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The Role of Vitamins and Minerals in Energy Metabolism and Well-Being

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Physicians are frequently confronted with patients complaining of fatigue, tiredness and low energy levels. In the absence of underlying disease, these symptoms could be caused by a lack of vitamins and minerals. Certain risk groups like the elderly and pregnant women are well-recognized. Our aim was, therefore, to find out if other, less well-established groups might also be at risk. Thus, the objectives of this review are: to describe the inter-relationship between micronutrients, energy metabolism and well-being; identify risk groups for inadequate micronutrient intake; and explore the role of micronutrient supplementation in these groups. A review of the literature identified an important group at risk of inadequate micronutrient intake: young adults, often women, with a demanding lifestyle who are physically active and whose dietary behaviour is characterized by poor choices and/or regular dieting. Micronutrient supplementation can alleviate deficiencies, but supplements must be taken for an adequate period of time.

KEY WORDS: Vitamins; Minerals; Micronutrients; Micronutrient supplementation; Energy metabolism; Well-being

Introduction

Every doctor is familiar with the patient who presents complaining of a lack of energy, tiredness and exhaustion, and for whom thorough examination and even routine laboratory tests do not provide a satisfactory explanation for their symptoms. Without any underlying diseases, might these symptoms be caused by a lack of vitamins and minerals?

Research in the latter half of the 20th century has dramatically increased our understanding of the biochemical processes of cellular energy generation and demonstrated the fundamental role of a large number of vitamins and minerals as coenzymes and cofactors in these processes. This paper is based on the recognition that a lack of micronutrients may impair cellular energy production, resulting in symptoms of tiredness and lack of energy. In the first part of the paper, we summarize the current understanding of the role of micronutrients in energy generation and discuss the implications of micronutrient deficiency for energy and well-being. In the second part of the paper, we discuss the potential role of micronutrient supplements in improving the well-being of patients complaining of lack of energy and whether doctors should recommend such supplements.

This review focuses on 'healthy' adults

with active and demanding lives. It refers only briefly to athletes and sports performance, because comprehensive reviews about these groups and their specific needs can be found easily in the literature. For the same reason, we will also exclude very well-known risk groups, such as the elderly and those with vitamin B_{12} and iron deficiency.

Energy metabolism in the body

Energy to power the body's metabolic processes is derived from the food that we eat. Various reactions in catabolic pathways release this energy and store it in the high-energy phosphate bonds of the body's energy storage molecule, adenosine triphosphate (ATP). The process by which energy is transformed into ATP is known as cellular respiration (Fig. 1). The main part of this cellular respiration happens in the mitochondria, often referred to as the power plants of the cell. Glucose is the body's preferred source of energy for the production of ATP but, if necessary, other carbohydrates, fats and proteins can also be metabolized to acetyl coenzyme A (CoA), enter the citric acid (Krebs) cycle and be oxidized to carbon dioxide and water.

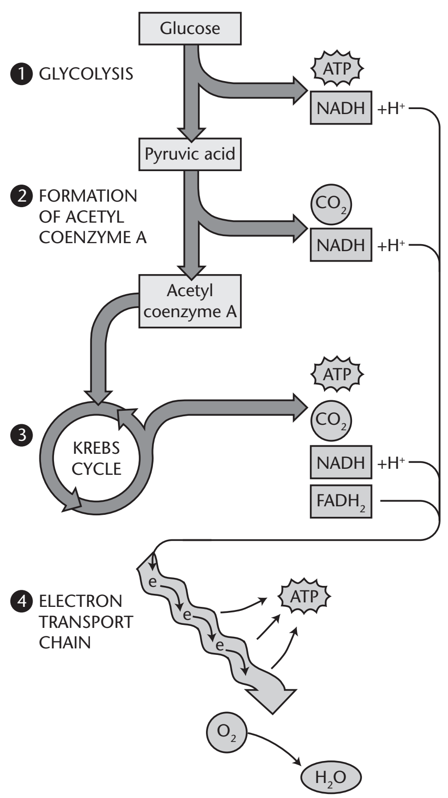

FIGURE 1: A simplified representation of cellular respiration with its four main steps. From each molecule of glucose, a total of up to 38 molecules of adenosine triphosphate (ATP) are produced. NADH, nicotinamide adenine dinucleotide (reduced form); $FADH_2$, flavin adenine dinucleotide (reduced form)

ROLES OF MICRONUTRIENTS IN ENERGY METABOLISM

The transformation of dietary energy sources, such as carbohydrates, fats and proteins into cellular energy in the form of ATP requires several micronutrients as coenzymes and cofactors of enzymatic reactions, as structural components of enzymes and mitochondrial cytochromes, and as active electron and proton carriers in the ATP-generating respiratory chain:[1,2] (i) thiamine pyrophosphate (TPP; vitamin B_1), CoA (containing pantothenic acid), flavin mononucleotide (FMN; derived from vitamin B_2), flavin adenine dinucleotide (FAD; derived from vitamin B_2) and nicotinamide adenine dinucleotide (NAD; derived from nicotinamide) are involved in the Krebs cycle and complexes I and II of the respiratory chain; (ii) biotin, CoA and FAD are involved in haem biosynthesis, which is an essential part of the cytochromes and important for the latter part of the mitochondrial respiratory chain; (iii) succinyl-CoA can feed into either the respiratory chain or the Krebs cycle depending on the needs of the cell.

In addition, the respiratory chain in the mitochondria also involves iron – sulphur (Fe – S) centres containing either two or four iron atoms that form an electron transfer centre within a protein.

The role of vitamins in energy metabolism continues to attract research interest. Depeint *et al.*[2] confirmed the essential role of vitamins B_6, B_{12} and folate in maintaining the mitochondrial one-carbon transfer cycles by regulating mitochondrial enzymes. The same authors also emphasized the essential role of the B vitamin family in maintaining mitochondrial energy metabolism and how mitochondria in their role as the cellular organelles responsible for energy metabolism are compromised by a deficiency of any B vitamin.[3]

As with the B vitamins, the role of certain minerals in energy metabolism is the subject of increasing interest. For example, a recent review noted the importance of adequate amounts of magnesium, zinc and chromium to ensure the capacity for increased energy expenditure and work performance, and that supplemental magnesium and zinc apparently improve strength and muscle metabolism.[4] A subsequent paper investigated the effects of magnesium depletion on physical performance and found that it resulted in increased energy needs and an adverse effect on cardiovascular function during sub-maximal work.[5] Most recently, Lukaski has shown that low dietary zinc also impairs cardiorespiratory function during exercise.[6] Table 1 summarizes the present state of knowledge with regard to the role(s) of individual micronutrients in energy metabolism.[7 – 10]

Inadequate micronutrient intake

The serious consequences of profound vitamin deficiency have been recognized for more than a century. Mainly as a result of better general nutrition and of micronutrient supplementation in at-risk groups, the deficiency diseases, such as rickets, pellagra, scurvy and beriberi, are now relatively uncommon, at least in the developed world. But, within the past two decades, a number of investigators[11,12] have re-introduced the concept of marginal micronutrient deficiency, first proposed by Pietrzik in 1985.[13] This showed that, long before the clinical symptoms of deficiency appear, micronutrient deficiencies develop progressively through several sub-clinical stages (Table 2).

Marginal deficiencies may occur as a

TABLE 1:
Present state of knowledge with regard to the role(s) of individual micronutrients in energy metabolism[7 – 10]

Micronutrient	Function in energy metabolism
Vitamins	
Thiamine (B_1)	• Essential cofactor in the conversion of carbohydrates to energy. • Needed for normal muscle function, including the heart muscle. • Involved in oxidative carboxylation reactions, which also require manganese ions.
Riboflavin (B_2)	• As a cofactor in the mitochondrial respiratory chain, helps in the release of energy from foods. • Component of the main coenzymes FAD and FMN.
Nicotinic acid, niacin (B_3)	• As a cofactor in the mitochondrial respiratory chain, helps in the release of energy from foods. • Transformed into NAD and NADP, which play a key role in oxidation – reduction reactions in all cells.
Pyridoxine (B_6)	• Helps in the release of energy from foods. • Used as a cofactor by nearly 100 enzymatic reactions, mainly in protein and amino acid metabolism.
Vitamin B_{12}	• Essential for metabolism of fats and carbohydrates and the synthesis of proteins. • Interacts with folic acid metabolism.
Biotin	• As a cofactor, involved in metabolism of fatty acids, amino acids and utilization of B vitamins.
Pantothenic acid	• Plays an essential role in the Krebs cycle. • Component of coenzyme A.
Vitamin C (ascorbic acid)	• Essential for synthesis of carnitine (transports long-chain fatty acids into mitochondria) and the catecholamines, adrenaline and noradrenaline. • Ascorbic acid facilitates transport and uptake of non-haem iron at the mucosa, the reduction of folic acid intermediates, and the synthesis of cortisol. • Potent antioxidant.
Folic acid	• Folates function as a family of cofactors that carry one-carbon (C1) units required for the synthesis of thymidylate, purines and methionine, and required for other methylation reactions. • Folate is essential for metabolic pathways involving cell growth, replication, survival of cells in culture. • Around 30 – 50% of cellular folates are located in the mitochondria.
Minerals	
Calcium	• Essential for the excitability of muscles and nerves. • Activates a series of reactions including fatty acid oxidation, mitochondrial carrier for ATP (with magnesium), glucose-stimulated insulin release.
Phosphorus	• Structural component of nucleotide coenzymes; ATP contains phosphorus, as does creatine phosphate, another high-energy compound. • ATP is involved in energy transformation and molecular activation.

TABLE 1 (continued):
Present state of knowledge with regard to the role(s) of individual micronutrients in energy metabolism[7 – 10]

Micronutrient	Function in energy metabolism
Magnesium	• Essential for the excitability of muscles and nerves. • Cofactor in over 300 enzyme reactions, particularly those involving metabolism of food components. • Required by all enzymatic reactions involving the energy storage molecule ATP.
Trace elements	
Copper	• Essential cofactor of cytochrome C oxidase, a component of the mitochondrial respiratory chain. • Involved in iron metabolism.
Chromium (III)	• Potentiates insulin action, thus promoting glucose uptake by the cells. • Individuals who exercise strenuously have been reported to have higher urinary levels of chromium.
Iron	• Essential part of haemoglobin for oxygen transport, of myoglobin for transporting and storing oxygen in the muscle and releasing it when needed during muscle contraction. • Facilitates transfer of electrons in the respiratory chain and is thus important in ATP synthesis. • Necessary for red blood cell formation and function.
Manganese	• Cofactor of several enzymes involved in metabolism of carbohydrates and gluconeogenesis.
Zinc	• Essential part of more than 100 enzymes, some of which are involved in energy metabolism.

FAD, flavin adenine dinucleotide; FMN, flavin mononucleotide; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; ATP, adenosine triphosphate.

result of inadequate micronutrient intake, caused by poor diet, malabsorption or abnormal metabolism. Whether in the developed or the less developed world, the overwhelming majority of cases fall into stages 1 – 3 (Table 2) and are further referred to as an inadequate micronutrient status.

Ideally, a sufficient and balanced diet should cover the overall micronutrient requirements. Unfortunately, even in developed countries, many sections of the population do not receive the essential vitamins and minerals needed from their diet. Several groups in the population are at increased risk for inadequate micronutrient status, usually due to insufficient intake caused by weight-reducing diets, insufficient and/or imbalanced nutrition, eating disorders, or demanding periods such as extensive exercise or emotional and/or physiological stress. Increased requirements may also cause an inadequate vitamin and mineral status; for example, as may occur in pregnancy and lactation, during growth, in the elderly, smokers and chronic alcohol abusers, and in patients with certain underlying diseases.[14 – 17]

Even otherwise 'healthy' individuals can

TABLE 2:
The sub-clinical stages of marginal micronutrient deficiency[13]

Stage	Aetiology	Evidence
Stage 1	Depletion of vitamin stores (more rapid for water-soluble than for fat-soluble vitamins).	Measurement of vitamin/mineral levels in the blood or tissues.
Stage 2	Non-specific biochemical adaptation.	Decreased excretion of metabolites in the urine.
Stage 3	Secretion of micronutrient-dependant enzymes or hormones reduced.	First physical signs; lack of energy, malaise, loss of appetite, insomnia.
Stage 4	Reversible impairment of metabolic pathways and cellular function.	Morphological, metabolic or functional disturbances. More pronounced physiological changes.
Stage 5	Irreversible tissue damage.	Clinical signs of micronutrient deficiency.

be at risk due to lifestyle-related factors. The 'lifestyle' category typically includes young to middle-aged adults with high occupational pressure or the double burden of family and work, for whom time is always in short supply. In this group, the risk for an inadequate micronutrient status is often the result of lifestyle-associated behaviour, such as rushed meals, unhealthy food choices, chronic or periodical dieting, and stress-related behaviour, such as smoking, excessive alcohol and coffee consumption.[18] Even mild micronutrient deficiencies can result in a lack of well-being and general fatigue, reduced resistance to infections or impaired mental processes (e.g. memory, concentration, attention and mood).[8,9] Recent studies have indicated that an optimal intake of certain vitamins is also crucial for long-term health maintenance and to help prevent diseases, such as osteoporosis, coronary heart disease and cancer.[19,20]

The risk of developing an inadequate micronutrient status is more common in industrialized populations than is generally assumed. In the 1987 – 1988 Dutch National Food Consumption Survey,[21] combinations of low thiamine, riboflavin, vitamin B_6 and vitamin C intakes were found among adults. A double-blind study demonstrated that a state of depletion of thiamine, riboflavin, and vitamins B_6 and C can be induced within 8 weeks by a diet composed of normal food products.[22] Within 3 – 6 weeks, deterioration of the vitamin status was indicated by decreased vitamin concentrations in the blood, decreased erythrocyte enzyme activities, elevation of stimulation tests of these enzymes and lower vitamin excretion in the urine.[22] Although no vitamin-specific clinical signs and symptoms of deficiency were observed, this depletion study showed that the combined marginally deficient status of thiamine, riboflavin, vitamin B_6 and vitamin C resulted in decreased physical performance. Marginal vitamin B_6 intake is among the nutritional risks prevalent in The Netherlands.[23]

Vitamin and mineral intake was recently assessed in the UK in an extensive survey carried out in adults aged 19 – 64 years living in private households.[24] Data from more than 2250 dietary interviews were gathered, along with more than 1700 7-day dietary records. In general, the intake data for vitamins and minerals were satisfactory, showing an average intake from food sources and supplements combined that met or exceeded the local recommended daily allowance (RDA) for each individual micronutrient.[24] However, when only dietary intake was considered and when looking at the stratified intake data, significant proportions of the population were found to have intakes below the RDA, as shown in Table 3.[24]

Data from the USA have shown that, even in the general population, the prevalence of low serum folate (18.4%) and of low red-blood cell folate (45.8%) was quite high.[25] This, in addition to the well-recognized roles of folate in human health, prompted the start of the mandatory folic acid fortification programme in 1998 in the USA.[25] Dutch data also indicated that around 50% of a representative Dutch population sample did not meet current recommendations for folate intake.[26] Recently, it was reported that folic acid deficiency in adolescent teenage girls in Turkey ranged between 14.7% and 20.1% in rural and urban areas, respectively.[27]

Another vitamin of concern is vitamin D; inadequate vitamin D status is becoming more common in developed countries. Vitamin D inadequacy is found in approximately 36% of otherwise healthy adults overall, in up to 57% of patients seen in general medicine in the USA and at even higher percentages in Europe.[28]

Dietary magnesium does not generally meet recommended intakes for adults. Results of a recent national survey in the USA, for example, indicated that a substantial proportion of women do not consume the recommended daily intake of magnesium; with the menopause this problem increases among women over 50 years old.[5] The average magnesium intake for women was found to be 228 mg/day compared with the recommendation of 320 mg/day by the US Institute of Medicine.[5] This average intake amount was derived from a 1-day diet recall and, thus, may be an overestimate of actual magnesium intake. Magnesium has also been proposed as a limiting nutrient for exercise and performance. Surveys of physically active individuals indicate that magnesium intakes among certain groups of athletes do not meet recommendations for adults.[4] A few reports have indicated that magnesium supplements enhance strength and improve exercise performance.[29] However, it is unclear whether these effects are related to

TABLE 3:
The results of an extensive survey of the diets of adults aged 19 – 64 years in the UK[24]

	Proportion of adults with an intake below the RDA	
Micronutrients	**Men (%)**	**Women (%)**
Vitamin B_1	12	13
Vitamin B_2	20	28
Vitamin B_6	6	10
Folate	11	30
Magnesium	50	74
Zinc	43	45

RDA, recommended daily allowance.

remediation of an existing magnesium inadequacy or a pharmacological effect.[5]

In both Europe and the USA, iron deficiency is considered to be one of the main nutritional deficiency disorders, affecting large proportions of the population, particularly children, and menstruating and pregnant women.[30 – 33]

Low consumption of foods rich in bioavailable zinc, such as meat, particularly red meat, and a high consumption of foods rich in inhibitors of zinc absorption, such as phytate, certain dietary fibres and calcium, impair the recommended zinc status. Inadequate zinc intake, resulting in a suboptimal zinc status, has been recognized in many population groups, both in less developed and in industrialized countries. Although the cause of this may be inadequate dietary intake of zinc, the most likely reason is the consumption of inhibitors of zinc absorption.[34] Women, dieters and the elderly are particularly at risk of being low in zinc.[35,36] Surveys of physically active subjects also indicate that low dietary zinc is common, especially among individuals who participate in aerobic activities, such as those recommended to promote health and well-being.[6]

With respect to minerals and trace elements in general, it is well established that rigorous exercise leads to greater losses, particularly of magnesium, iron, zinc and chromium in sweat and urine.[37 – 40]

In conclusion, the risk of an inadequate micronutrient intake may be provoked by the following different conditions and situations:

(i) Elevated needs due to the induced synthesis of those enzymes important to energy metabolism which, in turn, increases the requirements for micronutrient cofactors.[41]

(ii) Increased loss of minerals, such as magnesium and iron, due to sweating during exercise and in the urine.[37 – 40] In general, micronutrient deficiencies caused by high physical activity (e.g. among active individuals and athletes) are well documented: B vitamins, vitamin C, iron;[42] vitamin B_2 in young women athletes;[43,44] B vitamins, vitamin C;[45] and vitamin B_6 following marathon running.[46]

(iii) Increased need because of dieting and/or a poor diet, especially in combination with a demanding lifestyle. This is especially true of women living an active life who frequently reduce intake of food to lose weight as well as making poor dietary choices. Such women have a particular risk for insufficient B vitamin status. Lifestyle-induced micronutrient deficiency results in reduced physical performance, increased fatigue and tiredness.[47,48]

(iv) Groups such as pregnant women or the elderly must be mentioned, although they are not further considered in this review.

Consequences of inadequate micronutrient intake for physical well-being

Given the importance of micronutrients in energy metabolism it is not surprising that mitochondrial functions are compromised by insufficient dietary intake of B vitamins and/or increased B vitamin needs.[3] Unfortunately, clinical data on the interactions between micronutrient metabolism and physical performance are limited. This is mainly because study designs have not been sufficiently comprehensive to allow reasonable conclusions to be drawn due to the complexity of cellular respiration and the body's ability to utilize alternative pathways of energy production in an emergency. Nevertheless, it has been shown that deficiencies in folate and vitamin B_{12} reduce endurance work performance and that an inadequate intake of minerals impairs performance.[29]

Studies of the effects of restricted diets on physical performance have not only emerged from sports medicine, but also as a 'women's health issue'. Concerns about the health effects of chronic dieting in order to reduce body weight have been regularly voiced in both the medical and the lay press. In a comprehensive review of the health consequences of dieting in active women, a 'chronic dieter' is defined as an individual who 'consistently and successfully restricts energy intake to maintain an average or below-average body weight'.[47] The author notes that individuals with a poor energy intake usually have poor micronutrient intakes, especially of calcium, iron, magnesium, zinc and B complex vitamins.[47] These micronutrients are particularly important for active individuals since, 'they play an important role in energy production, haemoglobin synthesis, maintenance of bone health and strength and an adequate immune function'.[47] Problems may arise for the active female who chronically diets and performance may suffer in athletes involved in aesthetic or 'lean-build' sports, such as dancers, long distance runners or gymnasts, who are under pressure to maintain a lean body shape for their sport.[47] For active females, 'poor physical performance can have a devastating psychological effect, especially if physical performance is tied to job-related expectations'.[47]

Support is given to these conclusions by a Spanish study that investigated energy intake as a determinant factor of vitamin status in healthy young women.[45] In this study, the vitamin status (B_1, B_2, B_6, retinol, β-carotene, C and E) of 56 healthy young women was analysed and related to energy intakes. A high percentage of these apparently healthy young women had deficient or marginally deficient blood levels of most of the vitamins, with adequate or optimal levels only shown for vitamins C, E and retinol. The authors concluded that young women, especially those consuming low-energy diets, are vulnerable to developing marginal vitamin deficiencies. Taken together, there is good evidence that dietary restriction does result in an inadequate micronutrient status and that this may, in turn, impair physical performance.[45,47]

If deficiency of micronutrients can impair physical performance, conversely physical activity may deplete micronutrient status. In a metabolic study, young women were fed various amounts of riboflavin (vitamin B_2) over a 10-week period and their riboflavin status was monitored.[43] When 20 – 50 min/day of exercise for 6 days a week was introduced, riboflavin levels declined but were restored when dietary riboflavin levels were concomitantly increased. A similar study found that, in the weeks when subjects exercised, riboflavin status declined significantly compared with the weeks in which no exercise was performed.[44]

More recently, a double-blind, randomized, crossover study investigated the effects of zinc deficiency on physical performance.[6] Fourteen young men were fed a low-zinc diet for 9 weeks and, following a 6-week washout period, they were then fed a zinc-supplemented diet for a further 9 weeks. Blood and faecal determinations of zinc status and balance, and physiological testing were performed at specific times during each dietary period. The authors concluded that low dietary zinc was associated with impaired cardiorespiratory function and impaired metabolic responses during exercise. In establishing the 1998 dietary reference intake (DRI) for riboflavin, the US Institute of Medicine considered data from a number of metabolic studies and concluded that requirements might be higher in active individuals, but the amount of existing data was not sufficient to quantify the requirement.[8]

A number of studies have indicated that vitamin B_6 is lost as a result of exercise, although the magnitude of the loss is small. Vitamin B_6 is required to maintain plasma concentrations of pyridoxal 5′-phosphate (PLP). Blood studies show that PLP levels rise rapidly during exercise, indicating consumption of vitamin B_6.[48] In subjects with an adequate B_6 intake, the levels fall back to baseline within 30 – 60 min after exercise.[48] As an example, it was calculated that marathon runners lose about 1 mg vitamin B_6 during a marathon, equivalent to the DRI for an adult.[46]

In a review of the effect of physical activity on thiamine, riboflavin and vitamin B_6 requirements[48] it was concluded that, because exercise stresses metabolic pathways that depend on thiamine, riboflavin and vitamin B_6, the requirements for these vitamins may be increased in active individuals. Since exercise seems to decrease nutrient status even further in those with pre-existing marginal vitamin intakes or body stores, individuals ‘who restrict their energy intake or make poor dietary choices are at greater risk for poor thiamine, riboflavin and vitamin B_6 status’.[48]

In 2001 Speich *et al.*[49] published a review of 24 studies carried out between 1994 and 2000 into the significance of levels of 16 minerals and trace elements for physical performance. They concluded that, although many of these minerals are involved in aspects of energy metabolism, for most their precise physiological role is still unclear. This uncertainty underlines the need for further research. A better understanding about micronutrients and energy metabolism is even more urgent because, besides the impact on physical well-being, currently the long-term health consequences for humans with marginal B vitamin deficiencies are not known.[3]

Micronutrient supplementation

It is a well-known fact that, often encouraged by their coaches, sports people and athletes are major consumers of multivitamins/mineral supplements. As an example, Armstrong and Maresh[42] cite studies from Australia showing that 30% – 100% of athletes in different sports have taken supplements. With regard to the effects of micronutrient supplementation on physical performance, the literature generally indicates that a positive effect on physical performance is only detectable when the dietary intake of these nutrients is not adequate. This is supported by the most recent review of this topic, in which the author concluded that the use of vitamin and mineral supplements did not improve measures of performance in people consuming adequate diets.[29] However, ‘young girls and individuals participating in activities with weight classifications or aesthetic components are prone to nutrient deficiencies because they restrict food intake and specific micronutrient-rich foods’.[29]

Do the findings in athletes also apply to ‘normal’ people with only moderate physical activity? Young women at risk of micronutrient deficiency because of chronic dieting have been identified[47] and, in a subsequent paper, it was shown that the risk of deficiency was greatest in physically active women with pre-existing marginal vitamin status.[48] Indeed, both Manore[48] and Lukaski[29] identified the same high risk group, but from different perspectives: Lukaski studied athletes and identified an 'at risk' subgroup of young women who restricted their diet;[29] while Manore studied chronic dieters and identified an 'at risk' subgroup who were physically active.[48] Both authors concurred that multivitamin/ mineral supplementation may be beneficial for such women.

Finally, a generally well-recognized group for inadequate micronutrient intake is the elderly. Diet, micronutrient status and the benefits of supplementation have been much studied in the elderly, however most studies have concentrated on the effects of deficiency on susceptibility to infection and, more recently, cognitive function.[18] However, lack of energy, tiredness, weakness and, paradoxically, loss of appetite are frequent complaints of older people. A recent study confirmed earlier pan-European findings that between 39% and 78% of elderly subjects had dietary intakes of vitamin A, calcium and iron below the lowest European RDA;[50] the relationship between micronutrient insufficiency and energy in this group warrants further study.

As to how long to continue supplementation, the evidence suggests that an inadequate micronutrient status may take several weeks to develop and, once it occurs, it may take an equally long time to replenish body stores. Although data are limited, an experimental study showed that it took around 6 weeks for daily supplementation of vitamin B_6 to restore optimum blood levels.[51] Based on this and clinical data with multivitamin products,[52,53] a treatment period of at least 40 days is usually recommended.

Lichtenstein and Russell[54] recently concluded that there are strong reasons to make recommendations for the use of dietary supplements by certain segments of the population. 'Supplements are relatively inexpensive and can be reliably used to administer nutrients in precise doses. If used consistently, supplements can ensure adequate intakes of specific nutrients in targeted groups that have increased needs for those nutrients because of physiologic limitations or changes'.[54]

Conclusion

An overwhelming body of physiological evidence confirms the fundamental role of vitamins and minerals in energy metabolism. In particular, the B complex vitamins are essential for mitochondrial function and a lack of just one of these vitamins may compromise an entire sequence of biochemical reactions necessary for transforming food into physiological energy. It is also clear that several minerals and trace elements are essential for energy generation, although more research is needed to elucidate their precise role.

Inadequate intake of micronutrients, or increased needs, impairs health and increases susceptibility to infection, but may also result in tiredness, lack of energy and poor concentration. Besides generally accepted risk groups like the elderly, an important group who are at risk of an inadequate micronutrient intake – especially of the B vitamins – are young to middle-aged adults. These are often women with a demanding lifestyle who are physically active and whose dietary behaviour might be characterized by poor choices and/or regular attempts to lose weight.

Given the importance of micronutrients for energy metabolism and the risk for an inadequate micronutrient status in otherwise healthy individuals, multivitamin – mineral supplementation is recommended for patients complaining of chronic lack of energy and in whom underlying disease has been excluded. Where such supplements are prescribed or recommended they should be taken for an adequate period of time, ideally not less than 6 weeks, to obtain a noticeable effect on physical well-being.

Conflicts of interest

Silvia Maggini and Michael Ruf are employed by Bayer Consumer Care, a manufacturer of multivitamins.

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References

1 Groff JL, Gropper SS, Hunt SM: *Advanced Nutrition and Metabolism,* 2nd edn. St. Paul: West Publishing, 1995.
2 Depeint F, Bruce WR, Shangari N, *et al*: Mitochondrial function and toxicity: role of the B-vitamin family on mitochondrial energy metabolism. *Chem Biol Interact* 2006; **163:** 94 – 112.
3 Depeint F, Bruce WR, Shangari N, *et al*: Mitochondrial function and toxicity: role of B vitamins on the one-carbon transfer pathways. *Chem Biol Interact* 2006; **163:** 113 – 132.
4 Lukaski HC: Magnesium, zinc, and chromium nutriture and physical activity. *Am J Clin Nutr* 2000; **72(suppl):** 585S – 593S.
5 Lukaski HC, Nielsen FH: Dietary magnesium depletion affects metabolic response during submaximal exercise in postmenopausal women. *J Nutr* 2002; **132:** 930 – 935.
6 Lukaski HC: Low dietary zinc decreases erythrocyte carbonic anhydrase activities and impairs cardiorespiratory function in men during exercise. *Am J Clin Nutr* 2005; **81:** 1045 – 1051.
7 Institute of Medicine: *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride*. Washington DC: National Academic Press, 1997.
8 Institute of Medicine: *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin and Choline*. Washington DC: National Academic Press, 1998.
9 Institute of Medicine: *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids.* Washington DC: National Academic Press, 2000.
10 Institute of Medicine: *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc*. Washington DC: National Academic Press, 2001.
11 Brubacher GB: Assessment of vitamin status in pregnant women. In: *Vitamins and Minerals in Pregnancy and Lactation* (Berger H, ed). Nestle Nutrition Workshop Series, Vol 16. Vevey: Nestec / New York: Raven Press, 1988; pp 51 – 57.
12 Bässler KH: Definition und Relevanz subklinischer Vitaminmangelzustände. *VitaMinSpur* 1995; **10:** 112 – 118.
13 Pietrzik K: Concept of borderline vitamin deficiencies. *Int J Vitam Nutr Res Suppl* 1985; **27:** 61 – 73.
14 Baessler KH, Golly I, Loew D, *et al* (eds): *Vitamin-Lexikon fuer Aerzte, Apotheker und Ernaehrungswissenschaftler*, 3rd edn. Muenchen-Jena: Urban & Fischer, 2002.
15 Shankar AH: Nutritional modulation of immune function and infectious disease. In: *Present Knowledge in Nutrition,* 8th edn (Bowman BA, Russel RM, eds). Washington DC: ILSI Press, 2001; chapter 59, pp 686 – 700.
16 Meydani SN, Han SN: Nutrition regulation of the immune response: the case of vitamin E. In: *Present Knowledge in Nutrition,* 8th edn (Bowman BA, Russel RM, eds). Washington DC: ILSI Press, 2001; chapter 41, pp 449 – 462.
17 Rucker RB, Suttie JW, McCormick DB, *et al* (eds): *Handbook of Vitamins*, 3rd edn. New York: Marcel Dekker, 2001.
18 Huskisson E, Maggini S, Ruf M: The influence of micronutrients on cognitive function and performance. *J Int Med Res* 2007; **35:** 1 – 19.
19 Fairfield KM, Fletcher RH: Vitamins for chronic disease prevention in adults. *JAMA* 2002; **287:** 3116 – 3126.
20 Fletcher RH, Fairfield KM: Vitamins for chronic disease prevention in adults. *JAMA* 2002; **287:** 3127 – 3129.
21 van der Beek EJ, Löwik MRH, Hulshof KFAM, *et al*: Combinations of low thiamin, riboflavin, vitamin B_6 and vitamin C intake among Dutch adults (Dutch Nutrition Surveillance System). *J Am Coll Nutr* 1994; **13:** 383 – 391.
22 van der Beek EJ, van Dokkum W, Schrijver J, *et al*: Thiamin, riboflavin, and vitamins B-6 and C: impact of combined restricted intake on functional performance in man. *Am J Clin Nutr* 1988; **48:** 1451 – 1462.
23 Löwik MRH, van den Berg H, Schrijver J, *et al*: Risk assessment regarding vitamin B_6 among elderly people (Dutch Nutrition Surveillance system). *Age Nutr* 1993; **4:** 126 – 132.
24 Food Standards Agency: *The National Diet and Nutrition Survey: Adults Aged 19 to 64 Years*, Vol 3. London: The Stationery Office, 2003.
25 Ganji V, Kafai MR: Trends in serum folate, RBC folate, and circulating total homocysteine concentrations in the United States: analysis of data from National Health and Nutrition Examination Surveys, 1988 – 1994, 1999 – 2000,

and 2001 – 2002. *J Nutr* 2006; **136**: 153 – 158.

26 Konings EJM, Roomans HHS, Dorant E, *et al*: Folate intake of the Dutch population according to newly established liquid chromatography data for foods. *Am J Clin Nutr* 2001; **73:** 765 – 776.

27 Oner N, Vatansever U, Karasalihoglu S, *et al*: The prevalence of folic acid deficiency among adolescent girls living in Edirne, Turkey. *J Adolesc Health* 2006; **38:** 599 – 606.

28 Holick MF: High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006; **81:** 353 – 373.

29 Lukaski HC: Vitamin and mineral status: effects on physical performance. *Nutrition* 2004; **20:** 632 – 644.

30 Hercberg S, Preziosi P, Galan P: Iron deficiency in Europe. *Public Health Nutr* 2001; **4:** 537 – 545.

31 Looker AC, Dallman PR, Carroll MD, *et al*: Prevalence of iron deficiency in the United States. *JAMA* 1997; **277**: 973 – 976.

32 Centers for Disease Control (CDC): Recommendations to prevent and control iron deficiency in the United States. *MMWR Recomm Rep* April 3, 1998/47(RR-3): 1 – 36. http://www.cdc.gov/mmwr/preview/mmwrhtml/00051880.htm

33 Centers for Disease Control (CDC): Iron deficiency, United States, 1999 – 2000. *MMWR Morb Mortal Wkly Rep* October 11, 2002/51(40): 897 – 899. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5140a1.htm

34 Lönnerdal B: Dietary factors influencing zinc absorption. *J Nutr* 2000; **130:** 1378S – 1383S.

35 Hambidge M: Human zinc deficiency. *J Nutr* 2000; **130:** 1344S – 1349S.

36 Sandström B: Zinc: the functional significance of marginal deficiency. In: *Modern Lifestyles, Lower Energy Intake and Micronutrient Status* (Pietrzik K, ed). London: Springer, 1991; pp 181 – 189.

37 Anderson RA, Polanski MM, Bryden NA: Strenuous running: acute effects on chromium, copper, zinc and selected clinical variables in urine and serum of male runners. *Biol Trace Elem Res* 1984; **6:** 327 – 336.

38 Brouns F: Haben Sportler spezielle Ernährungsbedürfnisse? *Deutsche Lebensmittel Rundschau* 1995; **91:** 181 – 185.

39 McDonald R, Keen CL: Iron, zinc and magnesium nutrition and athletic performance. *Sports Med* 1988; **5:** 171 – 184.

40 Córdova A, Navas FJ: Effect of training on zinc metabolism: changes in serum and sweat zinc concentrations in sportsmen. *Ann Nutr Metab* 1998; **42:** 274 – 282.

41 Bässler KH: Vitaminbedarf unter besonderen physiologischen und pathologischen Bedingungen. *VitaMinSpur* 1992; **4:** 176 – 180.

42 Armstrong LE, Maresh CM: Vitamin and mineral supplements as nutritional aids to exercise performance and health. *Nutr Rev* 1996; **54**: S149 – S158.

43 Belko AZ, Obarzanek E, Kalkwarf HJ, *et al*: Effects of exercise on riboflavin requirements of young women. *Am J Clin Nutr* 1983; **37**: 509 – 517.

44 Winters LR, Yoon JS, Kalkwarf HJ, *et al*: Riboflavin requirements and exercise adaptation in older women. *Am J Clin Nutr* 1992; **56**: 526 – 532.

45 Carbajal A, Núñez C, Moreiras O: Energy intake as a determinant factor of vitamin status in healthy young women. *Int J Vitam Nutr Res* 1996; **66:** 227 – 231.

46 Rokitzki L, Sagredos AN, Reuss F, *et al*: Acute changes in vitamin B6 status in endurance athletes before and after a marathon. *Int J Sport Nutr* 1994; **4**: 154 – 165.

47 Manore MM: Chronic dieting in active women: what are the health consequences? *Women's Health Issues* 1996; **6**: 332 – 341.

48 Manore MM: Effects of physical activity on thiamine, riboflavine, and vitamin B-6 requirements. *Am J Clin Nutr* 2000; **72(suppl):** 598S – 606S.

49 Speich EJ, Pineau A, Ballereau F: Minerals, trace elements and related biological variables in athletes and during physical activity. *Clin Chim Acta* 2001; **312:** 1 – 11.

50 Martins I, Dantas A, Guiomar S, *et al*: Vitamin and mineral intakes in the elderly. *J Nutr Health Aging* 2002; **6:** 63 – 65.

51 Kübler W: Pharmacokinetic implications of single and repeated dosage. *Int J Vitam Nutr Res Suppl* 1989; **30:** 25 – 34.

52 Singh A, Moses FM, Deuster PA: Vitamin and mineral status in physically active men: effects of a high-potency supplement. *Am J Clin Nutr* 1992; **55:** 1 – 7.

53 Heseker H, Kübler W: Chronically increased vitamin intake and vitamin status of healthy men. *Nutrition* 1993; **9:** 10 – 17.

54 Lichtenstein AH, Russell RM: Essential nutrients: food or supplements? Where should the emphasis be? *JAMA* 2005; **294:** 351 – 358.

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