The role of trace elements in uraemic toxicity

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Abstract
Although most research on uraemic toxicity has focused on the retention or removal of organic solutes, subtle changes in the concentration of inorganic compounds are also of importance because these compounds may have significant clinical consequences. Potential clinical implications include increased risk of cancer, cardiovascular disease, immune deficiency, anaemia, renal function impairment and bone disease. In uraemic patients, the most important factor affecting trace element concentration is the degree of renal failure and modality of renal replacement therapy. Accumulation of trace elements in haemodialysis patients has resulted from dialysate contaminated with aluminium and strontium. Several trace elements have been implicated in the decline of renal function. These include arsenic, cadmium, copper, germanium, lead and mercury. In uraemic patients, aluminium, cadmium, chromium, lanthanum, strontium and zinc have been shown to accumulate in bone. In addition to substantial evidence linking aluminium to renal osteodystrophy, studies have also implicated cadmium, iron and strontium in bone disease. Studies using a rat model of chronic renal failure have demonstrated an association between lanthanum accumulation and mineralization defects characteristic of osteomalacia. Investigations of arsenic accumulation in animal models have demonstrated that speciation of trace elements potentially may alter toxicities of trace elements accumulated in uraemic patients. Conversely, the presence of uraemic toxins may also alter the uptake and toxicity of certain trace elements. Although research in uraemic patients has focused primarily on total concentrations of trace elements, the evolution of both inorganic and organic species should be considered separately.

Keywords: accumulation; bone; depletion; toxicity; trace elements; uraemia

Introduction
Uraemia is characterized by functional and biochemical disturbances that result primarily from the diseased kidney’s diminished capacity to remove organic solutes from the body. Most research on uraemic toxicity has focused on retention and removal of these organic compounds. However, subtle changes in the concentration of inorganic compounds, including trace elements, may also cause functional or biochemical disturbances.

The term ‘trace element’ dates back to the 19th century. The term referred to those elements found in the body at concentrations below accurate detection limits of that time. The term persists today, despite new analytical techniques that allow the accurate measurement of most trace elements.

Excessive accumulation or depletion of trace elements may have significant clinical implications,
including increased risk for cancer, cardiovascular disease, immune deficiency, anaemia, renal function impairment and bone disease. While very little is known about trace element concentration and metabolism in healthy individuals, even less is known about the physiology of trace elements in uraemia.

Factors affecting trace element concentration and toxicity

The concentration and toxicity of trace elements in body fluids can be affected by multiple factors (Table 1). Most factors cause a decrease rather than an increase in trace element concentration. In renal failure, trace element decreases mainly occur through losses to the dialysate and through urinary losses. However, the most important factor affecting trace element concentration in uraemic patients is the degree of renal failure [1].

Decreased concentrations are related mainly to nutritional intake, intestinal uptake and altered distribution. In addition, protein-bound trace elements may be lost more readily in the presence of proteinuria. Increased trace element concentrations can result from excessive homeopathic intake, industrial or environmental exposure, inhalation of cigarette smoke, administration of parenteral fluids or blood contact with contaminated dialysate. Although decreases in trace element concentrations occur more frequently in end-stage renal disease (ESRD) and in dialysis patients, the greatest pathophysiological impact may actually result from the accumulation of trace elements in these individuals [1].

Accumulation of trace elements in dialysis patients may result from exposure to contaminated dialysate. Overt aluminium intoxication as a result of dialysate contamination was first recognized in 1976 in patients receiving chronic dialysis [2]. Dialysate contamination can result from addition of aluminium components to tap water to induce sedimentation of impurities, from the release of aluminium into the river water from industrial waste and/or from contamination of river water by aluminium, which is present as a natural element in the soil of some geographic areas.

Table 1. Factors affecting concentration and toxicity of trace elements

<table>
<thead>
<tr>
<th>Inadequate intake</th>
<th>Malabsorption</th>
<th>Altered distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnutrition</td>
<td>Intestinal dysfunction</td>
<td>Changes in transport</td>
</tr>
<tr>
<td>Low income diets</td>
<td></td>
<td>Changes in receptors</td>
</tr>
<tr>
<td>Alcoholism</td>
<td></td>
<td>Inability to store</td>
</tr>
<tr>
<td>Increased requirement</td>
<td>(anabolism, etc.)</td>
<td>Transient changes:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>myocardial infarction</td>
</tr>
</tbody>
</table>

Table 2. Reported evolution of serum/plasma concentrations of various trace elements in renal failure (range of mean values as reported)

<table>
<thead>
<tr>
<th>Element</th>
<th>Out-patient (CRF patients without dialysis)</th>
<th>Haemodialysis</th>
<th>CAPD</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminium</td>
<td>50.0–186.3</td>
<td>50.0–183.6</td>
<td>105.3</td>
<td>[5,6]</td>
</tr>
<tr>
<td>Arsenic</td>
<td>–</td>
<td>↓ 8.5–79.8</td>
<td>–</td>
<td>[3,4,7,8]</td>
</tr>
<tr>
<td>Cadmium</td>
<td>–</td>
<td>= /1.2?</td>
<td>–</td>
<td>[3]</td>
</tr>
<tr>
<td>Cobalt</td>
<td>–</td>
<td>–</td>
<td>0.3</td>
<td>[9]</td>
</tr>
<tr>
<td>Copper</td>
<td>= /0.8–1.3</td>
<td>= /0.8–1.5</td>
<td>= /1.1–1.2</td>
<td>[3,6,9,10]</td>
</tr>
<tr>
<td>Iron</td>
<td>= /1.2</td>
<td>= /1.0–1.6</td>
<td>= 0.7</td>
<td>[3,9,10]</td>
</tr>
<tr>
<td>Mercury</td>
<td>0.5–1.2</td>
<td>2.5</td>
<td>–</td>
<td>[3]</td>
</tr>
<tr>
<td>Selenium</td>
<td>= /0.2</td>
<td>= /0.05–0.1</td>
<td>= /0.06–0.1</td>
<td>[3,9,11]</td>
</tr>
<tr>
<td>Vanadium</td>
<td>–</td>
<td>18.4</td>
<td>–</td>
<td>[12]</td>
</tr>
<tr>
<td>Zinc</td>
<td>↓ 0.7–0.9</td>
<td>↓ 0.7–0.9</td>
<td>0.8</td>
<td>[6,9,10]</td>
</tr>
</tbody>
</table>

\* defined as no significant difference compared with the reference value; \(\uparrow\) and \(\downarrow\) defined as significant increase or decrease, respectively, compared with the reference value. Note that reference values may be different from study to study.
Other inconsistencies in trace element profiles stem from a lack of uniformity in the reported results. Values are reported inconsistently from various sources, including whole blood, serum, plasma, packed cells or erythrocytes. In addition, various tissue concentrations are markedly different from blood or plasma concentrations for the majority of trace elements. Finally, concentrations differ from organ to organ. For example, kidneys and skin are known to sequester trace elements, including arsenic and cadmium [1].

**Clinical implications**

*Cancer susceptibility, cardiovascular disease, anaemia*

Cancer susceptibility is increased in patients with ESRD. Excess concentrations of arsenic and cadmium, as well as selenium deficiency, have been linked to carcinogenicity in non-uraemic populations [1]. Epidemiological studies, reviewed by Bates et al., demonstrated a relationship between arsenic concentration in well water and cancers of the skin, bladder, kidney lung, and liver [13]. It is impossible to compare this exposure with that in uraemic patients, because serum concentrations in the affected subjects were not reported.

Cardiovascular morbidity and mortality is enhanced and accelerated in uraemic patients [1]. Several studies link increased and decreased levels of various trace elements with cardiovascular disease. In individuals without renal disease, high levels of blood lead and plasma aluminium were associated with essential hypertension [14]. Oxidative mechanisms are affected by arsenic, cadmium and copper. Studies in rats demonstrated that arsenic induced lipid peroxidation in the liver, kidney and heart [15], and cadmium produced enhanced lipid peroxidation in the liver, heart and spleen [16]. Studies have related iron excess to lipid oxidation, accelerated arterogenesis and excess risk of acute myocardial infarction [17]. On the other hand, copper deficiency has been associated with cardiovascular disease [18]. *In vitro* experiments showed that Na-K-ATPase was inhibited by mercury, lead and cadmium [19], and increased systolic and diastolic blood pressure was caused by long-term vanadium exposure in rats [20]. In six chronic dialysis patients, Richard et al. demonstrated a strong correlation between selenium and plasma glutathione peroxidase and showed that selenium deficiencies could be reversed [21].

Anaemia continues to be problematic for uraemic patients, despite the advent of erythropoietin. Excess arsenic, aluminium and vanadium, as well as copper deficiency, are all related to anaemia. Competition by arsenic for transport on transferrin, together with enhanced uptake of this complex, is thought to lead to high bone marrow concentrations of arsenic that might contribute to renal anaemia [22–24]. A small study of five non-dialysed patients with chronic renal failure showed a negative correlation between blood haemoglobin and elevated levels of bone marrow arsenic. Haemoglobin levels in affected patients were in the range of 69–105 g/l compared with 142 g/l in controls, while arsenic levels ranged between 36 and 89 ng/g, compared with 19 ng/g in controls. Arsenic may have acted in parallel with or together with other accumulated compounds to inhibit erythropoiesis [24].

Investigators hypothesize that the inhibitory effect of aluminium on erythropoiesis is mediated by the interference of aluminium with iron bioavailability. In a case study of a patient who developed haematological evidence of aluminium accumulation, the inhibitory effect of aluminium was reversed with aluminium chelation therapy [25]. Furthermore, Jain et al. demonstrated a relationship between aluminium overload and the accumulation of lipid peroxides and lipofuscin products in red blood cells of haemodialysis patients. The data suggest that aluminium overload may increase membrane peroxidation and reduce red blood cell life span [26].

Although the uraemic state generally causes increased concentrations of copper, a deficiency of this metal has been associated with diminished growth of individual bone marrow cell lines and pancytopenia [27,28]. A study of 80 chronic haemodialysis patients demonstrated an inverse correlation between serum vanadium and red cell count and haemoglobin [12].

**Renal failure**

Several trace elements have been implicated in the decline of renal function. These include arsenic, cadmium, copper, germanium, lead and mercury (Table 3). In healthy individuals, normal functioning kidneys eliminate trace elements from the body. However, in uraemia, declining kidney function leads to an accumulation of potentially nephrotoxic trace elements, which may contribute to the deterioration of renal function [1].

Tubulointerstitial nephritis is associated with an elevated urinary arsenic concentration. Symptomatic improvement, normalization of abdominal radiographs and stabilization of renal function resulted after removal of the arsenic source, suggesting that this trace element provokes tubulointerstitial nephritis [29]. According to reports by Fowler et al., tubular transport defects leading to the equivalent of the Fanconi syndrome may result from preferential accumulation in kidney tissue of cadmium, copper, lead and mercury [30].

Lead and germanium accumulation are especially significant in renal decline. In the study of a random population sample of 965 men and 1016 women, the creatinine clearance rate was found to be inversely correlated with blood lead and zinc protoporphyrin values. Furthermore, a 10-fold increase in blood lead concentration was associated with a 10–13 ml/min reduction in creatinine clearance. Although the study found that exposure to lead may impair renal
function in the general population, the alternative hypothesis that renal impairment results in blood lead accumulation could not be ruled out [31].

In a case study of two young HIV-infected patients, the ingestion of germanium as an immunostimulant for 9 months produced extremely high concentrations of germanium in renal tissue (10–70 times normal) and liver tissue (140 times normal). The male patient continued to have renal dysfunction (creatinine clearance of 43 ml/min/m²) 9 months following cessation of germanium supplements. The female patient presented with severe renal dysfunction (creatinine clearance of 7 ml/min/1.73 m²), which persisted for 2 years after cessation of germanium supplements (14 ml/min/1.73 m²) [32].

Bone disease

The spectrum of renal osteodystrophy covers two general types of bone disease: a low turnover disease characterized by osteomalacia and adynamic bone disease, and a high turnover disease that includes osteitis fibrosa or mild secondary hyperparathyroidism. A mixed or transitional bone disorder may contain histological features of both low and high turnover lesions [33]. Several trace elements, including aluminium, cadmium, iron and strontium, have been implicated in renal osteodystrophy.

In vitro experiments and studies with dialysis patients show an association between aluminium and bone disease. In a study of 48 dialysis patients undergoing bone biopsy, all patients with a positive biopsy for aluminium staining (n=21) showed an abnormal morphology. The majority of aluminium-positive biopsies showed osteomalacia (n=13). However, in aluminium-negative biopsies (n=27), osteomalacia was absent. Furthermore, among aluminium-positive patients, hyperparathyroidism was rare (n=1) [34]. In vitro studies found that aluminium concentrations of 4 and 40 μM inhibit the affinity of parathyroid hormone (PTH) receptor and suppress PTH-stimulated adenylate cyclase. No PTH-responsive adenylate cyclase or binding to receptor was demonstrated at 200 μM [35].

Cadmium was reported to induce osteomalacia in ovariectomized rats, and cadmium concentrations were increased in bone of ESRD patients [36,37]. D’Haese et al. also reported an increased bone strontium and chromium content in patients with ESRD and an association of bone strontium with osteomalacia [33].

Research interests: arsenic as a special case

In recent years, several questions have gained importance among uraemic research interests. Which trace metals show the most spectacular changes? Can trace metal concentrations be influenced by the dialysate?
These questions have led some research groups to focus on the behaviour of arsenic, which has shown important changes in uraemia and potential for toxic side effects, not yet reported in the literature.

In a study of five uraemic patients on haemodiafiltration, deviations of trace element concentrations from normal reference values showed increasing or decreasing trends (Table 4). However, large interindividual differences were observed and arsenic showed the most marked increase, exceeding the reference value by a factor of 50 in one patient [3].

Although caesium, iron, rubidium, selenium and zinc showed trends for decreased concentrations, the trends were not consistent throughout the five patients. While four patients showed a decrease in iron and caesium concentrations, one patient unexpectedly had an increased concentration of these trace metals. Patient 5 showed a normal zinc concentration, compared with the other four patients with decreased zinc concentrations [3].

Consecutively, arsenic concentrations were studied in seven chronic haemodialysis patients, and showed a correlation between intracellular arsenic and serum arsenic concentrations. Arsenic accumulations of >10-fold were determined in serum and packed cells of chronic haemodialysis patients. However, arsenic concentrations remained unaltered, before and after a single haemodialysis treatment, with no arsenic detectable in the dialysate or heparin solution [8].

The magnitude of arsenic accumulation may be related to the degree of chronic renal insufficiency. Arsenic is already increased for moderate degrees of renal failure as demonstrated in pre-dialysis outpatients [49]. Zhang et al. determined serum arsenic to be 5.8 ± 3.3 µg/l compared with a normal value of 0.382 µg/l for a mean serum creatinine of 4.4 ± 3.3 mg/dl. In addition, higher arsenic concentrations were found in serum and in packed cells of patients having a greater degree of chronic renal insufficiency [49].

**Arsenic species and uraemic toxicity**

Too often, the metabolism of inorganics has been neglected in trace element research. In a study of arsenic metabolites in Flemish giant rabbits, De Kimpe et al. observed disparate behaviour between organic and inorganic species that resulted from arsenate metabolism. Following the administration of a bolus of inorganic arsenic, high concentrations of inorganic species, such as arsenate and arsenite, peaked very early and then gradually decreased thereafter. These inorganic species are thought to exert the highest toxicity [50].

The organic species monomethylarsenic acid and dimethylarsenic acid were registered soon after the inorganic peaks. For dimethylarsenic acid, the gradual decrease was less dramatic than either of the inorganic species. Protein-bound arsenic appeared only after a few hours and showed no decline. When the same amount of arsenic was administered to uraemic rabbits, inorganic species tended to peak higher and to disappear more slowly, whereas the appearance of organic species was postponed. Arsenic distribution in tissues varied widely, with the highest concentrations in kidneys, liver and lungs. Arsenic accumulated in bone, compared with rapid clearance rates in other tissues and blood [50].

In humans with renal failure, the main detectable species were the relatively innocuous arsenobetaine (3.6 ± 4.6 µg/l) and dimethylarsenic acid (0.8 ± 1.1 µg/l) [51]. Toxic inorganic species such as arsenite and arsenate were below the detection limit, making a comparison with healthy controls impossible. In animals, more inorganic species were accumulated in those with renal failure than in those with normal renal function [52,53].

**Uraemic compounds may alter toxicity and kinetics of trace elements**

Certain uraemic compounds may influence the cellular accumulation of trace elements. In vitro experiments demonstrated that uraemic solutes present in ultrafiltrate fractions were related to an increased cellular uptake and toxicity of aluminium. Dose-response curves confirmed that aluminium uptake and cell toxicity were proportional to p-cresol concentrations in culture medium. p-Cresol and other uraemic compounds from these ultrafiltrate fractions may

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Table 4. Trace elements in haemodiafiltration

<table>
<thead>
<tr>
<th>Trend</th>
<th>Element</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased trace element concentrations compared with normal reference</td>
<td>As (µg/l)</td>
<td>43.1</td>
<td>3.8</td>
<td>7.5</td>
<td>12.5</td>
<td>9.6</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Cd (µg/l)</td>
<td>3.1</td>
<td>3.7</td>
<td>&lt;0.4</td>
<td>&lt;0.5</td>
<td>&lt;0.3</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td></td>
<td>Cu (µg/l)</td>
<td>1.4</td>
<td>1.6</td>
<td>1.5</td>
<td>1.4</td>
<td>1.8</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Hg (µg/l)</td>
<td>4.0</td>
<td>4.8</td>
<td>1.1</td>
<td>1.4</td>
<td>1.4</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Mo (µg/l)</td>
<td>2.0</td>
<td>1.8</td>
<td>4.0</td>
<td>2.7</td>
<td>1.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Decreased trace element concentrations compared with normal reference</td>
<td>Cs (µg/l)</td>
<td>0.3</td>
<td>0.5</td>
<td>0.7</td>
<td>1.1</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Fe (mg/l)</td>
<td>1.5</td>
<td>0.8</td>
<td>0.6</td>
<td>4.1</td>
<td>1.0</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Rb (µg/l)</td>
<td>56</td>
<td>100</td>
<td>102</td>
<td>104</td>
<td>95</td>
<td>170</td>
</tr>
<tr>
<td></td>
<td>Se (mg/l)</td>
<td>0.06</td>
<td>0.07</td>
<td>0.09</td>
<td>0.07</td>
<td>0.06</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>Zn (mg/l)</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.7</td>
<td>1.1</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Adapted from [3].
play a role in the accumulation and toxicity of aluminium in the liver of ESRD patients [54].

Detoxification of arsenite can be altered by uraemic toxins. p-Cresol and other uraemic toxins, including oxalate, hypoxanthine, homocysteine and myo-inositol, were found to inhibit arsenic methylation [55].

Conclusions

Plasma concentrations of several trace elements are altered in uraemia and may play an important role in mediating a variety of pathophysiological events affecting the general condition of uraemic patients. Clinical implications from uraemic trace elements include increased cancer susceptibility, enhanced cardiovascular morbidity/mortality, anaemia, renal failure and bone disease. Several trace metals have been shown to accumulate in bone of uraemic patients, including aluminium, cadmium, chromium, lanthanum, strontium and zinc. The potential use of certain metal-containing therapeutics requires further health risk analysis. Although bone disease resulting from aluminium intoxication has declined, renal osteodystrophy still persists. Further research is necessary to determine accurately the effect of trace metal accumulation in relation to bone disease.

Among the various factors influencing trace element accumulation, the most important factors are the stage of renal failure and the type of renal replacement therapy. The metabolism of inorganics has been neglected in trace element research. Trace element accumulation and toxicity may differ depending on the retained inorganic species. Arsenic behaviour in uraemia illustrates the importance of inorganic metabolism. The inorganic species, arsenate and arsenite, are thought to exert the highest toxicity. The uraemic syndrome may also partially alter the uptake and toxicity of trace elements. Uraemic compounds have been related to increased cellular uptake and toxicity of aluminium and arsenic.

While little of the behaviour of trace elements is understood in healthy individuals, even less is known about trace element disturbances in uraemic patients. Although research has focused on total concentrations of trace elements, the evolution of both inorganic and organic species should be considered separately.

References