

MEGADOSES OF VITAMINS C, D, AND E

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INTRODUCTION

After the vitamins were discovered during 1915-1948 and their chemical and physical properties as well as physiological roles were learned, the importance of vitamins became accepted. However, there has been a great deal of controversy about the amounts of vitamins that should be consumed daily to support optimal health. Also there has been confusion about the difference between the terms "physiologic" and "pharmacologic" as applied to doses of vitamins (1). Different orders of magnitude of intake of vitamins C, D, and E are compared in Table 1. "Physiologic doses" represent the amounts of these vitamins recommended in 1974 by the Food and Nutrition Board of the National Research Council (NRC-RDA) (2) to meet the known nutritional needs of practically all healthy young male adults. A "pharmacologic dose" is generally in the range of ten times the physiological dose; it may be used to treat an illness or a condition quite unrelated to the generally recognized manifestations of a vitamin deficiency. A "toxic dose" of 100 times or more the physiologic dose may induce undesirable or toxic signs and symptoms.

Supplementation with vitamins has value for persons in certain situations: the elderly, those on low-calorie reducing diets, those taking certain medications (such as oral contraceptives and anti-epilepsy drugs), pregnant women, and infants who are not breast-fed. Some persons say they feel better and have more energy when taking vitamin supplements, even when no deficiency can be demonstrated. However, a common approach to vitamins has been: "If a little bit is good, a lot will be better, and enormous quantities still better". When excessive vitamins are taken into the body, they function as chemicals instead of vitamins. The body must

TABLE 1

Effects of varying doses of vitamins C, D, and E (1)

Substance	Physiologic Dose	Pharmacologic Dose	Toxic Dose and Manifestations of Toxicity
Vitamin C	45 mg	100-2000 mg	2000-4000 mg Reproductive failure Interferes with tests for glycosuria Reverses effects of anticoagulants May induce nephrolithiases Inactivates vitamin B ₁₂ Induction of vitamin C dependent ayndrome
Vitamin D	400 IU	50,000- 100,000 IU Hypophosphatemic rickets	1000-3000 IU-(children)-Hypercalcemia 15,000 IU-(adult)-renal failure
Tocopherol	15 mg	300-1200 mg Cardiovascular disorder	1000 mg / kg (experimental animals) Increase deposition of cholesterol in aorta Decrease hepatic tolerance to ethanol

excrete excess chemicals which may interact with other substances and cause toxicity. However, according to a recent concept, some vitamins can be used in pharmacological dosages to prevent and treat certain diseases such as some forms of cancer. The purpose of this report is to review and discuss the uses and effects of megadoses of vitamin C, D, and E by animal and human beings.

VITAMIN C

Human requirements

Ascorbic acid is necessary for the hydroxylation of proline and lysine in the amino acid chain of collagen (3). The function of ascorbic acid in collagen formation makes it indispensable for the growth of fibroblasts, osteoblasts, and odontoblasts (4). The primary defect in scurvy, ascorbic acid deficiency disease, is the failure of collagen formation in the fibroblast in connective tissue (4).

Results of numerous studies have indicated that a daily intake of 10 mg of ascorbic acid is sufficient to alleviate and cure the clinical signs of scurvy in human subjects (5). This amount, however, may not be satisfactory for the maintenance of optimal health over a long period of time. Anderson (6) stated that the vitamin C level of blood can be increased only to a certain point by increasing the daily intake of vitamin C. Maximum blood concentrations are reached with intakes of 60 to 120 mg ascorbic acid per day. Tissue levels also appear to reach a plateau---referred to as "saturation of tissues". In this state, body stores of the average adult (estimated at approximately 4000 mg) decline at a constant rate of about 3 % per day. The 1974 NRC-RDA of 45 mg will maintain a body pool of 1500 mg which is 300 mg above the level that symptoms of scurvy begin to appear. Recently, there have been many claims for benefits of pharmacological doses of ascorbic acid. However, there are doubts about the safety of taking large amounts for long periods of times.

Vitamin C and the common cold

In his 1970 controversial book, "Vitamin C and the Common Cold",

Linus Pauling (7) suggested that individuals should take one gram or more of ascorbic acid daily to protect against the common cold. Since that time and despite warnings of possible adverse effects of large doses of ascorbic acid, many persons have consumed large amounts of vitamin C each day.

Pauling (8,9) was influential in opening serious consideration of the possible merits of ascorbic acid for prevention and treatment of the common cold. In 1972, Anderson et al. (10) studied 1000 volunteers in Toronto, Canada . The subjects took 1 g of ascorbic acid or a placebo daily for 14 weeks; they increased the dose to 4 g daily during the first three days of any illness. Of the 818 volunteers who completed the trial, 407 had received ascorbic acid, and 411 had received a placebo. A number of sickness indices were compared. Total days of disability (confined to house and off work) and number of individuals free of illness during the test period are shown in Table 2. Although the total number of episodes of illness was 7 % lower in the vitamin group, this difference was not statistically significant. Similarly, although there was 12 % difference in the total days of recorded symptoms in the two groups, that difference was not statistically significant. However, there was a highly significant difference in the amount of disability experienced by the two groups.

The vitamin group had recorded 531 days confined to the house, 30 % fewer than the 769 days recorded by the placebo group. In an attempt to acquire clear quantitative measures of both prophylactic and therapeutic effects of ascorbic acid, Anderson et al. (11) carried out a double-blind randomized study in 1974. Eight different treatment regimens were established, with approximately 400 subjects in each group. In this study, all the

TABLE 2

Total days of disability and number of individuals free of illness in the ascorbic acid group and the placebo group. (10)

	Treatment	
	Ascorbic acid	Placebo
Subjects who completed study	407	411
Total days confined to house per subject**	1.30 \pm 0.101	1.87 \pm 0.138
Total days off work per subject *	0.88	1.31
No.(%) of subjects who remained free of illness \ddagger	105 (26)	76 (18)

** t test, $p < 0.001$

* t test, $p < 0.01$

\ddagger $\chi^2 = 5.92$, $p < 0.05$

differences between measures of illness were small compared to the standard errors, and none approached statistical significance. They failed to replicate the earlier findings and no clearly reproducible pattern of efficacy emerged.

A 14-week study of 641 Navajo boarding school children by Coulehan et al. (12) revealed 26 % fewer symptomatic days in treated younger children and 33 % fewer in older girls but no effect in older boys. However, these results could not be confirmed in his subsequent trial in 1976 (13).

Effect on uric acid metabolism

In 1976, Stein et al. (14) reported the effects of ascorbic acid on uric acid metabolism of ten men and five women maintained on a purine-free diet which provided about 2600 kcal and 70 g of protein. Five of the subjects had gout, four had asymptomatic hyperuricemia and six had normal levels of uric acid. In nine fasting subjects, the administration of 4 g of ascorbic acid caused a significant increase in clearance of uric acid; doses of 0.5 or 2 g did not increase the clearance. They concluded that the increase in clearance with the large dose of ascorbic acid was not due to changes in urate binding to serum proteins since in vitro studies did not show a change in binding. Ascorbic acid did not change the creatinine clearance and thus the glomerular filtration rate was not changed. They suggested that a change in tubular function might explain the results since three of four patients demonstrated a complete inhibition of the ascorbic acid induced uricosuria when acetylsalicylic acid and pyrazinamide were given.

Stein et al. (14) also observed that chronic administration of 8 g of ascorbic acid daily to three subjects resulted in an increased

clearance of uric acid to 174 % of control values. The increased loss of uric acid was maintained throughout the study and for one or two days thereafter. Serum uric acid declined in all three subjects by 1.5, 3.1 and 1.2 mg per 100 ml while they were receiving ascorbic acid. These data may be relevant to the formation of uric acid stones or in the management of gouty individuals.

Hemolytic anemia

Mengel and Greene (15) studied the pharmacologic effects of ascorbic acid on hemolysis of human red cells. They tested the lytic sensitivity of erythrocytes to hydrogen peroxide in 14 healthy volunteers with no previous history of hemolysis. Five grams of ascorbic acid were given daily, 1 g at breakfast and 2 g after the noon and evening meals. The percent lysis was approximately 3 % prior to the administration of ascorbic acid and rose to approximately 9 % after administration of ascorbic acid. None of the subjects showed any evidence of hemolysis in vivo. The investigators speculated that ascorbic acid might increase hemolysis in patients who have depressed mechanisms for handling oxidant stress, such as glucose-6-phosphate dehydrogenase deficiency.

Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency

Campbell et al. (16) discussed a case study in which megadoses of ascorbic acid were a contributing factor to the death of a 60-year-old black man admitted to the hospital for treatment of acute renal failure. Six days prior to admission he had suffered second degree burns of the hand. After admission he received 80 g of ascorbic acid intravenously on each of two consecutive days. Before treatment, his urinalysis and hemoglobin concentrations were normal but on the third day of ascorbic acid

treatment he became oliguric. The urine was dark in color and the serum was red. Creatinine concentration was 4 mg per 100 ml and hemoglobin concentration was 6 g per 100 ml. He was transferred first to a regional hospital and given two units of blood and corticosteroids and then transferred again to a university hospital. Upon admission to the university hospital, he was comatose and in respiratory distress. Physical examination revealed right-sided hemiparesis. The liver and spleen were not enlarged and there was no purpura. At this time the hemoglobin concentration was 12 g per 100 ml, the platelet count was 45,000 per mm, an abnormal bone marrow was noted and the serum creatinine concentration was 14 mg per 100 ml. The patient was anuric. The erythrocyte G-6-PD was only 1.76 units per gram of hemoglobin (normal: 8.4 ± 1.3 units per gram). Electrophoresis revealed the isoenzyme GdA⁻ which is relevant since individuals of African decent with G-6-PD deficiency show this isoenzyme. About 50 % of the patient's erythrocytes lacked G-6-PD (normal: less than 5 %). The patient was dialyzed with little change in clinical status. Platelet levels returned to normal suggesting that disseminated intravascular coagulation had abated. The neurological status deteriorated, however, and the patient died on the twenty-second day. Compbell et al. concluded that while ascorbic acid has a low toxicity in most individuals, patients, such as this one with G-6-PD deficiency, appear to be unusually sensitive to large amounts of ascorbic acid.

Destruction of vitamin B₁₂

Herbert and Jacob (17) evaluated the vitamin B₁₂ status of persons ingesting 0.5 g or more of ascorbic acid. Their data indicated destruction of vitamin B₁₂ contained in food was increased by increasing pharmacological

doses of ascorbic acid, 0.1 g, 0.25 g, and 0.5 g. The degree of destruction of vitamin B₁₂ in food by pharmacological doses of ascorbic acid appears from the data to be different for different meals. This implies that various ingredients in different foods play a role in augmenting or reducing the destructive effect of ascorbic acid, possibly in proportion to their oxidation or reducing capacity. A strong oxidant could rapidly destroy ascorbate and thereby eliminate its damaging effect; this might occur with foods of high nitrate content. Herbert and Jacob (17) suggested the possibility that large oral doses of ascorbic acid may destroy some vitamin B₁₂ in serum and in body stores.

Hines (18) assessed vitamin B₁₂ concentrations in serum and peripheral blood smears of three subjects, aged 50 to 60 years, who had been taking a minimum of 1000 mg of ascorbic acid with each meal for more than three years. Those three subjects showed subnormal serum vitamin B₁₂ concentrations. Two of the three had hypersegmented neutrophils and occasional ovalomacocytes which is indicative of a morphologic expression of vitamin B₁₂ deficiency but none were anemia. In one subject, the serum vitamin B₁₂ level increased within three months following cessation of the megadose regimen of ascorbic acid. They concluded that possibly 2 to 3 % of subjects on megadose regimens of ascorbic acid may well be at risk for ultimate development of vitamin B₁₂ deficiency.

Role in atherosclerosis

Many claims have been made that vitamin C might play a protective or curative role in diseases resulting from atherosclerosis. There is some evidence of a preliminary nature that ascorbic acid can have an effect on lipid metabolism. Kretchevsky (19) called attention to work indicating that

the livers of scorbutic guinea pigs do not oxidize cholesterol at an optimal rate, but he suggested that the effect of ascorbic acid on cholesterol metabolism may not be direct. Spittle (20) reported that daily administration of 1000 mg of ascorbic acid resulted in lower cholesterol levels in the serum of young people under 25 years of age, had no consistent effect in older people and actually increased the levels in patients with atherosclerosis. Ginter (21) observed that concentrations of cholesterol increased in the serum and livers of guinea pigs with vitamin C deficiency while the rate of conversion of cholesterol to bile acids by the liver was decreased. While studying factors that influence the rate of lipolysis, Tsai et al. (22) observed that ascorbic acid can inactivate lipase in the presence of ATP and $MgCl_2$. Their study indicated that ascorbic acid may have an effect on lipase activity as well as on cholesterol metabolism.

Both increases and decreases in the concentration of cholesterol have been attributed to ascorbic acid. It is not surprising that studies of the consumption of relatively large amounts of ascorbic acid without control of other variables have resulted in contradictions. Klevay (23) hypothesized that a high ratio of zinc to copper was associated with hypercholesterolemia and large amounts of ascorbic acid seemed to inhibit the absorption of ascorbic from the intestinal tract (24). Her data showed that addition of ascorbic acid to the diet of rats produced hypercholesterolemia. She suggested that this result should be consonant with data on men fed ascorbic acid under reasonable dietary control because rats do not require exogenous ascorbic acid.

VITAMIN D

Human requirement

The importance of vitamin D in human nutrition resides in its role as a regulator of the metabolism of calcium and phosphate. Vitamin D promotes the intestinal absorption of calcium and also mediates the mobilization of calcium from bone. In this function, vitamin D maintains blood calcium and phosphorus levels to permit normal calcification in bone matrix and cartilage (25, 26). In the absence of vitamin D, mineralization of bone matrix is impaired and collagen synthesis is defective, resulting in the disease called rickets in children and osteomalacia in the adults. According to the 1974 Recommended Dietary Allowances (2), 100 IU of vitamin D per day prevents rickets and ensures adequate absorption of calcium from the gut, satisfactory growth rate, and normal mineralization of the bone in infants. The ingestion of 300-400 IU promotes better calcium absorption and some increase in growth. Therefore this higher level is recommended as the daily allowance for all people under age of 22 (2).

Vitamin D metabolism and its metabolites

The recent identification of many vitamin D metabolites has yielded a complex pattern for vitamin D metabolism. The present known pathway as summarized by DeLuca (27) is shown in figure 1.

In 1968, Blunt et al. (28) isolated the predominant vitamin D₃ derivative in blood and determined its structure to be 25-hydroxy-vitamin D₃ (25-OH-D₃). This metabolite is the product of the initial step in the activation of the vitamin and also serves as the progenitor of other active vitamin D forms. Blunt and DeLuca (29) achieved the chemical synthesis of 25-OH-D₃ and proposed that it was the biologically active form of vitamin D₃.

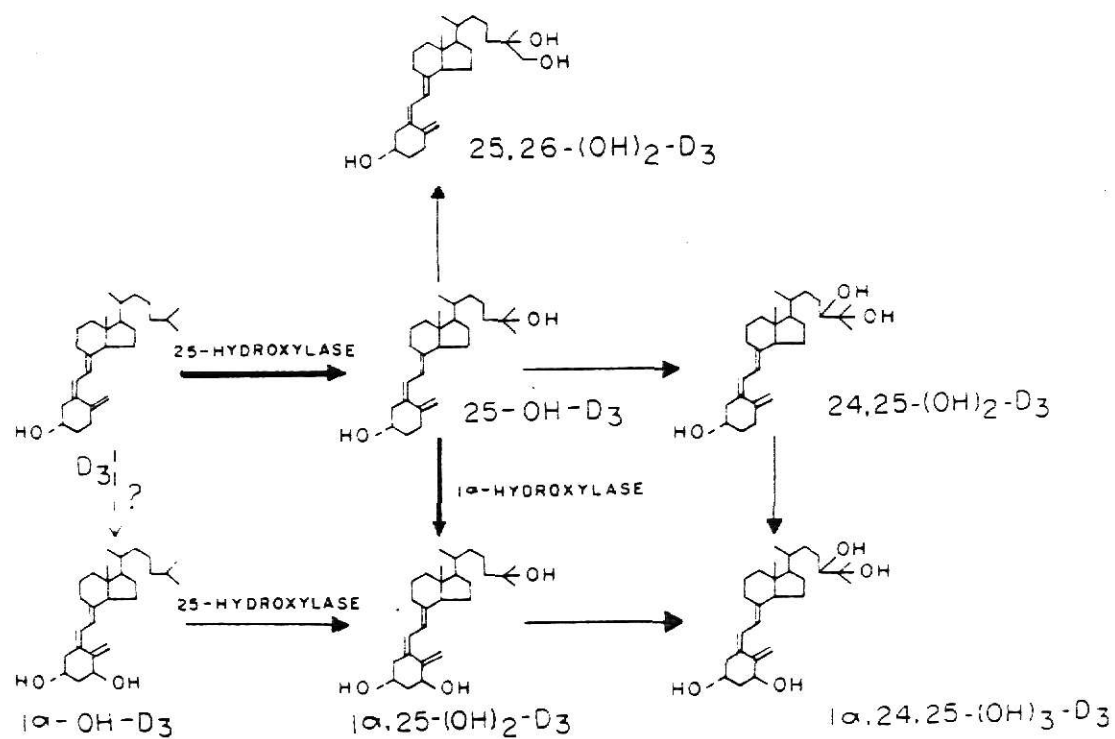


Fig. 1 Metabolism of vitamin D₃

in stimulating intestinal calcium transport and bone calcium mobilization in vivo. In 1971, $1,25-(\text{OH})_2\text{-D}_3$ was isolated and identified as the most potent metabolite of vitamin D by Norman et al. (30). Complete chemical synthesis of $1,25-(\text{OH})_2\text{-D}_3$ was achieved by Barton et al. (31). Both $24,25-(\text{OH})_2\text{-D}_3$ and $25, 26-(\text{OH})_2\text{-D}_3$ circulate intestinal calcium transport to some extent (32). A trihydroxy metabolite, $1,24,25-(\text{OH})_3\text{-D}_3$, first detected under in vitro conditions, has been produced biosynthetically with the aid of a kidney homogenate system (33). Although $1,24,25-(\text{OH})_3\text{-D}_3$ will stimulate intestinal calcium transport, it is less active than $1,25-(\text{OH})_2\text{-D}_3$ on a weight basis (33).

Vitamin D_3 is hydroxylated in the liver at the 25-position and then in the kidney at the 1-position. It has been shown that nephrectomized rats cannot convert 25-OH-D_3 to $1,25-(\text{OH})_2\text{-D}_3$ because they lack the renal enzyme, 25-hydroxy-cholecalciferol-1-hydroxylase. Administration of vitamin D_3 or $25-(\text{OH})\text{-D}_3$ to such animals fails to evoke the biological responses obtained with $1,25-(\text{OH})_2\text{-D}_3$ (34). Moreover, administration of either $25,26-(\text{OH})_2\text{-D}_3$ or $24,25-(\text{OH})_2\text{-D}_3$ cannot stimulate intestinal calcium transport in nephrectomized rats (35). This further indicates that hydroxylation in the 1-position is required for those compounds to be biologically active.

The synthetic analog, $1\alpha\text{-OH-D}_3$, displays biologic activity virtually identical to the $1,25-(\text{OH})_2\text{-D}_3$ (36). Barton et al. (31) have chemically synthesized $1\alpha\text{-OH-D}_3$ so that it may be tested for clinical use. It is then possible that $1\alpha\text{-OH-D}_3$ can be used as a therapeutic agent in the treatment of certain hypocalcemic disorders, especially those involving defective kidney $25-(\text{OH})\text{-D}_3$ -1-hydroxylase. The synthetic analog, $1\alpha\text{-OH-D}_3$, is easy and inexpensive to synthesize; its activation is carried out quickly

and efficiently by the widely distributed 25-hydroxylase enzyme and the rate limiting 1-hydroxylase in the kidney is circumvented (36).

The active forms and analogs of vitamin D are shown in Table 3. Some forms are not available for clinical use at this time.

Vitamin D metabolites and the treatment of metabolic bone diseases

The identification of various metabolites of vitamin D in the past few years, has led to the testing of new therapy for renal osteodystrophy. The skeletal abnormalities that occur in patients with chronic renal failure include retardation of growth, osteomalacia, osteitis fibrosa, osteoporosis, and osteosclerosis; collectively, these have been termed "renal osteodystrophy" .

Brickman et al. (38) successfully treated the hypocalcemia and negative calcium balance of chronic renal failure with $1,25-(\text{OH})_2\text{-D}_3$. Other evidence also suggested that long term administration of $1,25-(\text{OH})_2\text{-D}_3$ corrected both osteitis fibrosa cystica and osteomalacia associated with renal disease (39). The analog $1\alpha\text{-OH-D}_3$, also has been employed as a therapeutic agent in renal patients (36). It is evident that the availability of $1,25-(\text{OH})_2\text{-D}_3$ to patients on hemodialysis, especially those waiting long periods for a compatible transplant donor, offers great hope in alleviating the painful and serious bone disease which often accompanies chronic renal failure.

Another therapeutic use for vitamin D was reported by Fraser et al. (40) in patients with familial vitamin D-dependent rickets. Such individuals require higher than normal levels of vitamin D_3 or 25-OH-D_3 to prevent rachitic lesions, yet they respond to doses as low as $1\text{ }\mu\text{g}$ of $1,25-(\text{OH})_2\text{-D}_3$. Their data indicate that this genetic disease is characterized by either a

TABLE 3

Active forms and analogs of vitamin D (37)

a. Approved for clinical use

Vitamin D₂ (Ergocalciferol)

Vitamin D₃ (Cholecalciferol)

Dihydrotachysterol (DHT)

b. Analogs being evaluated (investigational use)

1,25-hydroxy-vitamin D₃ (1,25-(OH)₂-D₃)

25-hydroxy-vitamin D₃ (25-OH-D₃)

1 alpha-hydroxy-vitamin D₃ (1 α -OH-D₃)

c. Natural metabolites of uncertain physiological function

24, 25-dihydroxy-vitamin D₃

25,26-dihydroxy-vitamin D₃

1,24,25-trihydroxy-vitamin D₃ (in vitro)

total lack of the renal 1-hydroxylase enzyme or a defect in the regulation of this enzyme. Although they did not measure the circulating concentration of $1,25-(\text{OH})_2\text{-D}_3$, they assumed that the blood level is suboptimal in these patients and must be maintained by exogenous administration. Hypophosphatemic vitamin D-resistant rickets, another inherited disorder resulting in osteomalacia which is refractory to normal doses of vitamin D, apparently cannot be corrected by treatment with $1,25-(\text{OH})_2\text{-D}_3$ (41).

Haussler et al. (42) also found that $1,25-(\text{OH})_2\text{-D}_3$ significantly improved serum calcium levels in both postsurgical and idiopathic hypoparathyroid patients after administration of 1 μg per day of oral doses of $1,25-(\text{OH})_2\text{-D}_3$. The fact that the subjects were resistant to vitamin D doses as large as 400,000 IU (10 mg) per day indicated that $1,25-(\text{OH})_2\text{-D}_3$ represents a much more powerful agent for correcting low serum calcium levels and preventing tetany in severely hypoparathyroid individuals.

Overuse of vitamin D

A dietary intake of 400 IU by normal healthy persons of all ages incurs no risk of toxicity. Ingestion of vitamin D in excess of the recommended amount provides no benefit and large excesses are potentially harmful (43). Only individuals with diseases affecting vitamin D absorption or metabolism require more than 400 IU per day. The amount needed should be established by clinical evaluation; treatment should be specifically recommended and supervised by physicians (44).

Data from a small sample of children indicated that an intake of 1800 IU per day of ergocalciferol may impair linear skeletal growth (45), but this was not supported by more recent data on infants supplemented with up to 2170 IU per day (46). As much as 2000 IU per day have been

consumed by many infants regularly without ill effect (47). The Committee on Nutrition of the American Academy of Pediatrics has set a dose of 1000 to 3000 IU per kilogram of body weight per day as dangerous (47).

Because vitamin D promotes absorption of calcium from the intestine, a large excess of stored vitamin D can cause hypercalcemia. The resulting hypercalcemia affects calciphylaxis and deposition of mineral in soft tissues, including the basement membrane of renal tubules, myocardium, arterial walls, and stomach wall. Subsequent damage may result in hypertension and cardiac insufficiency with abnormal electrocardiograms; and in renal failure, azotemia and hypochromic anemia (48, 49).

Although excess mineralization is the most conspicuous result of overdoses of vitamin D, some cellular injury is not dependent upon calcium deposition (50). This is indicated by the data from new world monkeys that kidney malfunction and death can result from vitamin D intoxication without the usual observable pathologic changes such as nephrocalcinosis, the deposition of calcium phosphate in the renal tubules.

VITAMIN E

Human requirements

Vitamin E is important in the body because of the antioxidant properties of tocopherol which inhibits the oxidation of unsaturated fatty acids and has an apparent role in the maintenance of stability and integrity of biological membranes (51). It also may play a role in cellular respiration.

A recommended dietary allowance (RDA) of 30 IU per day for men and 24 IU per day for women was first proposed by the Food and Nutrition Board of National Research Council (NRC) in 1968 (52). This was intended to be an amount that would allow for a moderately increased consumption of polyunsaturated fatty acids. In 1974, a new subcommittee of the Food and Nutrition Board lowered the NRC-RDA to 15 IU for men and 12 IU for women with the provision that more vitamin E is needed if the consumption of polyunsaturated fatty acids (PUFA) is greater than usual (2). This decrease was based on the absence of available evidence of insufficient vitamin E intake in the adult United States population (53) and analysis of food as consumed. Daily intake of vitamin E from American adult diets ranges from 2.6 to 15.4 mg, with an average of 7.4 mg or 11 IU, according to Bunnell et al. (54), and from 4.4 to 12.7 mg, with an average of 9.0 mg or 13.4 IU, according to Biere and Evarts (55).

Horwitt (56) stated that among the factors which were considered in proposing the decreases in the NRC-RDA for vitamin E in 1974 were a) dietitians were having difficulty devising diets of natural foods which had the recommended amount of vitamin E and b) a different method of evaluating the vitamin E activity of the diet had been proposed which was

based on a summation of the activities of all of the compounds of vitamin E studied individually. Horwitt suggested that two separate factors needed to be considered in the evaluation of the requirement for vitamin E to prevent tissue lipid peroxidations. The first must allow for the synthesis and selective storage of PUFA in tissue lipid even when the diet is unusually low in PUFA. This amount is placed at the low level of 6 IU per day, and it is only enough to avoid obvious pathology in such unusual individuals whose depot fat may contain less than 2 % linoleic acid (57). The second allows for the difference in PUFA content of tissue lipids that depend on dietary habits. The variation of fat content in the diet may be 25-fold, since the linoleates of depot fat can easily be raised to more than 50 % of the total fatty acids (57). At present, the RDA for vitamin E is controversial.

Even though the United States population consumes adequate amounts of vitamin E in the usual diet to maintain a blood concentration of total tocopherols above 0.5 mg / 100 ml and only a limited number of deficiency symptoms have been noted in adults (53), many individuals continue to self-dose themselves regularly with relatively large doses of 100 to 1000 IU vitamin E daily . The public has used this vitamin at megadosage levels as a means of prevention or self-medication for heart disease, aging and many other conditions.

Possible benefits of supplementary vitamin E

Hemolytic anemia in premature infants. Because of poor transfer of vitamin E from mother to fetus across the placenta, both premature and full-term newborn infants may have relatively low levels of vitamin E in both tissues and blood. The need of the newborn for supplemental vitamin E

has been recognized. In recent well-controlled study (58), immature infants were shown to have a lower incidence of retrolental fibroplasia when given vitamin E. Children suffering from malabsorption syndromes that inhibited retention of dietary fat also have been shown to benefit from vitamin E supplementation(58).

Intermittent claudication. There is strong evidence of the usefulness of vitamin E therapy for intermittent claudication which is one kind of occlusive arterial disease. It is hard to explain the physiological effect of long term treatment with vitamin E . To be sure of the clinical effect, patients with rather severe symptoms of claudication were chosen in Haeger's study (59). He found that patients on 300 mg Ido E-Novum (d-alpha-tocopheryl acetate) per day for 4-6 months had greater walking ability than those given either vasodilating agents, anticoagulant therapy or plain vitamin tablets without vitamin E. In addition there was an increase of arterial flow to the lower leg after 12 to 18 months of vitamin E treatment. He concluded that the addition of vitamin E to the general regimen of the life of claudicating patients is valuable. He could offer no explanation for the molecular level mechanism of vitamin E therapy but he assumed that vitamin E given in megadose amounts in some way changes the walking ability of persons and that the changes in blood flow are secondary to increased muscular training.

Protection against air pollution. A number of investigators, stimulated by the recent increase in attention to environmental and pollution problems, have claimed a protective effect of alpha-tocopherol on lung damage caused by ozone, which is the predominant oxidant in photochemical smog (60,61). In one study (62), rats that received amounts

of vitamin E comparable to the average American consumption had marked lung damage when exposed to 0.1 ppm ozone for 7 days, whereas the undesirable effects were essentially absent in animals similarly exposed but fed 6 times as much vitamin E. Because the basic features of these animal tests may not be similar to conditions affecting humans, it is difficult to speculate about the application of these results to human beings.

Aging. It has been claimed that the antioxidant properties of vitamin E help slow the aging process. Aging is a very complex process and many theories have been advanced to explain it (63). There is some support for the theory that free radicals formed in the tissues can interact with protein to form so-called "aging pigments" that may be related to aging processes in various tissues. Laboratory tests indicate that vitamin E interacts with and "neutralizes" free radicals. Hence, the proposition was made that vitamin E can perform the same function in the body and slow the ravages of age (64).

This theory, like all theories on aging, needs to be studied for a long period of time because of the very nature of the aging process. Tappel (64,65) tested the effects on mice of mixtures of vitamin E and other nutrients and antioxidants that might give maximum protection against oxidative deterioration. For one such test, he started with an adequate basic mouse diet and added 0.3 % vitamin E. To other diets, he added butylated hydroxy-toluene, a commonly used food antioxidant; 0.1 % vitamin C; or 0.3 % methionine and 0.1 ppm selenium. The vitamin E level consumed in that diet was about equivalent to human's taking 2000 IU per day. After adult mice were fed these test diets for about a year, they were evaluated by various physiological and biochemical tests. Mice fed

vitamin E showed essentially no improvement in their walking capacity and coordination, kidney function, or muscle membrane function, and no decrease in mortality, but there were fewer age pigments in their cells. Whereas age pigments increased exponentially in test tissue of the control mice, they were present at one-half those values in the mice that only received the antioxidant supplements.

Heart diseases. Broad-based claims that large doses of vitamin E relieve most heart ailments were made in the mid-1940s and continue to be promoted today. However, there now seems to be sufficient evidence that vitamin E is ineffective in treating or preventing heart diseases (65). In one study (66), patients with chronic chest pains and arteriosclerotic and hypertensive heart disease were given 300 IU of vitamin E daily for an average of 16 weeks. Controlled observations were made by a blind test method; 19 patients received vitamin E, and an equal number received placebos. The doctors reported no significant differences between the vitamin E and placebo group as to chest pain, capacity for work of cardiac muscle, or capacity for work of skeletal muscle. Although many physicians continue to prescribe large amounts of alpha-tocopherol for heart ailments, the treatment of heart diseases with vitamin E never had a good rationale.

Toxicity from overdosage

In animals. If vitamin E does have a pharmacological effect, one must be concerned with the levels at which it is safe. Vitamin E is fat soluble and can be accumulated in the body. Thus cumulative effects are hypothetically possible.

Possible toxicity has led to experiments in animals. A study conducted by March et al. in 1973 (67) on hypervitaminosis E in the chick

suggested excess vitamin E must be considered as potentially toxic. Amounts of vitamin E ranging from 220 to 2200 IU per kilogram of diet were studied in relation to various metabolic parameters. Growth rate was depressed by 2200 IU of vitamin E per kilogram of diet. Excess vitamin E administered orally or parenterally to chicks depressed calcification when the diet was deficient in calcium or vitamin D. The vitamin D requirement for maximum calcification with a particular intake of calcium was increased in hypervitaminosis E. Excessive vitamin E (2200 IU per kilogram) induced both reticulocytosis and a reduction in hematocrit value. Prothrombin times were lengthened when 2200 IU vitamin E were fed, but were rapidly normalized by injection of vitamin K, indicating an increased dietary requirement for vitamin K in the presence of excess vitamin E.

In man. In 1957, Hillman observed that excess tocopherol (1200 IU per day) resulted in general muscular weakness accompanied by increased urinary creatine and elevated plasma creatine phosphokinase activity (68). This observation also was made by Biggs in 1974 (69).

Swedish investigators (70) noted prolonged plasma clotting time and decreased fibrinolysis after long term treatment with alpha-tocopherol. Corrigan and Marcus (71) conducted coagulation research in the United States. During the course of treating a patient with warfarin and clofibrate, they noted clinical evidence of vitamin K deficiency. Upon learning that the patient had been taking 1200 IU of vitamin E per day, they began a study of the combined effects of the therapy the patient was receiving. It was known that warfarin depresses levels of vitamin K dependent coagulation factors and that clofibrate potentiates the warfarin effect but they also were able to show that adding d,l-alpha-tocopheryl

acetate to the therapeutic regimen had an additional effect in depressing the vitamin K-dependent coagulation factors (71).

The effects of supplementation with vitamin E on the possible elevation of serum lipid and alteration of fatty acid pattern also has been studied. In 1975, Farrell and Biere (72) reported that plasma tocopherol levels of individuals ingesting 100 to 800 IU per day of tocopherol for an average of 3 years correlated positively with plasma triglyceride and cholesterol concentrations. Recently, Tsai et al. (73) showed that serum cholesterol levels were slightly elevated in both males and females after vitamin E supplementation of 600 IU per day for 28 days, but the elevations were not statistically significant. Serum triglyceride levels were significantly elevated in vitamin E -supplemented females, but only slightly increased in the supplemented males. Vessby et al. (74) reported that supplementation of vitamin E does not lower plasma cholesterol under controlled conditions, either in normal subjects or hyperlipidemic patients, although vitamin E is a good biological antioxidant.

SUMMARY

The human requirements of vitamins C, D, and E are controversial. The recommended dietary allowances of the National Research Council (NRC-RDA) represent physiological amounts which ensure that the needs of practically all healthy persons are met. Therefore, they are estimated to exceed to some extent the requirements of many individuals. The benefits and risks of pharmacological doses of approximately ten or more times the physiological dose also are controversial.

No clear and reproducible pattern of efficacy has emerged from those clinical data relating to the use of pharmacologic doses of ascorbic acid in prevention and treatment of the common cold. Pharmacologic doses of vitamin C increased uric acid excretion in urine and depressed blood uric acid. Furthermore, use of vitamin C at high dosage levels increased susceptibility of red cells to hemolysis and, in one instance, was apparently involved as a causative factor which produced death in a patient with G-6-PD deficiency. Subjects on megadose regimens of ascorbic acid may well be at risk for ultimate development of vitamin B₁₂ deficiency. Intake of ascorbic acid had been associated with both decreases and increases in cholesterol concentration.

In order to become biologically active, vitamin D is hydroxylated in the liver at the 25-position and then in the kidney at the 1-position. The analogs, 1,25-(OH)₂-D₃ and 1 α -OH-D₃, have been employed as therapeutic agents in renal osteodystrophy, hypoparathyroidism, and familial vitamin D-dependent rickets to correct serum calcium level. Such needs for individuals with defective vitamin D absorption and metabolism should be established by clinical evaluation and supervised by a physician. Otherwise, excess mineralization is the most conspicuous result of overdoses of vitamin D.

Vitamin E supplements have been beneficial in lowering the incidence of retrolental fibroplasia in immature infants. Long-term treatment with vitamin E has been suggested for claudicating patients to improve their walking capacity. Other possible benefits of supplementary vitamin E such as protection against air pollution, slowing the aging process and relieving heart disease have been studied in animals, but there is no good evidence that such benefits apply to human beings. Muscular weakness accompanied by increased urinary creatine and elevated plasma creatine phosphokinase activity and depressed vitamin K-dependent coagulation factors have been observed in individuals consuming excess tocopherol.

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MEGADOSES OF VITAMINS C, D, AND E

by

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The human requirements of vitamins C, D, and E are controversial. The recommended dietary allowances of the National Research Council (NRC-RDA) represent physiological amounts which ensure that the needs of practically all healthy persons are met. Therefore, they are estimated to exceed to some extent the requirements of many individuals. The benefits and risks of pharmacological doses of approximately ten or more times the physiological dose also are controversial.

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