PRESCRIBING TRACE ELEMENTS IN CLINICAL PRACTICE

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Editorial note:
There is great interest in, and sometimes controversy and confusion about, the clinical significance of trace elements. It is often difficult for health professionals to obtain reliable information. The Executive Editorial Board believes that this article is a unique and important reference source.

SYNOPSIS

Although most people in Australia are unlikely to suffer from acute trace element deficiencies in their diet, the intake of certain groups may be sub-optimal, while a greater number may be at risk from deficiencies arising as a consequence of their lifestyle, or from particular physiological or pathological conditions. Generally, improved trace element status is best achieved through better dietary practices, but in serious conditions of trace mineral depletion short-term oral or parenteral supplementation is indicated. Most trace elements are relatively non-toxic, but high intakes of some interfere with the availability and utilisation of others. All become toxic at levels of excess which vary with the individual trace element.

Biochemical role

Of the 100 or more elements in the biosphere, only 25 are essential for animal life, of which 14 are known as trace elements because they occur in biological tissue at concentrations less than 0.01%. Biochemically they function in many different ways, although most act in a regulatory capacity, forming part of complex metabolic systems which, if impaired, result in characteristic deficiency symptoms (Table 1).

Nutritional deficiencies

As a rule, the low level at which trace elements occur in the body reflects a correspondingly modest nutritional requirement, with the result that most trace elements are adequately supplied in the diet, particularly in Western countries, where food sources are varied and derived from different geographical regions (Table 1).

However, low levels of some elements do occur over broad areas, most notably iodine and fluorine, which can affect large communities even in developed nations, including Australia. Fortunately, both have been widely recognised and large scale supplementation programs through iodised salt (100 ppm) and fluoridated water (1 ppm) have all but eliminated the problem in Western countries.

Nevertheless, despite the fact that frank dietary trace element deficiencies are uncommon in Australia, some deficits have been noted in groups consuming poor quality diets through economic hardship or food faddism, as well as in individuals whose overall food intake is insufficient to supply their trace element requirements e.g. the elderly and some people on weight-reducing diets.

Compounding the problem is the more widespread occurrence of conditioned deficits, which arise as a consequence of factors which modify the availability or requirement of a trace element, so as to create a deficiency situation even in the presence of an apparent dietary sufficiency (Table 2).

Several conditioning factors of particular clinical significance are listed in greater detail in Table 3.

Diagnosis

Diagnosis of trace element deficiencies is often difficult, especially if the deficit is marginal. Estimates of nutrient intake provide useful information on a population basis. For the individual, variability in homeostasis and in nutritional requirements need to be taken into account. The availability of population-based centile distributions of nutrient intake (National Dietary Survey, 1983; Victorian Food and Nutrition Survey, 1985) allow the nutrient intake of an individual to be assessed in relation to these distributions when evaluating the likelihood of deficiency. The chemical analysis of accessible body tissues, although seldom unequivocal, does offer a more direct assessment of the individual status for several trace elements (Table 4). Measurement of the activity of a biological compound which is known to be dependent on the concentration of a trace element may also be of value e.g. activity of the selenium-containing enzyme glutathione peroxidase, or the levels of copper-containing ceruloplasmin or iodine-containing thyroid hormone.

The only definitive demonstration of a trace element deficiency lies in a positive chemical or biochemical response to supplementation. In practice, clinicians may believe that a short trial period of dietary enrichment is justified. It should be remembered that such trials are uncontrolled and that there is always a considerable potential for a placebo response.

Table 1

Essential trace elements

Trace element	*Biochemical function*	*Principal deficiency symptoms*	*Toxic intake (mg/day)*	*Toxicity symptoms*	*Mean Australian dietary intake (mg/day)*	*Recommended dietary intake (mg/day)*		*Food source and amount of trace element (mg/100 g fresh food)*
						Australia	*U.S.A.*	
Chromium (Cr)	Control of blood glucose	Impaired glucose tolerance in some undernourished infants and patients on TPN	Chronic > 100#	Growth depression, liver and kidney damage, cardiomyopathy#	0.06*	—	0.05–0.2**	Seafood 0.07; eggs, meat, whole grains 0.04
Cobalt (Co)	Component of vitamin B12	Anaemia	Chronic > 30	Polycythemia, thyroid hyperplasia, myxoedema, cardiomyopathy, heart failure. Potentiated by alcohol	Cobalt must be supplied as vitamin B12 (cyanocobalamin) in the human diet			
Copper (Cu)	Copper enzymes/proteins in oxidative metabolism and iron utilisation	Anaemia and bone disorders occasionally in infants. With adults, anaemia following excessive supplementation with zinc	Acute > 1000 Chronic > 10	Acute — vomiting, diarrhoea, shock, hypotension, renal and liver damage. Chronic — reduced absorption of zinc and iron	1.9	—	2–3**	Liver 8–12; shellfish 2–7; legumes 1–20
Fluorine (F)	Component of hydroxyapatite in bones and teeth	Reduced resistance to dental caries	Acute > 100 mg/L in water Chronic > 10 mg/L in water	Acute — angioedema and oedema of larynx. Polyarteritis nodosa. Chronic — mottled teeth, anorexia, exostoses	0.5–1.5 in non-fluoridated areas. Up to 3.5 with fluoridation	—	1.5–4**	Seafood 0.5; meat 0.1; fluoridated water 0.1
Iodine (I)	Component of thyroid hormone	Goitre, myxoedema and cretinism	Acute > 10 Chronic > 2	Acute and chronic — thyrotoxicosis, iodide goitre	0.7–0.8 including iodised salt	0.15	0.12–0.15	Milk contaminated with iodophores 0.1; seafood, meat, vegetables 0.03–0.07
Iron (Fe)	Iron enzymes/proteins in oxygen transport and oxidative metabolism	Anaemia, listlessness, reduced resistance to disease	Acute several grams Chronic > 500	Acute — vomiting, cyanosis, shock. Chronic — siderosis, liver and myocardial damage. Aggravated by alcohol	13.5	7–16†	10–18	Liver, meat 10–20; enriched breakfast cereals 10–20; green vegetables 2–8
Manganese (Mn)	Activator of many enzymes	In animals, reduced growth and fertility, bone and neurological disorders. Nothing definite in humans	Chronic — by inhalation of > 5 mg/m³ in ambient air	Neurological and psychological disorders	4.3	—	2.5–5*	Wheat bran 10; oatmeal 3–4; wholemeal bread 2–5
Molybdenum (Mo)	Molybdenum enzymes	In animals, reduced growth and uric acid synthesis. Nothing definite in humans	Chronic > 10	Possibly increased serum uric acid and gout	0.1–0.5*	—	0.15–0.5**	Meat 0.1–0.3; legumes 0.02–0.5; cereal grains 0.01–0.15
Nickel (Ni)	Possibly involved in membrane structure	In animals, reduced growth and anaemia. Nothing definite in humans	—	—	0.3–0.5*	—	—	Vegetables 2.5; whole grains 0.15; nuts 0.15
Selenium (Se)	Antioxidant function in part through enzyme glutathione peroxidase	In animals, reduced growth and muscular dystrophy. In humans, cardiomyopathy in children in China — Keshan's disease	Acute > 7 Chronic > 0.6	Acute — blindness, tetany, paralysis #. Chronic — gastric disturbance, dermatitis, brittle fingernails, hair loss, garlic breath, paraesthesia and polyneuritis.	0.11	0.07–0.085	0.05–0.2**	Brazil nuts 1.5; kidneys 0.35; seafood 0.07
Silicon (Si)	Possibly cross-linking agent in organic matrix of early bone	In animals, reduced growth and skeletal development. Nothing definite in humans	Chronic > 0.5	Silica urolithiasis, nephropathy #. Suggested cause of Balkan nephropathy in countries bordering River Danube	Up to 1200††	—	—	Whole grains, legumes approx 1000; meat 0.2 (connective tissues 5 times higher)
Tin (Sn)	Possibly involved in redox reactions	In animals, reduced growth. Nothing definite in humans	Chronic > 0.5	Nausea, vomiting, diarrhoea	0.2–3.5 — level depends on degree of consumption of food from unlacquered tinned cans	—	—	Acidic foods in unlacquered tinned cans 1–10; whole grains 0.5; nuts 0.25
Vanadium (V)	Possibly involved in redox reactions	In animals, reduced growth and increased blood cholesterol and triglycerides. Nothing in humans	Acute > 50	Intestinal cramps, vomiting, fever, chills	1–2*	—	—	Radish 0.08; other food < 0.01
Zinc (Zn)	Zinc enzymes involved in all aspects of metabolism and growth	Reduced growth, development, disease resistance and wound healing, skin lesions, birth defects and neurological disorders	Acute > 1000 Chronic > 150	Acute — nausea, vomiting, gastric pain, muscular incoordination, dizziness. Chronic — reduced copper absorption and copper deficiency anaemia.	11.6	12–16	15	Oysters 45; meat 4–8; nuts and legumes 2–4

#Animal data. No information on humans
*U.S.A. data
**Safe and adequate intakes (U.S.A.) not RDIs
†Lower value for men, upper for women
††U.K. data

Table 2

Aetiological factors capable of inducing trace element deficiencies in humans — 'conditioned trace element deficiencies'

Aetiological factor	*Mechanism of action*
Food processing	Loss of elements
Dietary constituents	Antagonism between elements, complex formation
Genetic disorders	Disturbed metabolism, decreased absorption, increased excretion
Medications (chelating agents, laxatives), drugs and alcohol	Disturbed metabolism, decreased absorption, increased excretion
Physiological conditions:	
(1) Disease (infection, parasitic infestation, intestinal, liver and renal disorders)	Redistribution within body, decreased absorption, increased excretion and loss
(2) Trauma (burns, haemorrhage, contusions)	Redistribution within body, increased excretion and loss
(3) Growth, pregnancy, lactation	Increased anabolic demand, hormonal effect
Total parenteral nutrition	Deficiency of element in infusion fluid
Dialysis	Excessive removal of element from blood

Thus, the clinical diagnostic sequence is:

1. Identify those at risk of micronutrient deficiency, namely where food intake is poor, bioavailability reduced or utilisation or losses increased (Table 2).
2. Estimate nutrient intake from food intake using food composition tables or computer software. Assess in relation to centile distributions of intake in apparently healthy populations. Take into account Recommended Dietary Intakes (RDIs). A dietition can assist with these assessments.
3. Where index of suspicion is high, perform tissue chemical analysis (see Table 4).
4. Where uncertainty persists or analysis is unavailable, conduct a therapeutic trial, preferably using a measurable outcome (e.g. enzyme activity). Keep in mind that an apparent clinical response may be a placebo effect.

As in other areas of clinical practice, no one line of assessment is usually sufficient in its own right.

Supplementation

Permanent correction of a nutritional trace element deficit is generally best accomplished by the deliberate inclusion in the diet of foods especially rich in the particular trace element, bearing in mind the amounts of the foodstuff that will be needed to provide the RDI (Table 1), which would ensure an adequate intake for almost all individuals.

In those cases where dietary modification is not feasible, therapeutic oral supplementation of the particular element in a readily absorbed and well tolerated form provides an acceptable alternative. Amounts should relate to the RDI, other than for repletion of body stores. In cases of severe deficiency, which sometimes accompany disease or trauma, or may be iatrogenically induced, parenteral therapy is recommended to provide an immediate, short-term improvement to nutritional status.

One of the problems with supplementation is the limited availability of both oral and parenteral preparations. For specific trace elements, oral formulations of fluoride (sodium fluoride 2.2 mg per unit), iron (as salicylate or gluconate, between 33 and 105 mg elemental iron per unit), selenium (selenenomethionine, 50 microgram elemental selenium per unit) and zinc (gluconate or sulphate, between 30 and 50 mg elemental zinc per unit) are available.

Table 3

Some aetiological factors of clinical significance

Aetiological factor	*Element affected*	*Clinical condition*
Genetic		
Menkes' disease	Copper	Disturbed copper metabolism resulting in mental retardation; abnormalities of muscle tone, bone and hair
Acrodermatitis enteropathica	Zinc	Impaired zinc absorption resulting in lethal zinc deficiency if untreated
Medications		
Laxatives	Zinc, copper, magnesium*	Uncommonly faecal zinc loss and zinc deficiency
Diuretics	Zinc, copper, magnesium*	Zincuria and mild zinc deficiency, anorexia and hypogeusia
Chelating agents e.g. penicillamine, ethylene diamine tetraacetic acid (EDTA)	Zinc, copper, magnesium*	Zinc deficiency, including skin lesions and alopecia. Copper deficiency with reduced haemopoiesis
Disease		
Inflammation	Copper, zinc	Mild copper and zinc deficiency
Diarrhoea	Zinc	Faecal zinc loss and zinc deficiency
Trauma	Copper, zinc	Mild copper and zinc deficiency

*Other trace elements may also be affected

Table 4

Normal values for tissue indices of trace element status in humans

Trace element	*Normal range*			*Preferred diagnostic index*
	*Serum**	*Urine*	*Hair***	
Chromium	0.1–1.0 microgram/100 mL	1–10 microgram/24 hr	0.5–1 microgram/g	Serum chromium
Copper	70–150 microgram/100 mL Ceruloplasmin: 20–40 mg/100 mL	32–64 microgram/24 hr	12–20 microgram/g	Serum copper or ceruloplasmin which represents 95% of copper
Iodine	Ionised: 0.01–0.3 microgram/100 mL PBI: 3.2–7.6 microgram/100 mL	Up to 465 microgram/24 hr	—	—
Iron	Female: 86–120 microgram/100 mL Male: 90–140 microgram/100 mL TIBC female: 250–350 microgram/100 mL TIBC male: 300–400 microgram/100 mL	0.06–0.1 mg/24 hr	—	Serum iron levels together with TIBC
Manganese	60–150 ng/100 mL	very low	1.5 microgram/g	Serum manganese
Selenium	10–50 microgram/100 mL	8–20 microgram/24 hr	13–140 ng/g	Serum selenium or erythrocyte glutathione peroxidase (normal value 12–40 units/g haemoglobin)
Zinc	80–145 microgram/100 mL	240–415 microgram/24 hr	90–200 microgram/g	Fasted serum zinc. Leucocyte zinc levels of some value but variable

* Serum or plasma

**Hair analyses are generally of limited value due to leaching out of minerals and contamination

As part of a formulation with vitamins and in accordance with RDIs, the Roche preparation 'Elevit RDI' has copper 1 mg, iron 5 mg, manganese 1 mg and zinc 7.5 mg per tablet unit for adults. Oral formula feeds for adult use may have no more than iron, although enteral feeds and infant formulae generally include copper, iodine, iron, manganese and zinc.

For parenteral supplementation, levels of trace elements for use in Australia have been recommended by the Australian Society for Parenteral and Enteral Nutrition.[1]

Toxicity

Although many trace elements are relatively non-toxic, the practice of dietary mineral supplementation does carry some risk. Unbalanced intakes can lead to competition and interference between elements at the level of absorption and physiological function, leading to an induced deficiency of one element by another. More importantly, all trace elements are toxic if taken in sufficient excess, the amount varying in relation to the efficiency of homeostatic control, and with the biochemical basis for toxicity. In some cases (e.g. iodine, iron, manganese, tin and zinc) homeostasis is good and comparatively high levels of the element are well tolerated. With others, notably fluorine and selenium, accumulation occurs more readily so that the range between safe and unsafe levels of intake is narrower (Table 1).

Elements of special interest

Iron:

In Australia, wheat is not routinely enriched with iron although some breakfast cereals are. Generally, dietary intakes of iron are adequate for men and for a proportion of menstruating women, but are inadequate during pregnancy. It is therefore frequently supplemented at levels around 80-120 mg/day, often together with folate (300 mg/day) in order to maintain or increase iron reserves. However, excessive dosages should be avoided as their possible adverse effect on zinc absorption has not been fully evaluated.

Selenium:

Selenium has lately attracted considerable attention as a possible agent in reducing the risk of cancer and coronary heart disease by protecting against free radical damage to DNA and diminishing the uncontrolled entry of oxidised low density lipoprotein from the blood into the arterial cells. However, these associations have not been well established in humans and in animal studies appear to require dietary intakes very much higher than the requirement in order to be effective. Overall, the dietary intake of selenium for most Australians seems sufficient not to justify special supplementation, particularly since selenium toxicity occurs at intakes only one order of magnitude greater than the RDI. National Health and Medical Research Council (NH&MRC) recommendations include that selenium and its salts in forms used as supplements should only be available on prescription (Schedule 4).

Zinc:

The recent wave of community zinc consciousness has led to massive self-medication with this element often at levels 5-10 times above the RDI, for treatment of a variety of conditions

including hypogeusia (diminished sense of taste), acne, lethargy, forgetfulness and growth retardation. While zinc intakes of some people (elderly, weight reducing dieters, vegans) may be sub-optimal, prolonged high intakes of zinc can interfere with the uptake of copper and lead to copper deficiency anaemia.

Boron:

Although not currently recognised as an essential trace element for humans and animals, a possible role has emerged recently for boron in improving calcium retention through an endocrine mechanism, which may be of importance in reducing the incidence of post-menopausal osteoporosis. Benefits appear to occur at boron intakes of 1.5-3.0 mg/day, which would be obtained from a diet rich in fruit and vegetables. NH&MRC recommends that boron and its salts for internal human use should only be available on prescription.

In any discussion of trace elements, mention should also be made of calcium and magnesium, even though they are macroelements and occur in the body at levels far higher than the trace elements. Dietary aspects of calcium are adequately covered in text books and journals.

Magnesium:

Magnesium is unlikely to be deficient in the average Australian diet but certain conditions, especially relating to reduced absorptive capacity of the intestine (malabsorption syndromes, surgical resection), loss of body fluids (prolonged diarrhoea, laxative abuse) and increased excretion (diuretic therapy, alcoholism, primary and secondary aldosteronism, diabetes) can lead to severe magnesium depletion which, because of the wide role of the element in many enzyme systems, results in disturbed muscular function (tremor, weakness, ataxia, tetany), gastrointestinal symptoms and cardiovascular aberrations (ventricular tachycardia, fibrillation and ectopic beats). When symptoms are slight, daily oral dosing of about 350 mg is recommended. With pronounced symptoms, intravenous magnesium (up to 700 mg/12 hr) should be given immediately, but needs to be monitored and is contraindicated in patients with renal or respiratory insufficiency, or with disturbance of cardiac conduction.

Conclusions

In practice, patients with trace element intakes significantly below the RDI, or with biological indices indicating sub-optimal nutrition should receive immediate attention by revised dietary practices or therapeutic supplementation. Postulated benefits associated with supranormal intakes of trace elements in providing added resistance to a wide range of diseases are not accepted nutritional practice and will need to be weighed against possible individual variations in requirement, personal lifestyle factors and the patient's psychological need for nutritional supplementation.

REFERENCE

1. Phillips GD. Vitamin and trace mineral supplementation for total parenteral nutrition. Trans Aust Soc Parenter Enteral Nutr 1984;1:22–4.

FURTHER READING

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(See also *Dental implications:* this page)

Dental implications

Prepared by Dr R. G. Woods of the Australian Dental Association.

Prescribing trace elements in clinical practice (page 39)

The trace element of most significance to dentistry is fluorine. Most domestic water supplies were low in this trace element but fluoride is now added to the domestic water supplies and reaches 10.5 million people (approximately 65% of the population of Australia).[1] The fluoridation of these water supplies has been most effective in reducing dental caries in Australia.

Fluoridation of water supplies has been introduced to all State capitals (with the exception of Brisbane), Darwin and the Australian Capital Territory.

The percentage of the population served by fluoridated water in each State and Territory is set out in Table 1.

Table 1

Percentage of Australian population served by fluoridated water

State or Territory	%
New South Wales	81.9
Victoria	71.1
Queensland	5.1
South Australia	69.8
Western Australia	84.2
Tasmania	67.7
Northern Territory	68.6
Australian Capital Territory	99.7

In November 1985 the National Health and Medical Research Council (NH&MRC) at its 100th Session adopted a report which followed a re-examination of a number of aspects of fluoride therapy including the use of fluoride supplements where the fluoride concentration of the domestic water supply was low.

Because available dietary fluoride from foodstuffs manufactured in fluoridated areas had increased since the NH&MRC previously made recommendations for fluoride supplement doses, these were modified:

'The Council further recommends that in areas with less than 0.3 ppm of fluoride in the domestic water supplies the following dietary fluoride supplements should be taken:

Age	*Daily fluoride supplement*
Two weeks– 2 years	0.25 mg
2– 3 years	0.5 mg
3–16 years	1.0 mg

While there is some evidence indicating that the use of fluoride supplements during pregnancy may give some protection against dental caries of the offspring, the weight of evidence does not support the use of such supplements. However, there is no contra-indication to a pregnant woman living in a non-fluoridated area taking fluoride supplements.'

REFERENCE

1. Barnard PD, ed. Facts & Figures Australian Dentistry 1986-87. Sydney: Australian Dental Association, March 1988.