SAFETY OF MICRONUTRIENTS

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Micronutrients and their role in the prevention and treatment of disease are currently enjoying tremendous growth and interest. These nutrients may have functions other than the ones accepted up to now (i.e. gene regulatory functions) and their requirements for the maintenance of optimal health may be different from those for the prevention of conventional deficiency states.[1] Marginal micronutrient status can adversely affect morbidity and mortality, and although increased micronutrient intakes (in the form of dietary supplementation) in excess of the recommended dietary allowances (RDAs) may have beneficial effects in specific situations, such high intakes demand extreme caution in terms of long-term safety.

Since there is no satisfactory internationally accepted standard for the intake of micronutrients, the RDAs are used by most. These levels are by definition safe, but are designed to meet the needs of practically all healthy individuals. Various studies have been performed to determine a safe daily level for prolonged intake of vitamin supplementation in adults. Table I summarises the proposed safe level of intake in relation to the RDA for a specific vitamin. There appears to be a considerable margin of safety with most of the vitamins and, with the exception of adverse reactions after the long-term excessive ingestion of vitamins A, D and B_6, most of the side-effects that occur with vitamin supplements are rapidly reversible on withdrawal of the supplementation and leave minimal or no lasting effects.[2]

Table I. RDAs and safety levels in adults

Vitamin	RDA	Safe level of intake
Fat-soluble vitamins		
Vitamin A	1 000 µg RE	Approx 10 x RDA
Vitamin D	5 µg	Approx 10 x RDA
Vitamin E	10 mg	Over 100 x RDA
Vitamin K	70 - 140 µg	Approx 50 x RDA
Water-soluble vitamins		
Thiamin	1.4 mg	Over 100 x RDA
Riboflavin	1.6 mg	Over 100 x RDA
Niacin	18 mg NE	Approx 100 x RDA
Pyriodoxin	2.2 mg	100 x RDA
Folic acid	400 µg	Over 50 x RDA
Vitamin B_{12}	3 µg	Over 100 x RDA
Vitamin C	60 mg	Approx 100 x RDA

Adopted from reference 2.

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VITAMIN A

Clinical vitamin A deficiency (VAD) is one of the leading causes of childhood blindness.[3] It is, however, not only clinical vitamin A deficiency that is considerd of importance. In recent years, even marginal vitamin A deficiency has been linked to decreased immune function with subsequent increased predisposition to infections, poor growth, and iron deficiency anaemia (IDA). Vitamin A deficiency therefore plays an important role in child survival not only because it affects the severity of infections,[3-5] but also because vitamin A supplements administered to improve vitamin status are well documented to impact beneficially on childhood mortality.[3,6-8]

Treatment of clinical VAD

The treatment schedule for all stages of xerophthalmia, per age category, is outlined in Table II. The doses should be administered orally and should start immediately after diagnosis.

Table II. Treatment schedule for xerophthalmia for all age groups

Timing	Vitamin A dosage
Immediately after diagnosis	
< 6 months of age	50 000 IU
6-12 months of age	100 000 IU
> 12 months of age	200 000 IU
Next day	Same age-specific dose
2-4 weeks later	Same age-specific dose

Adopted from references 14 and 26.

Prevention of subclinical VAD

Various approaches to the prevention and treatment of subclinical VAD are available. They include, among others, supplementation, food fortification, dietary diversification/modification, promotion of breast-feeding, addressing conditions of public health importance, i.e. measles immunisation, parasitic control and oral rehydration,[7,9] and education on nutrition and health, with special emphasis on vitamin A. An interpersonal approach, the mass media, teacher programmes and medical personnel[10] are used to educate the public.

Periodic high-dose supplementation of vitamin A, whereby vitamin A reserves in the body are maintained at an optimal level, can only be considered a short-term solution to the problem of VAD.[9,11] Up to 30 - 50% of a 200 000 IU dosage is stored in the body for approximately 180 days (a protection period of about 6 months).[10]

Vitamin A supplementation programmes can be divided into two categories. Firstly, universal/mass supplementation programmes, which involve the periodic administration of large doses of vitamin A to all preschool-age children, children and adults living in high-risk areas, or all mothers living in high-risk areas within 4 weeks after delivery (Tables III, IV). Secondly, targeted or selective supplementation programmes, which are aimed at repleting vitamin A reserves drained by chronic or repeated infections, thereby protecting the high-risk child from vitamin A deficiency. Such programmes, therefore, target (*i*) susceptible age groups through the existing health services infrastructure; (*ii*) specific diseases in children (i.e. measles, protein-energy malnutrition, acute respiratory infections, and diarrhoeal disease); (*iii*) children with intestinal infestation with accompanying impairment of the absorption of supplementary retinol;[12] and (*iv*) very-low-birth-weight children.[9,13,14]

Table III. Prevention of vitamin A deficiency

Age category	Vitamin A dosage
Universal/mass supplementation programmes	
Infants < 6 months of age	
Non-breast-fed infants	50 000 IU orally
Breast-fed infants whose mothers have not received vitamin A supplements	50 000 IU orally
Infants 6-12 months of age	100 000 IU orally (every 4-6 months)
Children > 12 months of age	200 000 IU orally (every 4-6 months)
Targeted/selective supplementation programmes	
VLBW babies	1 500 - 2 800 IU/kg/day
Infants < 6 months of age	50 000 IU orally (every 4-6 months)
Infants 6-12 months of age	100 000 IU orally (every 4-6 months)
Children > 12 months of age	200 000 IU orally (4-6 months)

Adapted from references 14 and 26.

A single oral dose of vitamin A should be sufficient for 8 - 12 weeks.[15] However, whether vitamin A supplements should be given every 6 months or 4 months depends on a number of factors which may influence compliance. Moreover, the protective effect of supplementation seems to be greater with smaller frequent doses as compared with one large dose.[16] It would also appear that the effect of repeated (weekly) supplements is cumulative with the protective effect increasing after every dose.[11,17-20] Unfortunately, this mode of more frequent, small-dose supplementation can only be effective in the presence of an optimal infrastructure so as to ensure compliance.

Side-effects of vitamin A

Certain individuals are more susceptible to vitamin A toxicity than the general population owing to predisposing conditions such as viral hepatitis, cirrhosis and other forms of liver disease.[21] The dose and duration of exposure, as well as the age

Table IV. Vitamin A supplementation during pregnancy and lactation

Period	Vitamin A dosage
Safe vitamin A dosage during pregnancy	
Prevention	10 000 IU daily or 25 000 IU weekly
Treatment of night blindness/Bitot's spots	5 000 - 10 000 IU daily for 4 weeks
Treatment of severe xerophthalmia	200 000 IU divided in 3 dosages (as per Table II)
Safe vitamin A dosage postpartum	
Breast-feeding mothers	200 000 IU within first 60 days
	100 000 IU daily thereafter
Non-breast-feeding mothers	200 000 IU within the first 28 days
	10 000 IU daily thereafter

Adapted from reference 25.

of the individual, affects the adverse symptoms experienced. Vitamin A toxicity can be categorised as either acute, resulting from high doses (500 000 IU or 100 times the RDA) consumed over a short period of time, or chronic, as a result of long-term intakes of lesser amounts (50 000 - 100 000 IU per day for adults and 18 000 - 60 000 IU per day for children) and the tendency of vitamin A to accumulate.[21-23]

Acute intoxication, occurring within hours or at most a day or two after intake of a very large dose, is almost always accompanied by headache, as a result of increased intracranial pressure.[23] Other signs and symptoms in children include anorexia, bulging fontanelles, drowsiness, irritability and vomiting.[21] These symptoms should disappear within 12 - 24 hours without any specific treatment apart from stopping the next dose.

The essential feature of chronic hypervitaminosis A is peeling of the skin and bone pains, especially in the long, tubular bones.[23] Chronic vitamin A toxicity in children presents with alopecia, anorexia, bulging fontanelles, craniotabes, premature epiphyseal closure, pruritus and skin desquamation. Hepatomegaly and liver cirrhosis can also occur owing to excessive deposition of retinyl esters in the liver, leading to collagen deposition.[21]

Vitamin A in pregnancy

Since vitamin A is essential for growth and development, increased requirements occur during pregnancy. Breast-milk from vitamin A-deficient mothers is likely to contain insufficient vitamin A to maintain vitamin A stores in the infant. Since 90% of vitamin A in human milk is absorbed,[24] the vitamin A status of infants has been shown to improve with maternal supplementation. Advantages of maternal supplementation as opposed to direct supplements to the infant include improved safety (since the infant receives relatively low doses of vitamin A through breast-milk over a long period of time, instead of a single large dose), improved compliance, because of a reduced number of contacts necessary, and benefits accruing to both mother and child.[24]

In 1998, the WHO[25] recommended (Table IV) a safe vitamin A dosage for supplementation during pregnancy and lactation in areas where VAD is endemic. Treatment of clinical signs of VAD depends on the severity of the deficiency. Women of childbearing age with nightblindness or Bitot's spots should receive a daily oral dose of 5 000 - 10 000 IU vitamin A for at least 4 weeks. If severe signs of xerophthalmia are present, irrespective of whether the woman is pregnant or not, the high-dose treatment schedule (Table II) is advisable.

Vitamin A supplementation to postpartum mothers living in vitamin A-deficient areas is regulated by the safe period of postpartum infertility. In breast-feeding mothers, high-dose vitamin A supplementation can be administered up to 60 days postpartum. Thereafter, the daily intake should not exceed 10 000 IU. In the non-breast-feeding mother, the high-dose supplement can be administered up to 28 days postpartum, thereafter 10 000 IU daily.[25]

Excessive doses of vitamin A administered during pregnancy have been controversially associated with teratogenic effects, depending on the concentration and stage of gestation. Women exposed to high doses of preformed retinoic acid derivates (> 10 000 IU retinol daily) within the first 6 weeks of pregnancy, are reported to have a higher incidence of spontaneous abortion, premature delivery and babies with central nervous system, craniofacial and cardiac development malformations. This probably results from the fact that retinoic acid acts as a ligand that binds to a nuclear hormone receptor, thereby affecting gene function at the critical periods of organogenesis and embryonic development.[25,26] The current recommendation of a daily intake of 10 000 IU retinol throughout pregnancy is considered to be safe for women who do not habitually take vitamin A at the level of the RDA (8 000 IU). There is no justification for a vitamin A supplement in cases of adequate dietary vitamin A intake.[27]

Vitamin B_6

Vitamin B_6 is a water-soluble vitamin required for the metabolism of protein, fat and carbohydrate. Because vitamin B_6 is required for amino acid metabolism, the need for the vitamin is related to protein intake. Symptoms of vitamin B_6 deficiency

in humans include poor growth, anaemia, impaired immune response and convulsions.[27,28]

Vitamin B_6 is well known to be associated with alleviating symptoms of the premenstrual syndrome. Recently a relationship between vitamin B_6 and cardiovascular health has also been suggested on the basis of abnormal homocysteine metabolism. The metabolism of homocysteine to methionine involves three enzymes, namely vitamin B_6, vitamin B_{12} and a folic acid-containing enzyme. A defect in any of these enzymes (especially for vitamin B_6-dependent enzymes) can cause homocystinaemia. The latter may contribute to atherosclerosis in humans.[27]

Large intakes of pyridoxine (2-6 g/day) have been associated with the development of sensory neuropathy. The neuropathy is usually reversible on discontinuation of pyridoxine.[2] An intake of 50 - 100 X the RDA for up to 6 months appears to be safe.[27]

Folic acid

Folic acid is a precursor of certain important enzyme cofactors required for the synthesis of nucleic acids and the metabolism of certain amino acids. An insufficient intake results in the inability to produce deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and certain proteins, resulting in impaired cell growth. Because the demand for folic acid is highest during periods of rapid growth, the risk of deficiency is highest during growth phases and is therefore prevalent in newborn infants, pregnant women and adolescents. The elderly is another high-risk group because their dietary intake is often inadequate.[29] Folic acid supplementation is associated with a decreased incidence of neural tube defects[30] as well as reduced risk for cardiovascular disease by lowering homocysteine levels.[28]

Very high levels of intake have been associated with reduced zinc absorption, although much controversy exists on this matter, since there are studies that do not confirm such an effect. It can also mask the clinical signs of pernicious anaemia, thus making its timely diagnosis difficult. A safety level of 50 - 100 X RDA is recommended.[2,29]

Iron

Anaemia is the most common nutritional disorder in developing and developed countries. According to current estimates approximately 2 billion people worldwide are classified as anaemic, with iron deficiency being considered to be the principal cause.[31]

Complications of iron deficiency anaemia (IDA) are population-specific and are thought to be associated with pregnancy outcome (increased maternal and fetal morbidity and mortality, as well as premature delivery); physical growth (low birth weight and retarded physical development); mental development (retarded cognitive development) and physical performance (fatigue, decreased work capacity and decreased resistance to infections/impaired immunity).[31-36]

In view of the claimed extent and important consequences of iron deficiency, a number of strategies for its 'elimination' have been developed and include, at population level, improved sanitation, control of parasitic infestations, food fortification, improved breast-feeding and dietary practices.[37-39] At the individual level, though, the most important strategy is to identify and treat those at risk[37] by means of iron supplementation. The latter has been a key strategy for the short-term control of IDA for more than 70 years.

Treatment of IDA

In children, iron supplementation should be targeted to those individuals with poor iron status (Table V). Known high-risk groups include low-birth-weight babies, preterm babies, infants breast-fed for less than 6 months without the addition of adequate complementary foods and infants with protein-energy malnutrition.[40] In adults, at-risk groups for IDA include women who are pregnant, of low socio-economic status, with low levels of education, with high parity and multifetal gestations and those who consume diets low in meat and meat products and who are frequent blood donors.[41]

Table V. Treatment schedule for IDA

Category	Elemental iron dosage
Children	
VLBW infant (< 1 000 g)	4 mg/kg/day
VLBW infant (1 000 - 1 500g)	2-3 mg/kg/day
LBW infant	2 mg/kg/day
Full-term infant	1-2 mg/kg/day
Children 3-6 years	2 mg/kg/day 3 mg/kg/week
Pregnant women	
Treatment of IDA	60-120 mg/kg/day or 120 mg per week
Prevention of IDA	30 mg/day

Adapted from references 31, 33, 41, 44.

Studies on the effect of iron supplementation on growth have shown that supplementation of anaemic, underweight children resulted in increased weight gain, increased appetite and decreased morbidity.[34] Furthermore, supplementation of iron combined with vitamin A is reported to protect against any harmful effects of iron supplementation in communities where infections are highly prevalent, owing to the immuno-enhancing role of vitamin A.[42] Iron supplementation during pregnancy benefits the mother by improving maternal iron stores within 3 months. The improved maternal iron status has been documented to last up to 6 months postpartum.[43,44] In this regard, it is also suggested that maternal iron status during pregnancy is a strong predictor of infant iron status later in life.[43]

Frequency of dosing

Emerging evidence indicates that a weekly or twice-weekly iron supplementation regimen produces similar results to the one employing daily dosing; the former dosage schedule is associated with a lower prevalence of side-effects and improved compliance.[31,45,46] This has been ascribed to the fact that in iron-deficient individuals, iron absorption is about 30 - 40% after a single dose. The absorption of iron decreases to about 3 - 6% with a daily dose regimen. It has also been proposed that dosing once a week allows the renewal pattern of intestinal mucosal cells to occur, thereby increasing iron absorption and decreasing the possibility of mucosal iron overload that is thought to be responsible for the side-effects usually reported with iron supplementation. In view of the better iron absorption attained with a weekly dosing regimen, the supplemental dose can be smaller, thus reducing costs and improving compliance.[31] Iron supplements are optimally taken at bedtime or between meals to facilitate absorption. If the supplement contains only an iron salt, the absorption is also better than when it is part of a multivitamin.[41]

Possible adverse effects of iron supplementation and/or excessive iron intake

In the short term, the prevalence and severity of side-effects following iron supplements are dose-related and vary depending on the individual. Side-effects of supplementation include heartburn, nausea, abdominal discomfort, constipation and diarrhoea. These side-effects are reported to subside after a few days of treatment.[41]

In the longer term a few important complications have been associated with inappropriate iron supplementation practice:

1. Retarded growth — routine supplementation of iron to iron-sufficient children is reported to result in a significantly lower rate of weight gain.[47]

2. Bacterial growth — iron supplements given to iron-deficient individuals living in an area with inadequate sanitation and socio-economic circumstances has been associated with an increased incidence and longer duration of diarrhoea. This could be ascribed to the contamination of the environment by bacteria and parasites and the fact that these organisms require iron to proliferate.[48]

3. Catabolism of vitamin C — iron deposits lead to increased catabolism of vitamin C, resulting in reduced release of iron into the circulation from the reticulo-endothelial cells and inappropriately low serum ferritin concentrations.[49]

4. Haemochromatosis — dietary iron overload, resulting from the consumption of alcoholic beverages with a very high iron content (brewed in iron pots) is still reported to be a major problem in South Africa.[49,50]

Iodine

Iodine deficiency disorder (IDD) is one of the three micronutrient deficiencies that are currently recognised to be of public health significance,[51,52] since IDD is known to be one of the most common preventable causes of mental defects in the world.[53]

Salt iodisation is seen as a simple and cost-effective method to provide the iodine needs of any population. In South Africa salt iodisation has been voluntary for a number of years and has normally been in the region of 20 ppm. Compulsory legislation for iodisation of table salt at the level of 40 - 60 ppm has been in place since December 1995.[54]

Iodine intakes of < 1 mg/kg are probably safe for the majority of the population, but may cause adverse effects in some individuals.[55] Those most likely to respond adversely to excessive intakes of iodine include inhabitants of endemic goitre areas, those with habitual low dietary intakes of iodine, those with other forms of thyroid diseases and pregnant women.[55]

Adverse or side-effects to excessive exposure to iodine include thyroiditis, goitre, hypo- and hyperthyroidism and hypersensitivity reactions. Various reports of increased incidence of thyrotoxicosis in endemic goitre areas after increased iodine ingestion following supplementation programmes have been reported. Some of these cases resulted in heart failure and death. The importance of some form of biochemical monitoring of target populations in cases of universal salt iodisation has been emphasised repeatedly.[56,57]

Conclusion

The first rational approach to optimal health has been, and should be, food. When food/nutrient intake is inadequate, significant health benefits have been shown to accrue from supplementation. The latter, however, must be practised with great circumspection and with due consideration to the desired endpoint as well as to the possibility of doing harm. Future developments promise to provide us with a more sound scientific basis both for the recommendations we make in terms of healthy eating and well-defined indications for nutrient supplementation.

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