Trace element metabolism in chronic renal failure: update and perspectives

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RESUMEN

Metabolismo de elementos traza en la insuficiencia renal crónica: revisión y perspectivas.
Se revisa la importancia de la depleción y acumulación de elementos traza en la insuficiencia renal crónica, haciendo énfasos en el valor de las determinaciones en suero y en tejidos. Otros elementos potencial tóxicos, como hierro, cinc, cobre, cobalto, cromo y níquel, son evaluados.

SUMMARY

Trace element metabolism in chronic renal failure: update and perspectives.
Depletion and accumulation of trace elements occur during the development and treatment of renal disease. The most satisfactory measure of trace elements status is obtained from tissue analysis; however, for practical reasons indirect evidence from plasma serum or whole blood is more often quoted. The likely role of trace elements other than aluminium, such as iron, cooper, cadmium, chromium and zinc is reviewed.

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Introduction

Alterations in trace element metabolism occur alongside the more major changes caused by the various stages of renal disease its treatment.

Much impetus was given to the investigation of trace metal disorders by the belated realisation that aluminium (Al) accumulation was the cause of certain degenerative changes in renal dialysis patients [1].

There is now a considerable literature which describes alterations in more than 30 trace elements. These can include deficiency of essential nutrients and/or accumulation of inorganic elements in toxic excess [2].

The clinical relevance of many of the observations remains uncertain but should not be completely discounted.

Analytical considerations

Trace elements are by definition present at low concentration. Which elements are determined by an investigator is decided by the analytical techniques available rather than by a systematic examination of elements of known biological activity.

An arbitrary definition of "Trace Elements" would be those present in tissue or body fluids at micromolar (μmol) concentration or less. The various unit systems are confusing and for present purposes we will consider that μmol/l = mg/l = μg/g = parts per million (ppm); and that nmol/l = μg/l = ng/g = parts per billion (ppb).

Numerous methods are available to determine a range of elements at such concentrations. Neutron activation, variants of atomic spectroscopy, X-Ray analytical methods and mass spectometry and many other procedures have been used to investigate trace elements in renal disease. No single technique can encompass the entire range of elements of interest. Commonly used methods such as atomic spectroscopy are most sensitive for metals and important non-metals such as Iodine (I) or Fluorine (F) are somewhat neglected.

Doubt must exist as to the validity of some early reports due to a failure to limit sample contamination during collection and preparation for analysis, or to employ adequate laboratory quality control procedures. These are problems common to all areas of trace element analysis [3]. Furthermore, most investigators rely upon the indirect evidence as to trace element metabolism obtained from analysis of extracellular body fluids such as whole blood, blood plasma or urine. Better information is obtained by tissue analysis which more directly reflects intracellular concentration of essential or toxic elements. A survey of autopsy tissue samples obtained in two countries (USA and Australia) is reported by Smythe, Alfrey et al [4]. They examined samples from 120 dialysis patients, 29 chronic renal failure patients and 64 "controls". Thirteen elements were determined by an x-ray fluorescence technique.

From these studies and the other valid literature it is possible to make some generalisations with respect to trace element metabolism in renal disease.

Deficiency of Essential Trace Elements

This could arise from a combination of dietary restriction when following a low protein intake diet, with losses caused by diuretic therapy, losses during dialysis, and as part of the general excretion of proteins and other metabolites in the nephrotic syndrome. Individual elements considered in this category are:

Zinc: There is a large literature, mainly from the USA, which seeks to show that zinc deficiency occurs in uraemia and is related to clinical effects such as sexual impotence and loss of the sense of taste. Tissue zinc concentrations are not in fact low in uremia [2, 4] and observations of low plasma Zn levels are explained by a parallel fall in plasma albumin, the main transport protein for zinc in plasma. There are conflicting claims as to the effect of oral Zn supplementation as judged on both clinical and biochemical responses [5].

Selenium: There is a marginal fall in serum Se and red cell glutathione peroxidase (a Se dependent enzyme) in patients on CAPD [2].

This can be linked to the lowered protein intake in diet. The extent of the depletion does not seem large but there may be sub-groups of renal patients susceptible to Se deficiency and who could benefit from supplementation.

Other elements

From tissue studies, Smythe, Alfrey et al [4], were able to show a variable but consistent fall in Rubidium (Rb). However, a clinical trial of Rb supplementation showed no apparent effect. Similarly, there may well be losses of bromine (Br) and perhaps other "borderline" essential elements. Such changes are of unknown importance.

Accumulation of Potentially Toxic Elements

Due to various methods of clinical treatment and the nature or renal disease there is a general tendency for small amounts of metals to accumulate in the tissues of renal patients. This is due to excessive input and/or a reduced ability to excrete via the kidney. The most striking example is Aluminium (Al), but other elements fall into this general category:

Iron (Fe)

Renal disease results in failure or reduction of the production of erythroprotein. This in turns contributes to the anemia of renal failure and to an increase in tissue iron deposition. There may however also be iron losses which can be replaced by either oral or intravenous supply of iron salts, yet iron overload caused by repeated blood transfusions is a serious problem.

The effects of chronic renal disease on iron status are obviously complex and variable [6].

Zinc (Zn) and Copper (Cu)

Contamination of dialysate fluid by both Zn and Cu has been associated with severe haemolytic episodes.

Cobalt (Co)

Treatment of refractory anaemia with Co salts has been used but is associated with a toxic cardiomyopathy. Use of Co containing haematinic pharmaceuticals is not advised.

Chromium, Nickel and Cobalt (Cr, Ni, Co) and other metals

There is clear evidence of increased serum Cr, Ni and Co in renal patients on dialysis. These metals present as contaminants at low concentration in dialysate fluid, become bound to plasma proteins but cannot be excreted via the kidney as would happen in healthy subjects. Accumulation of Cr, in liver and spleen, has been demonstrated but measurements of tissue Ni and Co are not yet reported.

The clinical significance of these observations is not apparent. Both Ni and Cr are associated with skin hypersensitivity reactions. Patch testing of selected renal patients could be of interest.

Other metals present in stainless steel like Molybdenum (Mo) and Vanadium (V) may behave similarly. That is they may be low level contaminants of dialysate or other intravenous fluids, and in normal health these metals are excreted via the kidney.

Trace Elements as Nephrotoxic Agents

It is known that occupational and/or environmental exposure to "heavy metals" such as lead (Pb), cadmium (Cd) and mercury (Hg) is associated with renal damage. Similarly chromate and bromate are known to be nephrotoxic, in addition, certain compounds of gold (Au) and platinum (Pt) while of therapeutic benefit, also cause renal damage [7]. Investigation of possible exposure to these and other substances in otherwise unexplained renal disease, should be considered and previous as well as present occupational histories should be obtained.

Studies of blood levels of Pb and Cd during CAPD do not suggest that "heavy metal" contamination is a problem in standard treatment [2].

Contamination of Products given by Intravenous Injection

As well as dialysis fluid, all other fluids given by intravenous injection to renal patients, need to be examined for low level metal contamination. It is known that protein hydrolysates used for intravenous feeding contain numerous "metal impurities". The level of Al can be relatively high and is thought to have been associated with bone disease [8].

Plasma albumin solutions, coagulation factors and a number of additives such as concentrated phosphate solutions, have significant amount of Al, and possibly other metals [9].

Retention of aluminium by patients with compromised renal function is likely and may eventually cause problems. The extent of other trace element contamination of intravenous fluids is not known since manufacturers do not commonly determine the trace element content of their products.

Conclusions

Modern analytical methods when carefully applied can reveal a wide range of trace element abnormalities in renal disease. These may be quite unsuspected clinically and may be associated with non-specific degenerative changes.

Prevention of either nutritional deficiency or toxic accumulation of trace elements could be achieved by screening dietary and intravenous inputs. It is to be hoped that none of the changes in trace element metabolism which are now being uncovered will be of as much clinical importance as those associated with aluminium.

Careful clinical and laboratory studies are required, to establish the true extent of the disorders. To this end it would be valuable to organise a European based study of autopsy tissue obtained from various categories of renal patient. This would establish whether or not there were any important differences from the findings of the American/Australian study [4] and allow an extension of the range of elements investigated.

References

1. Kerr DNS and Ward MK: The history of aluminium related renal disease. In *Aluminium and other trace elements in renal disease.*

Editor, A. Taylor. Publisher Bailliere, London, 1986, 1-15.
2. Fell GS: Trace Elements in renal failure. In *Aluminium and other trace elements in renal disease*. Editor, A. Taylor. Publisher Bailliere Tindall, London, 1986, 325-331.
3. Versieck J: Trace elements in human body fluids and tissues. *Critical Reviews in Clinical Laboratory Sciences* 22:97-184, 1985.
4. Smythe WR, Alfrey AC, Craswell PW, Crouch CA, Ibels LIS, Kubo H, Nunneley LL and Harvey R: Trace element abnormalities in chronic uremia. *Ann Int Med* 96(2), 96:302-310, 1982.
5. Rodger RSC, Sheldon WL, Watson MJ, Dewar JH, Wilkinson R, Ward MK and Kerr DNS: Zinc deficiency does not cause sexual dysfunction in men with renal failure. In *Aluminium and other trace elements in renal disease*. Editor, A. Taylor. Publisher Bailliere Tindall, London 343-347, 1986.
6. Streicher E: Discussion, Iron metabolism. In "Trace Elements in Renal Insufficiency", in *Contributions to Nephrology* 38:174, 1984.
7. Bach PH, Bonner FW, Bridges JW and Lock EA (Editors): *Nephrotoxicity assessment and pathogenesis*. Publisher, Wiley Heysen, Chichester, 1982.
8. Klein GL, Alfrey AC, Miller NL, Sherrard DJ, Hazlet TK, Ament ME and Coburn JW: Aluminium loading during parenteral nutrition. *Amer J Clin Nutr* 35:1425-1429, 1982.
9. Fell GS, Shenkin A and Halls DJ: Aluminium contamination of intravenous pharmaceuticals and blood products. *Lancet* 1:380, 1986.