

Module 2.3

Metabolism of Minerals and Trace Elements

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Learning Objectives

- To list the trace elements which need to be supplied to patients receiving artificial nutrition;
- To know the effects of deficiency of trace elements;
- To understand the reasons why patients receiving artificial nutrition may have increased requirements;
- To understand the value and limitations of methods of assessing trace element status in patients receiving nutritional support.

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Key Messages

- Trace elements are an essential part of all diets, both in normal individuals and in those requiring nutritional support;
- Patients requiring intravenous nutrition should receive trace elements from the beginning of their IV nutrition;
- Requirements in disease are often greater than in health, to cope with increased metabolic requirements and increased losses;
- Optimising intake of micronutrients in nutritional support is difficult since laboratory tests are rarely sufficiently sensitive and specific in patients with an inflammatory response.

1. Trace Elements - biochemical function, effects of deficiency and methods of assessment

This is a large topic and readers are referred to textbooks of nutrition (1), and to the most recent Dietary Reference Intakes from the USA (2, 3) for a more detailed discussion.

1.1 Zinc

Zinc has three main types of functions, catalytic, structural and regulatory. Approximately 100 enzymes require zinc for their catalytic activity, especially the enzymes of protein and nucleic acid synthesis. This accounts for the importance of zinc in growth and tissue repair. Zinc also permits the folding of other proteins by binding to cysteine and histidine residues, forming zinc fingers. These have extensive roles in controlling gene transcription, and in facilitating enzyme action, although not actually catalysing the enzyme e.g. zinc - copper superoxide dismutase. Zinc may also directly affect gene expression e.g. metallothionein synthesis in the liver.

Zinc is absorbed after digestion of macronutrients in the gut. Absorption can be markedly affected by ingestion of large amounts of other elements such as iron or copper, or by the amount of phytate or fibre, which reduce the bioavailability. Homeostasis of body zinc is largely controlled by the amount of zinc absorbed or secreted into the gut. Zinc is mainly transported in plasma bound to albumin. Urine zinc is usually less than 10% of faecal zinc, unless there is increased muscle protein catabolism.

Deficiency of zinc is well characterised. Reduced growth in children is an early sign. Severe zinc deficiency gives rise to alopecia, diarrhoea, delayed sexual maturation, and eczematous skin rash especially on the face and in body flexures, and impaired appetite. There are also important effects on immune function.

The most widely used marker of zinc status is plasma zinc concentration which correlates reasonably well with intake, provided there is no inflammatory response. However, in a hospital population, surgery, infection, or other inflammatory disease cause an acute fall in plasma zinc. Changes in plasma zinc concentration must therefore be interpreted together with changes in the binding protein, albumin, and also changes in the acute phase response, possibly by measuring C-reactive protein at the same time. Other methods of assessing zinc such as the zinc concentration in erythrocytes has not proved useful, whereas zinc in hair is too susceptible to methodological variation. Enzyme activity has also not proved sufficiently specific. Organ failure does not lead to significant changes in zinc requirement, with the exception of major burns where exudative losses of zinc can be substantial.

1.2 Copper

Copper has primarily a catalytic role for certain metalloenzymes which act as oxidases. For example, cytochrome C oxidase is especially important in energy metabolism, lysyl oxidase produces cross-linkages in collagen and elastin, and ferroxidase oxidises iron to bind to transferrin for circulation in the plasma and delivery to the tissues.

Copper homeostasis is controlled by modulation of copper absorption from the small intestine and its excretion in the bile. Urinary losses are very low. Copper is transported in plasma bound to caeruloplasmin, which participates in tissue iron release.

Deficiency of copper is rare, but it has been observed in TPN and causes normocytic hypochromic anaemia, neutropenia and skeletal disturbances.

The best markers of copper status are plasma copper or caeruloplasmin, although the acute phase response will cause an increase due to increased caeruloplasmin synthesis. Concentrations also increase in pregnancy and with the oral contraceptive pill. Erythrocyte superoxide dismutase may be helpful, although it can be elevated in situations of oxidative stress.

1.3 Iron

The main function of iron is for oxygen transport within haemoglobin, although a substantial amount is also required for myoglobin function in skeletal muscle.

Iron status is largely maintained by regulation of absorption in the upper small bowel. Haem iron is absorbed separately and more efficiently than non-haem iron, which is improved by reducing agents such as vitamin C, which also form chelates with iron.

Mucosal cells regulate the amount of iron absorbed, which is then carried by transferrin to the tissues where uptake is controlled by expression of a membrane bound receptor for transferrin. Iron is stored in the liver and bone marrow in the form of ferritin.

The signs of iron deficiency become progressively severe, with microcytic hypochromic anaemia, impaired physical activity and endurance in adults and cognitive impairment in children.

There are many laboratory tests for iron status. Serum iron and iron binding capacity (transferrin) are widely used, but the concentrations of both of these are markedly reduced by the acute phase response. Serum ferritin is usually the best marker of iron status, but it is increased in the presence of an acute phase response. Soluble serum transferrin receptor increases in iron deficiency and it may be the best marker in inflammatory diseases, but it is not yet in widespread use.

Iron status is not directly affected by severe illness. There is however concern that excess iron provision may exacerbate certain bacterial infections, possibly by providing iron as a substrate for the microorganisms, and hence iron provision must be very cautious in such patients.

1.4 Selenium

Selenium functions through its presence in selenocysteine, which is incorporated into a number of proteins, selenoproteins. The functions of these are not fully elucidated but glutathione peroxidases are essential defence agents against oxidative stress, and iodothyronine deiodinases are central for thyroid hormone metabolism.

Absorption of selenium from the diet is very efficient - much is in the form of selenomethionine, a plant amino acid, or selenocysteine. Commercial selenium supplements in the form of selenite or selenate are well absorbed. All selenium species in the diet will eventually all be converted to selenophosphate, which is the precursor of selenocysteine. Excess selenium is excreted in the urine.

Inadequate selenium intake gives rise to a wide spectrum of diseases. Keshan disease is a cardiomyopathy of children in China and Kashin-Beck disease of cartilage in adolescents were the main syndromes from which the deficiency was first identified. In clinical nutrition, skeletal and cardiomyopathy have both been observed.

It seems likely that selenium deficiency alone does not cause obvious illness unless some other stimulus, such as a viral infection, is also present.

Assessment of selenium status is most frequently by use of plasma selenium, although plasma or erythrocyte glutathione peroxidase measurements are also widely used. Plasma selenium is affected by an acute phase response, but not as markedly as zinc or iron. Organ failure is not considered to have too much effect on selenium metabolism, although severe burns are associated with marked losses.

1.5 Chromium

Chromium increases the action of insulin, possibly through amplifying insulin receptor tyrosine kinase activity. This may lead to an improvement in glucose tolerance in some individuals.

Chromium is absorbed largely in the form of chromium³⁺. Homeostasis is mainly by altering the excretion in the urine.

A very small number of cases of chromium deficiency have been observed during TPN. They had weight loss, glucose intolerance, and peripheral neuropathy, which responded to chromium provision. Sub-clinical deficiency may lead to impaired glucose tolerance in type II diabetes, but further evidence is still needed regarding the significance of this.

Assessment of chromium status is extremely difficult due to the very low plasma concentrations and the difficulty in obtaining non-contaminated specimens. However plasma concentration may help in specialised laboratories. The best assessment may be the response of glucose and insulin to chromium supplements. Organ failure is not known to cause major effects on metabolism.

1.6 Molybdenum

Molybdenum is a co-factor for several oxidiser enzymes, especially sulphite oxidase and xanthine oxidase. These are of special importance in disposal of sulphite which otherwise causes neurological damage, and in catabolism of purines.

Deficiency of molybdenum is generally a genetic disorder. Nutritional deficiency has only been reported in one patient who developed tachycardia, headache and night blindness, which were corrected by molybdenum supplements.

Assessment is rarely done. Plasma concentration is very low and difficult to measure. The best markers are metabolic, molybdenum deficiency being linked to low serum urate, low urine sulphate and elevated urine xanthine and hypoxanthine. Since the primary route of excretion is the urine, renal failure will be associated with molybdenum retention and the risk of toxicity.

1.7 Manganese

Manganese metalloenzymes are involved in amino acid, cholesterol and carbohydrate metabolism. Glycosyl and xylosyl transferases are important in proteoglycan synthesis, which is required for bone formation.

Dietary manganese is poorly absorbed (less than 5%). It is transported in the blood bound to transferrin and albumin. Excretion is via the bile to the faeces, with little excretion in urine.

Manganese deficiency is extremely rare, and only under experimental conditions have signs of a scaly rash and low plasma cholesterol been observed.

The best estimates of manganese status are from whole blood manganese since this is less affected by haemolysis or contamination during collection. Plasma manganese may be helpful but collection of suitable specimens is critically important. Cholestatic liver damage leads to manganese accumulation, and this may reach toxic levels with subsequent accumulation in central nervous tissue and extrapyramidal syndrome. Many preparations of trace elements for TPN have contained excessive amounts of manganese, leading to toxicity, so monitoring is important, especially in long-term provision.

Trace elements are essential inorganic micronutrients, which are required in the diet in very small amounts but nonetheless they are critical both for maintenance of health and treatment of disease. The function of trace elements and effect of their deficiencies are summarised in Table 1. A more complete account can be found in various textbooks of nutrition (1, 4).

Table 1 Trace elements - Functions, biochemical model of action, effects of deficiency and methods of assessment (6)

	Function(s)	Biochemical modes of action	Effects of deficiency	Assessment of status	Comments
Zinc	Protein synthesis Control of differentiation	Enzyme cofactor "Zinc fingers" in DNA	Growth ↓ Hair loss Skin rash Immune function. ↓	Plasma zinc - with albumin and C-reactive protein	Plasma Zn falls in acute phase reaction
Iron	O ₂ transport Electron transport	Haem/myoglobin Cytochromes	Hypochromic anaemia Possibly increased resistance to infection	Serum iron/ IBC Serum ferritin with CRP Blood Hb and film	Serum Fe falls and ferritin increases in APR - care needed not to exceed IBC

Copper	Collagen/elastin synthesis Antioxidant	Lysyl oxidase Zn/Cu superoxide dismutase Caeruloplasmin	Subperiosteal bleeding Cardiac arrhythmia Anaemia Neutropenia	Plasma copper or caeruloplasmin with CRP	Plasma Cu increases in acute phase reaction
Selenium	Antioxidant Thyroid function Immune function	Glutathione peroxidase Tyrosine deiodinase T lymphocyte receptor expression	Cardiomyopathy Skeletal myopathy Nail abnormalities Macrocytosis Neoplastic risk ↑	Plasma Se RBC glutathione peroxidase Urine Se Whole blood Se Platelet glutathione peroxidase	Se depletion may be asymptomatic
Manganese	Not clear Some antioxidant	Enzyme cofactor Mitochondrial superoxide dismutase	Cholesterol↓ Red blood cells↓ Possibly mucopolysaccharide abnormalities	Whole blood Mn	Deficiency state not confirmed in man
Chromium	Carbohydrate metabolism	Insulin activity Lipoprotein metabolism Gene expression	Glucose intolerance Weight loss Peripheral neuropathy	Plasma Cr	Contamination free blood sampling required Cr is present as a contaminant of most TPN solutions Rarely measured
Molybdenum	Amino acid metabolism Purine metabolism	Sulphite oxidase Xanthine oxidase	Intolerance to S amino acids: - tachycardia - visual upset	Urinary hypoxanthine sulphite	
Iodine	Energy metabolism	Thyroid hormones	Hypothyroidism	Serum T ₄ T ₃ TSH	
Fluoride	Bone/tooth mineralization	Calcium fluorapatite	Dental caries	Urine excretion	Provision in nutritional support is controversial

2. Trace elements in clinical nutrition

2.1 Introduction

The provision of an adequate amount of trace elements is an integral part of all nutrition support regimens by both parenteral and enteral routes.

2.2 Individuals at risk of deficiency

By the time a patient commences nutritional support, he/she may already have developed a whole body depletion of one or more essential nutrients. The extent of this will depend on a number of factors:

- The nutritional state of the patient on admission to hospital. The pre-existing illness may have caused a period of anorexia, or inadequate digestion or absorption of nutrients;
- The duration and severity of inadequate nutritional intake whilst in hospital, as a result of surgery or other treatment;

- Any increased losses through small bowel fistula/aspirate (rich in zinc), biliary fluid (rich in copper) burn exudate fluid (rich in zinc/copper/selenium), or dialysate (rich in water soluble nutrients);
- Moreover, some individuals will have an increased daily requirement, partly to keep up with increased losses, and partly to meet metabolic requirements - these are particularly important when patients become anabolic after a period of catabolism or when normal growth resumes in a child.

Identification of potential micronutrient deficiencies should be part of the nutritional assessment of every patient, since conditions such as alcoholism, coeliac disease, inflammatory bowel disease, etc., predispose to such deficiencies. Students should make themselves familiar with the more common associations found in medical and surgical practice and be alert to their occurrence.

2.3 Clinical deficiency syndromes and sub-clinical deficiency states

“Classical” nutritional deficiency usually results in a complex syndrome of typical signs and symptoms, and these have now been fully characterized for each of the vitamins and trace elements. These syndromes were the basis on which the essential micronutrients were initially identified, and there is now a reasonable understanding of the nutritional consequences of severe deficiency, and the intake necessary to prevent clinically obvious deficiency from developing.

It is, however, now clear that as an individual develops progressively more severe depletion of one or more micronutrients, he/she will pass through a series of stages with biochemical or physiological consequences. The metabolic or physiological penalty of such a sub-optimal nutritional status is usually not clear, but the assumption remains that this impaired metabolism is likely to result in detrimental effects. Similarly, specific and localized tissue deficiencies can occur which can lead to pathological changes. Such situations can be defined as sub-clinical deficiency. The time course for development of a sub-clinical deficiency state varies for each individual micronutrient, and depends upon the nature and amount of tissue or body stores. The consequences of an inadequate intake are more clearly delineated in Figure 1.

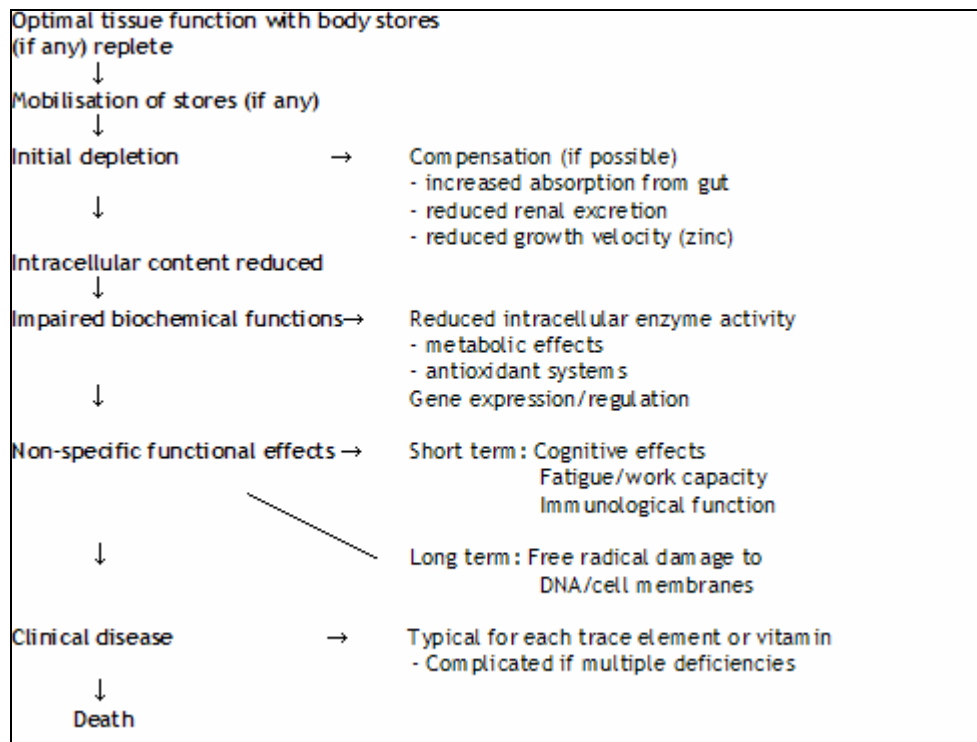


Figure 1 Consequences of inadequate micronutrient intake

A sub-clinical deficiency state can be either absolute or relative. Thus an intake less than the requirement in normal health will lead to sub-clinical deficiency, or to a typical clinical deficiency state. However, certain patients have significantly increased requirements as a result of their

disease process, and hence an intake normally regarded as adequate may be relatively insufficient and lead to a sub-clinical deficiency state. Most of the recommendations for vitamin and trace element supplements in TPN, and the content in enteral feeds, include an allowance for an increased requirement in disease.

2.4 Optimisation of provision of trace elements

Defining the optimal intake of micronutrients is far from ideal. It is possible to make a reasonable assessment of the requirements of an individual, based upon the requirements in health, the likely underlying nutritional state of the patient at the time of presentation, and the ongoing effects of the disease process. Such a level of provision using the enteral feeds and intravenous additives, which are currently commercially available, has been proved to be adequate in most cases to prevent the development of a deficiency state. However, provision of micronutrients to ensure the best possible tissue function remains poorly defined. Possible methods of trying to optimise provision in relation to function can be considered with respect to the antioxidant system, and also to the immune system.

It is to be expected that in the next few years, well controlled clinical trials will help to clarify the situations where increased provision of these micronutrients is or is not helpful, both in reducing the biochemical effects of reactive oxidant species (ROS), and also in altering complication rates and outcome in serious illness. Many of the disease states thought to be associated with ROS are chronic degenerative conditions, such as atherosclerosis and neoplastic disease. The increasing number of patients dependent on life-long TPN makes the long-term provision of adequate amounts of micronutrients an important part of nutritional therapy.

2.5 European Union Legislation and Enteral Nutrition

The European Union has issued a directive on Dietary Foods for Special Medical Purposes (FSMPs). This includes guidelines on vitamin and trace element content. In many cases, the minimum intake suggested for an individual with an energy intake of 2000 kcals is in excess of the reference intake in a normal population. This allows for the increased requirement of most individuals receiving enteral nutrition. The directive defines FSMPs as:

- **nutritionally complete standard formula** - which can be used as a sole source of nutrition - these must comply with the guidelines for micronutrient composition, as shown in Table 3 and Table 4;
- **nutritionally complete, nutrient adapted disease specific formula** - which also must be suitable as a sole source of nutrition;
- **nutritionally incomplete formulas** - which are not suitable as a sole source of nutrition.

Selection of the most appropriate tube feed often requires assistance from an experienced dietician. Students should be aware that although the micronutrient composition must lie within the ranges quoted, these are wide and they have been designed for a 2000 Kcal intake, which is rarely achieved enterally. Different commercial products can have quite different amounts of micronutrients. 1500 kcals of feed is an intake, which is more widely met in clinical practice. The range of amounts present in this amount of feeds, which are currently available in Europe, is therefore also shown as a guide in Table 2.

2.6 Trace elements in parenteral and enteral nutrition

Many of the trace elements now recognized as being essential for human nutrition have been better characterized as a result of studies in patients who were depending totally upon their intravenous intake during total parenteral nutrition (TPN), especially for prolonged periods.

The key features of an essential trace element are that its removal or inadequate supply in the diet is associated with reproducible structural or biochemical changes, and that these are reversible on provision of the element. This has been convincingly demonstrated in TPN for zinc, copper, selenium, iron, molybdenum, and chromium. In addition, there is good evidence of biochemical essentiality of iodine and of manganese, and the nutritional benefits of fluoride on bones and teeth. Cobalt is also recognized as being essential, although all requirements seem to be met by supply of vitamin B₁₂ alone.

A summary of suggested intravenous and enteral intakes of trace elements in nutritional support is provided in Table 2. It is important to note the significant difference between intakes by the intravenous and enteral routes, which are largely due to the efficiency of absorption from the gut.

Table 2 Trace Elements in parenteral and enteral nutrition

- Fresenius-Kabi
- Baxter Health Care
- Various commercially available standard feeds

	Units	IV Supplement		Enteral Nutrition		
		Additrac (1)	Decan (2)	EC Directive		Approximate amount (3) in feed providing 1500 kcal
				Minimum	Maximum	
Zinc	mg	6.5	10.0	10	30	15-23
	μmol	100	153	153	459	230-353
Copper	mg	1.3	0.48	1.2	10	2-3
	μmol	20	7.6	19	157	31-46
Iron	mg	1.2	1.0	10	40	20-30
	μmol	20	17.9	179	714	358-537
Manganese	mg	0.3	0.2	1	10	3-6
	μmol	5	3.6	18	180	54-108
Selenium	μg	30	70	50	200	70-112
	μmol	0.4	0.89	0.63	2.5	0.89-1.4
Chromium	μg	10	15	25	300	100-150
	μmol	0.2	0.29	0.48	5.8	1.9-2.8
Molybdenum	μg	19	25	70	360	150-225
	μmol	0.2	0.26	0.73	3.75	1.6-2.4
Iodide	μg	131	1.5	130	700	150-300
	μmol	1	0.012	1	5.3	1.2-2.4
Fluoride	mg	0.95	1.45	0	4	0-3
	μmol	50	76	0	210	0-156

2.6.1 Bioavailability of trace elements in enteral nutrition

The bioavailability of micronutrients is the efficiency with which each micronutrient is used in the body. It depends on absorption from the gut and utilization by the tissues. Gut factors are considered to be of most importance and depend on:

- Dietary composition e.g. the chemical form of a nutrient (iron in heme, selenium in selenomethionine); the presence of antagonistic ligands (e.g. phytate, fibre); and competitive interactions (e.g. iron, zinc and copper can compete for absorption);
- Luminal /mucosal factors;
- Redox state, dietary hydrolysis, and binding to amino acids or carrier proteins may all modify absorption.

2.6.2 Overprovision of trace elements

Excess trace elements may be provided inadvertently as contaminants of other nutrients - in TPN e.g. Al in Ca/P supplements, Cr in amino acids. Some older commercial trace element supplements contain excess manganese (> 5 μmol/d), which has been shown to be related to a toxicity condition in some patients after long-term use.

2.6.3 Assessment and monitoring of trace element status

An accurate assessment of trace element status during nutritional support is difficult, especially in seriously ill patients (5). Some guidelines are:

- Tests of plasma concentration are a poor reflection of tissue status;
- Plasma concentration of Zn, Fe, Se all falls during an acute phase response (APR), whereas Cu increases (see Fig. 2);
- Plasma concentration may be of value in stable patients without an active APR;
- For some elements, measurement of enzyme activity may be helpful e.g. red blood cell or plasma glutathione peroxidase as a marker of selenium status;

- Plasma concentration may be helpful in identifying over-provision.

2.7 Pharmaceutical aspects of provision of trace elements in intravenous nutrition

Care must be taken to minimize interactions between nutrients, or between individual micronutrients and the infusion bags or giving sets. Instability caused by trace elements is unusual, although there are limitations to the amount of inorganic iron which is stable in infusion mixtures. Chemical interaction with trace elements, especially the oxidative effect of copper on vitamin C is minimized by addition immediately before infusion.

2.8 Assessment and monitoring in clinical practice

Some tests commonly used to assess trace elements are included in Table 1. The acute phase reaction associated with trauma and infection markedly affects plasma concentration of many trace elements (Fig. 2).

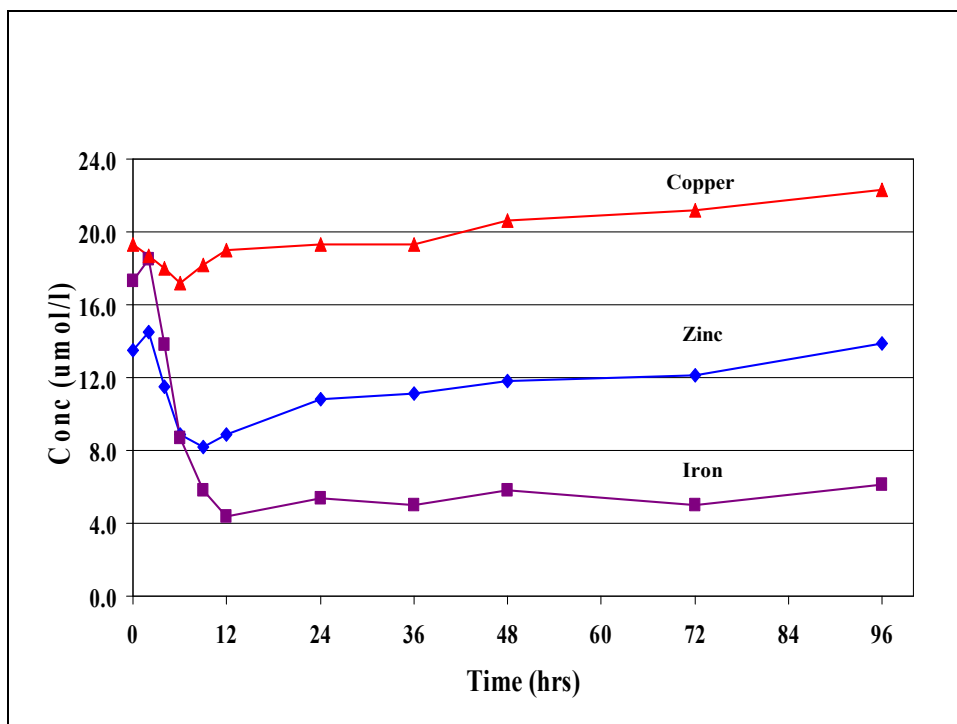


Figure 2 Changes in plasma iron, zinc and copper after elective surgery. Similar changes occur after any acute trauma, infection or inflammation

Because of the limitations in interpretation of these data, it is common practice, especially in patients receiving TPN, only to assess on a regular basis the status of zinc, copper, selenium (mainly in long-term nutritional problems) and iron. The other laboratory tests which are available to assess micronutrients are usually only used when there is a particular clinical problem where confirmation of micronutrient deficiency or excess is necessary. If such tests are not available, and a deficiency is suspected, a therapeutic trial of increased intake can usually be safely given if renal function and liver function are satisfactory. In patients receiving enteral nutrition or TPN where some intestinal absorptive capacity may still be present, an oral or enteral multi-mineral supplement may also be provided.

A two-week course of a well balanced micronutrient supplement is unlikely to cause any harm, and may occasionally be beneficial. Alternatively, an increase in intravenous supply can be given for a limited period, with careful clinical monitoring. In such cases a blood/plasma sample at the beginning of supplementation should be stored for possible analysis at a later date.

3. Summary

Trace elements are an essential part of all diets and should be given in full daily amounts with all forms of artificial nutrition. Requirements in disease, although difficult to quantify, are often greater than those in health. In some conditions, e.g. burns or small bowel fistulae, losses may be greatly in excess of normal and, in those who are likely to be already depleted an initial catch up replacement dose may be required. Although major deficiencies give rise to characteristic syndromes, it is possible that subclinical deficiencies, single or multiple, may affect clinical outcome adversely although more evidence is needed before this is established. Optimising intake of trace elements and minerals in patients undergoing nutritional support is difficult since laboratory tests often lack sensitivity and specificity in the presence of inflammation e.g. effects on Zn, Fe, and Cu blood levels. As a practical policy, therefore, it is wise to give at least the RDI, with additions to counteract any prior deficit, to meet continuing losses, and to meet the metabolic demands of the response to disease and injury.

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