

Physiological and medicinal zinc

Zinc is present in a number of products available from pharmacies and its efficacy in “boosting the immune system” has been much debated. In this article, **Pamela Mason** gives an overview of this important trace mineral and its possible uses



Shellfish are a good source of zinc

The human body contains around 2g of zinc. Approximately 95 per cent of this zinc is found within cells. About 57 per cent of the body pool is stored in skeletal muscle, 29 per cent in bone and 6 per cent in skin, but zinc is found in all body tissues and fluids.

Functions of zinc

Zinc is critical for the function of about 60 enzymes in humans. It is a co-factor in a range of biochemical processes, including the synthesis of deoxyribonucleic acid, ribonucleic acid and proteins. Zinc is required for the hepatic synthesis of retinol binding protein, the protein involved in transporting vitamin A. Without adequate zinc, symptoms of vitamin A deficiency can appear even if vitamin A supplements are taken.

Zinc also acts as an antioxidant, restricting endogenous free radical production and acting as a structural component of the extracellular antioxidant enzyme, superoxide dismutase. It also helps to protect against depletion of vitamin E and maintains tissue concentrations of metallothionein, a possible scavenger of free radicals.

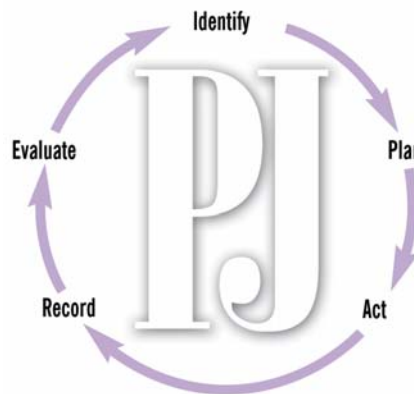
Other biochemical processes that require zinc include carbohydrate metabolism, protein digestion, blood clotting and bone metabolism.

Structural and regulatory role Zinc plays a role in the structure of biomembranes. A reduction in the concentration of zinc in these membranes results in increased susceptibility to oxidative damage and alteration in specific transport systems and receptor sites and these may underlie some of the disorders associated with zinc deficiency.

Zinc is also important for the structure of some proteins, known as “zinc finger proteins”. Polypeptides that are too small to fold by themselves can do so when stabilised by bound zinc. Zinc finger proteins regulate gene expression by acting as transcription fac-

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Identify knowledge gaps

1. What is the evidence behind using zinc for colds or wound healing?
2. What foods are high in zinc?
3. What is Wilson's disease?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in “Plan and record”, (available at: www.rpsgb.org/education). This article relates to “giving informed and accurate pharmaceutical advice”.

tors (binding to DNA and influencing the transcription of specific genes). Prostaglandins and nuclear receptors for steroids are also zinc finger proteins.

Zinc has regulatory roles in cell signalling and influences nerve impulse transmission. It also plays a role in apoptosis, a critical cellular regulatory process with implications for growth and development, as well as a number of chronic diseases.

Panel 1 (p272) describes current issues involving zinc.

Immune function Zinc is involved in the function of cells contributing to non-specific immunity, such as neutrophils and natural killer cells. Zinc also plays a role in T-lymphocyte function and in the development of acquired immunity.¹

Reproduction Zinc is essential for the metabolism of reproductive hormones (eg, androgens, oestrogens and progesterone), ovulation, testicular function, the formation and maturation of sperm, fertilisation and the health of the fetus and mother during pregnancy. Deficiency of zinc during early development can be teratogenic.

In men, the prostate gland has the highest concentration of zinc of any organ in the body.

Panel 1: Current issues involving zinc

Common cold The use of zinc lozenges within 24 hours of the onset of symptoms and every two to three hours while awake has been advocated for reducing the duration of the common cold. It is proposed that zinc binds with proteins of critical nerve endings in the respiratory tract and rhinovirus surface proteins to interrupt infection. However, results from randomised controlled trials in humans are conflicting. A meta-analysis of six RCTs reported no statistical benefit of using zinc lozenges to reduce cold duration.² Two additional analyses of RCTs of zinc for the common cold found that evidence is inconclusive.^{3,4} Up until 2005, a total of 10 RCTs were conducted to evaluate the use of zinc lozenges on the duration of colds. Of these, five showed a positive effect and five reported no effect.

Researchers have suggested that discrepancies may have been caused by inadequate placebo control and differences in lozenge formulation, administration and dosage. The amount of available ionised zinc, which varies with different lozenge formulations, could affect efficacy. For example, the addition of flavouring agents such as citric acid, mannitol or sorbitol to zinc gluconate lozenges decreases zinc ionisation (and hence its release) while the addition of glycine to zinc gluconate lozenges does not. Positive effects were generally associated with zinc gluconate or zinc acetate, while other forms of zinc were less effective.

Some researchers question the relevance of oral zinc because rhinoviruses replicate in the nasal mucosa. Zinc nasal preparations have also been investigated for the common cold. One study showed that a zinc nasal gel reduced cold duration compared with placebo when used within 24 hours of onset of symptoms,⁵ although another study showed no effect of a zinc nasal spray on duration of cold symptoms.⁶

Taking lozenges every two to three hours while awake may result in daily zinc intakes above the safe upper level of 25mg/day. Short-term use of zinc lozenges (up to five days) has not resulted in serious side effects but some individuals experience gastrointestinal irritation. Use of zinc at above the safe upper level for over six weeks is not recommended and may lead to copper deficiency.

Wound healing Zinc supplementation is valuable for wound healing where there is zinc deficiency or malnutrition. According to one review,

zinc administered orally or topically to wounds can promote healing and reduce infection.⁷ In patients with low serum zinc levels, topical zinc oxide has been shown to promote cleansing and re-epithelialisation of leg ulcers, reducing deterioration of ulcers and infection risk.⁸ One Cochrane review assessing six placebo-controlled trials of zinc supplementation in arterial and venous leg ulcers found no overall benefit on the number of ulcers healed⁹ but, in people with low serum zinc levels, there is some evidence that oral zinc might improve healing of leg ulcers.

Male fertility It has been reported that infertile men have reduced seminal and serum zinc levels compared with fertile men. However, other research has shown no statistically significant relationship between zinc in serum or seminal plasma and semen quality or IgA or IgG antisperm antibody. In the same study, zinc levels had no influence on sperm capacity to penetrate cervical mucus *in vitro* or *in vivo* and had no effect on subsequent fertility.¹⁰

Age-related macular degeneration Several studies have investigated the effects of zinc and antioxidant vitamins on the progression of age-related macular degeneration. The highest profile study is the age-related eye disease study (AREDS) in which 80mg of zinc daily (about 10 times the RNI) together with other antioxidants were shown to reduce the risk of progression to advanced AMD among patients who already had extensive signs of degeneration.¹¹ A Cochrane review looking at the evidence to date (including AREDS) concluded that current data are insufficient to state that antioxidant vitamin and mineral supplementation should be taken during early signs of the disease and said that more research is needed.¹²

Anorexia nervosa Zinc status is compromised in people with anorexia, partly due to poor food intake. It has been argued that zinc deficiency is a cause of anorexia, but it is also possible that poor zinc status exacerbates the condition. In patients with anorexia, zinc supplementation (50mg daily) has been shown to reduce anxiety and depression, prevent further weight loss and improve weight gain.¹³

Vision Present in high concentrations in the eye, particularly in the retina and choroid, zinc plays a role in the maintenance of vision.

Sources of zinc

Foods vary widely in their zinc content. Concentrations can range from 0.02mg/100g for egg white to 1mg/100g for chicken and 75mg/100g oysters. Shellfish and red meats are good sources of zinc. The bioavailability of zinc is high in these foods because of the relative absence of compounds that inhibit zinc absorption (eg, phytic acid) and the presence of amino acids, such as cysteine and methionine, that enhance absorption.

Wholegrain cereals are relatively rich in zinc but nearly 80 per cent of it can be lost in the wheat milling process. Nuts and legumes are also good sources of zinc. The zinc concentration in plant sources might be enhanced if plants are grown in zinc-rich soil. However, zinc in plants is less bioavailable than that in animal sources because of the high content of phytic acid. Fermentation of wholemeal bread reduces the phytic acid content and significantly improves zinc absorption. Leavened breads, therefore, have more bioavailable zinc than unleavened breads. Techniques used for cooking breakfast cereals seem to inhibit

degradation of phytic acid in the gut and results in less efficient absorption of zinc.

Supplements Many over-the-counter multivitamin and mineral supplements contain zinc. Those sold in pharmacies commonly contain a daily dose of 5–15mg of elemental zinc. Elemental zinc is also available as single supplements in the form of zinc acetate (30 per cent), zinc amino acid chelate (10 per cent), zinc gluconate (14 per cent), zinc orotate (17 per cent), zinc picolinate (35 per cent) and zinc sulphate (23 per cent).

Human requirements

Zinc requirements are based on a number of different indicators because a sensitive indicator of zinc status is not available. In the UK, these indicators include measurement of zinc losses in faeces, urine, skin, hair and menstrual blood or semen during metabolic studies of zinc deprivation. Turnover time of radio-labelled endogenous zinc pools and deduction from metabolic studies of patients receiving total parenteral nutrition (TPN) are also used.

Minimal zinc losses have been estimated to be 2.2mg/day in men and 1.6mg/day in women. Based on 30 per cent absorptive efficiency, these figures correspond to estimated

average requirements (EARs) of 7.3mg/day in men and 5.5mg/day in women. The reference nutrient intakes (RNIs) are 9.5mg/day for men and 7.0mg/day for women while lower reference nutrient intakes (LRNIs) are 5.5mg/day for men and 4.0mg/day for women.

Mean intake of zinc in the UK is 10.2mg/day in men and 7.4mg/day in women. Overall intakes are, therefore, higher than the RNI. However, 43 per cent of men and 45 per cent of women fail to achieve the RNI. In addition, 4 per cent of both men and women fail to achieve the LRNI, a level that fulfils the requirements of relatively few people and below which deficiency is likely to occur.¹⁴

The EU recommended daily amount (RDA) for zinc is 15mg. This is judged to be sufficient for most people. However, this is an approximate figure, based on the requirements of adult men, and does not take into account the needs of other population groups.

Zinc deficiency

Serious zinc deficiency is rare in the UK, but inadequate intake and marginal deficiency are not uncommon. Clinical manifestations of severe zinc deficiency include growth retarda-

Zinc deficiency can develop as a result of diseases, such as sickle cell anaemia, Wilson's disease, cirrhosis, or malabsorption syndromes

tion, delayed sexual maturation, hypogonadism, diarrhoea, alopecia, skin lesions and nail dystrophy. Immune system deficiencies and susceptibility to infection, behavioural disturbances, impaired taste, delayed wound healing, impaired appetite and food intake may also indicate zinc deficiency. Eye lesions, photophobia and lack of adaptation to the dark can occur.

Mild or marginal deficiency is more difficult to characterise. However, there is likely to be a graded response to progressive degrees of deficiency. Thus, while growth may cease in severe deficiency, growth may slow in mild deficiency. Maternal zinc deficiency before and during pregnancy is associated with intrauterine growth retardation, low birthweight, teratogenicity and increased risk of miscarriage and stillbirths. Zinc deficiency is also associated with increased morbidity, pre-eclampsia and toxæmia.

There is no reliable clinical test to determine zinc deficiency. Serum or plasma zinc on its own is neither sensitive nor specific. This is because zinc is primarily found intracellularly. The small proportion in the plasma is bound to plasma proteins. Plasma zinc is influenced by conditions unrelated to zinc status (eg, infection and inflammation) and does not

Panel 2: Zinc and its medical uses

Wilson's disease Wilson's disease is an inborn defect of copper metabolism, where the protein (caeruloplasmin) that normally forms complexes with copper is deficient. In patients with Wilson's disease, free copper is deposited in the liver (causing cirrhosis and jaundice) and brain (causing mental retardation and parkinsonism).

Penicillamine is generally regarded as the drug of choice for the initial management of Wilson's disease because it produces a rapid reduction in copper levels. However, it can exacerbate neurological symptoms so some practitioners suggest starting with zinc. Zinc prevents the absorption of copper. It induces synthesis of metallothionein in the intestine so that absorption of copper from the gastrointestinal tract is blocked. It is usually given as the acetate because this form is less irritating to the stomach than zinc sulphate.

Zinc is not suitable for those requiring rapid reduction of copper levels because it has a slow onset of action. Once a negative copper balance is achieved, maintenance therapy must be continued for life. Zinc, penicillamine or trientine can be used for maintenance, but the adverse effects of penicillamine are often a problem during long-term use and zinc is often preferred. However, prospective RCTs have not been conducted.

When transferring to zinc therapy from penicillamine, the British National Formulary suggests that the two treatments should be co-administered for two to three weeks until zinc takes maximum effect. Zinc therapy should be initiated under specialised supervision.

Topical preparations Zinc oxide is a constituent of several traditional skin preparations (eg, zinc and castor oil ointment, zinc and coal tar paste, zinc and ichthammol cream, and zinc and salicylic acid paste). Zinc oxide is claimed to have antiseptic, astringent and soothing properties and provides a mechanical protective barrier on damaged skin. These preparations have been popular for several generations.

Zinc preparations have been investigated in herpes infections. Zinc sulphate gel, zinc sulphate solution and zinc oxide cream have all been found to be effective in herpes simplex infections if started as soon as possible after the onset of the attack.

Zinc is also found in topical combination products for acne, containing erythromycin and zinc acetate. Within the first 12 weeks'

treatment, significant benefits (in terms of severity grades and papule, pustule and comedone counts) have been observed, with the combination product being more effective than topical preparations containing erythromycin alone. Research in the 1970s and 1980s looked at the effect of oral zinc sulphate in acne, with mixed results. No further research on oral intake has been conducted since 1989.

Zinc sulphate eye drops are another traditional topical preparation. They have astringent properties and were at one time used for red, irritated eyes. They are still available but are little used.

Zinc sulphate Zinc sulphate is available on prescription, but should be given only when there is good evidence of deficiency or in zinc-losing conditions (eg, malabsorption, burns). Zinc sulphate tablets (eg, Solvazinc) may be given until clinical improvement occurs. In cases of severe malabsorption or zinc loss they may need to be continued. TPN regimens usually contain only trace amounts of zinc. If necessary, further amounts of zinc can be added to TPN feeding regimens. A suggested dose for intravenous nutrition is elemental zinc 6.5mg (100µmol) daily.

Oral zinc sulphate has been investigated for the treatment of warts. One open label RCT involving 80 people compared oral zinc sulphate up to a maximum of 600mg/day with placebo. Treatment continued until the warts resolved or for a maximum of two months. Zinc sulphate significantly increased the proportion of people who had complete resolution of their warts at two months but this trial had several design flaws.

Zinc bandages Zinc paste bandage remains one of the standard treatments for leg ulcers and can be left undisturbed for up to a week. These bandages can be used under appropriate compression bandages or hosiery in chronic venous insufficiency. Containing zinc oxide, these bandages have antiseptic and astringent properties and are used to treat the skin around the leg ulcer and to act as a protective buffer between the skin and compression bandage. Zinc paste is also combined in bandages with calamine, coal tar or ichthammol for use in chronic skin conditions such as eczema where occlusion is indicated.

fluctuate with modest changes in dietary zinc intake. Until better markers are developed, an estimate of zinc status can be made from a combination of dietary zinc intake and plasma zinc concentration. If usual intake is below the EAR and plasma zinc is low, poor zinc status can be considered possible.

Zinc deficiency can result from inadequate dietary intake, poor absorption or increased loss. Vegetarians are at risk because the high levels of phytic acid in plant foods reduce the absorption of zinc. Some patients receiving TPN have been reported to develop symptoms of zinc deficiency. Zinc deficiency can also develop as a result of diseases, such as sickle cell anaemia, Wilson's disease (see Panel 2, p273) and cirrhosis, or recurrent infections. It is also associated with anorexia nervosa and alcoholism.

Malabsorption syndromes such as coeliac disease or chronic diarrhoea and inflammatory bowel conditions, such as Crohn's disease and ulcerative colitis, can lead to increased zinc losses and zinc deficiency in this way. Other conditions of increased zinc loss include severe burns, major surgery and HIV or AIDS.

Diabetes, particularly if poorly controlled, is associated with increased zinc loss in urine, reduced absorption and decreased total body zinc. However, the role of zinc and the influence of zinc deficiency in diabetes is currently unclear. It has been suggested that zinc deficiency may exacerbate destruction of islet cells in type 1 diabetes and adversely affect synthesis, storage and secretion of insulin — processes that require zinc. Zinc supplementation is sometimes used in diabetes to try to prevent deficiency, but it is not yet known whether this is of benefit in preventing or treating diabetes.

Interactions and toxicity

Zinc can interact with a number of other minerals, foods and medicines. High intakes of dietary calcium and calcium supplements have been shown to impair zinc absorption in some studies, but not others. Supplemental iron at prescription doses reduces zinc absorption. Long-term folate supplementation may also reduce zinc levels. Thiazides, loop diuretics and, possibly, angiotensin-converting enzyme inhibitors increase urinary excretion of zinc and the possibility of zinc deficiency during long-term use of these drugs should be considered.

High zinc intake (100–150mg/day) reduces copper absorption by competition. Zinc forms complexes with tetracyclines, quinolones and also non-steroidal anti-inflammatory drugs and doses should be separated by two hours. Acute zinc toxicity is rare, but typical signs include epigastric pain, diarrhoea, nausea, vomiting, bad taste and discomfort in the mouth and throat. Doses above 200mg/day are typically emetic and may be vomited before absorption can occur. The major consequence of chronic long-term ingestion of excessive zinc supplements (ie, 100–150mg zinc/day) is induction of a secondary copper deficiency with anaemia and neutropenia. Impaired



Zinc supplements commonly contain a daily dose of up to 15mg of elemental zinc

immune function and an adverse effect on the ratio of low-density lipoprotein to high-density lipoprotein cholesterol can also occur.

The UK Food Standard Agency's Expert Group on Vitamins and Minerals has set a safe upper level for zinc from supplements alone of 25mg daily. This level applies to long-term use of supplements in the normal healthy population. It does not apply to patients who receive zinc on prescription. Panel 2 (p273) discusses the medical uses of zinc.

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Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Compare the recommended dose of zinc sulphate used for zinc deficiency with that of zinc acetate used for Wilson's disease.
2. Make your staff aware of the zinc-containing products available in your pharmacy.
3. Make a list of people you would consider might need extra zinc.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt?

How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?