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Micronutrients in Health and Disease

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"We know accurately only when we know little; with knowledge doubt increases".

—Goethe"

The story of micronutrients in disease and health is still not settled. Called *micronutrients* because they are needed only in minuscule amounts, these substances are the "magic wands" that enable the body to produce enzymes, hormones and other substances essential for proper growth and development. As tiny as the amounts are, however, the consequences of their absence are severe. Micronutrients play a central part in metabolism and in the maintenance of tissue function. An adequate intake therefore is necessary, but provision of excess supplements to people who do not need them may be harmful[1]. Recently an editorial in Lancet wrote: The prospect that a vitamin pills may not only do no good but also kills their customers is a scarry speculation given the vast quantities that are used in certain communities[2]. Micronutrients are basically vitamins, minerals and trace elements. Following micronutrients are being discussed.

VITAMINS

Vitamin A and beta-carotene, Vitamin D, vitamin E, Vitamin C or ascorbic acid, Thiamin, Riboflavin, Niacin, Folic Acid, Vitamin-K, Vitamin $B_{12,}$

MINERALS

Sodium, Potassium, Calcium, Phosphorus, Magnesium.

TRACE MINERALS

Iron, zinc, Copper, Selenium, Iodine, Manganese, Chromium, Fluoride and cobalt. Omega-fatty acid, Coenzyme Q and Glucosamine will be not discussed, as there are not confirmed deficiency states.

Micronutrients in Relation to Specific Diseases

Reducing the Risk of Cancer

Micronutrients may play important roles in the prevention of human cancers. Greater consumption of vegetables and fruits is associated with decreased risk of lung, esophageal, stomach, and colorectal cancer[3]. Vitamin A is needed to maintain healthy tissues. Vitamin A supplements, whether in the form of beta carotene or retinol, have not been shown to lower cancer risk, and high-dose supplements may, in fact, increase the risk for lung cancer in current and former smokers[4,5]. Many studies have linked consumption of vitamin C–rich foods with a reduced risk for cancer[6]. The few studies in which vitamin C has been given as a supplement, however, have not shown a reduced risk for cancer. There is a growing body of evidence from epidemiologic studies (not yet tested in RCTs) that vitamin D may have beneficial effects on some types of cancer, including cancers of the colon, prostate, and breast. The promise of alpha-tocopherol as a cancer prevention agent appears to be dimming[7]. One experimental trial has shown selenium supplements might reduce the risk of cancers of the lung, colon, and prostate. Folate deficiency may increase the risk of cancers of the colorectum and breast, especially in people who consume alcoholic beverages. Current evidence suggests that to reduce cancer risk, folate is best obtained through consumption of vegetables, fruits, and enriched grain products. Extensive research has examined the effects of fluorides given as dental treatments, or added to toothpaste, public water supplies, or foods on cancer risk. Fluorides have not been found to increase cancer risk[8].

Several studies have suggested that foods high in calcium might help reduce the risk for colorectal cancer[9]. There is also evidence, however, that a high calcium intake, primarily through supplements, is associated with increased risk for prostate cancer, especially for prostate cancers that are more aggressive[10]. Clinical studies of antioxidant supplements are currently under way, but studies have not yet demonstrated a reduction in cancer risk from vitamin or mineral supplements[11]. To reduce cancer risk, the best advice presently is to consume antioxidants through food sources rather than supplements. A deficiency of any of the micronutrients: folic acid, Vitamin B_{12}, Vitamin B_6, niacin, Vitamin C, Vitamin E, iron, or zinc, mimics radiation in damaging DNA by causing single- and double-strand breaks, oxidative lesions, or both. Folate deficiency causes extensive incorporation of uracil into human DNA (4 million/cell), leading to chromosomal breaks. This mechanism is the likely cause of the increased colon cancer risk associated with low folate intake. Micronutrient deficiency may explain, in good part, why the quarter of the population that eats the fewest fruits and vegetables (five portions a day is advised) has about double the cancer rate for most types of cancer when compared to the quarter with the highest intake. Remedying micronutrient deficiencies should lead to a major improvement in health and an increase in longevity at low cost.

Cardiovascular Diseases

It has been expected that an increased intake of antioxidants would reduce the incidence and complications of heart disease. Some small studies did initially suggest beneficial effects from taking vitamin E supplements. However, more recently a number of large-scale trials have failed to show such a benefit, for example, the HOPE study[12]. A comprehensive review of studies by the American Heart Association concluded that cardiovascular disease reduction can be achieved by long term consumption of a well balanced diet together with regular physical activity, and that there was no additional benefit from consumption of micronutrients at levels exceeding these obtained from such a diet[13]. There is mystery surrounding folate and homocysteine.The essential requirement for folate, in the form of methyltetrahydrofolate, in ensuring homocysteine is converted to methionine has been recognized for some time. Homocysteine metabolism also requires vitamin B_{12} and vitamin B_6. Homocysteine is an independent risk factor for coronary artery disease, and a number of trials are currently underway to investigate clinical benefit of reducing homocysteine plasma concentration. It seems clear from some studies that folate does not reduce the risk of atherosclerosis by reducing homocysteine. The relation between intermediates in the homocysteine pathway and mediators of atherosclerosis is therefore complex and requires much further study[14].

Diabetes

There is no clear evidence of benefit from vitamin or mineral supplementation in people with diabetes (compared with the general population) who do not have underlying deficiencies. Routine supplementation with antioxidants, such as vitamins E and C and carotene, is not advised because of lack of evidence of efficacy and concern related to long-term safety. There is growing evidence for the value of added chromium in maintaining glucose tolerance, reducing body fat, and increasing lean tissue mass, although some of the evidence is conflicting[15]. Benefit from chromium supplementation in individuals with diabetes or obesity has not been clearly demonstrated and therefore can not be recommended. There is now sufficient compelling evidence to justify support for a randomized prospective clinical trial to test the effect of consuming major food sources of Mg, such as whole grains, nuts, and green leafy vegetables, on the development of type 2 diabetes in a high-risk population. If increased Mg intake is beneficial, it could provide a new cost-effective way to reduce development of type 2 diabetes[16].

HIV / AIDS

Of special significance is the role of trace elements and other micronutrients in antioxidant defence .Zinc and copper are essential for cytoplasmic superoxide dismutase, manganese for the mitochondrial enzyme, and selenium is part of the prosthetic group of glutathione peroxidase. Loss of antioxidant activity will lead to increased activation of nuclear factor-kB (NF-kB), which is a key regulator of HIV replication[17]. There is evidence that decline in plasma selenium parallels the loss of CD4+ cells, and that low levels of selenium in children is related to faster disease progression and to mortality. Although supplementation may lead to biochemical improvement, showing that this leads to improved clinical outcome remains controversial[18]. However, one study does suggest that supplementation will delay progression of the severity of HIV[19].

Oxidative Damage and Eye Disease

Significant reduction in the progression of age related macular degeneration has been shown with the combination of antioxidants. (zinc being most effective).

There was no significant difference in development or progression of age related cataract[20].

Infections in the Elderly Population

Taken overall, a meta-analysis showed that there is little if any benefit from a multivitamin and mineral supplement, in terms of incidence of infections in an elderly population[21].

Cognitive Function

It has long been thought that supplements of vitamins and trace elements may improve aspects of cognitive function. Some studies have suggested that concentration ability may be improved as a result of supplements.But these results are inconclusive[22].

Osteoarthritis and Bone Function

Longitudinal evidence of the effect of vitamin D on osteoarthritis was recently provided by Lane and colleagues[23] who found that high levels of vitamin D protected against both incident and progressive hip osteoarthritis. A small trial of calcium, zinc, manganese, and copper supplements showed a positive effect on spinal BMD in postmenopausal women. There is growing evidence of the importance of optimal vitamin K intake in carboxylation of bone proteins and complexation of calcium, to increase bone mass[24].

Outcome in Critically Ill

One meta-analysis has suggested that overall there may be a reduction in mortality from the use of antioxidants in critically ill. In this regard selenium and zinc are of major importance[25].

Infections in Children

Zinc deficiency is prevalent in children in developing countries where diarrhea is also an important problem. In six of nine trials, zinc supplementation significantly reduced the incidence of diarrhea, and in five of these there was a lower incidence of pneumonia[26].

Status of Multivitamin (MVM) Supplements

Most people assume that the ingredients in MVM supplements are safe. There is evidence, however, that certain ingredients in MVM supplements can produce adverse effects, including reports from RCTs that noted excess lung cancer occurring in asbestos workers and smokers consuming β-carotene. In addition, esophageal cancer excess was found with long-term follow-up of older Chinese patients treated with selenium, β-carotene, and vitamin E supplements[23]. In another study, patients with elevated prostate-specific antigen levels at baseline who were receiving an MVM intervention had higher incidence of prostate cancer[27].Vitamin D and calcium may increase the risk for kidney stones for certain people. These data raise safety questions both in general and in special populations. Although these studies are not definitive, they do suggest possible safety concerns that should be monitored for primary components of multivitamins. Minerals taken as supplements can also be toxic. For example, magnesium can cause diarrhea at doses above 400 mg/d; phosphorus can cause diarrhea at doses above 750 mg/d, and mild nausea and vomiting at lower doses; iron can cause constipation, nausea and vomiting, reduced zinc uptake, and iron overload in hemochromatosis; zinc can cause nausea and vomiting, immunosuppression and impaired copper uptake; and selenium at doses above 0.91 mg/d can cause brittle hair and nails, peripheral neuropathies and gastrointestinal upset.

Final Points

Micronutrients play a central part in metabolism and in the maintenance of tissue function. An adequate intake therefore is necessary to sustain metabolism and tissue function. Provision of excess supplements to people who do not need them may be harmful. Clinical benefit of micronutrient supplements is most probable in those people who are severely depleted and at risk of complications, and is unlikely if this is not the case. Most clinical trials have failed to show a benefit from supplements in reducing the incidence of infections in the elderly population, coronary artery disease, or malignant disease. Supplements of zinc and vitamin A in children in developing countries have led to reduced diarrhea and pneumonia. The evidence for benefit from supplements in HIV is weak. There is some evidence for benefit of supplements on cognitive function in marginally malnourished children, but no evidence of such benefit in the elderly population. There is good evidence of benefit in critical illness. There is special interest in selenium supplements. Most benefit from micronutrients seems to come from a well balanced diet.

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