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Supraphysiological dosages of vitamins and their implications in man

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Summary. Some recent evidence on the benefits and hazards of elevated dosages of vitamins is summarized. Special emphasis is given on the safety of vitamins A, D, K_1 and B_6. Furthermore, the possibly beneficial effects of vitamins for athletic performance as well as the preventive potential of antioxidative vitamins and of carotenoids against cancer are discussed.
Key words. Vitamins; antioxidative vitamins and cancer; vitamins and athletic performance; carnitine; toxicity of vitamins A, E, K_1, B_6.

Everyone knows that vitamins are essential for health and that a good supply is ensured if we eat the right food. Because people are often uncertain whether they are really getting enough of each vitamin, they tend to supplement their food with high-dosage vitamin pills or capsules. In addition, many vitamins have become known as having additional, beneficial effects. Even 'magic' properties have been claimed for them, if they are taken in large dosages. The question, therefore, arises: How much is enough, and what happens if large dosages are taken up – are they beneficial or toxic? In order to answer those questions, Stähelin, Brubacher and myself organized a symposium on this topic in 1987, and this paper is based on the symposium book issued in 1989. It will, however, not be possible to give a complete overview. After a short general introduction, I will mainly discuss the oral uptake of supraphysiological dosages by healthy adults, and will not include clinical cases where the supplementation with vitamins is of importance. It will also not be possible to cover all the vitamins.

Recommended dietary allowances

Before discussing supraphysiological dosages, it is necessary to give some thought to the difficulty of determining the so-called recommended dietary allowance (RDA). Each vitamin has many functions in our body. When the daily intake is reduced, the most sensitive function of each vitamin will be affected first, and if the insufficient uptake is continued, further functions will be impaired. Finally, the first signs of the specific vitamin deficiency disease will appear[4]. In order to make a recommendation for the daily intake we have to know the minimal requirement for maximal protection for each vitamin-dependent function. This *functional requirement* shows a large individual variation, and a *safety margin* has to be defined when a country sets its RDA values. It has, furthermore, to be taken into consideration that all vitamins can be stored in our bodies, but the storage capacity for each vitamin is different. We therefore also have to take into account a *storage requirement*, i.e. a minimal requirement to allow for adequate storage pools of each vitamin.

At present, we do not have all the necessary information concerning functional and storage requirements for each vitamin. The published RDA values from different countries are therefore only partially based on scientific data. They are the result of a compromise between scientific judgement and other considerations such as the size of the safety margin, special risk factors, and also economic arguments. It is therefore not surprising that the RDAs set by various countries differ considerably[4].

Definition of supraphysiological dosages

As mentioned above, a certain safety margin is always included in the RDA values in order to take into account individual variation and other factors. Therefore in certain cases the RDA value may already be somewhat higher than what is physiologically needed. Nevertheless, to simplify matters I shall use the term 'supraphysiological dosages' for those intake values that are above the 1980 RDA values for the USA.

The safety of supraphysiological dosages of vitamins

Marks[9] has divided the vitamins into two broad categories:

a) Those vitamins with a safety level at least 50–100 times greater than the RDA, and no clear indication of serious adverse reactions above that level. This level should be adequate to match any required pharmacological dose, and these vitamins should be regarded as safe for use at elevated dosages, not necessarily under medical supervision.
b) Those vitamins with a safety ratio of about 10 times the RDA value (this is often influenced by the health status of the individual), and/or those vitamins with serious irreversible adverse reactions. These vitamins can be used safely at the RDA level, but should only be administered at higher dosages under medical supervision to avoid dose escalation.

Marks[9] considers that most vitamins can be put into category (a) and that only vitamins A, D, K and B_6 belong to the more dangerous category (b). I will first discuss some aspects of these four vitamins.

The RDA for vitamin A (retinol) amounts to 1 mg per day (3333 IU). We cover our retinol requirement mainly by eating meat, fish, milk and eggs. Plants do not contain retinol itself, but do contain carotenoids from which retinol can be split off in the digestive tract; the best known example is β-carotin, consisting of two retinols and occurring in carrots. Part of the ingested carotenoid is split in the digestive tract, but another part is directly absorbed into the lymph, from which it goes into the blood[17]. The most common manifestations of vitamin A overdosage are skin redness, disturbed hair growth, nausea and anorexia. These adverse effects are extremely rare to dosages below 0.9 mg retinol daily, and the majority arise at much higher dosages[9,17]. In recent years, it has been shown that both retinol and retinyl esters are teratogenic in animals. Until more is known about the mechanism of placental transfer and its control, and also about the dose-related teratogenicity of vitamin A, it is generally recommended[17] that fertile and especially pregnant women should limit their daily intake to not more than 10,000 IU, i.e. $3 \times$ RDA. No teratogenic effect has been reported for β-carotin. However, at dosages higher than 15 mg per day a strong carotenodermia is observed. As will be discussed later, carotenoids may play an important role as radical scavengers in the prevention of cancer.

Vitamin A deficiency is known to be a serious public health problem in at least 26 countries, especially in Asia and Africa[15]. An estimated 5–10 million children suffer from xerophthalmia and 250,000–500,000 go blind every year. Vitamin A deficiency has also been associated with a 10–14-fold increase in mortality. Because it is very difficult to change the diet of these persons in such a way that they take enough vitamin A every day, single high dosages are given. In a recent study[15] it has been shown that administration of 200,000 IU every 4–6 months to children one year and older reduces mortality, stimulates growth, and prevents xerophthalmia and nutritional blindness. Because the liver can store relatively large amounts of retinol and retinyl esters, side effects of this administration have been minimal. Special WHO programs have now been initiated to continue this treatment, in order to prevent vitamin A deficiency. This administration of large dosages of vitamin A is an example which shows that one very large dose is not harmful, whereas the chronic administration of a 20 times lower dosage may be toxic.

In the case of vitamin D, it has been known for a long time that the intake should not exceed 10 times the RDA. The toxic symptoms are hypercalcemia, anorexia and renal calcification[6]. Vitamin D supplementation is a special problem in newborn or preterm infants, but this will not be discussed here in detail[11].

Vitamin K_1, phylloquinone, may reverse anti-coagulant therapy. Therefore a safety ratio of about 15 times the normal intake has been recommended. No official RDA for this vitamin has been determined; however, it has been estimated to be in the area of 100 µg per day[2].

The fourth vitamin of the risk group is vitamin B_6, with an RDA value of 2.2 mg per day. The administration of this vitamin at chronic dosages higher than 600 mg per day, i.e. $\approx 270 \times$ RDA may be critical. Especially for the treatment of the pre-menstrual syndrome, dosages of several grams may be prescribed, and several cases of side effects such as reversible peripheral sensory neuropathies have been described. According to Bässler[1], treatment with dosages higher than 200–500 mg per day may be considered to be the upper limit of a daily prescription. However, such treatment should always be under medical supervision.

For certain vitamins that were not put in the risk group by Marks, the question of safety above 100 times the RDA has to be mentioned. Of special interest is vitamin C (RDA: 60 mg per day), of which many people take up to 10 g daily over long periods of time. The main reason for taking these high dosages is that there are reports indicating a beneficial effect on certain types of cancer. Marks, who has reviewed the literature in detail[9], concludes that the safe daily level is at least 100 times the RDA. Even with doses up to 10 g per day, the risk of oxalate stones is not increased except for persons with severe renal insufficiency. Furthermore, the evidence that vitamin C leads to cyanocobalamine depletion, to a decrease in immunological tolerance, or to mutagenic effects, could not be confirmed.

Also in the case of vitamin E (RDA: 10 mg per day), chronic dosages of 2–3.5 g for several months showed only very minor side effects that might not even have been related to the administration of the vitamin. The only significant difficulty is that high dosages of vitamin E interfere with vitamin K_1, and are therefore contraindicated during anticoagulant therapy. With this exception, the safety factor appears to be substantially higher than 100 times the RDA[8,9].

A very special case concerns the pharmacological effects of niacin (RDA 18 mg per day), which is known to exert a cholesterol-lowering effect. Today the alcohol (pyridylcarbinol) and nicotinic acid are well-known drugs for the treatment of hypercholesterolemia[19]. The average dosages that are necessary for this treatment are about 6 g of nicotinic acid per day.

Evidence for beneficial effects of supraphysiological dosages of vitamins

The potential beneficial effect of elevated dosages of vitamins on adults is at present a wide open field. Many observations have been reported of beneficial changes in one way or another after the intake of high dosages of one or several vitamins. In most of these cases it is not possible to decide with certainty whether the changes were related to the intake of the vitamin. It is, for example, possible to measure the intake, the blood levels and the excretion of vitamins in cyclists taking part in the Tour de France[14], but it is not possible to relate these levels to the performance of the respective athletes because all of them take vitamins. The same is true for certain illnesses such as cancer, where no patient wants to be deprived of vitamin C if there is a hope that it could help. In the following, I will concentrate on only a few aspects of the effects of elevated dosages of vitamins.

Vitamins and sports

Recent reviews by Williams[18] and Nöcker[12] concluded that physical performance may be impaired if there is a vitamin deficiency. Under these conditions it is also possible to show that vitamin supplementation improves physical performance. Such vitamin deficiencies may occur in disciplines where dieting is used to reduce body weight, for instance among weight lifters, wrestlers and boxers.

Whether or not vitamin supplements can improve the athletic performance of athletes who are on a well-balanced diet is a matter of great controversy. Nöcker[12] reported that the need for vitamins A, B_1, B_2, niacin, C, D, E and B_6 is higher when there is a high energy demand over a prolonged period of time. In general, our storage capacity for these vitamins is large enough to satisfy the increased demand. It is clear that after the athletic performance, the storage pools have to be replenished. There is, however, very little if any conclusive evidence to support the contention that vitamin intake above and beyond normal RDA will significantly enhance physical performance[18]. There is one interesting study[5] in which a statistically significant improvement of target shooting was shown after an oral intake of elevated dosages of a combination of vitamins B_1, B_6 and B_{12}. It was suggested that an excess of these B-vitamins may influence receptor affinity for neurotransmitters or their binding capacity; this may indeed implicate an influence on the fine tuning for sensory motor control, leading to better results in shooting.

In recent times, the 'semi-vitamin' carnitine has been attracting special attention, especially in Italy, where it is believed to improve athletic performance especially in endurance tests. Its role in fatty acid oxidation is well known. As in the case of vitamins, there is little evidence to show that athletic performance can be improved in well-nourished athletes by carnitine supplementation. On the other hand there are two studies showing that administration of 1–2 g of carnitine to untrained athletes increased the ratio of oxygen utilization to heart-rate, mainly because the latter decreased[5,7]. Also, the intravenous injection of carnitine in patients with ischemic heart disease resulted in a lowering of the heart rate.

These results may reflect a second function of carnitine in addition to its role in fatty acid oxidation. This function is related to the fact that during oxidation in the mitochondria most of the CoA is bound to fatty acids or acetate. However, CoA is needed for the oxidation of pyruvate and certain amino acids. Addition of carnitine leads to the formation of acetyl-carnitine, thereby liberating CoA. In this way carnitine can enhance the oxidation of pyruvate derived from glucose. Since the output of energy in relation to oxygen consumed (i.e. the energy equivalence of O_2) is higher in the case of glucose than in the case of fatty acids, this function of carnitine would lead to a higher utilisation of glucose, resulting in a higher energy output per unit of oxygen used, resulting in a lowering of heart rate. Carnitine could therefore be potentially useful in enhancing athletic performance when carbohydrates are used as the main source of energy. For further details see references[3,10,13].

Preventive potential of antioxidative vitamins and carotinoids against cancer

In a prospective study performed in Basel in 1971 with 2974 male participants, cancer mortality and vitamin status were found to be correlated [16]. This as yet uncompleted study demonstrates a significant inverse correlation between plasma β-carotin and all types of cancer, as well as cancer of the lung and of the stomach. Retinol was related only to gastric cancer, whereas low vitamin C and low vitamin E were related to all types of cancer, including gastric cancer. These results point to the fact that the antioxidative vitamins may be more important than has been thought so far. At present, several intervention studies throughout the world are going on to investigate this point. A possible implication of these studies that must be considered is that the RDAs of the antioxidative vitamins may have to be increased.

Final remark

In the present paper some of the 'hot topics' in vitamin application have not been reviewed, in particular the controversial evidence on the application of megadosages of vitamin C and E. Further research has to be carried out, especially to distinguish between the physiological and pharmacological effects of vitamins.

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The physiological and nutritional importance of dietary fibre

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Summary. Fibrous material is an integral part of the daily diet, and it exerts direct physiological effects throughout the gastrointestinal tract, in addition to affecting metabolic activities more indirectly.
The interplay of these effects is responsible for the presumed desirable influence of fibre on weight regulation, carbohydrate and lipid metabolism, and on colon function. Numerous mechanisms of action have been identified which are related to the type and the physicochemical nature of the fibre. This review concentrates mainly on the serum cholesterol-lowering effect of dietary fibre, its colonic fermentation, and finally on some possible adverse effects that one should be aware of when consuming high amounts of dietary fibre.
Key words. Dietary fibre; nutrition; review; health; cholesterol; minerals; fermentation; gastrointestinal tract; cancer.