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Micronutrient deficiencies

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Summary *Objective* The aim of this study was to consider the risk of micronutrient deficiencies and approaches for intervention, and to summarize existing knowledge and identify areas of ignorance. *Design* Experts from a range of relevant disciplines received and considered a series of questions related to aspects of the topic. *Intervention* The experts met and discussed the questions and arrived at a consensus. *Conclusion* Though healthy balanced diet is available for the general European population, a few defined groups are at risk of micronutrient deficiencies. In addition, the intake of specific micronutrients such as iron, folic acid, vitamin D and vitamin B12 are often marginal. To overcome these deficiencies, either selected micronutrients or a mixture of different micronutrients might be recommended. However, to define and detect micronutrient deficiencies, specific biomarkers are only available for a few micronutrients (e. g. vitamin D, folic acid, vitamin C, iron). The definition of a risk group, based on scientific data, might be an appropriate way to justify intervention with supplements.

Key words micronutrients – risk groups – supplements

Introduction

From May 30 to June 2, 2002, a group of scientists met at Hohenheim University, Stuttgart, in the fifteenth of a series of Consensus Meetings, to consider the occurrence and effect of micronutrient deficiencies in European countries. The panel considered a series of questions until a consensus developed. The questions (in bold), the consensus (in italics), and some literature intended to allow the topic to be considered further are listed below. Due to the special type of conference and the preparation of the scientific text by different authors, one will find substantial redundancies that make each section understandable in itself. With respect to the available space, the accompanying text will focus only on a few studies which are important to understand the consensus answers.

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Are there any groups at risk for micronutrient deficiencies in western countries?

Micronutrients in general

Consensus: Yes, there are selected groups of people at risk for general micronutrient deficiencies. These populations include: elderly, pregnant women, vegans, people on a weight reduction diet, some groups of athletes, hospitalized and institutionalized people, subjects with a chronic inflammatory disorder, subjects with chronic administration of certain drugs, and clinically defined groups of patients.

Background: Elderly people are generally considered at risk of developing vitamin and trace element deficiencies, especially vitamins A, D, and folate, as well as iron and calcium [1, 2]. The multifactorial causes of this health hazard comprise quantitative and qualitative decreased food intake, reduced energy expenditure due to sedentary life style and loss of metabolically active body cell mass, and the development of chronic age-associated disorders. Furthermore, chronic inflammatory conditions, age-related degenerative disorders as well as the biology of the ageing process itself are associated with increased oxidative stress and impaired anti-oxidative networking, which emphasize the importance of an adequate intake of anti-oxidative nutrients. Adequate nutrition during pregnancy plays an important role in the well-being of mother and child and influences health of the offspring during childhood and adulthood. Nutritional requirements are increased during pregnancy, but will generally be met by dietary intake and adaptive physiological changes [3]. However, the micronutrient status of vitamin D, folic acid, iron, and zinc may become compromised without supplementation [3–5]. Folic acid supplementation is generally recommended to decrease the risk of serious birth defects. Especially in multifarious women, the essential fatty acid status may become impaired and negatively affect the neurological and cognitive development of the offspring [6]. There are indications that n-3 fatty acids are involved in gestation and parturition and that n-3 fatty acid deficiencies are associated with premature delivery [7]. The micronutrient intake of vegans is easily imbalanced with respect to the recommended dietary allowances. In particular, the intake of vitamin B12, riboflavin, and selenium is often inadequate. Even the use of dietary supplements often does not meet the recommended intake of vitamin B12 and selenium [8, 9]. The micronutrients at risk appear to be iron, magnesium, zinc, fat soluble vitamins and essential fatty acids. Although a nutritionally adequate low-fat diet seems feasible in a motivated, free-living population, special attention should be paid to the issue of potential essential fatty acid deficiency. Energy-restricted diets and traditional cholesterol-lowering diets are typically focused on the reduction of total fat intake and shift from saturated fatty acids to polyunsaturated fatty acids (PUFAs). However, these PUFAs usually contain high concentrations of n-6 fatty acids and low amounts of n-3 fatty acids. This may have an adverse effect not only on reducing the risk for obesity-related metabolic disorders, such as vascular disease and heart rhythm disturbances, but also on the regulation of the intermediary metabolism of brain monoamines such as serotonin, which may lead to impaired mood status and depression. Many micronutrients play key roles in energy metabolism. During strenuous exercise in well-trained athletes, energy metabolism in skeletal muscle tissue may be increased up to 100 times the resting rate. This implies an increased rate of micronutrient turnover and, together with the increased micronutrient losses that sometimes occur during prolonged strenuous exercise, may compromise micronutrient status. However, the increase in energy expenditure is normally accompanied by an increased energy (food) intake, which will in turn increase the micronutrient intake. Hence, in general, there is no scientific evidence for micronutrient deficiencies in highly trained athletes and people with moderate physical activity [10]. It is well known that malnutrition is far more common among institutionalized and hospitalized elderly compared to free-living subjects in the community and that its prevalence is associated with the severity of morbidity, functional impairments and mental state [11]. Malnutrition affects a broad spectrum of micronutrients, such as the B vitamins, especially B1, B6, folate and B12, vitamin C, vitamin D and E, essential fatty acids and selenium [12]. Thiamine and folate status need special attention in this respect as a deficiency of these nutrients is associated with depression, and impaired cognition and dementia [13]. Intervention trials with micronutrient supplementation consisting of zinc and selenium, vitamin C, beta-carotene and alpha-tocopherol have been associated with a reduction of infectious events [14]. Chronic inflammatory disorders are associated with increased oxidative stress, which in the case of a compromised antioxidative networking may exaggerate the inflammatory response. This applies for chronic inflammatory disorders including chronic obstructive pulmonary disease, rheumatic disorders, and various dermatologic disorders [15] and others. Trace elements including zinc and selenium, various vitamins, and essential fatty acids play a pivotal role in either the antioxidative networking (e. g. glutathione peroxidase) or the inflammatory response. Chronic inflammatory bowel diseases (IBD), i. e. Crohn's disease and ulcerative colitis, are associated with not only increased expenditure of antioxidants, but also increased intestinal losses of micronutrients [16]. Micronutrient deficiencies are often seen in these diseases [17]. Nutritional therapy in IBD takes these considerations into account [18].

Chronic use of drugs may lead to micronutrient deficiencies, either by decreasing food intake mainly due to impaired appetite or upper GI motility, by decreasing the bioavailability of micronutrients, for example cholestyramine which impairs the absorption of fatty acids and fat-soluble vitamins, or by interfering with metabolism [19]. A number of micronutrients, such as zinc and magnesium, play a role in phase I oxidation reactions involved in drug metabolism. Typical examples are the increased folate requirements with chronic use of sulphasalazine, methotrexate, or valproic acid. However, a relevant interaction between drugs and specific micronutrients only occur in case of prolonged use of specific drugs in high doses in susceptible subjects.

Selected micronutrients

Consensus: There exist groups within the general population whose intakes of specific micronutrients are below the recommended intakes. These groups, depending on the region, may be at risk of deficiency of specific micronutrients, including iodine, vitamin D, iron, folic acid, vitamin B12 and n-3 fatty acids. The most critical groups at risk are the elderly, women of child-bearing age, the developing newborn, vegans and specific ethnic groups.

Background: **Iodine.** In 1999, WHO estimated that about 15 % of the population in the European region was affected by goitre [20]. Subclinical hypothyroidism during pregnancy and early infancy (with a concomitant risk of minor brain damage and irreversible impairment of the intellectual development of offspring) may be another consequence of an insufficient iodine intake.

Vitamin D. Although sunlight is the major source of the body's store of vitamin D, diet plays an important role for the whole population during inadequate light exposure. Low or inadequate vitamin D status [defined by blood 25(OH) vitamin D levels] is common in subgroups of the population in countries with low exposure to sunlight, particularly in the winter months [21]. Vitamin D intakes have a greater effect on vitamin D status in the winter than in the summer [22]. Dietary intake of vitamin D is also essential for those who, for various reasons, do not expose their skin to sunlight. Vitamin D insufficiency is common in the elderly, partly due to the decreased ability to synthesize vitamin D, as well as low intakes and inadequate light exposure. Low status can lead to an increased risk of osteoporosis, osteomalacia and fractures in this group. Vitamin D status is inadequate in the elderly in many countries throughout Europe [21].

Iron. Iron deficiency is a particular risk for women and girls of child-bearing age, because of menstrual losses. In a recent Irish food consumption survey, almost half of women aged 18–50 years had inadequate iron intakes when compared with national average requirements. In the British National Diet and Nutrition Survey, iron intakes were found to be low in girls (aged 7–18 years), with iron intakes decreasing with age. Adolescent females (15–18 years) were found to have extremely low intakes of iron when compared with UK dietary reference values. Dietary supplements made no difference to mean intakes and iron status was also low in these groups.

Folic acid. In European countries, the average folate intake in adults was found to be remarkably similar, around 300 μg/day in adult males and 250 μg/day in adult females [23]. This is about the recommended intake level, but lower than recommended for pregnant women and women wishing to become pregnant. For these groups, an intake of > 400 μg/day is considered protective against neural tube defects. More than 90 % of women of childbearing age have dietary folate intakes below this optimal level

Vitamin B12. Vitamin B12 is found only in animal products. In a recent UK study of 250 vegetarian and 250 vegan men, approximately one-quarter of vegetarians and more than half of vegans had sub-optimal intakes of vitamin B12. Plasma vitamin B12 levels were low in the vegetarians and extremely low in the vegan group, with more than a quarter below the threshold level where neurological signs may develop (130 ng/L) [24]. The elderly are also at risk of vitamin B12 deficiency, due to physiological changes resulting in reduced absorption.

Selenium. Although selenium is widely distributed in the environment, the selenium content of foods is greatly affected by soil on which crops grow or animals graze. Recent evidence suggests that selenium intakes in most parts of Europe are falling and are low when compared with recommended intakes [25]. Declining intakes in the last three decades have been attributed mainly to a change in the source of wheat for bread and cereal products, from predominantly North American to European origin (from a high to low selenium content). In the UK, selenium intakes were low in the majority of the elderly (aged 65 and over) in the British National Diet and Nutrition Survey when compared with UK dietary reference values [26]. Selenium intakes decreased with increasing age in this population subgroup.

Calcium. Although there is good evidence, at extremely low intakes, that calcium intake affects bone mass in all age groups, uncertainty exists about the required intakes for various age groups and physiological levels. In the British National Diet and Nutrition Survey, infants and children (< 4.5 years) had adequate calcium intakes as assessed against the UK dietary reference values. However, average calcium intakes from food sources were below the reference nutrient intakes for both boys and girls aged 11–18 years (1000 mg for boys, 800 mg for girls). A proportion of free-living elderly women (approximately 10 %) had very low calcium intakes. In Ireland, a recent survey demonstrated that almost a quar-

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ter of women (aged 18–64 years) had calcium intakes below the average requirement. Vegans have been reported to have low calcium intakes when compared with the UK dietary reference values [9].

Vitamin K. Low phylloquinone intakes were observed in free-living British elderly people (> 65 years), when compared with current guidelines of 1 μg/kg body weight/day. Intakes were lower in older people living in Scotland or northern Britain than in the south of England, particularly due to differences in vegetable intakes [27].

Do dietary food supplements play a role in supporting nutrition for those individuals? If so, are there special micronutrients for selective groups at risk?

Consensus: Yes. (see above)

Do we have any reliable clinical or analytical biomarker for either suboptimal micronutrient intake or marginal deficiency?

Consensus: There are a few valid biomarkers that reflect either suboptimal micronutrient intake or marginal deficiency (Table 1).

Suboptimal or marginal intake, in cases of components related to signs and symptoms of deficiency, should be based on three lines of evidence: Suboptimal intake (compared to RDA); Marker; Importance to groups within the general population. Biomarkers are influenced by Bioavailability: Inflammatory diseases (including subclinical inflammation); Gender; Pregnancy; Seasonal variation of supply; Genes. Low levels of non provitamin A carotenoids (compared to the median level in the general population) may be taken as biomarkers for a low intake of fruit and vegetables.

Background: There are basically two types of biomarkers: biomarkers of dietary intake and biomarkers of exposure. What we are concerned with here is biomarkers of intake. Biomarkers of dietary intake can generally be categorized into two types: 1) those biomarkers which provide an absolute quantitative measure of dietary intake related to a time dimension such as 24 h; and 2) those biomarkers which measure the concentration of a given factor, i. e. concentration in blood or other tissues, but without relation to a time dimension [28].

Homocysteine. Plasma homocysteine levels are inversely related to plasma levels of folic acid, vitamin B12 and pyridoxal-5'-phosphate in adult and elderly populations; therefore, plasma homocysteine has been suggested to be a valid biomarker for these vitamins. Plasma homocysteine is strongly inversely related to folic acid intakes in young and older adult and elderly populations [29–32]. Plasma homocysteine is also more weakly inversely related to vitamin B6 intakes [30]. However, although plasma homocysteine levels inversely correlate with folate and B6 status, they do not correlate with vitamin B12 status [29, 30].

Vitamin C. Vitamin C is required as a cofactor for many enzymes and is transported to tissues in the blood; therefore, plasma vitamin C concentrations should be a good indicator of vitamin C intake. Brubacher et al. [33] carried out a meta analysis on 35 studies of the intake-plasma relationship for vitamin C in different adults and elderly smokers and nonsmokers. The results suggest that plasma vitamin C is a good biomarker of vitamin C intake. Bates et al. [34] reported a strong correlation between vitamin C intakes and status in a cross-sectional study of approximately 1,000 British elderly people. Plasma vitamin C correlates well with fruit and vegetable intake, suggesting it is a biomarker for intake of these foods [35].

25-hydroxy vitamin D is a better marker than Parathyroid hormone (PTH)

PTH can be considered a functional marker of vitamin D insufficiency. There is a well-established inverse relationship between plasma PTH levels and plasma 25(OH) vitamin D in adult and elderly populations [36].

Low levels of non-provitamin A carotenoids may be taken as biomarkers for a low intake of fruit and vegetables

Epidemiological studies suggest that a high fruit and vegetable diet may reduce risk of diseases such as cancer and cardiovascular disease. Although several factors affect the bioavailability of carotenoids (e. g. other nutrients) and blood/tissue concentrations of carotenoids (e. g. season), the concentration of carotenoids in blood is a biomarker for fruit and vegetable intake. Epidemiological studies have demonstrated a relationship between fruit and vegetable intake and plasma lutein, alpha carotene, betacarotene and beta crypto-xanthin [35]. Intervention studies demonstrate that circulating

Table 1

Micronutrient(s)	Biomarker (functional)
Folic acid B-Vitamins (B6 and B12)	Homocysteine
25 OH-D	Parathyroid hormone
Essential FA	Ratio of PUFA to selected FA
Iron	Transferrin Receptors
Vitamin C	Plasma Vitamin C

carotenoids are a biomarker of fruit and vegetable intake. Increased fruit and vegetable intakes lead to increases in circulating carotenoids including total carotenoids (excluding lycopene), lutein, beta-cryptoxanthin, alpha and beta carotene. Those with lower fruit and vegetable intake in control groups had lower levels of plasma carotenoids.

In the case of special risk groups for micronutrient deficiencies (to be defined), should a continuous or interval supplementation be recommended?

Consensus: Choice of supplement depends on: the biological half-life; bioavailability and interaction of micronutrients; single high dose toxicity and effectiveness; accumulation.

Background: If supplements are recommended for special risk groups, the time period of supplementation depends on the special conditions whether a short-term deficiency might be compensated or a more or less general problem of inadequate nutrition is addressed. Consequently, the decision to supplement continuously or only for a given time period must be made in the special case. On the other hand, the above-mentioned aspects have to be considered, if possible. Concerning toxicological effects, the tolerable upper levels must be respected. However, up to now we do not have data dealing with long-term intake of supplements in concentrations at the tolerable upper level. Consequently, if high doses are needed, an interval supplementation would be safer.

Health effects of micronutrients

Are there specific health effects of selected micronutrients, based on valid scientific data?

Consensus: There is good evidence from epidemiological studies that a high intake of micronutrients has an impact on risk for diseases such as: bone fracture, coronary heart disease, neurodegenerative disorders, diabetes, cancer, age-related macular degeneration and others. There is evidence from in vitro and in vivo studies that micronutrients modulate the pathophysiology of various diseases.

Background: Nutritional status can be simply categorized as deficiency and adequacy: however, in recent years, there have been an increasing number of attempts to add the concept of optimal nutrition. Epidemiology may have contributed to this. Dietary deficiency is well known to reduce immune function and increase susceptibility to disease. Whether there is a difference in disease susceptibility between adequate and optimal nutrition is much more difficult to discern. Frequently, epidemiological studies categorize nutritional status by dividing into tertiles, quintiles, etc. and determine effects by examining differences between the groups with the widest differences in intakes or blood levels, etc. When differences are revealed, then health benefits are attributed to the higher intake, whereas, in reality, it may be that the health benefit is lost by or is absent from those in the lower group. This may seem just a question of semantics, but epidemiological data often suggest a gradation of response between the groups (or intermediate groups where there is no apparent response) giving rise to the impression that the higher intake groups are better off than those below, and that health benefits increase even after dietary adequacy has been achieved. However, while the intake of one nutrient may appear to show increasing amounts through the intake groups, it may be the adequacy of another nutrient or other nutrients that determines the utilizability of the first nutrient, and only when both are adequate in the diet is the full benefit on health achieved. Thus, a gradation of health effect may be seen and the highest intakes of a specific nutrient regarded as optimal since they are very much higher than those required to meet recommended daily allowances. However, the optimal concentration may only be optimal because all other nutrients in that specific group are all present in adequate amounts.

Coronary heart disease, hypertension. Arteriosclerosis is a chronic inflammatory process occurring within the arterial wall. It is believed to be linked to the oxidation of low density lipoproteins (LDLox). LDLox are scavenged by macrophages which migrate through the vascular walls. Some of these accumulate within the endothelium of vascular tissues releasing mediators of inflammation and leading to plaque formation within the vascular epithelium. The pivotal role of oxidation within the inflammatory process has led to much research to identify protective dietary antioxidants capable of preventing arteriosclerosis or minimizing or preventing its effects once initialled.

Epidemiology: The WHO MONICA project included a series of epidemiological investigations of risk factors for heart disease in northern and southern European countries. Gey [37] studied micronutrient status and initially suggested the idea of prudent diets to protect against ischaemic heart disease (IHD) and cancers, and, subsequently [38], that the intakes of vitamins A, C, E and β-carotene were inversely associated with the risk of IHD. On the basis of these studies, it was suggested that specific plasma concentrations of these nutrients were necessary for IHD protection [38]. However, concentrations of several of these plasma micronutrients are determined by other factors as well as diet [39]. Thus, while the specific concentrations of the above micronutrients might not differ in populations with different cardiovascular risks [40], the difference in plasma lutein concentrations indicated a large difference in fruit and vegetable consumption. Thus, other components in fruits and vegetables such as the polyphenols [41] or wine [42] with or without the above antioxidant micronutrients may be necessary for protection against IHD. The WHO and other international bodies [43] have recommended that five portions of fruit and vegetable per day is necessary to lower the risk of IHD. Strain and co-workers have recently shown that only 4.3 % of men in the Caerphilly studies in South Wales (UK) consumed intakes of this order and 33 % only one portion or less per day [44]. Likewise, the UK national survey of adults showed similar results for the whole country [45].

Intervention: Little evidence from intervention studies with the antioxidant micronutrients vitamins E and C or β-carotene has emerged to suggest that these micronutrients give protection against IHD. For example, in the most recent study of > 40.000 adults (40–80 years) with CHD, occlusive artery disease or diabetes, there was no evidence of protection by daily β-carotene (20 mg), vitamin E (600 mg) and vitamin C (250 mg) given for 5 years. There was no difference in all-cause mortality between treatment and placebo groups or any other parameter of morbidity [46].

There is some evidence that larger amounts of vitamin C than those used by the Heart Protection Group might help to prevent endothelial dysfunction possibly by enhancing the delivery of nitric oxide to the vascular wall from the plasma [47]. Thus, 2 g vitamin C in a placebo-controlled double-blind study was associated with a significant reduction in arterial stiffness in healthy male subjects 20–42 years, 6 h after acute oral administration [48]. However, acute (2 g po) or chronic (500 mg/day for 1 month) treatment of hypertensive patients with vitamin C did not reverse conduit vessel endothelial dysfunction, although both systolic and mean blood pressure was reduced in the patients [49].

Cancer. It is suggested that appropriate diets may prevent on a global basis 3–4 million cases of cancer every year and that the main dietary change would be to increase the consumption of fruit and vegetables which would prevent 20 % or more of all cases of cancer. Vegetables and fruits contain many potentially active components; the antioxidant vitamins, hundreds of carotenoids and thousands of simple and complex polyphenols. Many studies have been done to identify the active components with conflicting results, as indicated below. Some studies have produced evidence of beneficial effects, but it has to be realized that no single substance may emerge with protective properties against any specific cancer and that protection can only arise from lifestyle changes with major effects on dietary patterns (Table 2).

Age-related macular disease (AMD). *Epidemiology:* When nutritional data from the NHANES I were re-evaluated for links with AMD, it suggested that subjects who ingested fruit and vegetable portions rich in pro-vitamins A and vitamin C equal to or greater than 7 times per week had a significantly lower risk of AMD [60]. Further support for these observations was also reported by Seddon and colleagues [61], who studied 356 patients with neovascular AMD and 520 controls. They found that those in the highest quintile for carotenoid ingestion had a 43 % significantly lower risk of AMD. Furthermore, it was the macular carotenoids (lutein and zeaxanthin) ingested mainly in the form of spinach that were most strongly associated with the lower risk of AMD. The data also suggested that the risk of AMD in current smokers was somewhat lower in those with the greatest intake of lutein and zeaxanthin. Similar beneficial links with a risk of AMD were reported also by the Eye Disease Case-Control Study Group [62] for serum carotenoids and by workers in the Beaver Dam Eye Study [63] for dietary carotenoids [64]. Thus, although some studies have shown that high dietary intakes of fruit and vegetables or high serum carotenoid concentrations are associated with a lower risk of AMD, most epidemiological studies reported so far have not found correlations between lutein and zeaxanthin concentrations in blood or diet and a risk of AMD [65].

Table 2

Type of cancer	Prevention	Intervention
Prostate	High intake of tomatoes, high serum lycopene up to 20 % lower risk [50–53]	Up to now, no results from intervention studies
Gastric	High vitamin C consumption lowers risk [54]	Intervention trial in China with β-carotene (15 mg), vitamin E (30 mg), selenium (50 µg) resulted in a 13 % reduction of gastric cancer
Lung	High serum β-carotene, reflecting hig intake of vegetables is correlated with a lower risk [55] High antioxidant intake lowers risk [56]	Two intervention studies failed to document protection from high β-carotene intake (20 or 30 mg/day 5 years) Instead they showed a negative effect (increase of lung cancer) [57]; a further study using 50 mg β-carotene/day showed neither benefit nor hazard [58]
Colon cancer	High intake of vegetables, fruits and fibres	β-carotene failed to show an effect on polyp reoccurrence
Skin non melanomous	No epidemiological evidence	50 mg β-carotene/day over 5 years did not reduce reoccurrence in patients with previous skin cancer [59]

Intervention: Daily consumption of vitamin C (500 mg), vitamin E (400 IU), β-carotene (15 mg) and zinc (80 mg) by 3,640 persons aged 55–80 years in the Age-Related Eye Disease Study (AREDS) found an 18 % reduction in risk of development of advanced AMD against the placebo group [66]. Of the carotenoids, however, only lutein and zeaxanthin are obtained in extracts of excised human maculae measured by liquid chromatography [67, 68]. The interrelationships between the dietary intake and plasma concentrations and the amounts of these carotenoids found in the retinal pigment epithelium are not resolved.

Selected Micronutrients. *Consensus:* Based on meta analysis and systematic reviews of intervention studies, there is good evidence that high-dose supplementation studies have a favourable effect on: Duration of Common Cold (10 %) – Vitamin C, Duration of pre-menstrual syndrome – Vitamin B6, Hypertension and Pre-eclampsia – Calcium. These effects can only be achieved with high (pharmacological) doses and not via nutrition. There are many intervention studies dealing with other diseases which have not been subjected to meta analysis or systematic reviews, but have shown benefits in particular groups. There are only a few dietary intervention studies using food which showed an impact of nutrition and optimization on risk of different diseases: e. g. Colon cancer, Hypertension, Coronary heart disease HD. From these studies, the "causal" component cannot be extracted.

Background: **Calcium.** Supplementation with calcium may lead to a small reduction in blood pressure. Pooled analysis showed a reduction in systolic blood pressure of –1.27 mm Hg (95 % CI –2.25 to 0.29; P = 0.01) and in diastolic pressure of –0.24 mm Hg (95 % CI –0.92 to 0.44; P = 0.49) [69], confirming epidemiological findings of an inverse association between the dietary calcium intake and blood pressure [70]. Furthermore, a modest reduction of systolic and diastolic blood pressure has been demonstrated in pregnant women with hypertension, just as supplementation can reduce the risk of pre-eclampsia.

Magnesium. Also, an inverse association has been found between dietary magnesium intake and blood pressure [71]. A meta analysis of randomized controlled trials found a small, but non-significant, overall reduction in blood pressure following magnesium supplementation, with an apparent dose-dependent effect, specifically reductions of 4.3 mm Hg (95 % CI 6.3–2.2; P < 0.001) systolic blood pressure and 2.3 mm Hg (95 % CI 4.9–0.0; P = 0.09) diastolic blood pressure for each 10 mmol/day increase in magnesium dose.

Zinc. Zinc-deficient individuals demonstrate slower wound-healing and are more prone to infections. However, studies of the effect of zinc supplementation aimed at the healing rate of venous leg ulcers have been inconclusive. A Cochrane review concluded that oral zinc did not appear to aid the healing of leg ulcers, and that there was only weak evidence that zinc was of benefit in patients with venous leg ulcers and low serum zinc. Zinc has been found to inhibit rhinovirus replication in vitro. Some studies have demonstrated that zinc lozenges may beneficially affect cold symptoms; however, a meta analysis of randomized controlled trials concluded that the evidence for the effectiveness of zinc lozenges in reducing the duration of common cold symptoms is lacking. Finally, in settings with high rates of stunting and low plasma zinc concentrations, zinc supplementation may improve children's growth.

Chromium. Lack of chromium reduces insulin sensitivity and increases blood glucose possibly through its participation in the still hypothetical glucose tolerance factor. Obviously, chromium supplementation has been an attractive option for glycaemic control in diabetes mellitus. A recent meta analysis showed no effect of chromium on glucose or insulin concentrations in non-diabetic subjects; too few studies in glucose-intolerant and diabetic subjects were performed to allow conclusive findings.

Selenium. Selenium is often considered as belonging to the group of antioxidant nutrients, since it is incorporated into the enzyme glutathione peroxidase, which acts as a cellular protector against free radical oxidative damage. A secondary end-point analysis of a randomized placebo-controlled skin cancer prevention trial suggested that supplemental selenium might reduce the incidence of and mortality from cancers at several sites [72].

Vitamin B_6. Somatic and psychological symptoms in conjunction with the pre-menstrual syndrome seem to improve from the intake of high-dose (50–100 mg daily) B^6-vitamin (pyridoxine). A systematic review of placebo-controlled trials demonstrated that pyridoxine was significantly better than placebo in relieving overall pre-menstrual symptoms and in relieving depression associated with pre-menstrual syndrome, but the effect was not dose-dependent [73]. There are not enough data from clinical trials to draw conclusions on the efficacy of pyridoxine in reducing nausea and vomiting in pregnancy [74] and pain in carpal tunnel syndrome [75].

Are there dietary intervention studies using food which have an impact on optimal nutrition and risk of disease?

Consensus: Although dietary intervention studies have reported reductions in clinical risk factors for disease, there have been relatively few dietary intervention studies using food (rather than supplements) that have shown an impact of nutrition and optimization on disease risk. It is not possible from these limited studies to extract the causal component.

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Background: Food-based intervention studies have been carried out for reduction of risk factors associated with chronic diseases such as cardiovascular disease (e.g. cholesterol-lowering) and non-insulin-dependent diabetes mellitus and its cardiovascular risks (e.g. glycaemic control). However, only a few food-based intervention studies have been reported which have demonstrated a benefit on risk of disease.

Cardiovascular disease

A systematic review of 27 randomized trials has examined the efficacy of reduced total and saturated fat intake – and increased intake of complex carbohydrates and fibre – on total and cardiovascular mortality. The dietary changes did not decrease total mortality (RR 0.98; 95% CI 0.86–1.12), but decreased cardiovascular mortality non-significantly (RR 0.91; 95% CI 0.77–1.07) and cardiovascular morbidity significantly (RR 0.84; 0.72–0.99) [76]

Two recent food-based intervention trials have reported up to 70% reduction in recurrence after a first myocardial infarction. These trials tested the impact of a low intake of total and saturated fatty acids, increased intake of n-3 fatty acids and a high intake of fruit and vegetables on recurrence of disease. The most promising results came from the Lyon Diet Heart Study [77, 78] where a significant beneficial effect of diet on secondary prevention of ischaemic heart disease was observed and was maintained up to 4 years after the first infarction. This Mediterranean-type diet was lower in total and saturated fat, cholesterol and linoleic acid (18:2 n-6), higher in oleic and alpha linolenic acid (18:3 n-3) and had a higher content of fruit and vegetables, legumes and fibre-rich cereals (with high amounts of antioxidants, B vitamins, minerals and vegetable proteins) than the control diet. Therefore, it is impossible to dissect the active components.

A previous randomized controlled trial investigated the effects of a low fat, high fruit and vegetable, nut and grain diet compared with a low fat control diet on secondary prevention of myocardial infarction [79]. The incidence of cardiac events was significantly lower in the group on the higher fruit and vegetable-containing diet after 1 year (24.5 vs. 40.5%), as was total mortality (10.3 vs. 18.8%).

Hypertension. The Dietary Approaches to Stop Hypertension (DASH) study utilized a diet high in fruit and vegetables or a combination diet rich in fruit, vegetables, low-fat dairy products, nuts, fish, poultry and wholegrains and low in fats, red meats, sweets and sugar-containing beverages with a constant sodium intake [80]. This multicentre, controlled-feeding trial compared the effects of these diets with a more typical control American diet on systolic and diastolic blood pressure of subjects with above optimal range or Stage I hypertension. The results demonstrated that the combination diet, when compared with the control diet, significantly reduced blood pressure (11.4/5.5 mm Hg in hypertensive subjects and 5.5/3.0 in those without hypertension) and persisted during the 8-week trial [81]. Although the combination diet also produced significantly greater effects than the fruit and vegetable diet, the latter also reduced systolic and diastolic blood pressure. Because of the multiple changes in the diet, the causal component could not be established. A further trial (DASH-Sodium), based on the DASH trial, investigated the impact of sodium within the context of the typical control diet or the DASH diet. Varying levels of sodium were consumed with either the DASH diet or control diet and the results demonstrated that reducing dietary sodium reduced blood pressure in both groups. Although the sodium-related reductions in blood pressure were greater in the control group, the lowest blood pressures were observed in the DASH group with the lowest sodium [82].

Cancer. A large American intervention study randomized 2.079 men and women, who all had a colorectal adenoma removed within 6 months before inclusion, to their habitual diet and to a diet with a low fat content (20% total energy) and a high intake of fruit and vegetables (3.5 portions per 10 MJ) [83]. After 4 years, no difference in recurrence of colorectal adenomas in the two groups was found. These results are in accordance with the result from two earlier, but smaller, controlled dietary intervention studies from Canada [84] and Australia [85].

Application

Does the long-term use of micronutrient supplements within the RDA (in addition to diet) have side-effects?

Consensus: There is no evidence for this.

Do we have evidence from long-term studies?

Consensus: There are no long-term studies.

Are there any advantages or disadvantages of micronutrients in a supplement vs. the endogenous micronutrients in food?

Consensus: Advantages are: Fixed dose, Known bioavailability, Control of interactions, Achievability, Controllability.

Disadvantages: Discouraging proper nutrition, Covering only a few important micronutrients and "questionable" safety, Risk of overdosing and abuse, Potential biological network imbalance.

Are there any advantages or disadvantages of supplements compared to fortified food?

Consensus: There is a need for sufficient regulatory controls for supplements and fortified food to avoid uncontrolled overdosing.

Which studies do we need to further define groups at risk and to document effects of micronutrients on human health?

Consensus: Studies validating biomarkers for: Intake, Activity/biofunction, Disease relationship, Safety, Susceptibility, selected micronutrients and diet-related health risks. These validated biomarkers must be a basis for future intervention studies.

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