Trace elements in renal failure: are they clinically important?

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Introduction

For decades nephrologists have been troubled by electrolyte disturbances. The clinical consequences of altered concentrations of potassium, sodium, phosphorus, calcium and magnesium have focused attention on the importance of maintaining concentrations and balance of these electrolytes within the normal range. Compared to these classical electrolytes less attention has focused on trace elements, which have remained the Cinderella of clinical nephrologists. Such relative neglect is explained by several factors: (i) substantial methodological difficulties exist to obtain precise measurements of these elements, (ii) the role of tissue concentrations of many trace elements under normal circumstances is not well defined, i.e. whether they are contaminants or essential elements, (iii) whether it is the trace element concentration itself which is biologically important or its concentration in relation to other elements, and (iv) even less is known with respect to their potential role in chronic renal failure.

Intense interest had been generated by the recognition that in dialysed patients an elevated body burden of aluminum may cause encephalopathy, aluminium-related bone disease, and anemia [1], even at very low concentrations. Although the role of this trace element is beyond doubt, the role of other trace elements has remained unclear, particularly the issue whether clinical disturbances result from their accumulation (toxicity) or depletion (deficiency).

Which methods are appropriate for measuring trace elements?

One major limitation to valid studies on trace elements levels in biological materials is the methodology: Nomiyama and Nomiyama [2] reviewed accurately methodological aspects of trace elements analysis in biological samples and suggested that precise metal determination requires a very high level of skill, clean sampling, a suitable method of determination, internal and external quality controls, careful consideration of biological factors in the assessment (for example dietary patterns), and a sufficient number of samples to assure an accurate and meaningful analysis. They also underlined the importance of a critical review of experimental data before assuming a cause–effect relationship between a specific disease and altered serum or tissue levels of a metal. Neutron activation analysis (NAA) is the ‘gold standard’ of methods to determine trace elements: the excellent sensitivity for a great number of elements, the high specificity, the simultaneous determination of many trace elements, the virtual absence of matrix effects, and its relative freedom from errors due to the contamination of samples prior to the instrumental measurement are the most striking advantages of NAA [3]. However, NAA is very expensive, requires sophisticated technology, and is not widely available; therefore, in the hands of an experienced operator, atomic absorption spectrophotometry (AAS) can be also considered a suitable routine method [2]. A more recent method for trace elements determination is inductively coupled plasma mass spectrometry (ICP-MS): it is very sensitive but has not yet been fully validated [4].

Which type of changes has been documented by measurements of blood and tissue concentrations?

Serum and tissue levels of eleven trace elements have been reported by Smythe et al. [5] and by Alfrey and Smythe [6]. According to these authors, trace-element disturbances can broadly be categorized into three groups (Table 1). The first group comprises the elements the concentrations of which are either globally increased (aluminium, strontium, zinc, tin) or decreased (rubidium, bromine). A second group of disturbances comprises the elements the concentrations of which are increased in some tissues and/or decreased in others (e.g. iron, which is only increased in liver and spleen; or copper, which is increased in the lung and decreased in heart). The third group of alterations in trace element distribution concerns elements which appear to have been translocated between visceral

| Table 1. Types of trace elements disturbances in tissues of dialysis patients |
|-------------------------------------------------|-----------------|-----------------|
| Global increase | Al, Sr, Zn, Sn | Cr |
| Global decrease | Br, Rb | Br, Rb |
| Selective increase | Fe, U | As, Au, Cd, Co, Cu, U |
| Selective decrease | Se |
| Combined alterations | Co |
| Translocation | Mo, Cd |

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organs, e.g. molybdenum and cadmium (reduced in the kidney and increased in the liver). Other elements, in particular selenium and lead, were found normal in uraemic patients, while inadequate information is available for chromium. Surprisingly, the role of the dialysis procedure in trace elements abnormalities was considered to be of limited importance, although the authors correctly pointed out the clear role of dialysis for rubidium depletion and aluminium intoxication [5].

What are the mechanisms for such changes? In uraemic patients the balance between intake and excretion found in normal subjects can be altered in several different ways. First, disturbed renal function can cause either reduced or excessive excretion of an element. Second, the uraemic patient on dialysis can accumulate elemental impurities present in dialysis and infusion fluids. Third, some elements can be excessively removed from the patient during dialysis, if concentrations in the dialysate are sufficiently low.

The role of dialysis fluids in generating trace-element abnormalities is clearly of great importance. We therefore determined dialysate levels of 44 elements in fluids for haemodialysis, haemofiltration, and CAPD [7]. These data can be useful in determining trace element transfer from dialysate to blood and vice-versa, although the actual contamination (or depletion) of a specific element could be markedly influenced by other factors, such as the chemical form of the element, its ability to bind to carriers, or its adsorption to dialysis materials (membranes and tubings). It should be underlined that while the actual transfer of trace elements from the dialysate to the blood can be markedly different from what could be expected on theoretical grounds, contamination from infusion fluids (replacement fluids for haemofiltration and haemodialfiltration, or even normal saline, all of which enter directly into the blood stream) can take place very easily if the quality of the infused fluid is not optimal. While it might be argued that the use of reverse osmosis will probably prevent any major episode of trace element intoxication, the progressive spreading of dialysis technology in developing countries can increase the possibility of trace elements imbalance if the quality of water treatment is not considered of the utmost importance.

What is known (and what is unknown) with respect to some individual trace elements?

In the following we wish to summarize the currently available information with respect to individual trace elements and discuss potential clinical consequences of deviations in their concentration (Table 2).

**Lead (Pb)**

Many studies suggest that lead may play a role in the development of chronic renal failure [8]. Lead can also be increased in dialysis patients, especially if high concentrations are present in drinking water [9]. However, the incidence of lead overload in patients with normal renal function is similar to that in patients with end-stage renal failure. Consequently renal failure per se does not appear to facilitate the accumulation of lead in the body [9].

**Selenium (Se)**

Selenium deficiency has been reported in patients with chronic renal failure [10], but recent studies show that plasma and serum selenium levels are not decreased in renal failure [11,12]. However, we found selective selenium deficiency in the heart [12]. Severe nutritional selenium deficiency has been associated with cases of congestive cardiomyopathy [13,14]; nevertheless, the prevalence and significance of selenium deficiency in the uraemic syndrome is still not clearly defined.

**Chromium (Cr)**

Elevated chromium concentrations have been described in chronic haemodialysis patients and it has been shown that dialysate contamination leads to systemic absorption of chromium during dialysis [15]. This was confirmed in CAPD patients [16]: mean serum chromium levels were about 26 times higher than the normal mean; the concentration of chromium in the fresh dialysate was markedly high, up to eight times the normal serum value. As far as the mechanism is concerned, lactate facilitated peritoneal transfer of chromium has been considered to play an important role [17]. We confirmed the presence of a clear increase in serum and tissue chromium levels in haemodialysis patients [18]: mass balance experiments proved an increase of serum levels of chromium at the end of dialysis along with a decrease in dialysate chromium concentrations, pointing to chromium gain during dialysis; moreover, we were able to detect release of substantial amounts of chromium from needles used for the dialysis procedure. Therefore both dialysate and needles could be sources of chromium release in haemodialysis patients, causing an increased body burden of this element [18]. Although the clinical relevance of these very elevated chromium levels in dialysis patients is not yet clear, an exposure to such impressive amounts of this element should be possibly avoided. Solutions for total parenteral nutrition are also potential sources of large amounts of chromium, as plasma levels up to 21-fold the upper reference range have been described even in patients with normal renal function [19,20].

**Vanadium (V)**

Tsukamoto et al. [21] determined plasma vanadium concentrations in dialysis patients and in patients with chronic renal failure: only haemodialysis patients showed a clear increase in vanadium plasma levels to more than 10 times the normal values; tissue levels were also increased (skin and aorta). Similar findings were reported by Hosokawa and Yoshida [22]. The likely cause of vanadium intoxication in this group of patients was oral ingestion of vanadium-contaminated...
Table 2. Summary of relevant trace elements alterations in dialysis patients and potential clinical consequences

<table>
<thead>
<tr>
<th>Element</th>
<th>Type of alteration</th>
<th>Clinical consequences</th>
<th>Induced by dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td>Decreased</td>
<td>Sleep disturbances (?)</td>
<td>Yes</td>
</tr>
<tr>
<td>Cr</td>
<td>Increased</td>
<td>Hypertension, CNS disturbances abdominal pain</td>
<td>No</td>
</tr>
<tr>
<td>Pb</td>
<td>Increased</td>
<td>CNS disturbances (depression?)</td>
<td>Yes</td>
</tr>
<tr>
<td>Rb</td>
<td>Decreased</td>
<td>No</td>
<td>Not proved</td>
</tr>
<tr>
<td>Se</td>
<td>Decreased in heart (?)</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td>Sr</td>
<td>Increased</td>
<td>Osteomalacia (?)</td>
<td>Unknown</td>
</tr>
<tr>
<td>V</td>
<td>Increased</td>
<td>Inhibition of Na-K-ATPase</td>
<td>No</td>
</tr>
<tr>
<td>Zn</td>
<td>Decreased in serum (normal or increased in tissues)</td>
<td>PNS disturbances</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

CNS, central nervous system; PNS, peripheral nervous system.

water. Vanadium, which has been reported to inhibit several enzyme activities, including the Na-K-ATPase, is normally excreted by the kidney [23].

**Strontium (Sr)**

Increases of bone [5,24] and serum [25] levels of strontium have been reported, but an adverse effect of strontium on bone of uraemic patients has not been established so far. Strontium could adversely affect bone metabolism [26], but it should also be remembered that it has even been proposed as an effective agent against osteoporosis [27].

**Zinc (Zn)**

The finding of reduced serum levels of zinc in dialysis patients has been associated with disturbances in taste and sexual performance [28,29], but this finding was not confirmed and the efficacy of zinc supplementation in reversing these abnormalities remains in doubt [30]. On the other hand, more recently Bonomini et al. [31] found an improvement in nerve conduction velocity after 6 months of zinc supplementation through the dialysate. Despite the positive findings of the latter study, the finding of normal or increased tissue levels of the element [5,12] could explain the absence of a clinical response to zinc supplements in most studies; therefore the practice of zinc supplementation in dialysis patients is questionable, and should be abandoned unless its efficacy can be proved in future placebo-controlled clinical trials.

**Bromine (Br), rubidium (Rb)**

The depletion of bromide and rubidium in dialysis patients is of particular interest in the light of their possible relationship with disturbances of the nervous system. Subnormal blood and tissue bromine levels have been reported by different investigators [5,12,16,32] and have been related to the insomnia in dialysed patients [33].

There is consensus that rubidium levels are low in dialysis patients [5,12,34]. The working hypothesis has been proposed that rubidium depletion is responsible for some of the neurological abnormalities associated with the uraemic state [6,33]. Rubidium is handled by the organism like a potassium analogue, and is efficiently removed by dialysis. However, the food content of rubidium is much lower than that of potassium. Although a physiological role of rubidium in mammals has not been discovered, its high tissue concentrations could be compatible with an essential role in normal humans.

**Other trace elements**

An accumulation of cobalt, arsenic, bromine, and chromium in uraemic myocardium has been reported [35]. The same investigators also suggested a possible role of cobalt accumulation in uraemic heart failure [36], while they found normal levels of selenium in the heart [35]. Hosokawa and Yoshida [37] confirmed the presence of an increase of serum silicon levels in dialysis patients, which had been described previously [38]. Altered tissue levels of several elements (arsenic, As; gold, Au; cadmium, Cd; cobalt, Co; copper, Cu; uranium, U) in specific tissues, such as spleen or liver [5,12], are of uncertain significance because no clinically relevant signs of deranged function of these organs are apparent in uraemic patients.

In conclusion, the role of trace elements in dialysed uraemic patients has not yet been fully characterized. Nevertheless several abnormalities of potential clinical relevance have been recognized. Changes in the dialysis procedures as well as in measurement methodology caution against a comparison of recent to previous data. We believe that today it can be stated that a generalized increase of the body content of chromium and a decrease of bromine and rubidium are commonly present in dialysis patients, but anomalies of other trace elements in specific tissues may also be of importance.

Up to now, most attention has been focused on the potential toxicity of several trace elements in uraemia. This concern is still valid, and assumes particular importance whenever the purity of the dialysate is less than optimal. Nevertheless, a more comprehensive view of the problem should also consider that the dialysis patient is at risk of trace element imbalance, either in the direction of trace element accumulation
and toxicity, or in the direction of trace element depletion, when essential elements are involved.

References