ÜBERSICHT

Z. Ernährungswiss. **21**, 175–190 (1982)

ISSN 0044-264 X

Institute for Biological Chemistry and Nutrition, University of Hohenheim, West Germany[1]); and Department of Renal Medicine, Huddinge University Hospital, Karolinska Institutet, Sweden[2])

Recent advances in the pathogenesis and nutritional treatment of chronic uremia

P. Fürst[1]), A. Alvestrand[2]), and *J. Bergström[2])*

(Received March 8, 1982)

"The uremic death of the most highly integrated organism is strictly comparable to the dissolution of the most simple organism in an aging bacterial culture – both are destroyed in an environment poisoned by the product of their own metabolism."

Harrison and Mason (37)

Uremic toxicity

The chemical theory of causation of the uremic syndrome begins with Prevost and Dumas (49), who discovered in 1821 that extirpation of the kidney led to rise in the blood urea concentration. Since that time, it has been assumed that the clinical features of uremia in man are caused by retention in the body fluids of toxic substances which are normally excreted in the urine.

Table 1. Organic compounds which accumulate in uremia.

urea	phenols	growth hormone
creatinine	myoinositol	gastrin
methylguanidine	mannitol	renin
guanidinosuccinic acid	glucuronic acid	gastric inhibitory peptide (GIP)
other guanidines	oxalic acid	human pancreatic polypeptide (HPP)
uric acid	acetoin	calciotonin
cyclic AMP	2,3-butylene glycol	prolactin
pyridine derivatives	middle molecules	β_2-microglobulin
amino acids	lipochromes	α_1-microglobulin
aliphatic amines	insulin	lysozyme
aromatic amines	glucagon	retinol-binding protein
polyamines	parathyroid hormone (PTH)	β_2-glucoprotein
indoles	natriuretic hormone (?)	ribonuclease

With the refinement of the analytical techniques an ever increasing number of organic compounds have been found in raised concentrations in uremic plasma (cf. table 1), and many of them have at one time or another been suggested to be a uremic toxin or "the uremic toxin" (11). However, despite more than 150 years of research, it has not been possible to explain the full spectrum of uremic toxic manifestations by accumulation of known uremic compounds.

It is now recognized that the functions of the kidneys are not limited to the excreation of waste-products, electrolytes, and water. We are increasingly aware of the importance of the kidneys as endocrine organs affecting blood pressure regulation, calcium homeostasis, and erythropoiesis. It is also established that the kidneys catabolize a number of peptide hormones. Accordingly, some of the symptoms and signs of uremia may be due to endocrine disturbances, either of renoprival origin or secondary to impaired homeostasis.

A solute to be considered as a uremic toxin should fulfil certain criteria listed below:

1. The compound should be chemically identified and specifically and quantitatively measurable in biological fluids.
2. The plasma level and/or tissue concentrations of the compound should be higher in uremic than in non-uremic patients.
3. High concentrations should be related to specific uremic symptoms.
4. Toxic effects should be obtained in human subjects, experimental animals and/or in an appropriate in vitro system at concentrations comparable to those found in the body fluids of uremic patients.

If synergism is of importance, tests according to point 4 may have to be performed in uremic man or animals or in a "uremic" environment in vitro.

After having surveyed the literature in this field extensively for the last few months, we have come to the conclusion that – except for some hormones as PTH and renin – urea is the only organic compound which clearly fulfils all the afore-mentioned criteria. The symptoms of urea intoxication (addition of urea to the dialysate) include headache, fatigue, nausea, vomiting, glucose intolerance, and bleeding tendency. However, it should be pointed out that the most severe gastrointestinal and cardiovascular, mental, and neurological changes in uremia were not noticed (38). Thus it is not possible to explain the wide spectrum of uremic symptoms by urea intoxication only, and in any event urea should be considered a "mild" uremic toxin.

"New" uremic toxins. New candidates of uremic toxins appear from time to time, or old ones regain popularity. Among the most recent ones are choline, polyamines, cyclic AMP, polyols, and ribonuclease (RNAse); the middle molecules (MM) are still attracting interest. PTH has also recently gained new interest not only as a compound involved in uremic osteodystrophy, but also as a more general uremic toxin.

Choline concentration in plasma measured in azotemic subjects receiving hemodialysis was found to be about twice that of normal subject, and the degree of peripheral neuropathy was inversely correlated to the levels of free cholin in plasma, suggesting a cause-relationship. Reduced renal mass may play a role for the increased free choline levels in uremia, since

the kidney has a role in the homeostatic regulation of plasma choline (52). Choline is also a precursor to aliphatic amines, which are formed in the gut by bacterial action and are suggested to be toxic in uremia (59).

Polyamines, which are formed in animal tissues (putrescine, spermidine, and spermine) or by bacterial action in the gut (putrescine and cadaverine) are widely distributed in the human body. The urinary excretion of polyamines is increased in cancer patients and in patients with infections (27b). Recently it has been found that the free plasma spermine concentration is markedly increased in patients with chronic uremia and that hemodialysis lowers the plasma concentration (22). Polaymines have been found to impair in vitro glucose transport in rat jejunum and to modify the activity of many enzymes (61). Their role as uremic toxins is as yet unproved, but it has been suggested by Bagdade that the raised polyamine level in chronic dialysis patients may contribute to the rapidly accelerated cardiovascular disease, observed during dialysis, by stimulating proliferation of arterial smooth-muscle cells (8), a central procession in atherogenesis. This interesting hypothesis deserves to be tested in depth.

It appears that substantial quantities of polyamines can be obtained from serum and urine after acid hydrolysis, which has led to the postulate that polyamine conjugates play an important role in polyamine metabolism of man (54). In this connection it is of interest that Lutz (43) isolated a strongly basic peptide which contained spermidine, thought to be toxic in uremia. Seale et al. (57) found that the diamine, putrescine, and the polyamines, spermidine and spermine, could be detected in human amniotic fluid only after acid hydrolysis. All these findings suggest that the polyamines, toxic or not in uremia, may play a role not only as free compounds, but also as conjugates to peptides, thus linking them to the middle molecules. This opens interesting new possibilities for further research in this field.

Cyclic AMP, which is the second messenger of a number of hormones, is elevated in uremic plasma (9, 56). Toxic effects on in-vitro platelet aggregation have been recorded, and there is a correlation between aggregation response and plasma concentration of AMP in uremic patients, suggesting that cyclic AMP is involved in the platelet defect in uremia (65).

Myoinositol is a natural constituent of food and is synthetized in muscle, liver, brain, and kidneys. The major pathway for myoinositol catabolism requires initial oxidation to D-glucuronate in the renal cortex. In patients with renal failure, the plasma concentration and urinary excretion of myoinositol are elevated (48, 24, 58), suggesting that the production is increased or the metabolism decreased. A striking decrease in sciatic nerve conduction velocity was found in normal rats given high amounts of myoinositol orally or intraperitoneally (24). Dorsal root ganglion cells in tissue culture showed toxic changes in presence of myoinositol at concentrations know to occur in uremic plasma (42). Myoinositol was therefore suggested to be a uremic toxin which is causally related to the development of peripheral neuropathy. A correlation has also been found between sorbitol in cerebrospinal fluid and signs of peripheral neuropathy in uremic patients (48).

RNAse, which belongs to the low molecular proteins catabolized by normal kidneys, is markedly increased in uremic plasma (50). Purified

RNAse from human urine is capable of inhibiting lymphocyte proliferation, growth of red and white cells in bone marrow cultures, and also adversely affects the viability of cultured fat cells (41, 21).

PTH. The role of PTH as a uremic toxin has recently been reviewed by Massry (44). Effects ascribed to excessive PTH in uremia are osteodystrophy, ectopic calcifications, itching, encephalopathy, peripheral neuropathy, anemia, hyperlipidemia, and impotence. However, Slatopolsky et al. (60) reviewed the role of PTH as a uremic toxin and came to the conclusion that the only toxic effects substantiated are bone disease and abnormal electroencephalographic patterns, this latter being due to a potential role of PTH in increasing calcium content of brain. Schaefer et al. (55) failed to show a correlation between serum parathyroid hormone, nerve conduction velocity and serum lipids in hemodialysis patients. With regard to PTH as a pathogenetic factor for peripheral neuropathy, carbohydrate intolerance, hyperlipidemia and anemia, outstanding clinical research is lacking, and conclusive experimental data are practically nonexistent. Thus it is still an open question whether PTH as a uremic toxin has more generalized effects than its action on bone and perhaps on the central nervous system.

Middle molecules. The middle molecules still attract many research groups. This field was extensively reviewed by Bergström and Fürst (11, 12). It was concluded that most studies in which the dialysis regimen has been changed to specifically alter dialysance of small and/or MM and relate these changes to symptoms, suffer from the drawback that no methods were available for direct measurements of MM, or that measurements performed were crude, unspecific and at best semiquantitative. Some of these studies were conducted over too short periods of time, or in patients not well standardized with regard to diet and residual renal function.

Until now, only few MM compounds have been isolated in pure form and for even fewer of them the molecular structure has been identified. Lutz and co-workers (43) isolated four basic peptides with a molecular weight range of 1300–1800 daltons. Klein et al. (40) determined the chief peptide constituents of a fraction in MM range with a molecular weight of approximately 3000 daltons, especially abundant in lysine, glycine, glutamic acid and serine, but in low concentrations for aromatic amino acids. Abiko and co-workers were able to isolate four peptides: A heptapeptide which corresponded to position 13 through 19 of β_2 microglobulin (1). A tryptophan-containing pentapeptide (2), corresponding to position 123 through 127 of β-chain of fibrinogen, had an inhibiting effect on rosette formation between human lymphocytes and sheep erythrocytes in vitro, suggesting that they might cause or contribute to the impaired immune response in uremia (3). A tripeptide (H-His-Gly-Lys-OH) was isolated from uremic ultrafiltrate (4). Another tripeptide (H-Glu-Asp-Gly-OH), which was isolated from "neurotoxic" dialysate, inhibited LDH activity in vitro (4). These are the first reports in which the complete structure of new, biologically active MM peptides are given, and where it was possible to show that they consist of fragments of known proteins. However, each of these peptides was only obtained from one patient, and

it is not yet possible to evaluate their role as uremic toxins, since their concentrations in normal and uremic plasma were not reported.

The Necker Group in Paris is now in the process of isolating and identifying an MM compound (b_{4-2}), which appeared to be a carbohydrate with neurotoxic properties (32). In current studies it could be demonstrated that the b_{4-2} solute is a glucuronoide with a molecular weight of 568 daltons corresponding to a glucuron conjugate of an aglycon (not yet identified) with a molecular weight of 392 daltons (25).

In our laboratory in Stockholm, we used analytical isotachophoresis for further separation of three fractions of middle-molecules, which were isolated by gel-filtration and ion exchange chromatography (68). Each of three chromatographically homogenous uremic middle molecule fractions could be shown to consist of at least two subfractions. One of these subfractions which is the main component of peak 7c (28) has now been identified as a β-glucuronidated fraction of P-OH-benzoic acid and glycine (69, 70).

New data have recently been obtained which suggest that MM exert toxic effects in vitro at concentrations comparable to those found in uremic plasma (11, 12, 13). In vitro toxic effects of MM include: inhibition of hematopoietic cells, hemoglobin synthesis, glucose utilization, lymphoblast transformation, and rosette formation, fibroblast proliferation, leucocyte phagocytic activity, nerve conductivity, and sodium transport. These results suggest that MM cause or contribute to certain symptoms and signs in uremia, such as anemia, impaired glucose tolerance, immunological deficiency, susceptibility of infection and neuropathy. It was also reported recently that injection of MM material in rodents delays the rejection of skin allografts and inhibits graft-versus-host reaction, an observation which supports a role of MM in uremic immunosuppression (11). Some enzyme activities are also inhibited by MM fractions in vitro, namely lactate dehydrogenase, adenyl cyclase, pyruvate kinase, Na^+-K^+-ATPase, glucokinase, insulin stimulation of lipoprotein lipase, delta-aminolevulinic acid dehydratase and catalase activity (11).

In conclusion, it is today not possible to evaluate the exact role of the manifold compounds which accumulate in renal failure in causing or contributing to the various symptoms and biochemical abnormalities in uremia. The new information gathered in the last years has further shed light on the complexity of the problem but not yet led to a breakthrough in our understanding of the nature of uremic toxicity, which can only be achieved by combined efforts of clinical nephrologists, endocrinologists and biochemists, will lead to improvement of the conservative therapy and the development of more efficient and selective methods for purification of the body fluids.

Nutritional treatment

Protein and amino acid requirement in uremia

In order to achieve a nitrogen balance in healthy average adults, approximately 0.45 g protein/kg body weight/per day is required with an upper limit of 0.6 g/kg to cover the extreme range of needs in a population. Only 20 % of this has to be in the form of essential amino acids (45, 29).

Nitrogen balance studies in uremic patients showed that 0.4 to 0.5 g protein per kg body weight is required to obtain nitrogen equilibrations and that further reduction of the protein intake leads to negative nitrogen balance (37a, 27a). In patients with advanced renal failure, i.e., endogenous creatinine clearance below 5 ml/min, the protein intake may have to be considerably lower than 0.4 g/kg body weight to prevent excessive urea accumulation and symptoms of uremic toxicity.

Dietary requirements of protein appear to be higher in patients during intermittent dialysis than in normal subjects, and an intake of more than 1 g/kg body weight is recommended for dialysis patients. Borah et al. (19) reported results of nitrogen-balance studies during intermittent dialysis therapy in 5 patients on high 1.4 g/kg body weight and low 0.5 g/kg protein intake and found that the balance was negative on dialysis days associated with a higher rate of urea generation and was positive or neutral (at high and low protein intakes, respectively) on non-dialysis days. Supporting data came from Ward et al. (64), who found enhanced protein catabolism (increased urea generation rate) induced by dialysis. Adding glucose to the dialysate was not accompanied by significant fall in dialysis-induced protein catabolic rate suggesting that gluconeogenesis is not the major contributor to increased catabolism on dialysis.

The minimum requirement and the proportions of essential amino acids in normal man have been defined in carefully conducted nitrogen balance studies (53). Much less is, however, known about the amino acid requirement in severely uremic patients. This is of considerable importance because the diets prescribed often do not contain adequate amounts of essential amino acids.

Based on Giordano's original findings that uremic patients on protein-poor nutrition could be brought into positive nitrogen balance when given essential L-amino acids (33), a dietary regimen using low-protein diet (15–20 g protein/day) supplemented with essential amino acids + histidine was developed and successfully applied for conservative treatment of patients with glomerular filtration rate of 5 ml/min or less (14, 47). All results from balance studies indicate that uremic patients had an increased requirement of essential amino acids. This hypothesis is supported by the fact that nitrogen balance can only be achieved in severely uremic patients with a diet supplemented with essential amino acids, which provides a higher proportion of essential amino acids to total nitrogen than found in any natural protein (14, 15). It is now established from studies in Scandinavia, Germany, and the United States that this form of treatment leads to clinical improvement and better nitrogen balance.

In contrast, there is strong evidence that in HD patients receiving protein and energy > 1.0 g/kg and > 145 kJ/kg, respectively, adequate nutrition in relation to their requirements (19, 5a) is achieved.

Optimum dose and composition of the amino acid complement

There are numerous reports of abnormalities in the plasma amino acid pattern in uremia with low concentration of several essential amino acids and high concentrations of some non-essential amino acids, a pattern similar to that found in protein malnutrition. It has been suggested that

Table 2. Muscle and plasma amino acid levels in uremia.

	Chronic renal failure								Dialysed			
	Untreated (5.29)		Low-protein diet (LPD) only (5.29)		LPD supplement with amines (5.29)		LPD supplement with NAF (31)		Peritoneal dialysis (17)		Hemo-dialysis (5a)	
	M	P	M	P	M	P	M	P	M	P	M	P
Essential												
Threonine	↓	↓	↓	↓	↓	↑	N	↑	↓	↓	N	N
Methionine	N	↑	N	↑	N	↑	N	↑	N	↑	N	↑
Valine	↓	↓	↓		↓	↓	N	N	↓	↓	N	N
Isoleucine	N	N	N	↓	N	N	N	N	↑	N	N	↑
Leucine	N	↓	N	↓	N	↓	N	N	↑	↓	N	N
Phenylalanine	↑	↑	↑	N	↓	N	↑	↑	N	↑	↑	↑
Lysine	↓	↓	N	N	↑	N	↑	↑	↑	↓	↑	N
Histidine*	↓	↓	N	N	↑	N	N	↑	N	↓	↑	↑
Tyrosine*	↓	↓	N	N	↓	↑	N	↑	↓	↓	N	↑
Nonessential												
Aspartic acid	↑	↑	↑	↑	↑	↑	↑	↑	N	↑	↑	↑
Serine	N	↓	N	N	N	N	N	N	N	↓	N	N
Asparagine	N	N	N	N	N	N	N	N	N	↓	N	↑
Glutamine	N	N	↑	↑	N	↑	N	↑	↑	↑	N	↑
Glutamic acid	N	↑	N	N	N	↓	N	N	↑	↑	N	N
Citrulline	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Glycine	N	N	↑	↑	N	↑	↑	↑	N	↑	↑	N
Alanine	N	N	↑	N	N	↑	↑	↑	↑	↑	↑	N
Ornithine	↑	↑	↑	↑	↑	↑	↑	N	↑	↑	↑	↑
Arginine	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑

Symbols: M, muscle; P, plasma; N, normal; NAF, new amino acid formula; ↓ decreased; ↑ increased. Figures in parentheses are references. * considered as an essential amino acid in uremia.
From Fürst et al. Amer. Clin. Nutr. **33** 1387-1385, 1980.

these abnormalities reflect nutritional deficiency or altered metabolism in the uremic state. Specific abnormalities in the metabolism of certain amino acids have also been found. Thus it is known that the activity of the enzyme phenylalanine hydroxylase is inhibited in uremia resulting in reduced formation of tyrosine from phenylalanine by hydroxylation (66). Histidine is an essential amino acid in severe uremia (16, 30).

The occurrence of the afore-mentioned abnormalities in amino acid metabolism in uremia raises the question whether uremic patients possibly should be supplied with essential amino acids in other amounts and proportions than recommended for non-uremic individuals to optimize amino acid utilization. The difficulties of solving these problems are formidable, since a number of variables has to be considered, such as the degree of renal function impairment, the total supply of nitrogen, the relation between essential and non-essential amino acids, the proportions between the different essential amino acids, and the energy intake.

In order to increase understanding of amino acid metabolism, we have recently developed methods, by which the amino acid concentrations in intracellular water can be determined in sceletal muscle tissue, obtained by percutaneous needle biopsy. A fundamental question is whether a unique intracellular pattern of free amino acids exists which is distinctive

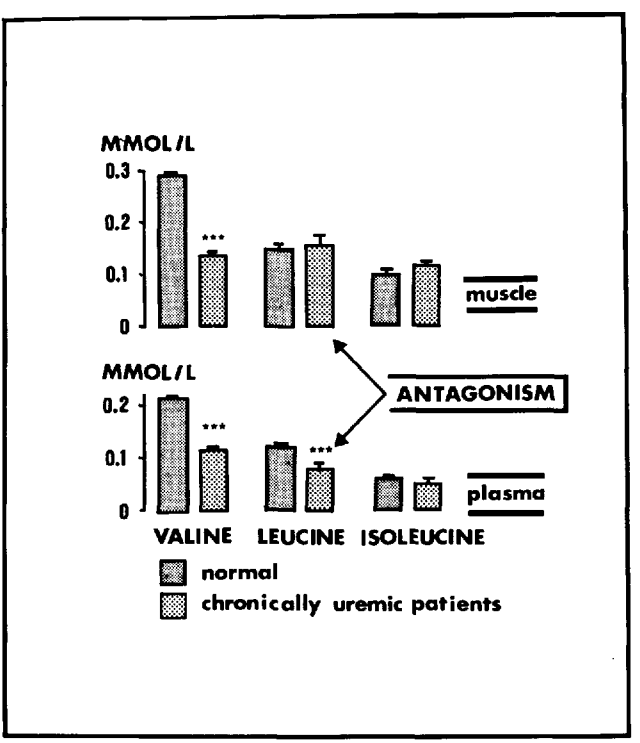

Fig. 1. Branched chain amino-acid antagonism in uremia.

for uremia and various therapeutical means. We have measured the plasma and intracellular muscle concentrations of free amino acids in untreated uremic patients, in patients treated with a 40-g protein diet, an 18-g protein diet alone and with amino acid supplementation, and also in patients on intermittent peritoneal dialysis and during regular hemodialysis treatment (17, 5, 5a, 31).

Uremic patients exhibit many abnormalities in intracellular amino acid concentrations (31). Typical features of uremia appear to be low muscle valine, threonine, tyrosine, histidine, and carnosine (cf. table 2). The low valine in presence of normal isoleucine and leucine in muscle (the latter two are elevated in patients on peritoneal dialysis) suggest an imbalance of the branched-chain amino acids with depletion of valine and abnormal distribution of the other two (fig. 1). This imbalance which persists even after prolonged treatment with low-protein diet and essential amino acids in proportions according to Rose, i.e., considered optimal for normal subjects, may decrease utilization of dietary protein and thus contribute to protein malnutrition. Low intracellular valine concentrations have also been found in uremic children, at early as well as at more advanced stages of renal failure (27, 20). A low valine pool and low turnover of valine were found by Jones and Kopple (39) in non-dialyzed uremic patients who were given ^{14}C-labelled valine. All these findings suggest that there is a specific defect in branched-chain amino acid metabolism induced by uremia. The low muscle-tyrosine concentration may be the consequence of reduced conversion of phenylalanine to tyrosine known to be present in uremia. Tyrosine has therefore been suggested to be an essential amino acid in uremia which should be included in amino-acid preparations intended for uremic nutrition (67). These results present strong evidence that an intracellular "pattern of uremia" does exist.

In an effort to improve the defects in the intracellular amino-acid pattern, a new oral essential amino-acid preparation was designed (31) for chronically uremic patients (fig. 2). Long-term nutrition with this amino-acid preparation normalized the low intracellular concentrations of

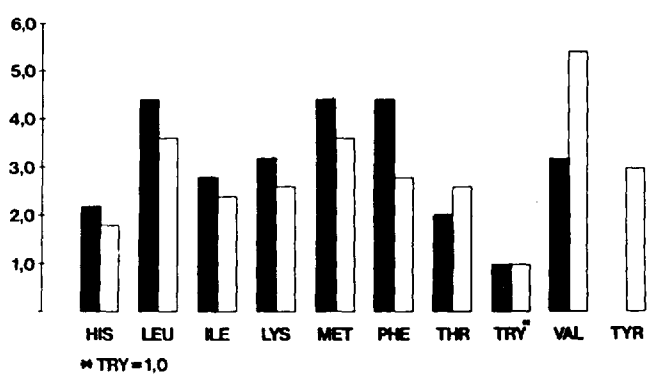

Fig. 2. Comparison of amino acid composition for nutritional supplements. Tryptophan is taken as the reference amino acid. ■ Aminess®; □ new formula.

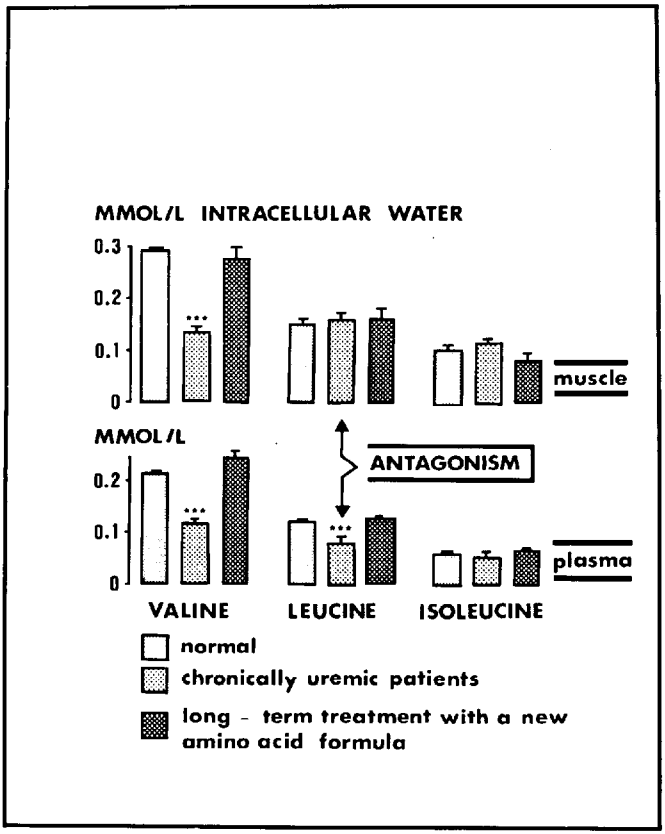

Fig. 3. The effect of nutrition on branched-chain amino-acid antagonism in uremia.

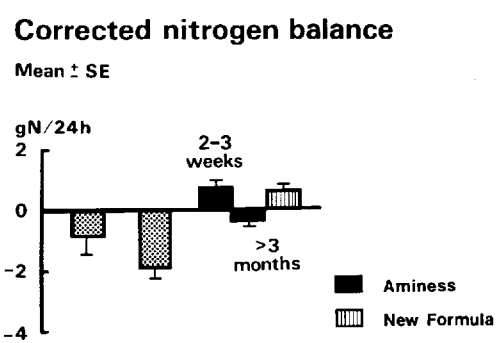

Fig. 4. Nitrogen balance in patients treated with protein-poor diets without (□) and with essential amino acid supplementation (■, □). The nitrogen balances were corrected for changes in total-body urea.

threonine, valine and tyrosine (fig. 3), and also a positive nitrogen balance was achieved (fig. 4). This finding is in contrast to the slightly negative nitrogen balance observed in patients treated with the old preparation (14, 29). However, the urea-cycle-related amino acids citrulline, ornithine and arginine remained high, indicating that these abnormalities are caused by uremic factors which are not controlled by diet.

Keto-acid analogues in uremia

By substituting 5 of the essential amino acids with the corresponding nitrogen-free keto-analogues, nitrogen balance has been maintained in some uremic patients on protein-poor diet, and it has been suggested that the keto-analogues may spare nitrogen more efficiently than the corresponding amino acids (62, 63).

We investigated the utilization of a preparation containing the ketoanalogues of 5 essential amino acids (cf. table 3) by nitrogen-balance studies in uremic patients on an 18-g protein diet (18). In all patients, the nitrogen balance improved, when the diet was supplemented with keto-acids. In 2 cases the improvement in nitrogen utilization occurred without a prior period of adaptation on the protein-poor diet only.

Whether the keto-acids will ultimately prove to be a better alternative to the essential amino acids, as has been suggested (62, 63), remains to be confirmed. Giordano (34) recently reviewed this subject and came to the conclusion that there are not enough data to support any positive benefits of keto-acids over essential amino acids.

The amino-acid preparations used today for nutrition of uremic patients are far from optimally proportioned, considering that the requirements of individual amino acids in uremia may be different from normal. This may even more be the case with the keto-acid preparation used, as practically nothing is known concerning the degree of utilization of individual keto-acid analogues in uremia (36).

Table 3. Composition of KA preparation administered per 24 hours.

	g
CO-valine-Ca	3.7
CO-leucine-Ca	3.5
CO-isoleucine-Ca	2.8
CO-phenylalanine-Ca	1.9
OH-methionine-Ca	2.1
L-threonine	0.67
L-tryptophan	0.33
L-lysine acetate	0.90
L-histidine	0.54
Carbohydrates (xylitol, sorbitol, sucrose, starch)	29.5
Total N	0.46

When metabolized, the keto-acids are not giving rise to increasing amounts of urea and presumably not of other nitrogenous compounds either. Hence they should be less toxic than the corresponding essential amino acids if not utilized for protein synthesis, e.g., in situations of increased net protein catabolism, provided that the keto-acids are not toxic per se, of which there is no evidence.

Another advantage might be that keto-acid supplementation can be instituted immediately when the patient is switched to the 18-g protein diet, i.e., no period of adaptation to the diet only is required, as is necessary when essential amino acids are given. This may imply that the period of negative nitrogen balance can be considerably shortened at the beginning of treatment.

Lipid metabolism and atherosclerosis

The characteristic features of the uremic dyslipoproteinemia are high triglycerides with increase of very-low-density lipoprotein (VLDL), decreased high-density lipoprotein (HDL) and a cholesterol : triglyceride ratio which is raised in VLDL and lowered in LDL. This is similar to the type-IV hyperlipoproteinemia, but not exactly the same, since in this condition the cholesterol : triglyceride ratio in VLDL is not increased (46). The hypertriglyceridemia has been attributed to reduced lipoprotein lipase activity thought to mediate removal of circulating lipoprotein triglyceride.

In a retrospective study we reported data from 68 patients treated with a diet contraining 15–20 g protein/day supplemented with essential amino acids or keto analogues beyond the time when they could not be supported by moderate protein reduction (40 g protein/day) (6). Results concerning mortality and life expectancy were at least as good as for patients on dialysis, which findings do not support a deleterious role of prolonged dietary treatment by accelerating atherosclerosis. The diet in this study was not modified to provide increased amounts of polyunsaturated fat or reduction in disaccharides. Attman and Gustavsson (7), who studied the influence of treatment with a protein-reduced diet and essential amino acids, similar to the one used by Alvestrand et al. (6), could not find any deterioration in total lipids and lipoproteins over an average 9.5 months in spite of continuous reduction in renal function over the observation period.

In view of the fact that we do not exactly know the importance of the lipid changes in uremic, although suggestive of being atherogenic, it is still of interest that dietary manipulation can chance the lipid patterns. Thus a decrease in dietary carbohydrate intake by 15 percent leads to a significant fall in post-prandial insulin response, very-low-density lipoprotein secretion and plasma triglyceride concentration (51). Cattran (23) also changed the composition of the diet and obtained similar results. Dietary manipulations remain the most practical way of changing blood lipids. Perhaps of equal value is increased exercise. Goldberg and his colleagues (35) reported on hemodialysis patients who within 4–7 months of exercise training showed significant improvement in oxygen consumption and excercise tolerance. The plasma triglycerides decreased, and the high-density lipoproteins increased. This was a carefully controlled study

which is not applicable to all patients but clearly indicates that greater use be made of sensible exercise. Other ways of manipulating blood lipids in uremia are by giving lipid-lowering drugs. Clofibrate should be used only after careful consideration of the risk, and doses should be reduced in uremic patients. In this connection it is of interest that the plasma level of L-carnitine decreases profoundly, while patients are undergoing hemodialysis as reviewed by De Felice and Klein (26). Carnitine has been administered orally or intravenously to dialysis patients in varying doses and found to have a lowering effect on triglycerides and free fatty acids, whereas cholesterol is not changed. Therapy also resulted in elevation of both plasma and muscle concentrations of L-carnitine. Giving DL-carnitine may induce a myasthenia-like syndrome in patients on long-term hemodialysis (10), an effect which can be prevented by treating with L-carnitine. The clinical value of L-carnitine therapy and exact dose and administration remain to be finally evaluated.

References

1. Abiko, T., M. Kumikawa, H. Higuchi, H. Sekino: Identification and synthesis of a heptapeptide in uremic fluid. Biochem. Biophys. Res. Commun. **84,** 184–194 (1978).
2. Abiko, T., I. Onodera, H. Sekino: Isolation, structure and biological activity of the Trp-containing pentapeptide from uremic fluid. Biochem. Biophys. Res. Commun. **89,** 813–821 (1979).
3. Abiko, T., M. Kumikawa, M. Ishizaki, H. Takahashi, H. Sekino: Identification and synthesis of a tripeptide in ecum fluid of an uremic patient. Biochem. Biophys. Res. Commun. **83,** 357 (1978).
4. Abiko, T., I. Onodera, H. Sekino: Characterization of an acidic tripeptide in neurotoxic dialysate. Chem. Pharm. Bull. **28,** 1629–1633 (1980).
5. Alvestrand, A., J. Bergström, P. Fürst, G. Germanis, U. Widstam: The effect of essential amino acid supplementation on muscle and plasma free amino acids in chronic uremia. Kidney Int. **14.** 323–329 (1978).

5a. Alvestrand, A., J. Bergström, P. Fürst: Intracellular free amino acids in patients treated with regular hemodialysis (HD). Proc. EDTA **16,** 129–134 (1979).

6. Alvestrand, A., M. Ahlberg, P. Fürst, J. Bergström: Clinical experience with amino acid and keto acid diets. Amer. J. Clin. Nutr. **33,** 1654–1659 (1980).
7. Attman, P. O., A. Gustafson: Lipid and carbohydrate metabolism in uremia. Influence of treatment with protein-reduced diet and essential amino acids. Nutr. Metab. **24,** 261–266 (1980).
8. Bagdade, J. D., P. V. Subbaiah, et al.: Polyamines: An unrecognized cardiovascular risk factor in chronic dialysis? Lancet **(1979) I,** 412–413.
9. Bartelson, N. M., T. Basil, A. L. Lavender: 3'5'-cyclic AMP levels in hemodialysis patients. In: Abstracts of 7th Annual Meeting of the American Society of Nephrology 7, (1974).
10. Bazzato, G., C. Mazzina, M. Ciman, et al.: Myasthenia like syndrome associated with carnitine in patients on long-term hemodialysis. Lancet **(1979), I,** 1041–1042.
11. Bergström, J., P. Fürst: Uraemic toxins. In: Replacement of renal function by dialysis, Chapter 18, p. 334, W. Drukker, F. M. Pearson, J. F. Maher, edited by Martinus Nijhoff Medical Division. (The Hague–Boston–London 1978).
12. Bergström, J., A. Alvestrand, H. Asaba, P. Fürst, V. Yahiel, L. Zimmermann: Uremic middle molecules. In: Controversies in Nephrology, Proceedings of the First Conference, edited by G. E. Schreiner, Nephrology Division, Georgetown University, 425–434 (Washington 1979).

13. Bergström, J., P. Fürst, L. Zimmermann: Uremic middle molecules exist and are biologically active. Clin. Nephrol. **11,** 229 (1979).
14. Bergström, J., P. Fürst, L. O. Norée: Treatment of chronic uremic patients with protein-poor diet and oral supply of essential amino acids. I. Nitrogen balance studies. Clin. Nephrol, **3,** 189 (1975).
15. Bergström, J., P. Fürst, B. Josephson, L. O. Norée: Factors affecting the nitrogen balance in chronic uremic patients receiving essential amino acids intravenously or by mouth. Nutr. Metabol. **14,** Suppl., 162 (1972).
16. Bergström, J., P. Fürst, B. Josephson, L. O. Norée: Improvement of nitrogen balance in a uremic patient by the addition of histidine to essential amino acid solutions given intravenously. Life Sci. **9,** part 2, 787 (1970).
17. Bergström, J., P. Fürst, L. O. Norée, E. Vinnars: Intracellular free amino acids in muscle tissue of patients with chronic uraemia: effect of peritoneal dialysis and infusion of essential amino acids. Clin. Sci. Mol. Med. **54,** 51 (1978).
18. Bergström, J., A. Alvestrand, P. Fürst: Metabolic studies with ketoacids in uremia. Amer. J. Clin. Nutr. **31,** 1761 (1978).
19. Borah, M. F., P. Y. Schoenfeld, F. A. Gotch, J. A. Sargent, M. Wolfson, H. Humphreys: Nitrogen balance during intermittent dialysis therapy of uremia. Kidney Int. **14,** 491–500 (1978).
20. Broyer, M., G. Jean, A. M. Dartois, C. Kleinknecht: Plasma and muscle free amino acids in children at the early stages of renal failure. Amer. J. Clin. Nutr. **33,** 1396–1401 (1980).
21. Brunner, B., A. Brunner, U. Essers, R. Heintz: Inhibition of bone marrow cell proliferation by undialyzable fraction. In: Renal Insufficience (Würzburg Symposium, 1974), edited by A. Heidland, H. Hennemann and J. Kult. Georg Thieme Verlag (Stuttgart 1976).
22. Campbell, R. A., Y. B. Talwalkar, D. Bartos, F. Bartos, J. E. Musgrave, M. Harner, D. Grettie, A. M. Dolney, B. Loggan: Polyamines, uremia and hemodialysis. In: Advances in Polyamine Research, vol. 2, p. 319, edited by R. A. Campbell, D. R. Morris, D. Bartos, G. D. Daves and F. Bartos. Raven Press (New York 1978).
23. Cattran, D. C., G. Steiner, S. S. A. Fenton, et al.: Dialysis hyperlipemia: response to dietary manipulations. Clin. Nephrol. **13,** 177–182 (1980).
24. Clements, R. S., P. V. De Jesus, A. T. Winegrad: Raised plasma myoinositol levels in uraemia and experimental neuropathy. Lancet **(1973) I,** 1137.
25. Cueille, G., N. K. Man, A. Sausse, J. P. Farges, J. L. Funck-Brentano: Characterization of sub-peak $b_{4\text{-}2}$, middle molecule. Artif. Organs **4** (suppl.), 28 (1980).
26. De Felice, S. L., M. I. Klein: Carnitine and hemodialysis – a minireview. Current Ther. Res. **28,** 195–198 (1980).
27. Delaporte, C., G. Jean, M. Broyer: Free plasma and muscle amino acids in uremic children. Amer. J. Clin. Nutr. **31,** 1647–1651 (1978).
27a. Dord, J., M. E. Philips, F. E. Yoye, V. A. Luck, H. E. Wardener: Nitrogen balance in patients with chronic renal failure on diet containing varying quantities of protein. Brit. Med. J. (1969) I, 735.
27b. Dreyfuss, F., R. Chayen, G. Dreyfuss, R. Dvir, J. Ratan: Polyamine excretion in the urine of cancer patients. Israel J. Med. Sci. **11,** 785 (1975).
28. Fürst, P., L. Zimmermann, J. Bergström: Determination of endogenous middle molecules in normal and uremic body fluids. Clin. Nephrol. **5,** 178–188 (1976).
29. Fürst, P., A. Alvestrand, J. Bergström: Principles of essential amino acid therapy in uremia. Amer. J. Clin. Nutr. **31,** 1744–1755 (1978).
30. Fürst, P.: ^{15}N-Studies in severe renal failure. II. Evidence for the essentiality of histidine. Scand. J. Clin. Lab. Invest. **30,** 307 (1972).
31. Fürst, P., A. Alvestrand, J. Bergström: Effects of nutrition and catabolic stress on intracellular amino acid pools in uremia. Amer. J. Clin. Nutr. **33,** 1387–1395 (1980).

32. Funck-Brentano, J. L., N. K. Man, A. Sausse, J. Zingraff, J. Boudet, A. Becker, G. F. Cueille: Characterization of a 1100–1300 MW uremic neurotoxin. Trans. Amer. Soc. Artif. Intern. Organs **22,** 163 (1976).
33. Giordano, C.: Use of exogenous and endogenous urea for protein synthesis in normal and uraemic subjects. J. Lab. Clin. Med. **62,** 231 (1963).
34. Giordano, C.: Amino acids and ketoacids – advantages and pitfalls. Amer. J. Clin. Nutr. **33,** 1649–1653 (1980).
35. Goldberg, A. P., J. N. Hazberg, J. A. Balmey, et al.: Exercise training improves abnormal lipid carbohydrate metabolism in hemodialysis patients. Trans. ASAIO **25,** 431–439 (1979).
36. Halliday, D., M. Madigan, R. A. Chalmers, P. Purkiss, S. Ell, J. Bergström, P. Fürst, M. Neuhäuser, P. Richards: The degree of conversion of α-keto acids to valine and phenylalanine in health and uremia. Quart. J. Med. **197,** 53–62 (1981).
37. Harrison, T. R., M. F. Mason: The pathogenesis of the uremic syndrome. Medicine (Balt) **16,** 1–44 (1937).
37a. Herdon, R. F., S. Freeman, A. S. Cleveland: Protein requirements in chronic insufficient patients. A study of the nitrogen minimum. J. Lab. Clin. Med. **52,** 235 (1958).
38. Johnson, W. J., W. W. Hagge, R. D. Wagoner, R. P. Dinapoli, J. W. Rosevear: Toxicity arising from urea. Kidney Int. **7,** Suppl 3, 288 (1975).
39. Jones, M., J. D. Kopple: Valine metabolism in normal and chronically uremic man. Amer. J. Clin. Nutr. **31,** 1660–1664 (1978).
40. Klein, A., M. Sarnecka-Keller, Z. Hanicki: Middle-sized ninhydrin-positive molecules in uraemic patients treated by repeated haemodialysis. II. Chief peptide constituents of the fraction. Clin. Chim. Acta **90,** 7–11 (1978).
41. Korz, R., U. Loebnitz, H. Brunner, R. Heintz: Lymphocyte enzymes of DNA-synthesis in chronic renal failure. Proc. Eur. Dial. Transplant Assoc. **13,** 528 (1976).
42. Liveson, J. A., J. Gardner, M. B. Bornstein: Tissue culture studies of possible uremic neurotoxins: myoinositol. Kidney Int. **12,** 131 (1977).
43. Lutz, W.: Chemical compositions and rate of passage across semipermeable membranes of basic peptides isolated from peritoneal dialysis fluid from patients with chronic renal failure. Acta Med. Pol. **17,** 137–147 (1976).
44. Massry, S. G.: Is parathyroid hormone a uremic toxin? Nephron **19,** 125 (1977).
45. Munro, H. N.: Amino acid requirements and metabolism and their relevance to parenteral nutrition. In: Parenteral Nutrition, edited by A. W. Wilkinson. Churchill Livingstone (Edinburgh and London 1972).
46. Norbeck, H. E., L. Orö, L.Å. Carlsson: Serum lipid and lipoprotein concentrations in chronic uremica. Acta Med. Scand. **200,** 487–492 (1976).
47. Norée, L. O., J. Bergström: Treatment of chronic uremic patients with protein-poor diet and oral supply of essential amino acids. II. Clinical results of long-term treatment. Clin. Nephrol. **3,** 195 (1975).
48. Pitkänen, E.: The serum polyol pattern and the urinary polyol excretion in diabetic and in uraemic patients. Clin. Chim. Acts **38,** 221 (1972).
49. Prevost, J. L., J. A. Dumas: Examen du sang et du son action dans les divers phénomènes de la vie. Ann. Chim. Phys. **23,** 90 (1821).
50. Rabin, E. Z., B. Tattrie, D. Algom, M. Freedman, F. Saunders, D. A. K. Roncari: Ribonuclease activity in renal failure: evidence for toxicity. In: Abstracts of 9th Annual Meeting of the American Society of Nephrology, **22** (1976).
51. Reaven, G. M., R. Swensson, M. L. Sanfelippo: An inquiry into the mechanism of hypertriglyceridemia in patients with chronic renal failure. Amer. J. Clin. Nutr. **33,** 1476–1484 (1980).
52. Rennick, B., M. Acara, P. Hysert, B. Mookerjee: Choline loss during hemodialysis: homeostatic control of plasma choline concentration. Kidney Int. **10,** 329 (1976).
53. Rose, W. C.: Amino acid requirements of man. Fed Proc **8,** 546 (1949).

54. Russel, D. H., B. G. M. Durie, S. E. Salmon: Polyamines as predictors of success and failure in cancer chemotherapy. Lancet **1975/II**, 797–799.
55. Schaefer, K., G. Oftermann, D. von Herroth, et al.: Failure to show a correlation between serum parathyroid hormone, nerve conduction velocity and serum lipids in hemodialysis patients. Clin. Nephrol. **14**, 81–88 (1980).
56. Schneider, W., G. A. Jutzler: Implications of cyclic adenosine 3'5'-mono-phosphate in chronic renal failure. New Engl. J. Med. **291**, 155 (1974).
57. Seale, T. W., W. Y. Chan, J. B. Shukla, et al.: Isolation and characterization of a polyamine-peptide conjugate from human amniotic fluid. Clin. Chim. Acta **95**, 461–472 (1979).
58. Servo, C., A. Bardy, A. Pasternack, E. Pitkänen: Plasma, red cell and cerebrospinal fluid concentrations of myoinositol in patients with severe chronic renal failure. Ann. Clin. Res. **8**, 374 (1976).
59. Simenoff, M. L., J. J. Saukkonen, J. F. Burke, R. W. Schaedler, W. H. Vogel, K. Bovee, N. Lasker: Importance of aliphatic amines in uremia. Kidney Int. 12, Suppl **8**, 16 (1978).
60. Slatopolsky, E., K. Martin, K. Hrusk: Parathyroid hormone metabolism and its potential as a uremic toxin, Amer. Phys. Soc. Ed. Rev. 1–12 (1980).
61. Tabor, H., C. W. Tabor: Spermidine, spermine and related amines. Pharmacol. Rev. **16**, 245 (1964).
62. Walser, M., A. W. Coulter, S. Dighe, F. R. Chantz: The effect of ketoanalogues of essential amino acids in severe chronic uremia. J. Clin. Invest. **52**, 578 (1973).
63. Walser, M.: Ketoacids in the treatment of uremia. Clin. Nephrol. **3**, 180 (1975).
64. Ward, R. A., M. J. Shirlow, J. M. Hayes, et al.: Protein catabolism during hemodialysis. Amer. J. Clin. Nutr. **32**, 2443–2449 (1979).
65. Wathen, R., M. Smith, P. Keshaviah, C. Comby, F. Shapiro: Depressed in vitro aggregation of platelets of chronic hemodialysis patients (CHDP): a role for cyclic AMP. Trans. Amer. Soc. Artif. Intern. Organs **21**, 320 (1975).
66. Young, G. A., F. M. Parsons: Impairment of phenylalanine hydroxylation in chronic renal insufficiency. Clin. Sci. Mol. Med. **45**, 89 (1973).
67. Young, G. A., J. B. Keogh, F. M. Parsons: Plasma amino acids and protein levels in chronic renal failure and changes caused by oral supplements of essential amino acids. Clin. Chim. Acts **61**, 205–213 (1975).
68. Zimmermann, L., A. Baldesten, J. Bergström, P. Fürst: Isotachophoretic separation of middle molecule peptides in uremic body fluids. Clin. Nephrol. **13**, 183–188 (1980).
69. Zimmermann, L., P. Fürst, J. Bergström, H. Jörnvall: A new glycine containing compound with a blocked amino group from uremic body fluids. Clin. Nephrol. **14**, 107–111 (1980).
70. Zimmermann, L., H. Jörnvall, J. Bergström, P. Fürst, J. Sjövall: Characterization of a double conjugate in uremic body fluids. Febs Lett. **129**, 237 (1981).

Authors' address:

Institute for Biological Chemistry and Nutrition, University of Hohenheim, Garbenstrasse 30, 7000 Stuttgart 70, West Germany