, which are involved in the destruction of bacteria by activated phagocytes (106). Hepatocyte aluminum uptake and the toxic effect of aluminum on the hepatocytes are increased in the presence of *p*-cresol (107).

p-Cresol is an end product of protein catabolism, produced by the intestinal bacteria, as a result of the metabolism of tyrosine and phenylalanine (108). Environmental sources include toluene, menthofuran, and cigarette smoke. Specific concern is warranted regarding menthofuran, which is present in several currently used herbal medicines, flavoring agents, and psychedelic drugs (109). Prevention of the intestinal absorption of *p*-cresol by administration of oral sorbents decreases the serum concentration in rats (110).

Homocysteine

Homocysteine (Hcy) is a sulfur-containing amino acid that is produced by the demethylation of methionine. Its retention results in the cellular accumulation of S-adenosyl homocysteine (AdoHcy), an extremely toxic compound that competes with S-adenosyl-methionine (AdoMet) and inhibits methyltransferases (111). Moderate hyperhomocysteinemia, which may be caused by a heterozygous enzymatic deficiency in Hcy breakdown or by vitamin B₆, B₁₂, or folate deficiency, is an independent risk factor for cardiovascular disease in the general population (112,113). The relationship is as strong as for smoking (114).

Patients with chronic renal failure have total serum Hcy levels two- to fourfold above normal. Hyperhomocysteinemia is the most prevalent cardiovascular risk factor in ESRD (115,116), and is present at increased concentrations in kidney transplant recipients with cardiovascular disease (117). Its serum concentration depends, however, not only on the degree of kidney failure, but also on nutritional intake (*e.g.*, of methionine), vitamin status (*e.g.*, of folate), genetic factors (118–120), and renal metabolism (121).

Hcy increases the proliferation of vascular smooth muscle

cells, one of the most prominent hallmarks of atherosclerosis (122). The administration of excess quantities of the Hcy precursor methionine to rats induces atherosclerosis-like alterations in the aorta (123). Hcy also disrupts several vessel wall-related anticoagulant functions, resulting in enhanced thrombogenicity (124).

Hcy levels can be moderately reduced by folic acid, vitamin B₆, and/or vitamin B₁₂ administration (125,126). To reduce Hcy, the population with ESRD might require higher quantities of vitamins than the nonuremic population (127). Direct clinical proof of the benefit of decreasing Hcy concentration in uremia is, to our knowledge, not yet available.

Indoles

Indoxyl sulfate is metabolized by the liver from indole, which is produced by the intestinal flora as a metabolite of tryptophan. It enhances drug toxicity by competition with acidic drugs at the protein binding sites (128), inhibits the active tubular secretion of these compounds (129), and inhibits deiodination of thyroxine 4 (T4) by cultured hepatocytes (130).

It is known that uremic retention solutes induce glomerular sclerosis (131); their removal by peritoneal dialysis or by oral sorbent administration retards the progression of intact nephron loss. Indoxyl sulfate might be one of the possible candidates for the enhancement of glomerular sclerosis. The oral administration of indole or of indoxyl sulfate to uremic rats increases the rate of progression of glomerular sclerosis and of renal failure (132).

Indoles are found in various plants and herbs, and some of them are also produced by the intestinal flora. Several metabolites of indoles are retained in uremia. Not all indoles show the same kinetic behavior. Some do not even conform with the definition of uremic retention solutes because their concentration is rather low in ESRD (*e.g.*, tryptophan, melatonin).

3-Carboxy-4-Methyl-5-Propyl-2-Furanpropionic Acid

3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid (CMPF) is one of the urofuranic fatty acids, a strongly lipophilic uremic solute, and one of the major inhibitors of drug protein binding (129). It inhibits the renal uptake of para-amino hippuric acid (PAH) in rat kidney cortical slices (133), and causes a decrease in renal excretion of various drugs, of their metabolites, and of endogenously produced organic acids, which are removed via the PAH pathway. *In vivo* CMPF clearance in the rat is inhibited by PAH and probenecid, the latter however at a molar dose at least fivefold greater than that of CMPF (134). CMPF inhibits hepatic glutathione-S-transferase (135), deiodination of T4 by cultured hepatocytes (130), and ADP-stimulated oxidation of NADH-linked substrates in isolated mitochondria (136). Costigan *et al.* demonstrated a correlation between neurologic abnormalities and plasma concentrations of CMPF (137).

Conclusion

The uremic syndrome is a complex mosaic of clinical alterations, based on functional changes that may be attributable to

one or more different solutes. Knowledge about the nature and the kinetic behavior of the responsible compounds might be of help when new therapeutic options are considered in the future. Biochemical alterations are provoked by a broad spectrum of compounds. Some compounds are small and water-soluble (*e.g.*, urea, the guanidines, phosphate, oxalate), some are lipophilic (*e.g.*, *p*-cresol, CMPF) and/or protein bound (*e.g.*, homocysteine, indoles), whereas others are larger and in the middle molecular range (*e.g.*, β_2 M, PTH, AGE). Optimal removal of each type of molecule might be achieved with a different type of extracorporeal treatment, *e.g.*, by using large pore membranes and/or dialyzers or devices with a high adsorptive capacity for some or several of the uremic toxins. Intestinal uptake can be reduced by influencing dietary habits, or by oral administration of absorbants. Preservation of residual renal function might be an important reason to pursue additional removal of retention solutes. Finally, the choice of marker molecules for uremic retention and dialytic removal should be reconsidered. It needs to be determined whether the current markers, which are all small water-soluble compounds (urea, creatinine), are representative in their kinetic behavior for middle molecules, and for the lipophilic/protein-bound compounds.

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