Vitamins and Minerals

Nutrition Biochemistry

Vitamins and minerals are essential to life. They act as cofactors or prosthetic groups for most enzymes, thus making biochemical reactions possible. Some cofactors are transiently associated with a given enzyme and in this capacity, they function as cosubstrates. They are also called **coenzymes**.

Besides being cofactors for enzymes some vitamins such as the fat-soluble vitamins A and D have been shown to exhibit hormone-like functions. Thus, vitamin A and its metabolites retinaldehyde and retinoic acids are involved in the growth, differentiation and maintenance of epithelial tissues as well as for reproduction. Retinoic acids can substitute for vitamin A —deficient animals in growth promotion and epithelial differentiation. As for vitamin D is interesting to note that the skin is both the site of vitamin $D_3$and 1,25-dihydroxy vitamin D_3 synthesis and a target organ for the latter. 1,25 $(OH)_2$ vitamin D_3 is essential for mineral homeostasis and bone integrity as well as the regulation of growth and differentiation in normal and malignant tissues.

Minerals are generally tightly bound to the protein moiety and are either directly involved in the catalytic process or help the protein perform its specific biological function. Among the former are metal ions such as Cu^{2+}, Zn^{2+}, Mn^{2+}, Se^{2+}, Fe^{3+}, which are part of the active site of enzymes involved in redox reactions while the latter group comprises cations that do not take part in catalytic reactions. A typical example is Zn^{2+}, which can function as a non-catalytic agent in the zinc-finger motifs found in the transcriptional factors that are proteins involved in DNA replication. These are specific repetitive amino acid sequences (some 30 residues long) that have Zn^{2+} covalently linked to Cysteine and Histadine residues.

Most of the higher organisms, including humans are not able to synthesize their own essential factors, which they must, therefore, acquire through diet. The high turnover of vitamins, especially the water-soluble ones, requires that they be replenished through food on a daily basis. It is well known that food processing causes the foodstuff we buy at the supermarket to be depleted of most vitamins and minerals. A diet rich in fresh fruits and vegetables restores the balance of essential nutrients in the body.

It is important to bear in mind that vitamins and in particular those in the B group are working and get absorbed synergistically that is they need each other and the presence of other factors, which could be other vitamins or minerals.

In vitamin deficiency, enzyme-catalyzed reactions may slow down or not occur at all. This leads to profound changes in the cellular metabolism and if vitamin/mineral deficiency is allowed to continue for a longer period of time degenerative diseases such as cardiovascular disease, rheumatoid arthritis, cancer and others may develop.

It is important to distinguish between severe vitamin deficiency—which is very rare nowadays in the Western world—and that which affects over half of the population in the Western hemisphere and is called subclinical deficiency by many nutritional experts. This means people may get most of their daily vitamin requirements from food but not in the optimal amounts. Over time this will lead to a partial breakdown of the finely-tuned cellular metabolism with unfavorable consequences for the body as a whole. Because these subtle changes occur over an extended period people are not aware that anything is going wrong.

Although most people believe that they might have an adequate supply of vitamins and minerals from various foods it has become apparent that even with a “normal” well-

Some sobering facts

Therefore, it would appear that it is quite improbable to get *all* the necessary nutrients from the diet alone, no matter how well balanced it is. A recent U.S. Department of Health, Education and Welfare report showed that:

- **over 90% of adults are chromium deficient**
- **over 60% of adults have an inadequate calcium intake**
- **over 30% have diets low in vitamins C and A**
- **over 50% have a low intake of vitamin B6 and folic acid**
- **over 50% have a low manganese intake**
- **over 40% have a low zinc intake**

How much we should get daily

We may ask then, what is the necessary daily intake of biocatalysts in order to maintain optimum health? According to many medical and government health organizations, optimum intake of vitamins and minerals should come mainly from food sources. This may be true when people eat a well-balanced diet with lots of fresh fruits and vegetables. However, a large segment of the population does not appear to follow this good advice particularly the young generation, always busy, always on the run. Today's lifestyles and the stress of the workplace together with the environmental conditions and the quality of food available in the grocery stores are forcing us to rely, at least in part on nutritional supplementation.

Although further research into the usefulness of nutritional supplementation in pill form is needed before making definite recommendations for additional vitamin and mineral supplements a large percentage of North Americans are already taking nutritional supplements on a daily basis. This is reflected by the sales of nutritional supplements in all forms that have reached some $25 billion worldwide in 2006.

So, how much vitamins and minerals should we have daily? Although there is not yet a wide consensus on a set of values for the daily intake of the most important biocatalysts most experts in nutrition suggested that the RDA issued almost 60 years ago must be amended. And so, it was. In 1989 the National Research Council of U.S.A. issued a new RDA (1) that took into account the developments in the nutritional sciences since late 1940s. However, as R.A. Sunde argued in a recent article (2) most of the nutrient requirements were still based on old methods of calculating the RDA, i.e. based on balance or factorial analysis rather than on biomarkers. Since many enzymes that require vitamins and minerals as cofactors are regulated by gene expression it is obvious that the analysis of that expression could form a better foundation on which to build a sound dietary allowances program for human nutrition. Since 1989 the new Dietary Reference Intakes guideline, which replaced the old RDA has been further amended (1998-2001) (3,4) but there is still a long way to go until all nutrient requirements could be set based solely on good biochemical markers. Meanwhile, based on several major scientific studies leading nutritionists recommend that a well-balanced diet should still be supplemented with vitamins and minerals in the range shown in the table below. This is to ensure optimal health and to reduce the risk of degenerative diseases and premature aging.

Recommended Daily Vitamins & Minerals Intake

Vitamin	**Range for Adults**	**Mineral**	**Range for Adults**
Vitamin A	1,000 - 5,000 I.U.	Boron	1 - 3 mg
Vitamin D	500 - 1000 I.U.	Calcium	250 - 1,000 mg
Vitamin E	200 - 400 I.U.	Chromium	100 - 300 mcg
Vitamin C	200 - 1000 mg	Copper	1 - 2 mg
Vitamin B1	10 - 100 mg	Iron	10 - 25 mg
Vitamin B2	10 - 50 mg	Magnesium	200 - 400 mg
Vitamin B3	10 - 50 mg	Manganese	5 - 10 mg
Vitamin B5	25 - 50 mg	Molybdenum	10 - 25 mcg
Vitamin B6	25 - 100 mg	Potassium	2000 - 3000 mg
Vitamin B12	25 - 50 mcg	Selenium	25 - 100 mcg
Folic Acid	200 - 400 mcg	Silica	5 - 10 mg
Biotin	100 -300 mcg	Zinc	20 - 50 mg

Adapted from "Encyclopedia of Nutritional Supplements" by Michael T. Murray, N.D., Prima Publishing, Rocklin, CA, 1996. Note: The recommended intakes of vitamins and minerals apply to healthy individuals eating a balanced diet and wishing to maintain good health. For certain medical conditions the daily doses of vitamins and minerals may need adjustment and the advice of a nutritionally oriented health care provider should be sought.

References

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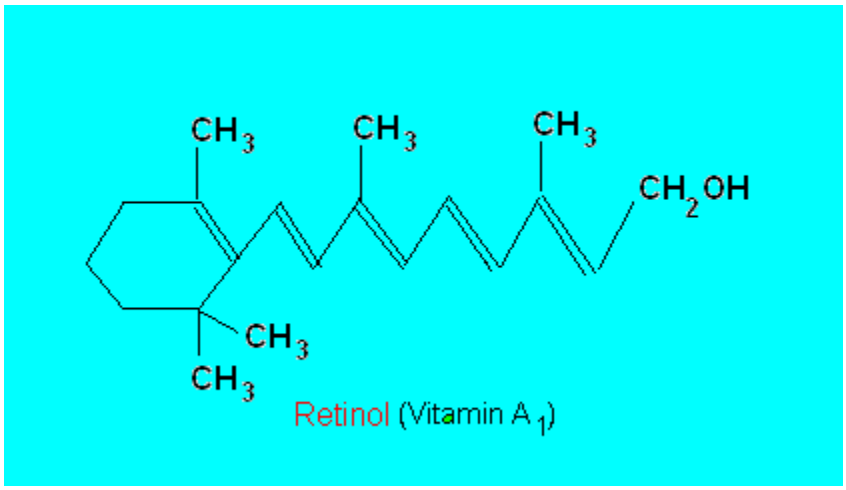
2. Sunde, R.A. (2001) Research Needs for Human Nutrition in the Post-Genome-Sequencing Era. J Nutr 131, 3319-3323.
3. Food and Nutrition Board (2000) Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids. National Academy Press, Washington, D.C.
4. Food and Nutrition Board (2001) Dietary Reference Intakes for Arsenic, Boron, Chromium, Copper, Iodine, Iron,
Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc. National Academy Press, Washington, D.C

Vitamin A

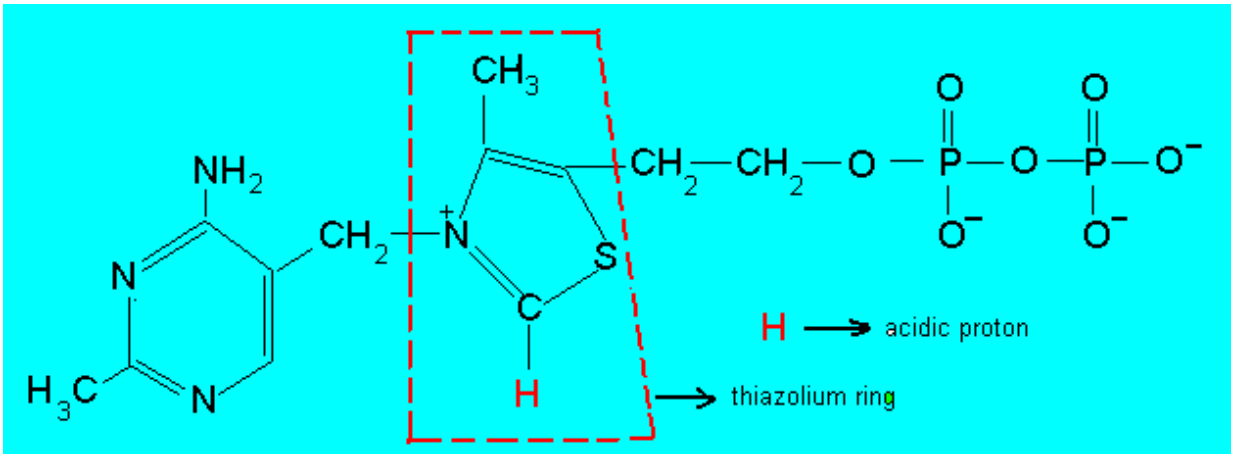
Vitamin A is synthesized in the liver of vertebrates from b-carotene. Retinol derivatives, i.e. *retinal* (carbon 15 becomes an aldehyde group) and *retinoic acid* (carbon 15 becomes a carboxylic group) act as visual pigment and hormone, respectively. Retinoic acid binds to receptor proteins in the nucleus, which then interact with transcription factors thus modulating gene expression in the development of epithelial tissue, including skin (1). Most of the biological activity of vitamin A is carried out by the above derivatives although in many research articles mention is made of vitamin A when describing the action of this vitamin.



- Involved in reproduction, growth and development, e.g. teeth and bone formation
- Essential for normal immune system maturation and function. There is evidence to suggest that vitamin A deficiency is a risk factor for low antibody production (2). In animal models it was shown that vitamin A supplementation enhanced cytokine production and secretory immunoglobulin A response to influenza virus infection although supplementation did not alter the clinical or virologic outcome of viral pneumonia (3). Vitamin A supplementation was also found to reduce morbidity and mortality in several infectious diseases such as severe diarrhea, measles-related pneumonia and malaria. Modulation of the immune response by vitamin A varies widely depending on the type of infection and immune response involved (4).

Vitamin B1 (Thiamine)

Thiamine is a water-soluble B vitamin and plays an essential role in normal cellular functions, growth and development. Thiamine is found in high concentrations in the skeletal muscle, heart, liver, kidneys and brain. Mammals, including humans cannot synthesize thiamine so it has to be obtained from diet via intestinal absorption. Absorption of vitamin B1 involves a specialized pH-dependent, Na^+- independent carrier mediated mechanism (1). In order to become a coenzyme thiamine has to acquire a pyrophosphate group. This process occurs intracellularly in a reaction catalyzed by the enzyme *thiamine pyrophosphokinase* at the expense of cellular ATP. Thiamine uptake is enhanced by thiamine deficiency and reduced by the thyroid hormone and diabetes (2).



Thiamine pyrophosphate (the coenzyme form of vitamin B1). The thiazolium ring is the moiety involved in the catalytic process.

- Essential for energy production in carbohydrate/amino acid metabolism. TPP deficiency may lead to pyruvate accumulation, hence inhibition of energy production.
- Essential for nerve cell function. A low level of thiamine in the brain impairs not only the energy production (ATP) but also the synthesis of the neurotransmitter acetylcholine. Acetylcholine is synthesized from choline and acetyl-CoA (reaction catalyzed by *choline acetyltransferase*).
- Potentiates and mimics the effects of the neurotransmitter acetylcholine in the brain. Total thiamine content in cholinergic nerve terminals is comparable with that of acetylcholine and the phosphorylation state of thiamine changes with the release of

Some of the reactions in which TPP is involved are listed below:
1. Thiamine pyrophosphate (TPP) is one of the coenzymes required by the pyruvate dehydrogenase multienzyme complex for the decarboxylation of pyruvate:

pyruvate + CoA-SH + NAD^+ ----> acetyl-CoA + CO_2 + NADH

2. TPP is also required in the degradation of branched-chain amino acids isoleucine, leucine and valine. The second stage in this process is catalyzed by a-ketoisovalerate dehydrogenase, a multienzyme complex that employs the coenzymes TPP, FAD, NAD^+ and the lipoamide.

3. TPP is involved in a reaction of the pentose phosphate pathway, i.e.in the formation of sedoheptulose-7-phosphate. The enzyme that catalyzes this reaction (transketolase) requires TPP as coenzyme. The pentose phosphate pathway is one of the generators of reducing power (NADPH) necessary for biosynthetic processes as well as for several reductive processes, such as the regeneration of GSH in the erythrocytes whose function is to protect the integrity of cell membrane by removing the hydrogen peroxide and lipid hydroperoxides through the reaction catalyzed by GSH-peroxidase.

References

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brush-border membrane vesicles.
2. Rindi, G. and Laforenza, U. (2000) Proc.Soc.Exp.Med. 224(4) 246-255. Thiamine intestinal transport and related issues: recent aspects.
3. Meador, K.J. et al. (1993) Ann.Neurol. 34(5), 724-726. Evidence for a central cholinergic effect of high-dose thiamine.

Vitamin B2 (Riboflavin)

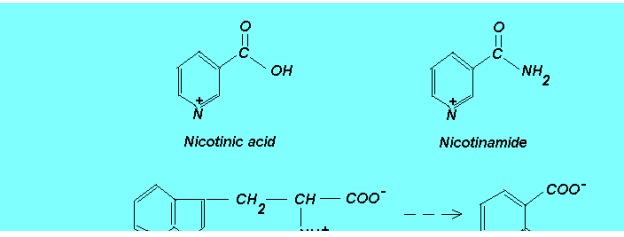
Riboflavin is the precursor of two prosthetic groups, flavin mononucleotide (FMN) and flavin dinucleotide (FAD) in flavoproteins. The two coenzymes, which are tightly bound to the protein moiety cycle between the reduced and the oxidized forms. FAD is more represented in these reactions than FMN. The chemical structures of riboflavin and the two coenzymes, FMN and FAD are presented below.

Some of the processes in which vitamin B2 is involved are listed below:

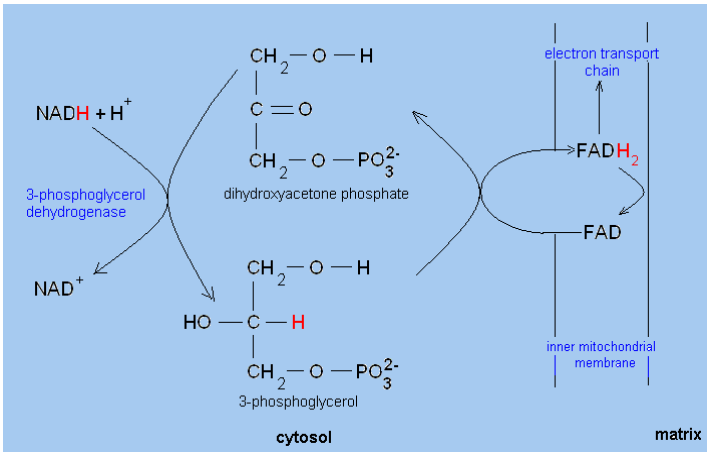
- Involved in energy production and the regeneration of cellular antioxidant glutathione; necessary for carbohydrate, fat and protein metabolism.
- Plays a crucial role in the formation of antibodies, red blood cells and cell respiration.
- Promotes healthy skin, nails and hair; alleviates eye fatigue.
- Mild deficiency may be associated with fatigue, migraine.
- Interactions: vitamin B2 works together with vitamins B1, B3 and B6. Vitamin B2 is inactivated by light, sulfa drugs, alcohol, estrogens. Riboflavin deficiency may exert some of its effects by reducing the metabolism of other B vitamins, notably folate and vitamin B6.
- Health benefits: supplementation is useful in conditions of stress and should be taken with other B vitamins and zinc.
- Best food sources: brewer's yeast, organ meats (liver, kidney, heart), almonds, mushrooms, whole grains.

Vitamin B3 (Nicotinic acid)

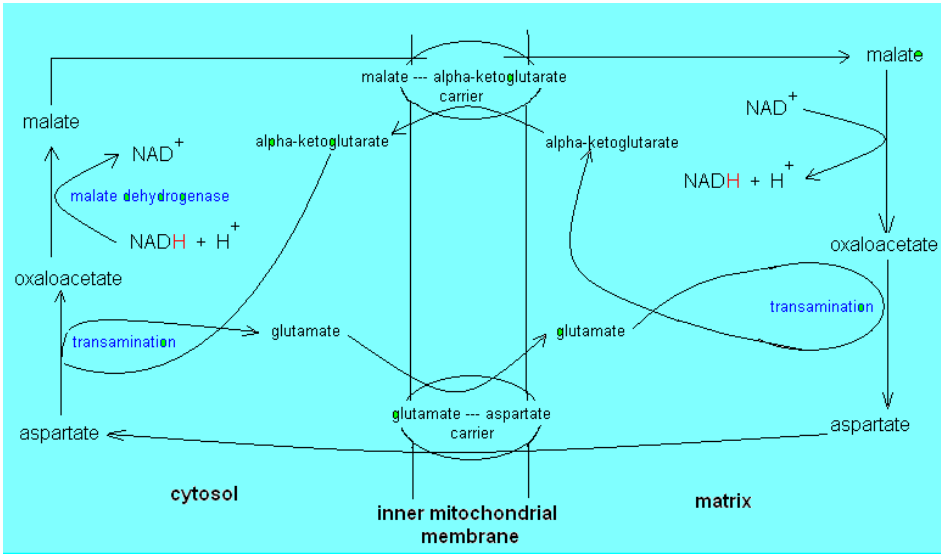
Vitamin B3, also known as niacin/nicotinic acid can be synthesized by the body from tryptophane. The nickname niacin came from linking several letters in the words *ni*cotinic, *ac*id and vitam*in*. As the story goes, when the properties of nicotinic acid (obtained through the oxidation of nicotine) were first discovered it was wisely decided that vitamin B3 or nicotinic acid should be named in such a way as to dissociate it from nicotine and not to create the impression that either smoking provided this vitamin or that wholesome food contained a poison. Niacin is required for processes such as cell respiration, synthesis of ATP, carbohydrate, fat and protein metabolism. Approximately 60 mg of tryptophan are necessary for the synthesis of 1 mg of niacin, which requires the presence of vitamins B6 and B2.



The main role of NADH (and $FADH_2$) is to provide free energy necessary for the synthesis of ATP. Since the cytosolic NADH, generated during glycolysis, cannot cross the mitochondrial membrane a shuttle system operates to carry the electrons across the membrane. Two well characterized shuttles are shown in the diagrams below.



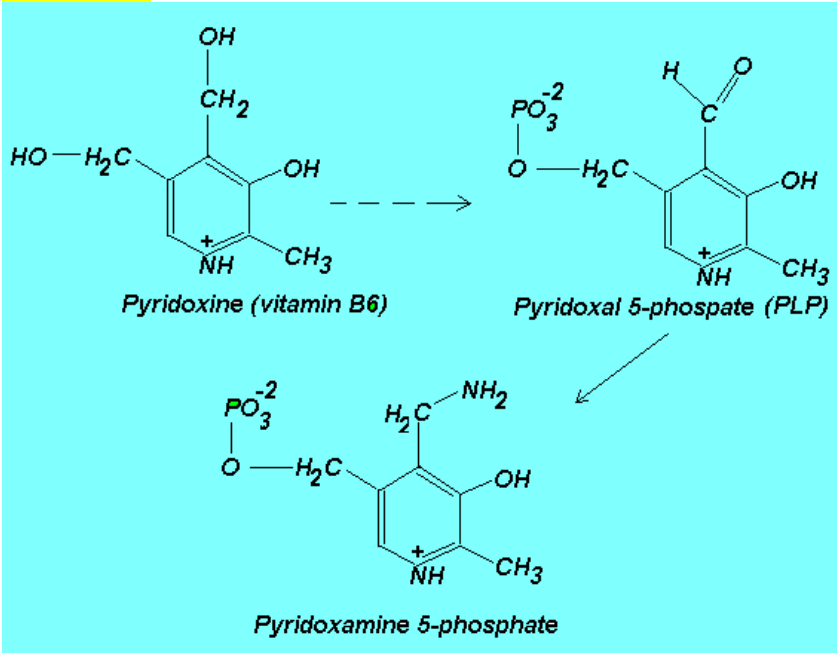
The glycerophosphate shuttle. The transfer of electrons is carried out in three steps. In the first step NADH is oxidized by dihydroxyacetone phosphate. In the second step the 3-phosphoglycerol is converted back to dihydroxyacetone by a FAD-depended dehydrogenase located on the inner mitochondrial membrane's outer surface. In the third step the electrons pass from $FADH_2$ to the electron transport chain and the coenzyme is oxidized in the process.



The malate-aspartate shuttle. This shuttle is more energy efficient than the glycerophosphate shuttle. Mitochondrial NAD^+ is reduced by the cytosolic NADH through the reduction and subsequent regeneration of oxaloacetate. The process involves two metabolite carriers, the malate -- a-ketoglutarate and the glutamate-aspartate transporters.

A summary of the generation of reducing powers (NADH and $FADH_2$) in glucose oxidation and fatty acid oxidation pathways and the location of these pathways in relation to ATP synthesis in the cell is shown below.

Vitamin B6 (Pyridoxine)

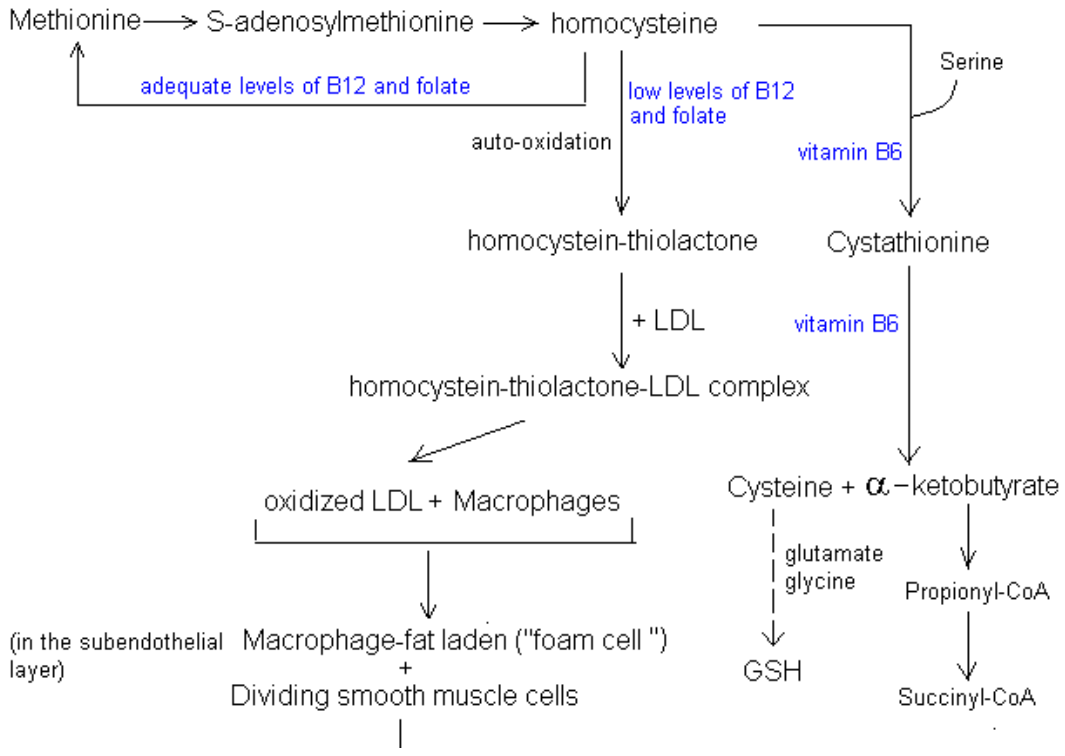


The coenzymes pyridoxal 5-phosphate and pyridoxamine 5-phosphate are derivatives of vitamin B6. The conversion of pyridoxine to the active form of vitamin B6 requires ATP and is catalyzed by pyridoxal kinase. It is part of the catalytic site of several enzymes involved in the amino acid and glycogen metabolism.

- Necessary for the synthesis and degradation of amino acids (the transaminase reaction

Homocysteine and heart disease

The original hypothesis that implicates homocysteine in the etiology of atherosclerosis was put forward some 40 years ago by McCully (1) and a short overview on the subject was published recently (2). Many experts in this field accept now the idea that hyperhomocysteinemia could be a risk factor for the cardiovascular disease according to several possible mechanisms (3,4). Homocysteine autooxidizes relatively easy and turns into homocystein-thiolactone. This is a highly reactive compound that can form a complex with LDL that makes the lipoprotein more prone to oxidation. In the subendothelial space the oxidized LDL is taken up by the macrophages that become "foamy cells" because of the large amount of LDL accumulated within cells. They become entrapped in the subendothelial space and eventually desintegrate releasing a large number of free radicals. The oxidative processes occurring in the sub-endothelial space lead to endothelial cells damage and the formation of the atherosclerotic plaque, which in most cases causes a stroke. If enough vitamin B6, B12 and folic acid are present in the body (5) the homocysteine is either converted back to methionine or catabolized to citric acid cycle compounds. In this way, the damaging effects caused by the oxidative reactions in which homocysteine plays a central role can be prevented. However, despite substantial progress in understanding the postulated role of homocysteine as a risk factor in atherogenesis that involves an oxidative stress mechanism it would appear that there is no conclusive evidence to support the homocysteine-induced oxidative stress mechanism. Along this line, in a recent paper Huerta and his associates have shown that in healthy elderly there was no lipid peroxidation associated with increased homocysteine plasma levels as determined by measuring plasma concentration of malone dialdehyde and the activity of two antioxidant enzymes, glutathione peroxidase and superoxide dismutase (6). Summing up, it appears that a clear answer regarding the involvement of homocysteine in atherogenesis through an oxidative stress-mediated mechanism is not forthcoming yet.



Zinc's Role in Heart Health

Did you know there's a molecule in your body that's designed to keep you "young" as long as possible?

Yet once you hit your forties, your body's levels start to decline rapidly. By the time you're 60, they've dropped by nearly HALF!

It's a major reason why you may feel tired all the time…more forgetful and "spacey" …and stiff, sore, and achy.

In honor of American Heart Month, we'd like to highlight an essential trace element that is a pretty important ally for the heart: zinc. Most celebrated for its immune-boosting/cold-kicking properties, zinc also helps facilitate hormone production, growth, and repair…digestion…and healthy cell division…and is a potent anti-inflammatory agent and free-radical-busting antioxidant. What's more, it's a primary nutrient for heart health, and the slightest deficiency can put you at risk for heart disease.

How Zinc Helps Your Heart

As an antioxidant, zinc helps protect the heart from cardiovascular disease by lowering inflammation and defending against oxidative stress. It keeps the cells that line the blood vessels healthy and promotes tip-top circulation, thereby defending against clogged or damaged arteries and helping to keep blood pressure and cholesterol levels in the healthy range. The relationship between zinc and the heart has been substantiated by studies, such as a 2011 study published in *Biological Trace Element Research* that showed that congestive heart failure patients had severe zinc deficiency.

A 2015 study published in the *Journal of Biological Chemistry* revealed that zinc also plays a primary role in controlling the movement of calcium through your heart cells. Calcium is released through portals called type-2 ryanodine receptors (RyR2). If these portals aren't working properly and too much calcium is continually released, heart failure may ensue. University of Leicester researchers discovered that zinc, found in individual heart cells, interacted with and directly regulated RyR2 function.

How Much Zinc Is Enough?

The RDA for zinc sits at 11 mg for male adults and 8 mg for female adults, with pregnant or lactating women requiring 3 more mg of zinc a day. An estimated 12% of adult Americans are at risk for zinc deficiency, while 40% of the elderly are at risk due to less food intake and a decreased ability to absorb zinc from foods. Zinc is best absorbed from animal foods, so those following a strict vegan or vegetarian diet may also carry a greater propensity for inadequate zinc levels. The following conditions may also increase your risk for zinc deficiency, and subsequent compromised heart health:

- Alcoholism
- Cirrhosis

- Kidney disease
- Celiac disease
- Inflammatory bowel disease (ulcerative colitis and Crohn's disease)
- Leaky gut syndrome

Where to Get Your Zinc

The best sources of zinc are protein-rich foods, particularly high-quality meats, seafood, and dairy. If consuming dairy, opt for unpasteurized and organic dairy products, such as raw milk.

Grains and legumes also contain zinc, but the body does not absorb zinc from these sources as easily. That's because grains and legumes also contain phytates, which have been dubbed "anti-nutrients" because they hinder zinc absorption. Of course, there are zinc-fortified foods, such as cereal, but they also contain phytates that interfere with the bioavailability of zinc. Some research suggests that the rising rates of zinc deficiency in Western nations may be in part due to the high intake of processed carbs such as these!

Better food choices for zinc include:

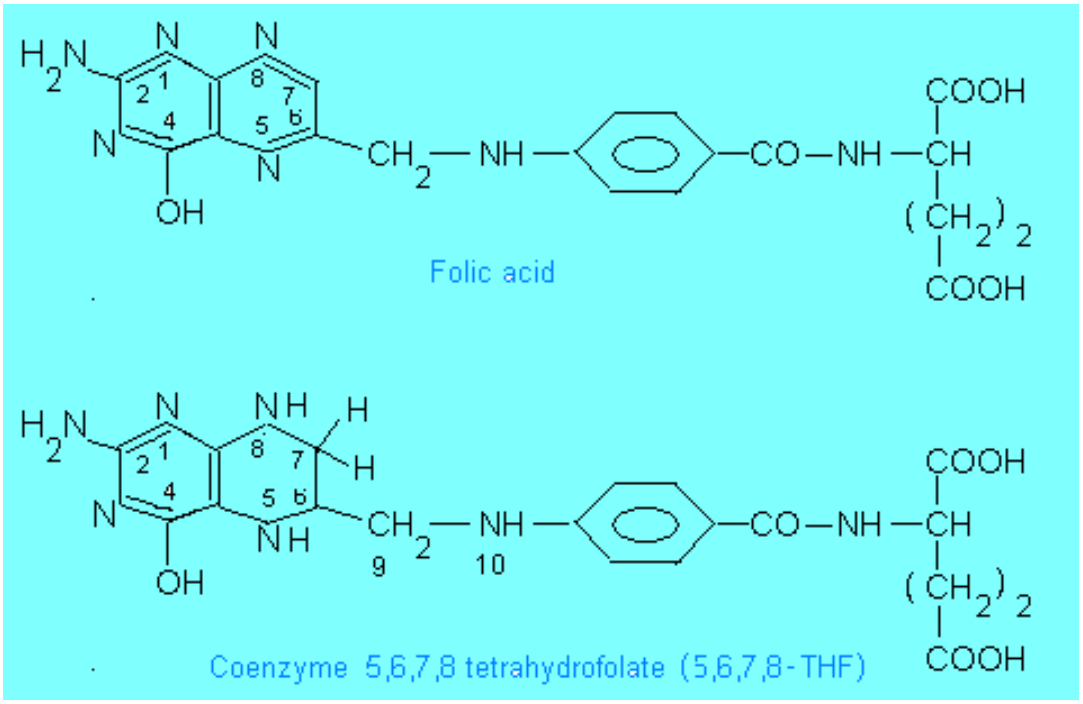
- Roasted pumpkin seeds
- Oysters
- Liver
- Tahini
- Almonds
- Roast beef
- Alaskan king crab

Should I Supplement with Zinc?

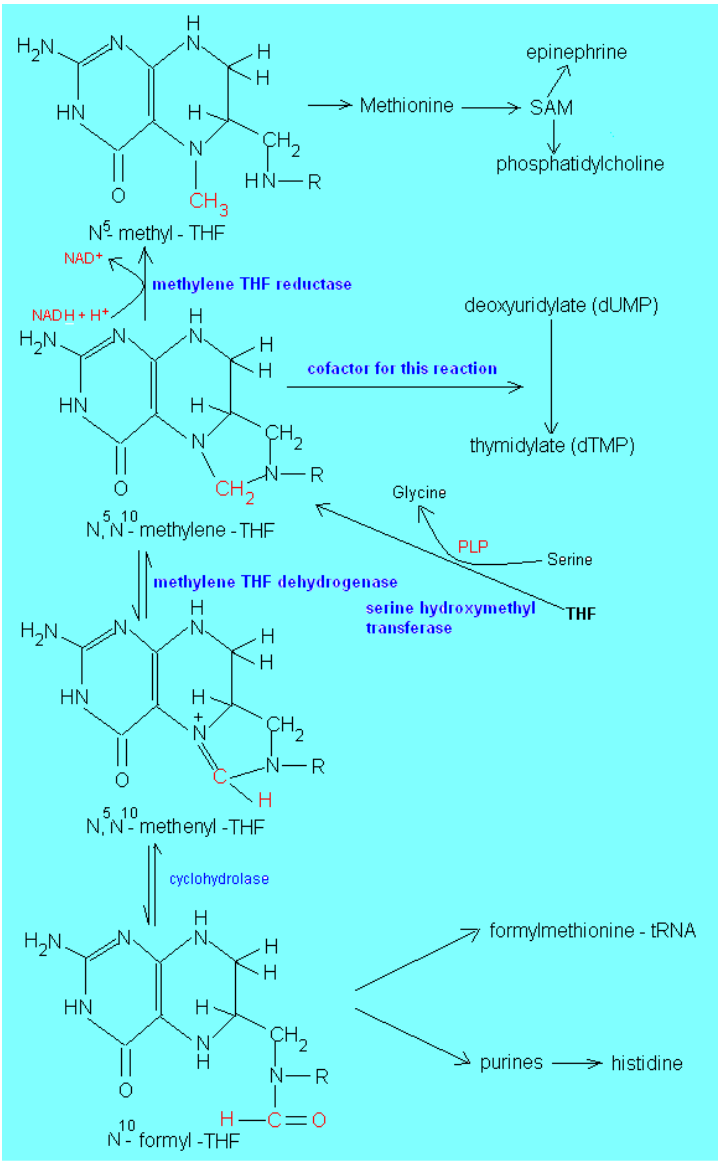
If you are deficient in zinc and need to supplement, do so under the supervision of a doctor. According to the University of Maryland Medical Center (UMMC), supplementing with zinc for too long of a time can deplete the body of copper. Copper deficiency can manifest as irregular heartbeats, so UMMC recommends a zinc supplement that includes copper.

Too much zinc from supplements can also upset your body's cholesterol balance, and high cholesterol is a marker for heart disease. Other side effects of taking too much zinc include chills, chest pain, and fatigue.

Folic acid



- Folic acid is seldom found as such in the human body or in foods. On the other hand, vitamin supplements contain mostly folic acid. So, to become biologically active the folic acid must be enzymatically reduced. This reaction is catalyzed by *dihydrofolate reductase*, which requires NADPH as coenzyme. Some of the active chemical forms are: 5,6,7,8 tetrahydrofolate (THF), 5,10-methenyl THF, 10-formyl THF. Folate coenzymes are involved in one-carbon unit (formyl and methyl groups) transfer reactions in the metabolism of nucleic acids (synthesis of dTMP) and certain amino acids (methionine, glycine, serine) as well as choline. The C_1 units are covalently attached to the N(5), N(10) or both positions of THF. They are generated through the conversion of serine to glycine (a reaction catalyzed by the *hydroxymethyl transferase*) and the cleavage of glycine (catalyzed by *glycine synthase* also called glycine cleavage enzyme). Histidine can also contribute C_1 units with the formation of N^5-formimino-THF. The various forms of C_1 units bound to THF easily interconvert between each other. The interconversion and the fate of the C_1 units in the THF pool is shown below.



- Essential for the synthesis of nucleic acids and thus critical to cellular division. Poor dietary habits and addiction to high alcohol consumption can lead to folate deficiency. Low cellular levels of N^5, N^{10}-methylenetetrahydrofolate (the cofactor for thymidylate synthase) decreases the synthesis of dTMP. As a result, there is an increased chance for the DNA polymerase-mediated dUTP misincorporation into DNA because of a higher dUMP/dTMP ratio (1). This can happen when the activity of methylene THF reductase is too high and as a result there is insufficient N^5, N^{10}-methylenetetrahydrofolate cofactor for the synthesis of dTMP. Two opposing nicks can lead to double strand breaks in the DNA molecule. Repeated chromosome breaks will result in impaired cell function and disease. Such DNA lessions can lead to cell cycle arrest in the S-phase of rapidly proliferating cells such as the hematopoietic cells. Folate deficiency symptoms mimics those observed in vitamin B12 deficiency.
- Critical to the development of the nervous system of the fetus. Deficiency of folic acid during pregnancy has been linked to neural tube defects like spina bifida, a birth defect.

- One of the folate coenzymes, i.e. N^5-methyl THF is involved in the conversion of homocysteine to methionine. Increased levels of plasma homocysteine have been associated with greater risk for developing heart disease.
- Cell culture experiments using a mouse fibroblast cell line suggested that folic acid may act as an iron modulatory factor by altering thr Fe^{2+}/Fe^{3+} ratio through Fe^{2+} oxidation. A folate-derived compound, 6-formyl pterin was found to possess an even greater iron-oxidizing power (2).
- Folate and vitamin B12 deficiency and elevated plasma homocysteine are significantly correlated with increased micronucleus formation and reduced telomere length, respectively (3).
- Interactions: Folate coenzymes work together with vitamin B12, vitamin B6 and choline (a component of the cell membrane and other intracellular structures). Alcohol, some chemotherapy drugs, barbiturates, anticonvulsants and sulfonamides (sulfa drugs) interfere with folic acid synthesis, absorption and function. Since the sulfonamides are structural analogs of the p-aminobenzoic acid (a constituent of THF) they competitively inhibit the biosynthesis of THF in procaryotes. Based on this property the sulfa drugs are widely used as antibacterial agents.
- Health benefits: Supplementation is useful in conditions such as acne, anemia, atherosclerosis, constipation, depression, fatigue, hepatitis, osteoporosis, gum disease, seborrheic dermatitis.
- Best food sources: Brewer's yeast, green leafy vegetables, whole grains.

References

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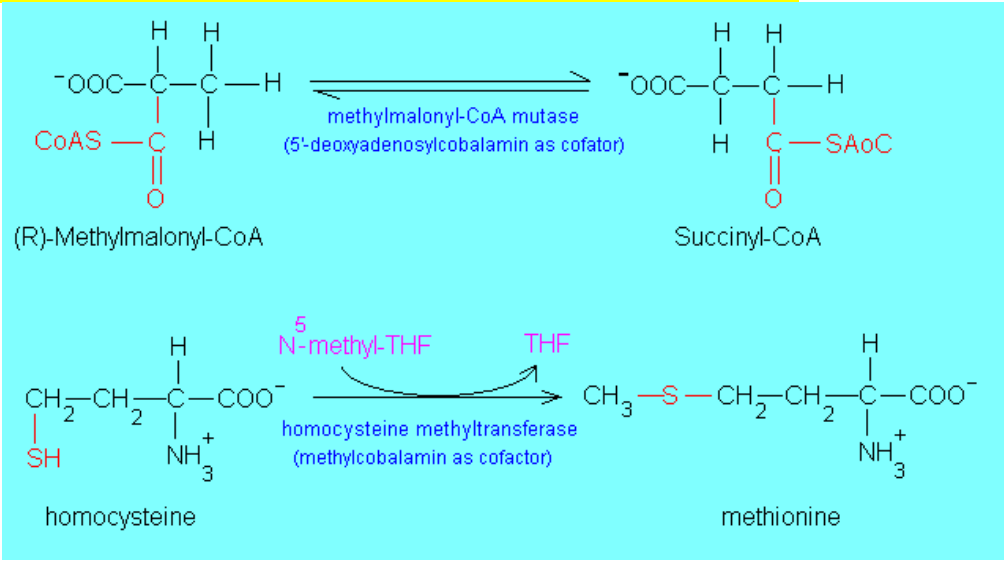
Vitamin B12 (Cobalamin)

Vitamin B12 has the most complex chemical structure of all vitamins. It exhibits a hemelike corrin ring system to which cobalt (as Co^{3+}) is coordinated. Its unique feature is that cobalt is

covalently bound to the 5' carbon of the deoxyribose moiety of deoxyadenosine. The C-Co bond is the only carbon-metal bond known in living systems. This bond is relatively weak for the mere illumination of cobalamin with visible light leads to the cleavage of the C-Co bond.

Vitamin B12 functions as coenzyme for several enzymes of which only two occur in mammalian systems: methylmalonyl-CoA mutase (5'-deoxyadenosylcobalamin as cofactor) and homocysteine methyltransferase (methylcobalamin as cofactor). The former catalyzes the last step in the conversion of propionyl-CoA to succinyl-CoA (the full path is shown on the Biotin page). The reactions catalyzed by these two enzymes are shown below:



It is interesting to note that in the reaction catalyzed by methylmalonyl-CoA mutase the 5'-deoxyadenosylcobalamin prosthetic group forms a free radical upon the homolytic cleavage of the C-Co(III) covalent bond (in most biological cleavage the process occurs via heterolytic cleavage). As a result Co^{3+} is reduced to Co^{2+}, then reoxidized in the later stage of the catalytic process with the re-formation of the C-Co bond just after the product, succinyl-CoA is released from the enzyme-cobalamin complex.

Some of the processes in which cobalamin is involved are listed below:

- DNA synthesis in body cells. Especially sensitive to vitamin B12 deficiency are the fast reproducing cells such as those lining the oral cavity, the gastrointestinal, urogenital and bone marrow.
- Erythropoietic cell development and maturation as well as other blood cells involved in defense against pathogens.
- Degradation of fatty acids with an odd number of carbon atoms in some marine organisms. The final round of b-oxidation of these fatty acids yields propionyl-CoA, which is then converted to succinyl-CoA for entry into the citric acid cycle.
- Amino acid metabolism, i.e. the conversion of homocysteine to methionine.
- Secretion of melatonin in the brain. Low levels of melatonin are associated with sleep-wake rhythm disorders.
- Essential for adrenal hormone synthesis, promotion of nerve growth and development as well as mood regulation. Normal B12 levels are associated with feelings of well-being.
- Interactions: Vitamin B12 works with folic acid in biochemical reactions involving methyl group transfers such as in the synthesis of methionine from homocysteine. The

buildup of homocysteine in blood plasma may be a factor in the formation of the atherosclerotic plaque. High alcohol and coffee consumption, heavy smoking, low intakes of calcium and iron and liver disease can cause vitamin B12 deficiency.

- Health benefits: Supplementation is useful in conditions like asthma, depression, impaired mental function in the elderly, HIV infection. A recent study showed that 39% of American adults age 26-83 have very low levels of B12 in their blood (1).
- Best food sources: Organ meats (liver, kidney), eggs, fish, cheese.

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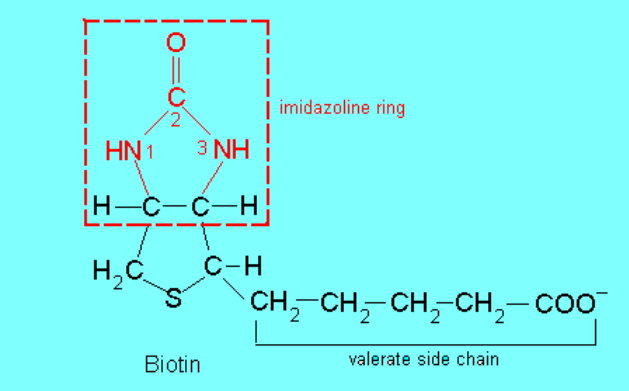
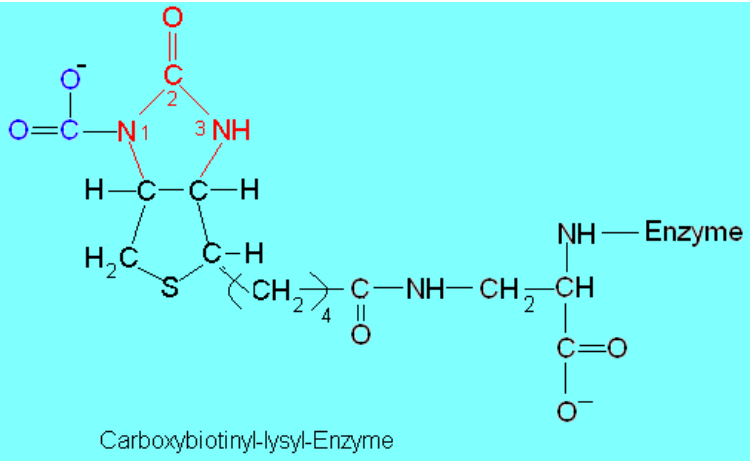
Biotin

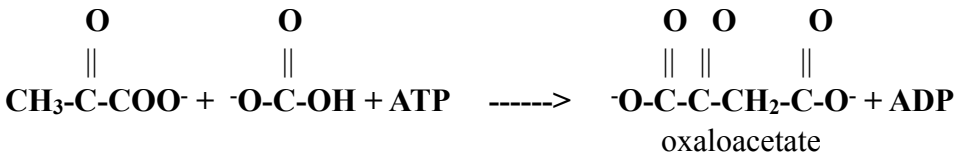
Biotin functions as a prosthetic group in several carboxylases. It is covalently bound to the enzyme by an amide linkage between the carboxyl group of the valerate side chain and the e-amino group of the lysine residue of the polypeptide chain.



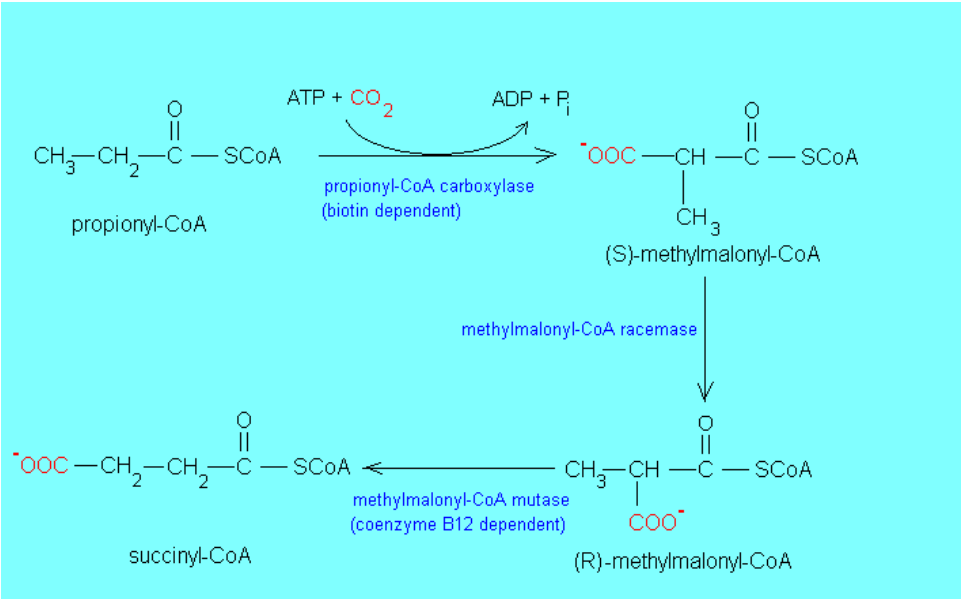


The prosthetic group functions as a CO_2 carrier (as bicarbonate) by forming an intermediate carboxyl substituent at its ureido group (N1 atom in the imidazole ring) followed by the attachment of the carboxyl group to various compounds. Three of the four biotin-dependent carboxylases in humans are located in mitochondria (pyruvate-, methyl crotonyl-CoA -, propionyl-CoA carboxylase). The fourth, acetyl-CoA carboxylase is located in both mitochondria and cytosol.

An example of such a compound is the pyruvate (an a-keto acid) and the enzyme that catalyzes the reaction is the *pyruvate carboxylase*.



Another reaction that requires the coenzyme biotin is the conversion of propionyl-CoA to (S)-methylmalonyl-CoA (catalyzed by *propionyl-CoA carboxylase*), the first step in the pathway from propionyl-CoA to succinyl-CoA, which is part of the degradation pathway for odd numbered fatty acids.

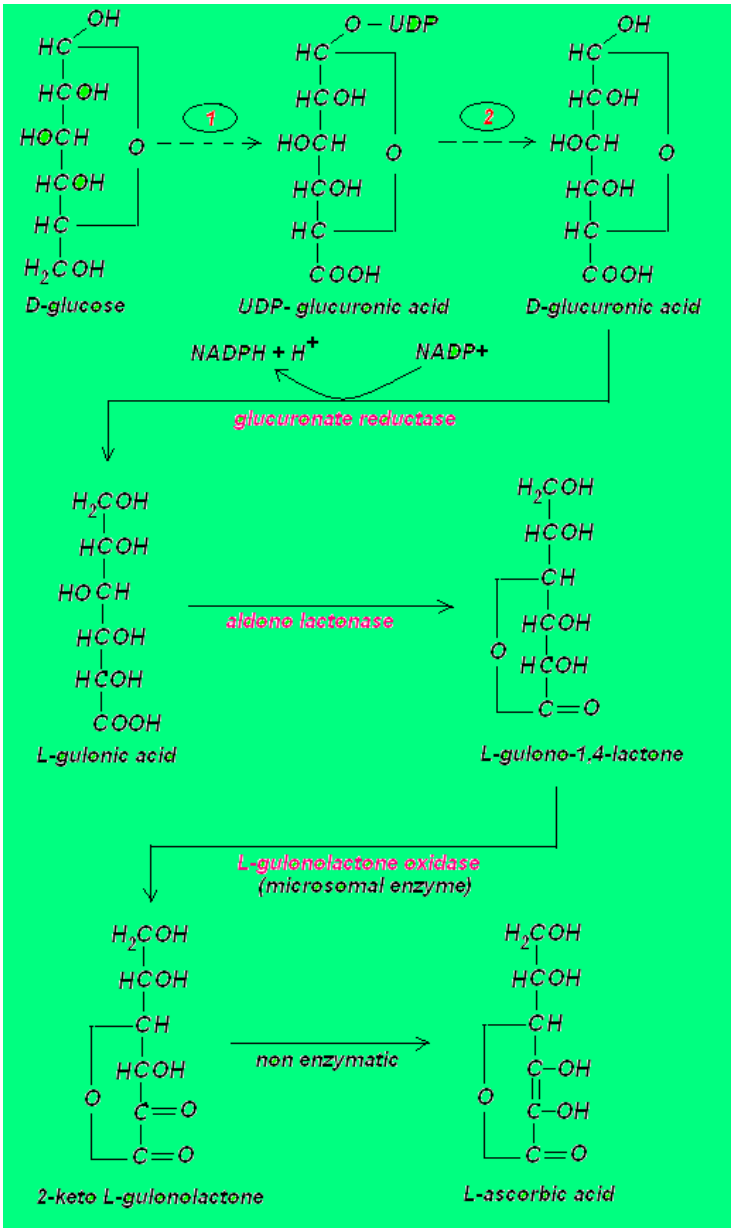


In the cell succinyl-CoA cannot be directly degraded by the citric acid cycle, which regenerates all its C_4 intermediates, which act as catalysts rather than substrates. So, the net degradation of succinyl-CoA takes place via the citric acid cycle where succinyl-CoA is first converted to malate, which may subsequently be transported to the cytosol. There it is decarboxylated to pyruvate. From here on, the aerobic degradation of this C_3 intermediate is well known to you and we need to elaborate no further.

- Essential in the metabolism of carbohydrates, fatty acids and amino acids.
- Biotin deficiency is rare because this vitamin occurs in many foods and is synthesized by intestinal bacteria. However, following excessive consumption of raw eggs biotin deficiency may occur because the egg white protein avidin prevents biotin absorption by forming a complex that does not cross the intestinal wall.
- Interactions: Biotin works synergistically with the other B-group vitamins, coenzyme Q as well as carnitine (4-trimethylamine-3-hydroxybutyrate). Carnitine is involved in the transport of fatty acids into mitochondria where they are degraded. This transport is mediated by a specific carrier protein that carries the acyl-carnitine across the mitochondrial membrane. The same protein carries the free carnitine back to the cytosol. Antibiotics destroy the biotin-producing bacteria in the gut. Alcohol inhibits the absorption of biotin in the gut.
- Health benefits: Biotin promotes strong nails and healthy hair and is useful in the management of seborrheic dermatitis and diabetes mellitus.
- Best food sources: Cheese, organ meats and soybeans, cauliflower, eggs, mushrooms, whole wheat.

Vitamin C (Ascorbic acid)

Ascorbic acid is a 6-carbon lactone whose biosynthesis occurs in the liver of mammals with the exception of guinea pigs, primates (apes and monkeys) and man (1). Ascorbic acid biosynthesis is absent in invertebrates, insects and fishes. In mammals, the synthesis of ascorbic acid starts from glucose and it involves nine steps. For those interested, the biosynthesis of ascorbic acid in plants is shown **on this page**.

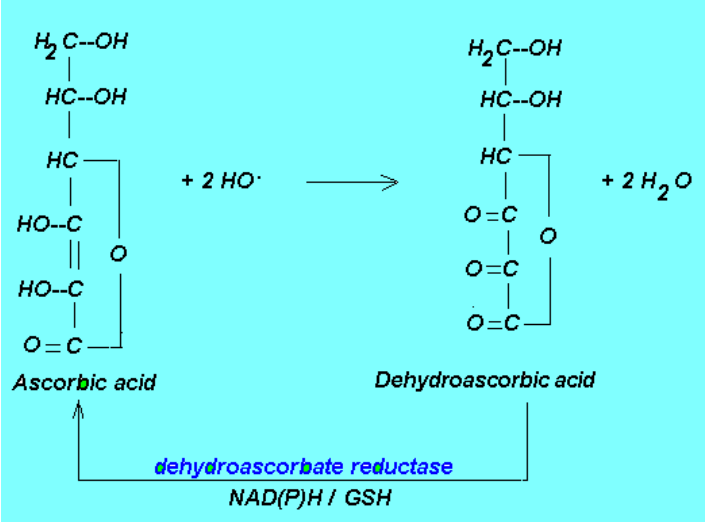


In the diagram above only the main steps are shown. As part of the first broken arrow the following reactions occur: D-Glucose ---> Glucose-6-P ---> Glucose-1-P ---> UDP-Glucose ---> UDP-D-glucuronic acid. As part of the second broken arrow the UDP-D-glucuronic acid is converted to D-glucuronate-1-P, which upon hydrolysis yields D-glucuronic acid.

It appears that some 25 million years ago a mutation occured in the gene that codes for the enzyme that converts L-gulono-1,4-lactone into the immediate precursor of vitamin C, namely 2-keto L-gulono-1,4-lactone (1). Thus,in order to survive, humans have to get the necessary vitamin C from their diet.

Ascorbic acid is an electron donor and therefore a reducing agent. It can be looked upon as a diacid whose pKs are 4.1 and 11.8, respectively. However, at the blood plasma pH of 7.4 over 99% of vitamin C is present as ascorbate($AscH^-$). By donating electrons, the ascorbic acid prevents sensitive biological molecules from becoming oxidized thus acting as an antioxidant. These electrons are lost sequentially with the formation in the first step of an *ascorbyl radical*, which upon the loss of another electron turns into dehydroascorbic acid. The formation of these molecular species in biological systems is mediated by a wide range of oxidants, such as oxygen and its reactive species (superoxide, hydroxyl radical), HClO, $NO^{\cdot}$ and the transitional metals

iron and copper. In both mammalian and plant systems, some of the oxidized ascorbic acid is converted back to its reduced form by *dehydroascorbate reductase* using NAD(P)H/GSH as hydrogen donor (2, 3). The rest is degraded and excreted.



For more on the chemistry of ascorbate and its antioxidant chemistry the reader is encouraged to look at **this short presentation.**

Below, some of the processes in which the ascorbic acid is involved are listed:

- Essential for collagen synthesis. Collagen is the main component of cartilage, tendons and connective tissue.
- Essential to the immune function by enhancing white blood cells activity and interferon levels.
- Acts as a general free radical scavenger in the body's aqueous environment, inside and outside the cells. Works synergistically with other antioxidants such as vitamin E and glutathione. Thus, the a-tocopheroxyl radical (generated when oxidants interact with the a-tocopherol-containing plasma LDL) is reduced back to a-tocopherol.
- Involved in the absorption of iron by reducing ferric to ferrous iron in the intestinal tract.
- Acts as co-factor for the hydroxylation reaction in carnitine biosynthesis.
- Acts as co-factor for dopamine b-hydroxylase, which catalyzes the conversion of dopamine to norepinephrine.
- Involved in enzymatic reactions (amidation) that yield biologically active oxytocin, vasopressin, cholecystokinin and a-melanotripin.
- Involved in the microsomal hydroxylation of cholesterol in the pathway that converts cholesterol into bile acids.
- Involved in the conversion of the amino acid tryptophan into 5-hydroxytryptophan, a precursor of serotonin.
- Involved in the conversion of p-hydroxyphenylpyruvate (an intermediate in the phenylalanine degradation pathway) to homogentisate.
- As mentioned on the Generation of Free Radicals page ascorbate can generate reactive oxygen species (ROS) through an "auto-oxidation" reaction. Since molecular oxygen

cannot react directly with most biomolecules because of spin restriction it became apparent that transition metal ions such as copper, which are redox catalysts can catalyze the reaction of molecular oxygen with ascorbate. Both ROS and ascorbyl radical are formed in the reaction (4). This may have biological as well as medical implications. Thus, it was shown that plasmin and other serine proteases were inactivated by the ascorbate-copper couple (5) and this may play a role in controlling the life span of thrombi at sites of injury. Platelets and leukocytes, which are always present at wound sites contain copper and ascorbate, respectively. Cellular toxicity caused by the ascorbate-copper pair was demonstrated in bovine corneal endothelial cells in vitro (6) and on sarcoma tumor cells in mice (7).

- Interactions: **Vitamin C synergists:** iron, selenium, nickel, germanium, vitamin A, bioflavonoids such as rutin and hesperidin. For instance, bioflavonoids function synergistically with the ascorbate (forming the so-called vitamin C complex) in scavenging ROS as well as in collagen synthesis and supporting a healthy immune system (recall that leukocytes are rich in ascorbate). Ascorbate and iron depend on each other for optimal absorption and selenium as part of the antioxidant enzyme glutathione peroxidase supports the ascorbate in scavenging the oxygen free radicals. **Vitamin C antagonists:** zinc, manganese, calcium, copper (II), vitamin E. High copper levels can deplete the ascorbate because as seen earlier the ascorbate-Cu^{2+} pair can generate ROS so additional ascorbate is required to scavenge those reactive species. High ascorbate intakes lower manganese levels and boosts insulin production, which is bad for those with hypoglycemic tendencies that exhibit low sodium for sodium slows insulin response. Low manganese also means decreased ability of the liver to store glycogen. Prolonged high intakes of vitamin C can affect calcium metabolism by lowering calcium stores, particularly the bones. However, high vitamin C intakes may be beneficial for people with high calcium levels as well as elevated levels of copper and zinc for vitamin C can lower the body levels of these minerals. That is why for healthy individuals a high intake of vitamin C may have harmful effects in the long run because of these interactions. Because of their synergism a higher vitamin C intake will require a higher vitamin E intake to balance the ratio between these two vitamins. An imbalance between vitamin C and E in regard to the trace mineral nickel can affect the vasodilating and vasoconstrictive properties of the coronary arteries. This may be a problem for those suffering from angina-related conditions. Aspirin was shown to interfere with ascorbate uptake by white cells.
- **Health benefits:** There have been suggestions that supplementation with doses above the RDA (recommended daily allowance of 100 mg of vitamin C) may be beneficial in several conditions, such as autoimmune disorders, bacterial and viral infections, cancer, capillary fragility, cardiovascular disease, fatigue, gum disease, skin disorders, etc. Clear signs of scurvy appear at vitamin C intakes below 10 mg. However, large controlled epidemiological studies have failed to show benefit. There is some evidence however, that ascorbic acid derivatives such as ascorbyl stearate inhibited the proliferation of certain human cancer cells by interfering with cell cycle progression and triggered apoptosis by modulating signal transduction pathways (9). For a review on the possible role of vitamin C in disease prevention see Ref. 8 & 9.
- Best food sources: fresh fruits and vegetables.

There is still a lot of debate among nutritionists as to what the optimum daily intake of vitamin C should be. Never in the history of research on the biomedical role of vitamins has there been so much debate raised as by vitamin C. To learn more about some of the less known aspects of the history of vitamin C research please go to **this page**

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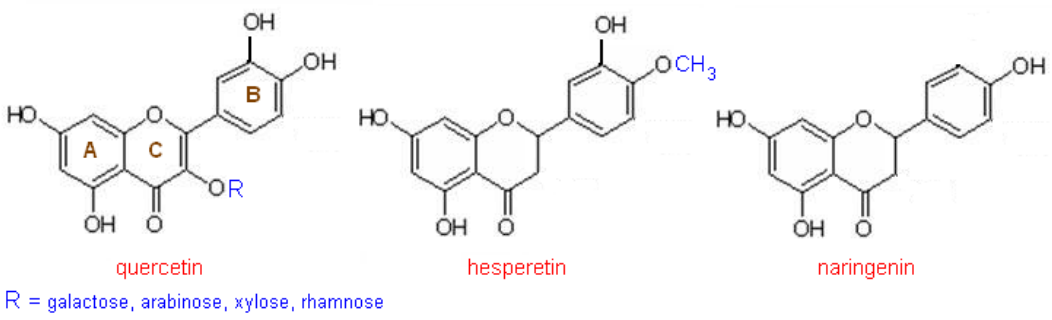
Bioflavonoids

- Bioflavonoids are a group of plant polyphenolic compounds that exhibit remarkable health promoting benefits although the mechanisms by which these benefits are brought about remain largely unknown. A well-studied group is the quercetin-based flavonoids such as the citrus flavonoids rutin, quercetin and hesperetin. Another class of biologically acitve flavonoids is that of the proanthocyanidins, which are usually present as oligomers (OPC).



The structure of three well known flavonoids.

- OPC are the most powerful antioxidants, being 20 times and 50 times more so than vitamin C and vitamin E, respectively. However, these findings from test tube experiments may have little relevance to the process in vivo. In fact, there is growing evidence to suggest that flavonoids undergo extensive transformation in vivo, which results in a significant alteration of their redox potentials. Many flavonoids, which occur as glycosides in plants are deglycosylated in the body then conjugated with monosaccharides, sulfur compounds or O-methylated. Flavonoids can also be degraded by the colon bacteria to simple phenols that are absorbed and further metabolized in the liver. The antioxidant function relies on the two OH groups in the B ring and /or the double bond and the OH group in the C ring. The catechol group in the B ring can also chelate metal ions thus removing one of the reactants in the metal-catalyzed reactive oxygen species generation reactions (1, 2). The concentration of flavonoid metabolites in blood plasma and several other tissues is much lower than that of ascorbate and a-tocopherol. It appears unlikely that flavonoids can exert their beneficial action only by virtue of their antioxidant function. It is interesting to note that flavonoids were found to protect neurons against oxidative stress more effectively than the ascorbic acid even when this was used at a concentration10-fold higher than that of the flavonoids. This led to the conclusion that flavonoids may act through a mechanism other than based on antioxidant activity (3).

  Flavonoids may act as modulators of cellular events through specific interaction with key proteins in the intracellular signaling cascade. One such pathway is the mitogen-activated protein kinase (the so-called MAP kinase) signaling pathway. By interacting with proteins such as phosphoinositide 3-kinase, tyrosine kinase, MAP kinase flavonoids or their metabolites can exert stimulatory or inhibitory actions, which are likely to influence the phosphorylation state of target proteins or to modulate gene expression. Flavonoids have been shown to interact with subcellular organelles such as mitochondria and to interfere with biochemical pathways of intermediate metabolism or downregulate the expression of adhesion molecules (4). For more information on this exciting field of research go to this excellent recent review article (5).
- OPC potentiate the action of vitamin C, which is essential for collagen synthesis. As a result, arteries and veins are strengthened because of increased collagen stability (collagen is the main protein in the wall of blood vessels).
- OPC inhibit the formation of nitrosamines (cancer-causing agents) from food additives and other environmental pollutants, such as pesticides and herbicides, car exhaust fumes, cigarette smoke, industrial emissions, etc. OPC exhibit significant antiviral activity against herpes virus type I, influenza virus, syncytial virus and others although the mechanism by which this is achieved is not clear at present.
- Health benefits: The scavenging of free radicals reduces the risk of: cardiovascular disease, cancer, allergic reactions, autoimmune disorders (rheumatoid arthritis, lupus), degenerative diseases (Alzheimer's disease, Parkinson’s disease, multiple sclerosis). OPC improve brain function, enhance the immune response, reduce diabetes symptoms, etc. Here again we must stress that when reference is made to the health benefits of flavonoids/OPC supplementation in fighting/prevention of cancer, proliferative disorders, chronic inflammation and neurodegeneration one should bear in mind the complex interactions of flavonoids or their derivatives with the various signaling and metabolic pathways as a means of cellular response to injury whether by internal or external factors

and less about the flavonoids exerting their biological action mainly as free radical scavengers as often portrayed in the popular science publications. In promoting the nutraceuticals industry's marketing executives are quick to exploit any data on the antioxidant activity of OPC/flavonoids (mainly from in vitro experiments) published in science journals, that may further their sales efforts. So, until solid information is acquired on the mechanisms by which bioflavonoids exert their biological action and the potential clinical benefits of flavonoids intake (coming from large scale double blind-controlled epidemiologic studies) caution should be exercised when taking OPC-based nutritional supplements.

- Best food sources: grapes (seeds), citrus fruits, berries, onions, parsley, apples, pears, apricots, cabbage, tomatoes, green tea.

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* OPC stands for oligomeric proanthocyanins. Although not vitamins in the strict sense of the word bioflavonoids, which were first called vitamin P by their discoverer, Albert Szent-Gyorgyi work together with vitamin C in many biological reactions and have common traits such as scavengers of oxygen reactive species. Because of that and to honor their discoverer we placed the OPC next to vitamin C in this table of vitamins and minerals.

The information given for the vitamins and minerals in the table above is by no means exhaustive. It is intended to be a brief reference guide and students are encouraged to find out more about the world of micronutrients by turning to articles and reviews in science journals and to what is available on the subject on the internet.

For an excellent source of information on human vitamin and mineral requirements interested students can take a look at this report: Human Vitamin and Mineral Requirements (Report of a Joint FAO/WHO Expert Consultation, Bangkok, Thailand, 2002)

Potassium

- Involved in water balance and distribution and hence in maintaining the osmotic pressure of cells.
- Involved in the maintenance of the acid-base balance in blood.
- Involved in membrane charge distribution in all animal cells. In nerve cells the interplay of sodium and potassium across the plasma membrane creates an electrical charge that ensures the transmission of the electrical impulse to the contractile fiber in the skeletal and cardiac muscle cells.
- Takes part in the kidney and adrenal cortex gland function.
- Involved in choline transport into brain cells. In nerve cell cultures the uptake of choline was increased at higher pH (8.1) or in the presence of excess K^+ in the medium (1).
- Health benefits: Supplementation may be useful in cases of high blood pressure. There is a positive correlation between low potassium intake and high blood pressure, which could be a risk factor for developing heart disease. It may also help in allergy treatment. In general, there is an excess of sodium in the diet of the western world and this can lead to various health problems. It is recommended that the potassium: sodium ratio should be at least 100:1 in order to maintain good health.
- Best food sources: Bananas, oranges, avocados, cantaloupe, raisins, tomatoes, potatoes, beans, nuts.

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Sodium

- Sodium is present in all body fluids and is involved in maintaining the acid-base balance of body fluids.
- Sodium is present mostly in the extracellular compartment. Together with potassium sodium helps regulate the movement of fluids in and out of tissues. These two ions are also involved in the propagation of the electrical signal along the axon by moving in and out of the nerve cell.
- Sodium concentration in the body is mainly controlled by the kidneys, adrenal glands and the pituitary gland. The concentration of sodium in urine is controlled by aldosterone.
- A high sodium (salt) intake has been positively linked to hypertension.
- Interactions: A high potassium intake was shown to increase the urinary excretion of sodium. High potassium intakes were found to inhibit the reabsorption of sodium in the urinary tract. This is beneficial in individuals with high blood pressure. An excess of sodium in the body can lead to increased urinary excretion of calcium, which may affect bone health and promote the formation of kidney stones.
- Best food sources: Most of the dietary sodium consumed by the North American population (some 90%) comes from salt (NaCl). The rest is represented by food additives such as monosodium glutamate, sodium nitrite, benzoate and citrate. The primary food source of sodium (as salt) are canned and processed foods where salt is added for flavor, prevention of spoilage and growth of hazardous bacteria such as C. botulinum. For more information on the role of salt and sodium-containing ingredients as food additives see **the review in ref.1**. It has been estimated that only about 12 percent of the total salt consumed comes from natural sources such as meat, milk, poultry, vegetables and drinking water, the rest comes from processed foods and condiments such as soy sauce, onion salt, ketchup, mustard, etc. According to the Institute of Medicine (US) the daily amount of sodium needed by healthy people 19-50 years old is 1500 mg, which corresponds to approx. 3500 mg salt (2).

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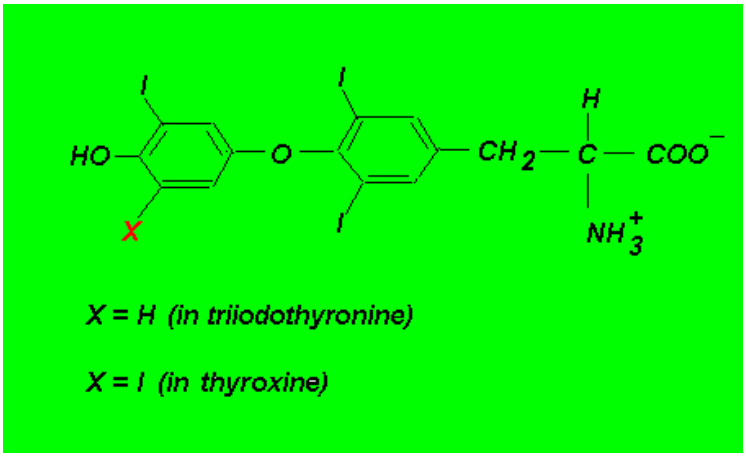
Phosphorus

- Phosphorus is found in the human body only in combination with oxygen as phosphate. Most of the phosphate (as calcium phosphate) is stored in the skeleton. Bone is connective tissue, which is composed of calcified extracellular matrix and bone cells. The organic portion is composed of collagen fibers (type I collagen) and ground substance (keratine sulfate, chondroitin sulfate, hyaluronic acid). The inorganic moiety accounts for about 65% of the dry weight of bone. Type I collagen fibers are embedded in a complex of calcium phosphate as hydroxyapatite $[Ca_{10}PO_4)_6(OH)_2]$.

- The phosphate group is also found in the composition of nucleic acids, proteins, phospholipids (in the cell membranes and blood lipoproteins), high energy compounds such as ATP and creatine phosphate.
- The phosphate group takes part in phosphorylation reactions catalyzed by the enzymes called kinases in many metabolic pathways as well as in the signal transduction pathway.
- Interactions: High phosphate intakes may impair the absorption of iron, copper and zinc. The overuse of aluminium-containing antacids may cause phosphate deficiency.

Iodine

- Essential for the synthesis of the thyroid hormones (triiodothyronine and thyroxine) which are required for the normal growth and development of young mammals, including humans.
- Involved (as elemental iodine) in the modulation of estrogen action on breast tissue.
- Health benefits: Adequate daily intake prevents hypothyroidism (the development of an enlarged thyroid gland, usually referred to as goiter), promotes healthy hair, nails, skin and teeth.
- Best food sources: seafoods, onions, vegetables grown in iodine-rich soil.



Boron

- Boron has long been known to be essential for plant growth and development, but its role remains elusive. Several roles have been postulated for boron in plant cells: cell wall synthesis, lignification and structure; nucleic acid synthesis and metabolism; carbohydrate, indole acetic acid and phenol metabolism (1). Since boron can form diester bridges between cis-hydroxyl-containing molecules it has been recently suggested that boron could serve to stabilize molecules with cis-diol groups, in plants at least and that would turn them effective, irrespectively of their biological function (2).
- It occurs in the human body in trace amounts. Its role in human nutrition is still sketchy and there is no clear evidence that boron is an essential element.
- As demonstrated in animal models there is evidence to suggest that boron supplementation at a physiological level affects a wide range of metabolic parameters.

Thus, it was found that boron stimulates growth in cholecalciferol-deficient chicks but not in the birds receiving adequate amounts of vitamin D3. This suggests boron may influence some aspect of vitamin D3 metabolism or is synergistic with vitamin D3 with respect to bone growth (3). In rats it was found that supplemental dietary boron has most marked effects when the diet is deficient in known nutrients. There was also a higher intake versus excretion ratio for calcium, magnesium and phosphorus in rats fed a vitamin D deficient diet supplemented with boron as compared to control animals (4).

- In mammals the boron transporter NaBCl functions as electrogenic sodium-coupled borate transporter. This transporter is essential for cell growth and proliferation (5).
- Boron supplementation to broiler chicks affected plasma levels of iron, copper, zinc and bone (tibia) concentration of boron, zinc and calcium. In addition, blood hematocrit and hemoglobin counts increased by boron supplementation (6). These results would suggest that boron may play an important role in mineral metabolism through biochemical and hematological mechanisms.
- In rodents (rats) a low boron diet was shown to impair early embryonic development (7).
- Health benefits: Boron supplementation may reduce body calcium loss by increasing the beneficial effects of estrogen on bone health. Thus, boron supplementation with amounts commonly found in diets high in fruits and vegetables to postmenopausal women markedly decreased the urinary excretion of calcium and magnesium, particularly when the magnesium intake was low (8). In the same time there was a marked increase of serum 17 b-estradiol and testosterone. In another study on postmenopausal women it was found that changing boron intake from low (0.33 mg/day) to high (3.33 mg/day) had no effect on mineral and steroid metabolism as shown by the bone mineral absorption and excretion and plasma steroid hormone levels. However, the low boron diet appeared to induce hyperabsorption of calcium since positive calcium balance were recorded in combination with elevated urinary calcium excretion (9). In healthy men it was found that boron supplementation (10 mg/day for 4 weeks) resulted in elevated plasma estradiol concentration but there was no difference in LDL susceptibility to oxidation between the control and the supplemented group and based on these findings it was suggested that boron may be involved in protection against atherosclerosis (10).
- Best food sources: fresh fruits and vegetables.

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Calcium

- Essential in bone and tooth mineralization (1, 2). Calcium metabolism is regulated by the parathyroid hormone, vitamin D and calcitonin (synthesized by specialized thyroid gland cells).
- Stimulates glycogen (a glucose polymer) breakdown in the liver when energy is needed, e.g. during intense physical activity.
- Regulates activity of several key enzymes in carbohydrate metabolism (related to energy production). Ca^{2+} together with ADP and ATP are allosteric regulators of several citric acid cycle enzymes (*pyruvate dehydrogenase (3), isocitrate dehydrogenase and a-ketoglutarate dehydrogenase*). It activates the enzymes catalyzing the following reactions:
  1) Pyruvate + CoASH + NAD^+ ----------> Acetyl-CoA + CO_2 + NADH
  2) Isocitrate + NAD^+ ----------> a-ketoglutarate + CO_2 + NADH
  3) a-ketoglutarate + NAD^+ --------> succinyl-CoA + NADH + CO_2
- Triggers muscle contraction—calcium ions are released from intracellular storage sites and bind to troponin C, a component of the contractile apparatus causing the fiber to contract (4). Regulates heart rhythm.
- Mediates many hormonal signals such as those triggered by epinephrine (for smooth muscle contraction) (5) and acetylcholine (a neurotransmitter involved in the transmission of nerve impulse).
- Involved in blood clotting by modulating the activity of the proteins that take part in the process (6). For instance, the sluggish prothrombin activation factor (a protein) becomes very active in the presence of Ca^{2+}, activated proaccelerin and a membrane phospholipid. Prothrombin and its activation factor require Ca^{2+} in order to bind to phospholipid membranes at the site of injury. These two proteins are anchored to the membrane via calcium bridges.
- Calcium can act as an intracellular second messenger when extracellular signals cause a transient rise in the cytosolic calcium concentration. As a result, processes such as muscle contraction (7) and glycogen breakdown are triggered.
- Involved in gastrointestinal physiology (8).
- Interactions: Calcium interacts with Zn^{2+}, Mg^{2+}, vitamin D and with vitamin K. Calcium absorption in the gut can be inhibited by aluminium (in cookware, aluminium foil, anticid products), high levels of sodium, magnesium, and dietary fiber. High levels of sodium,

alcohol, phosphates (in soft drinks), sugar and high protein intake increase calcium excretion.

- Best food sources: Dairy products, tofu, kale, green leafy vegetables, canned salmon, cooked soybeans, pecans, wheat germ, miso paste, romaine lettuce, dried apricots, roasted peanuts, blackcurrants, cabbage, whole wheat bread, eggs, globe artichoke, pumpkin seeds, celery, cashews, barley, carrots, sweet potatoes, brown rice, and fish.

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Magnesium

- In the human body most magnesium is stored in the skeleton followed by the muscle tissues.
- Critical to many cellular functions, such as energy production and cell replication. Controls the activity of over 300 enzymes of the carbohydrate, lipid and protein metabolism. As an example, there are five Mg^{2+}-dependent reactions out of 10 in the glycolysis pathway. Mg^{2+} is also an activator of pyruvate dehydrogenase phosphatase (1) and an inhibitor of pyruvate dehydrogenase kinase of pyruvate dehydrogenase multienzyme complex.
- Modulates activity of the ATP-dependent sodium and potassium pump that ensures the right distribution of these ions between the intra- and extracellular compartments of all animal cells. In nerve cells this balance is crucial to the proper flow of the electrical impulses along the nerve.
- Modulates intracellular Ca^{2+} in vascular smooth muscle cells (2). Earlier studies suggested a relationship between low plasma Mg^{2+} concentration and hypertension and heart disease (3).
- Involved in the regulation of calcium metabolism through its action on the *parathyroid hormone* (stimulates calcium uptake from bone, kidney and intestine) and *calcitonin* (a thyroid hormone that inhibits calcium uptake from bone and kidney). Helps prevent calcium deposits in kidneys and gall bladder.
- Involved in the proper function of the gastrointestinal tract (4).
- Known also for its antioxidant activity. As shown in animal studies magnesium deficiency led to increased production of reactive oxygen species (ROS). Mg^{2+}-deficient rats exhibited increased levels of plasma $NO\cdot$ (5). $NO\cdot$ reacts with O_2^- to generate $ONOO^-$, which can decompose into other more reactive species that can lead to oxidative damage. These findings provide additional support to earlier results that link magnesium deficiency to inflammation and oxidative stress. Moderate Mg deficiency through exacerbating chronic inflammatory stress may be contributing significantly to the occurrence of chronic diseases such as CVD, hypertension, osteoporosis, diabetes and cancer (6).
- Interactions: Magnesium interacts with calcium and vitamin K. It works with vitamins B1, B2 and B6 in many enzyme systems. Higher calcium and zinc intakes decrease magnesium absorption. Some drugs, e.g. diuretics and digitalis adversely affect magnesium status. Intense physical activity requires a higher magnesium intake. High alcohol, tea and coffee consumption decrease magnesium absorption.
- Best food sources: Kelp, tofu, seeds, nuts, whole grains, green leafy vegetables, corn, avocado, garlic, fresh green peas, sweet potato, blackberries, broccoli florets, cheddar cheese, cauliflower, carrots, white fish, celery, chicken, asparagus, stewing beef, potatoes, tomatoes, oranges, whole milk, eggs, black-eyed peas, lima beans.

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Silicon

- Essential for living organisms. Silicon (Si) performs an important role in the metabolism of connective tissue, cartilage and bone. In the latter Si appears to mediate the formation of the organic matrix. Collagen and glycosaminoglycan synthesis also require the presence of Si (1).
- Si and arginine are involved in collagen formation and bone mineralization. In rats it was found that Si deprivation decreased bone concentration of calcium, copper, potassium, zinc and manganese. Arginine supplementation increased bone concentration of sodium, potassium, manganese, zinc and iron in Si-deficient animals (2).
- Si deficiency may result in poor wound healing as well as a decreased liver ornithine aminotransferase activity, a key enzyme in proline synthesis (3).
- Biological role not fully determined in humans. In a recent study it has been shown that the silicon to calcium ratio varies along the human backbone suggesting that Si is compatible with the biokinetics of calcium in the vertebral bone structure (4).
- Health benefits: Silicon appears to be important for the growth and calcification of bones as well as for the normal growth of skin, hair and nails. There is some evidence to suggest that Si may play a role in delaying the onset of atherosclerosis (5). In an animal model study, it has been shown that Si inhibited the gastrointestinal absorption of aluminum, which may be relevant to the Alzheimer disease where aluminum is known to exert a neurotoxic effect (6).
- Best food sources: Unrefined grains, oatmeal and brown rice, root vegetables.

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Iron

- Iron plays a central role in the metabolism of all cells, i.e. prokaryotes and eukaryotes. It has a major contribution to such diverse processes as photosynthesis, free radical generation, DNA replication, protein synthesis and cell proliferation (1-3).
- Essential for synthesis of heme proteins such as hemoglobin, myoglobin, the cytochrome and several enzymes (peroxidase, catalase). Hemoglobin is the oxygen carrier protein of red blood cells. It also carries carbon dioxide from tissues to the lungs where it exchanges for oxygen.
- Involved in energy production (in the cytochromes and as iron-sulfur clusters bound to some proteins of the electron transport chain) and DNA synthesis. In the latter Fe^{2+} is involved as metal cofactor in a newly identified nuclear protein called pirin (a nonheme protein), a novel highly conserved 32-kDa protein with 290 amino acids (4). Although the exact function of pirin has not been established yet it appears that it has no enzymatic activity, but it can bind to a nuclear transcription factor (NFI). This suggests pirin may act as a transcription cofactor. NFI has been shown to stimulate DNA replication and RNA polymerase II-driven transcription (3).
- Involved in enzymatic and non-enzymatic activity of iron-binding nonheme proteins. For instance, transferrin, ferritin and lactoferrin are examples of non-enzymatic nonheme iron-binding proteins. The former two are involved in the transport and storage of iron, respectively while the third exhibits a wide spectrum of antimicrobial and immunotropic properties. Lactoferrin also plays a role in the absorption of nutrients such as the metal ions iron, manganese and zinc as well as sugars (5,6). The nonheme proteins with enzymatic activity such as diiron hydroxylases (AlkB - an omega hydroxylase, soluble methane monooxygenase and toluene monooxygenase) appear to have a ferryl species i.e. $[Fe(IV)O]^{2+}$ involved in the catalytic process. Such a molecular species can be formed under a variety of conditions including those that are characteristic of the Fenton reaction (7). Highly reactive intermediates are likely to be formed during the hydroxylation of an unfunctionalized alkyl group for this kind of substrate is very hard to attack unless it is "softened" by a highly reactive species like the ferryl ion. A typical example of such an oxidation is the hydroxylation of fatty acids in the omega position (8).
- Interactions: Copper, cobalt (as vitamin B12), manganese and vitamin C are necessary for iron absorption. High intake of calcium, magnesium and zinc can interfere with iron absorption. Animal studies showed that iron deficiency can cause altered folate utilization. This relationship is best seen during the reproductive and neonatal life cycle (9). Some anti-inflammatory drugs, such as aspirin and ibuprofen may contribute to iron loss through discreet gastrointestinal bleeding. Given the central role played by iron in the cellular metabolism a recent medical hypothesis put forward the idea that excess cellular iron together with low tryptophan, zinc and manganese may have a role in carcinogenesis

(10). Thus, besides its ability to catalyze Fenton-type reactions that generate oxygen reactive species excess iron may also interfere with energy production in mitochondria by complexing to citric acid and other Krebs cycle compounds and thus slowing down the reactions in the cycle. In the presence of iron, quinolinate an intermediate in the tryptophan degradation pathway was shown to cause an increase in lipid peroxidation. Excess iron may also interfere with MnSOD activity and the ability of cells to undergo apoptosis.

- Best food sources: Beef and pork liver, heart and kidney, raw clams, red meat, eggs, nuts, beans, molasses, oatmeal.

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Copper

- Copper (Cu) is a trace element found in all body organs; the highest percentage being in muscle. It forms part of the catalytic site of several enzymes such as superoxide dismutase (SOD), amino acid oxidases and mitochondrial cytochrome c oxidase (for a detailed description of mitochondrial Fe-Cu cytochrome c oxidase see ref. 1).
- Required for the crosslinking of collagen and elastin (proteins found in the blood vessel walls and responsible for their mechanical resistance) by the copper enzyme lysyl oxidase (2). Poor collagen integrity may lead to blood vessel fragility, osteoporosis and joint dysfunction.
- Disruption of normal Cu homeostasis can lead to severe medical conditions such as Wilson's disease and Menkes disease. The latter is a fatal childhood neurodegenerative disorder caused by a mutation in a gene (on the X chromosome) encoding a Cu-transporting ATPase; patients afflicted by this condition exhibit symptoms of Cu

deficiency. It has been recently shown that the Cu transporter ATPase functions by carrying Cu from a N-methyl-D-aspartate receptor-dependent releasable pool of Cu in hippocampal neurons (3). It was suggested that the neuronal degeneration may result from impaired Cu homeostasis brought about by an impairment of Cu efflux from its storage site.

- In the liver cells Cu is transported by chaperone proteins such as Cu-ATPase, which directs Cu to either ceruloplasmin for export or within the trans Golgi network to the proteins a amidating monooxygenase, lysyl oxidase, tyrosinase, dopamine b monooxygenase. Another chaperone delivers Cu to the mitochondrial cytochrome c oxidase (4,5). The so-called Menkes ATPase has been also shown to transport Cu to a secretory superoxide dismutase (SOD3) in the trans Golgi network of vascular cells (6).
- Metallothioneins are another class of proteins involved in Cu homeostasis. They function as an important storage protein for Cu as well as for zinc (7).
- Involved, as part of the copper carrier protein ceruloplasmin and the superoxide dismutase in free radical scavenging activity. The cytosolic SOD contains Cu^{2+} and Zn^{2+} in the catalytic site while the mitochondrial SOD contains Mn^{2+}.
- Takes part as enzyme cofactor in processes such as energy production (in cytochrome c oxidase), skin pigment melanin (in tyrosinase), amino acid metabolism (in amino acid oxidases).
- Interactions: A high intake of vitamin C, zinc and iron may impair the absorption of copper.
- Health benefits: Supplementation is not recommended if a diet rich in shellfish or nuts is consumed. An adequate level of copper in body tissues may prevent cardiovascular disease and arthritis.
- Best food sources: Oysters and other shellfish, nuts.

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Zinc

- Zinc is a component in over 200 proteins, mostly of them enzymes. Recall superoxide dismutase where Zn^{2+}pairs with Cu^{2+} in the catalytic site. Muscles contain over 60% of the zinc in the body. Cells and tissues with high zinc concentration: red and white blood cells, liver, kidney, pancreas, bones, skin, retina, prostate.
- Involved in the thyroid hormone metabolism (1). Zinc deficiency was found to lower the serum level of triiodothyronine in patients with hepatic and gastrointestinal disorders (2).
- Involved in insulin and steroid hormone metabolism. For instance, the glucocorticoids (a class of steroids that mainly affect carbohydrate metabolism) bind to their receptor and this complex interacts with a region of a DNA-bound protein. This protein contains the so-called "zinc fingers," which are amino acid motifs that fold around one or more zinc ions. By binding to specific DNA sequences these zinc fingers can activate the transcription of certain genes to elicit a response to the hormonal signal. Zinc fingers have also been shown to mediate protein-protein and protein-lipid interactions (3).
- Required for nucleic acid synthesis and cell growth. Plays an important role in immune function, wound healing.
- Interactions: High fiber and calcium intake as well as high iron to zinc ratio decrease zinc absorption. Zinc-rich foods should be taken apart from high-fiber foods.
- Health benefits: It is now widely accepted by nutritionists that a sizeable proportion of the population in the developed world has some form of zinc deficiency. Because of zinc involvement in several critical points of metabolism and the implications for human pathology there is a need for understanding of zinc biochemistry and homeostasis at molecular, cellular and organ-system level as well as of the factors that affect its bioavailability (4). Supplementation has been found useful in: rheumatoid arthritis and irritable bowel syndrome, acute infections, acne, Alzheimer's and Wilson's disease. In vitro studies (a cell-culture model) showed that low intracellular zinc levels increased oxidative stress and DNA single-strand breaks. In zinc deficiency there is an increased expression of DNA repair proteins as well as a decreased binding of transcription factors such as p53, nuclear factor B and activation protein 1. Repletion with zinc reversed these negative trends (5).
- Best food sources: Oysters, fish, red meat, nuts, whole grains, oats.

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Chromium

- Earlier studies indicated that chromium (III) compounds improved insulin efficiency in people with impaired glucose tolerance (1,2). Chromium supplementation was shown to improve glucose metabolism and decrease the total cholesterol/HDL cholesterol regardless of the status of glucose tolerance. Glucose tolerance is a term that defines the ability of muscle and liver cells to remove glucose from the blood stream. As you age the glucose tolerance decreases.
- Results from earlier studies have also suggested that the so-called 'glucose tolerance factor' (GTF), which appears to improve the impaired glucose tolerance in animals comprises a mixture of chromium-containing organic complexes (3-5). In one of these studies it was shown that the GTF activity was due to chromium complexed to amino acid/peptide-like molecules and these substances caused increased glycolysis in yeast as well as increased glycolysis and fatty acid synthesis in adipocytes in culture (4). In addition, a low molecular weight chromium-binding protein isolated from bovine liver was shown to activate phosphotyrosine phosphatase from adipocyte membrane (6). However, the results of these studies were later questioned as no chromium-containing GTF has been fully characterized, the purpose of low molecular weight chromium-binding protein is not well defined and no direct interaction between chromium and insulin has been demonstrated (7).
- Health benefits: Despite claims that chromium supplementation may be beneficial for the management of type 2 diabetes several randomized clinical trials failed to show an effect of chromium on glucose or insulin concentrations in nondiabetic subjects while the results with diabetic subjects were inconclusive (8).
- Best food sources: Meat and whole grains products, brewer's yeast.

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Manganese

- Manganese (Mn) is an essential trace element for higher animals including humans.

- Required for the activity of several enzymes in the intermediate metabolism (pyruvate carboxylase, succinate dehydrogenase and glutamine synthetase). It also plays a crucial role in glycogen synthesis. Mn^{2+} is bound to protein glycogenin, which serves as a primer for glycogen synthesis. The primer must be a least 8 glucose units long for glycogen synthase to start adding more glucose units to it. Mn^{2+} is believed to act as an electron-pair acceptor (Lewis acid).
  Glycogenin (Mn^{2+}) + UDP-glucose ------> Glycogenin (Mn^{2+})-glucose + UDP
  When the glucose chain has reached at least 8 residues, glycogen synthase takes over and starts adding more glucose units to the non-reducing end of the growing saccharide chain.
- Essential for the activity of Mn-dependent mitochondrial superoxide dismutase. It has been shown that MnSOD activity is decreased in conditions such as cancer, asthma and transplant rejection (1). On the other hand, overexpression of MnSOD inhibited tumor growth in many cell types (2). Mitochondrial decay has been linked to increased leakage of oxygen reactive species (O_2^-) from the electron transport chain and this is a critical factor in the aging process (3).
- Mn ascorbate together with glucosamine and chondroitin sulfate were able to retard the progression of cartilage degeneration in a rabbit model of osteoarthritis (4). Supplementation with either agent alone was much less effective than the three of them administered together to the animals.
- As demonstrated in adipose tissue culture Mn exhibits an insulin-mimetic effect when added to the tissue culture, i.e. causes an increased oxidation of glucose and a subsequent increase in lipogenesis (5).
- Exhibits antioxidant properties by inhibiting the Fe^{2+}-induced lipid peroxidation in the nigrostriatal system in the brain even in the absence of MnSOD (6).
- Interactions: High magnesium, calcium, iron, copper and zinc may inhibit the absorption of manganese. High fiber intake may also inhibit manganese absorption.
- Health benefits: Supplementation may be useful in conditions, such as strains, inflammation, diabetes and neurological disorders(epilepsy).
- Best food sources: Nuts, whole grains, green leafy vegetables, tea.

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Molybdenum

- Molybdenum (Mo) is an essential trace mineral in animal and human nutrition. Exerts its biological activity as a cofactor that forms the active site of all Mo enzymes, except nitrogenase. The Mo cofactor consists of the metal covalently bound to one or two dithiolates attached to a tricyclic pterin moiety referred to as molybdopterin (1). A defect in Mo cofactor synthesis results in the pleiotropic loss of all Mo-dependent enzyme activities. Mo enzymes catalyze redox reactions in purine catabolism (xanthine dehydrogenase), intermediate metabolism (aldehyde oxidase) and detoxification reactions (sulfite oxidase). Mo is also required for a class of hydroxylases that unlike the former three catalyze the hydroxylation of carbon centers using oxygen derived from water (2).
- It is now well established that Mo cofactor deficiency is a hereditary metabolic disorder characterized by severe neurodegeneration caused by anomalies in the functioning of xanthine dehydrogenase, aldehyde oxidase and sulfite oxidase. This disorder usually results in early childhood death. Characteristic biochemical defects in affected infants include hypouricemia, augmented urine sulfate and S-sulfocysteine (3).
- Exerts an insulin-like action as demonstrated by the improvement of carbohydrate and lipid metabolism in streptozotocin-diabetic rats (4). As cell culture experiments have shown, Mo salts treatment has also a positive effect on insulin secretion and function of pancreatic beta cells (5). In alloxan-induced diabetic rats it was found that sodium molybdate supplementation significantly reduced lipid peroxidation and increased the activity of antioxidant enzymes superoxide dismutase, catalase and GSH peroxidase (6).
- Interactions: Increased molybdenum intake leads to higher levels of urinary excretion of copper.
- Health benefits: Several pathological cases in animals and one in humans have been clearly attributed to Mo deficiency (7). The need for Mo supplementation in human nutrition appears to be supported by existing data suggesting that this ultratrace element as well as several others (Se, Mn, Cr, B and I) should be given essential element status and RDA values (8). On the other hand, experiments with animal models have shown that sodium molybdate can alleviate diabetes mellitus symptoms (6) and tetrathiomolybdate inhibits cytokines in lung inflammation and fibrosis (9). The latter effect may prove useful in cases of pulmonary inflammation/fibrosis often associated with bleomycin (an antitumor antibiotic) cancer therapy.
- Best food sources: Legumes, brewer's yeast, whole grains.

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Selenium

- Essential for proper functioning of the antioxidant enzyme glutathione peroxidase, which protects red blood and other cells against free radical damage. Selenium is a constituent part of up to 100 selenoproteins that may exist in mammalian systems. Some 25 of them have been partially or fully characterized (1).
- Required for the proper thyroid hormone synthesis, activation and metabolism (2,3). In humans, the thyroid gland has the highest selenium content per gram of tissue of all other organs.
- Exerts multiple actions on the endocrine system by modifying the expression of some 30 selenoproteins such as glutathione peroxidases, thioredoxin reductases and deiodinases. These groups of enzymes act as antioxidants, control the cellular redox status and modulate thyroid hormone (triiodothyronine) metabolism, respectively. Selenium was also found to stimulate the tyrosine kinases involved in the insulin signaling cascade. In this respect selenium exhibits insulin-like properties (4).
- Involved in cell growth, apoptosis and modifying the action of cell signaling systems and transcription factors.
- Selenium has a modulatory effect on the immune system (5).
- Interactions: Selenium absorption is adversely affected by heavy metals, such as lead and mercury. High zinc intake may decrease selenium absorption.
- Health benefits: Marginal selenium deficiency in humans may contribute to reduced immune function, some cancers and viral diseases (6). Animal model experiments indicated that selenium supplementation was associated with increases in natural killer cell activity, T cell proliferation, lymphokine- activated killer cell activity. In humans, selenium supplementation led to augmented cellular response through an increased production of interferon gamma and other cytokines, increased number of T helper cells in subjects challenged with attenuated live poliomyelitis vaccine (7). Supplementation was also found useful in patients with systemic inflammatory response syndrome and sepsis (8). Supplementation may also help prevent cardiovascular disease and cancer as well as inflammatory conditions, such as rheumatoid arthritis.
- Best food sources: Wheat germ, nuts, bran, garlic, whole grains. The concentration of selenium in the food is related to the level of the mineral in soil.

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Vanadium

- Although there is evidence to suggest that vanadium may be required in human nutrition the precise role played by this trace element in the cell metabolism is not fully understood. Vanadium salts exhibit insulin-like properties, which were demonstrated in tissue and cell culture from type I and type II diabetic animals. Vanadium salts treatment improved carbohydrate and lipid metabolism in diabetic rodents (1). Vanadium compounds are involved in the activation of key components of the insulin signaling pathway. Pharmacologic amounts of vanadium, i.e. up to 100 times the normal intake in diet have, in humans an effect on cholesterol and triglyceride metabolism and stimulate glucose breakdown and glycogen synthesis in the liver. For higher animals however, vanadium appears to be essential. Thus, the second generation of goat offspring's born from mothers fed a vanadium deficient diet died shortly after birth exhibiting skeletal damage (2).
- In animal models, vanadium supplementation in conjunction with ascorbate supplementation led to altered cholesterol metabolism as shown by the changes in the activity of hepatic 3-hydroxy-3-methylglutaryl CoA reductase (the rate-limiting enzyme in cholesterol synthesis) and plasma cholesterol concentration (3).
- Vanadium(IV) complex of 2-methylaminopyridine has been shown to afford a certain degree of radioprotection in gamma-irradiated rats, presumably by virtue of its superoxide dismutase-mimetic activity (4).
- Vanadium does not appear to be concentrated in any particular organ or tissue.
- Health benefits: Vanadium salts such as sodium orthovanadate and vanadyl sulfate could, similarly to insulin activate phosphatidylinositol 3-kinase, mitogen-activated protein kinase pathways, which led to increased glycogen synthesis in animals (5). Small clinical trials in humans showed that $VOSO_4$ improved hepatic and muscle insulin sensitivity in type 2 (insulin-dependent) diabetes mellitus (6).
- Vanadate was also found to act as an inhibitor of ptotein-phosphotyrosine phosphatase (7).
- Best food sources: mushrooms, black pepper, dill, shellfish.

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Strontium

If you are concerned about the bone-thinning disease osteoporosis, you may have heard about treatment with strontium. Some people say this supplement improves bone health, but it's important to think about its benefits and risks before you decide to take it.

What Is Strontium?

Strontium is a mineral found in seawater and soil. In your diet, you get it mainly from seafood, but you can also get small amounts of it in whole milk, wheat bran, meat, poultry, and root vegetables.

Strontium is similar to calcium. It seems to play a role in how your body makes new bone while it slows the breakdown of old bone. That means it may affect how strong your bones are. Some research says that women with osteoporosis may not absorb strontium as they should.

You can buy different forms of it, such as strontium citrate, in supplements at supermarkets and health food stores.

Scientists haven't tested these supplements to any great degree, so there's not enough research to know if they fight osteoporosis. Also, the FDA doesn't regulate supplements in the same way as prescription drugs, so it's not possible to know if they are safe or work well or even how much of the main ingredient they contain.

What is Strontium Ranelate?

In Australia and some countries in Europe, a form of strontium called strontium ranelate (Osseor, Protelos) is available as a prescription medication to treat and prevent osteoporosis and

bone fractures. But the FDA hasn't approved it for sale in the U.S., and it's different from the forms of strontium that come in supplements that are available in the U.S.

The drug makes your bones stronger and lowers your chances of getting fractures. Doctors aren't sure exactly how it works, but it seems to help the body make more bone and keep the bone you have from breaking down.

Strontium ranelate has risks though. Doctors can prescribe it only for postmenopausal women and for men with severe osteoporosis who can't take other drugs. It's also not for people who:

- Have blood clots or have had them before
- Can't move very much, either for a short time, such as after surgery, or for the long term, such as because of a disability
- Have a history of heart problems, like a heart attack, angina, or peripheral artery disease, which means there's less blood flow to your arms and legs
- Have high blood pressure that isn't under control

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WebMD Medical Reference Reviewed by Melinda Ratini, DO, MS on December 08, 2016

Vitamin D

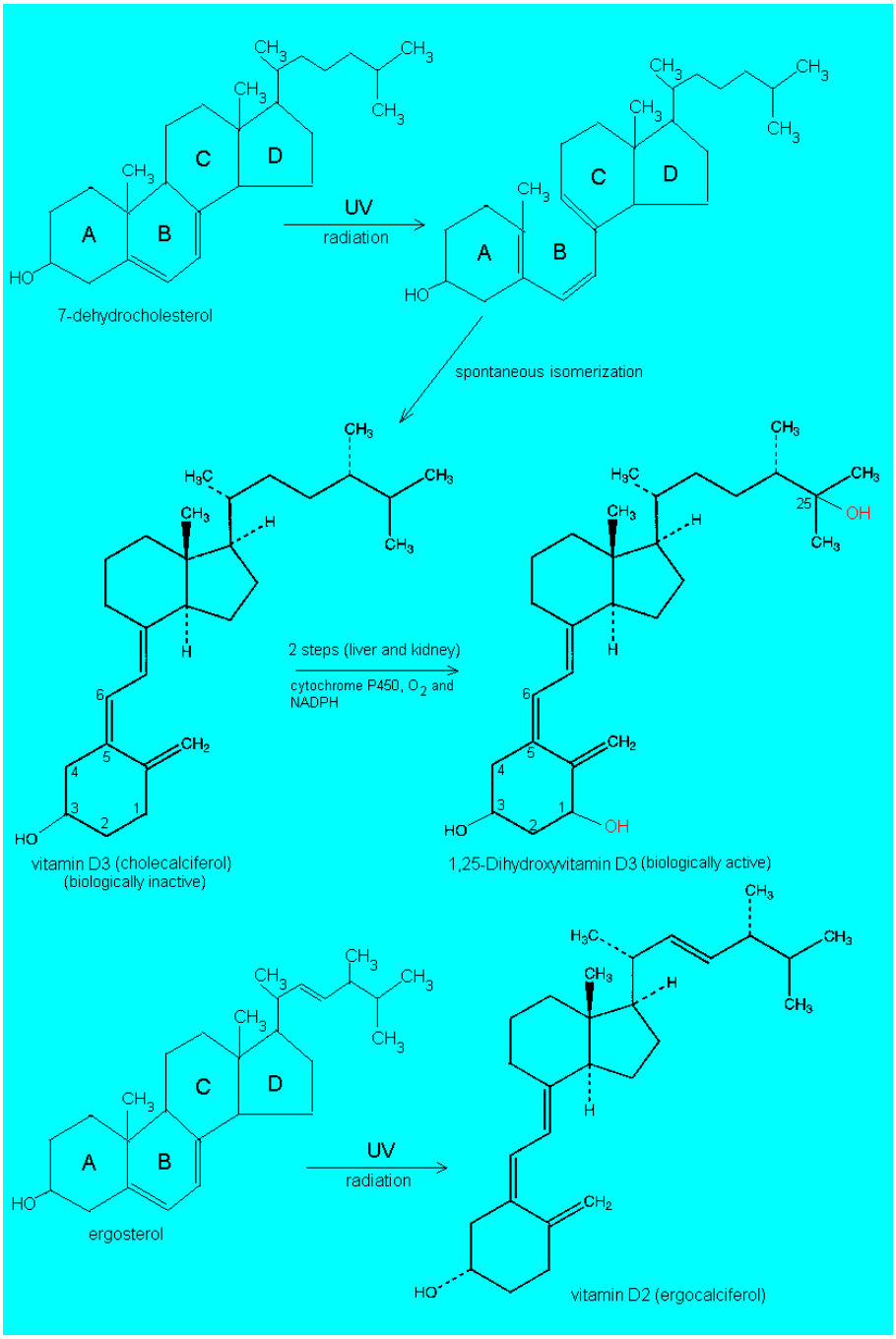
The D vitamins are sterol derivatives with hormone-like function. The natural form of the vitamin, i.e. vitamin D_3 (cholecalciferol) is formed nonenzymatically in the skin of animals through the action of UV light on 7-dehydrocholesterol. Vitamin D_2 is formed by the UV irradiation of the plant sterol ergosterol. It is noteworthy that both vitamins are inactive as such. 7-dehydrocholesterol in the epidermal layer of the skin absorbs solar UV (the effective range is 290-310 nm) and is converted to pre-cholecalciferol, which in turn undergoes a spontaneous isomerization to cholecalciferol (vitamin D_3). This form is not biologically active. Once formed cholecalciferol enters the circulation and is metabolized in the liver to 25-hydroxycholecalciferol (25(OH) D_3). This form of the vitamin re-enters the circulation bound to its binding protein and is converted in the kidney to its biologically active form 1a-,25-hydroxycholecalciferol [$1,25(OH)_2$vitamin D_3, also known as calcitriol. Both hydroxylations are catalyzed by the microsomal P450 enzyme. Blood plasma phosphorus and parathyroid hormone among other factors are involved in the regulation of renal production of $1,25(OH)_2D_3$. The production of this vitamin in the kidneys is tightly controlled as demonstrated by the fact that an increased intake of vitamin D or exposure to sunlight does not result in increased renal production of $1,25(OH)_2D_3$. This form of the vitamin acts to increase serum calcium concentration by promoting the intestinal absorption of dietary calcium (1). As a result, there is an increased uptake of calcium by the bone tissue. Besides this, $1,25(OH)_2D_3$ is involved in the regulation of cell growth and maturation, stimulation of insulin secretion and the modulation of the biological activity of activated T and B lymphocytes and macrophages.

It is noteworthy that cells of the epidermal layer in the skin were shown to also be able to convert 25(OH) D_3 to $1,25(OH)_2D_3$ (2). However, it is not clear what is the share of skin cells in the overall active vitamin D_3 production.

Vitamin D_3 is also known to possess anticancer activity by inhibiting cell cycle progression and inducing differentiation and apoptosis. In addition, vitamin D_3 increases the activity of anticancer agents that trigger an overproduction of reactive oxygen species in target cells. Treatment of the MCF-7 breast cancer cell line with vitamin D_3, in the absence of anticancer drugs resulted in a significant augmentation of oxidized GSH (oxGSH) and an increase in glutaraldehyde-3-phosphate dehydrogenase (GAPDH) activity (3). These results suggest that vitamin D_3 is responsible for an increase in the overall cellular redox potential, as reflected in the oxGSH/redGSH ratio and the production of NADPH, which may contribute to the modulation of redox-sensitive enzymes and transcription factors that control cell cycle, differentiation and apoptosis. However, the role played by vitamin D_3 in cancer prevention/treatment is far from being totally clear. For an update on vitamin D implication in cancer the reader is encouraged to look at this brief research article (4).

It is worth mentioning that the precursor [25(OH) D_3] to 1,25$(OH)_2$ D_3 thought until not long ago to be 'biologically inactive' was found to be able to induce in human macrophages stimulated with a mycobacterial lipoprotein, a peptide (cathelicidin) that exhibits antimicrobial activity (5).

It has been recently shown that vitamin D_3 deficiency is positively associated with an increased risk of cardiovascular disease in people with diabetes mellitus (6). Thus, macrophages from diabetics were cultured in the presence and absence of 1,25$(OH)_2$ D_3 and exposed to oxidized LDL (oxLDL). Vitamin D_3 suppressed foam cell formation by inhibiting oxLDL uptake in diabetic subjects. On the hand, deletion of vitamin D_3receptor in macrophages from diabetics accelerated foam cells formation. These results clearly identify vitamin D_3 receptor signaling pathway as a potential mechanism in turning macrophages into foam cells, which is a known step in atherosclerotic plaque formation.



Some of the most important functions of the biologically active D vitamins are listed below:

- Stimulates the calcification of matrix of bone and teeth.
- Promotes the absorption of calcium and phosphorus in the intestine, stimulates bone calcium mobilization and the increase of renal reabsorption of calcium in the distal tube.
- Stimulates calcium reabsorption in the kidney.
- Promotes a stable nervous system and heart function.
- Deficiency can lead to: tooth decay, softening of bones (osteoporosis), muscular weakness, impaired calcium absorption and a host of chronic conditions such as high blood pressure, atherosclerosis, autoimmune disorders (rheumatoid arthritis) and cancer.

There is strong evidence to suggest that the latter four conditions are linked to vitamin D_3 deficiency (7).

- Best food sources: cod liver oil, fresh water fish (salmon, herring), milk, butter.

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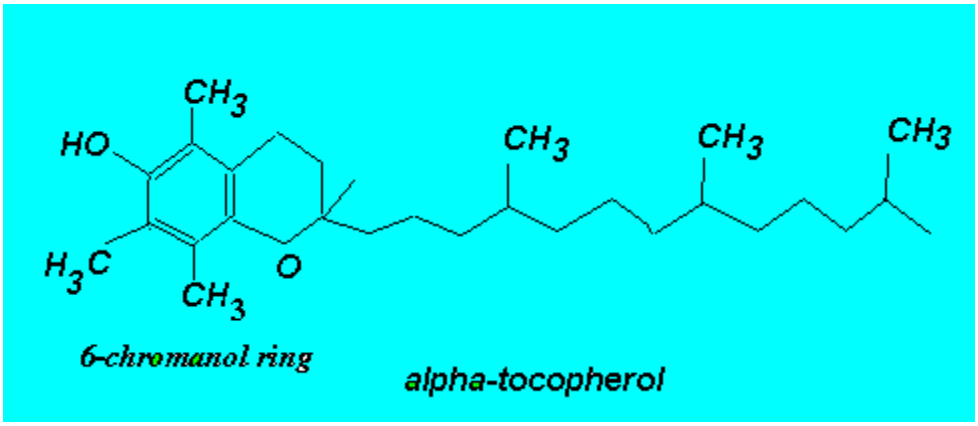
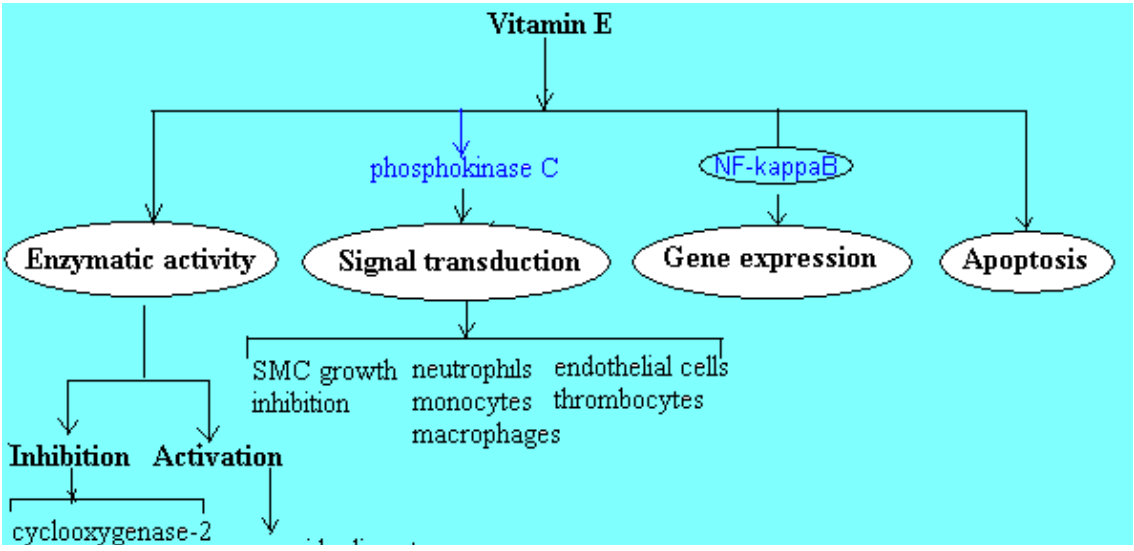
Vitamin E

Natural vitamin E is a mixture of tocopherols and tocotrienols (a, b, g, d) synthesized by plants. Chemically tocopherols consist of a chromanic ring and an aliphatic side chain (saturated for tocopherols and unsaturated for tocotrienols). There is no significant difference in antioxidant power between the various tocopherols. Vitamin E does not appear to have a specific plasma carrier protein as opposed to vitamins A and D. In plasma it is found in lipoproteins where it protects cholesterol and unsaturated fatty acids against oxidative stress.



Some of the biological functions of vitamin E are summarized below:

- Major antioxidant nutrient; it slows down the aging process, which is partly caused by oxidative stress.
- Protects circulating cholesterol in LDL and membrane lipids in red blood cells against oxidative damage.
- Protects immunocompetent cells such as phagocytic cells against oxidative damage that occurs in infections (1).
- Prevents damage to informational macromolecules such as nucleic acids by scavenging free radicals (mainly oxygen reactive species) generated within cells.
- Modulates enzyme activity through specific interactions with enzymes and gene expression through interactions with regulatory proteins such as transcription factors. These actions of vitamin E involve a non-antioxidant type of mechanism that may be relevant in cardiovascular disease (2). The main effects of vitamin E at cellular and molecular level that involve a non-antioxidant mechanism are depicted in the figure below.

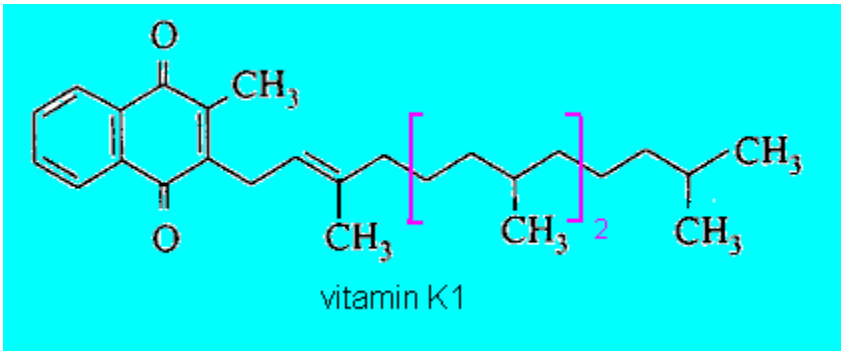


Vitamin K

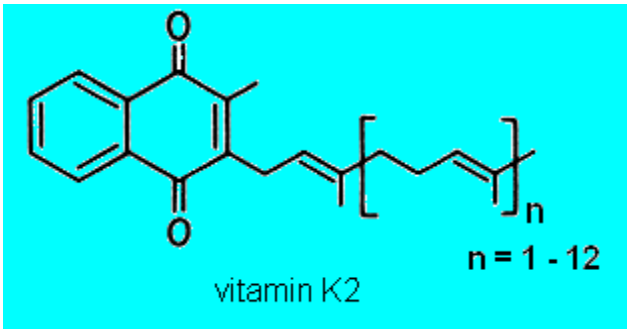
The most studied compounds in the vitamin K group include vitamin K1 (phylloquinone), vitamin K2 (menaquinone) and vitamin K3 (menadione). Vitamin K1 is also called phylloquinone because it is an indirect product of photosynthesis in plant chloroplasts. The naphthoquinone ring has a phytyl side chain.

Vitamin K2 has a poly-isoprenoid unsaturated side chain whose length varies from 4 to 12 units. These compounds are called menaquinones-n or MK-n for short. Animal experiments have shown that MK-7 may play an important role in the prevention of age-related bone loss (1). The results obtained by recent dose-response studies have suggested that the intake of vitamin K should be increased in order to optimize bone mineralization because the diet alone does not provide the adequate amount of vitamin K, particularly in post-menopausal women. In addition, menaquinone may be also effective in the prevention of arterial calcification (2).

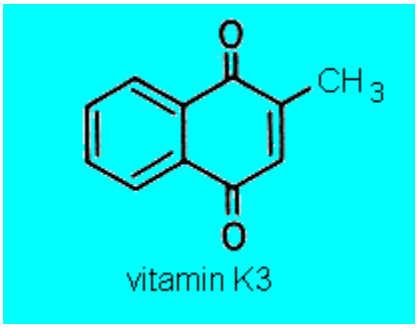
Vitamin K3 (2-methyl 1-4-naphthoquinone) has the same physiological activity in vivo as vitamin K1 after alkylation in position 3 with an isoprenoid chain in the liver.



vitamin K1

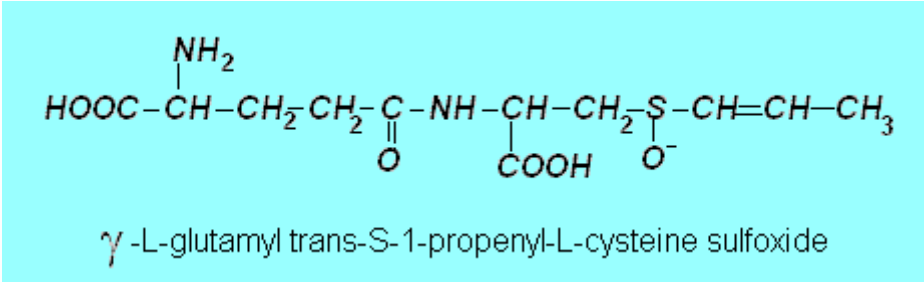


vitamin K2



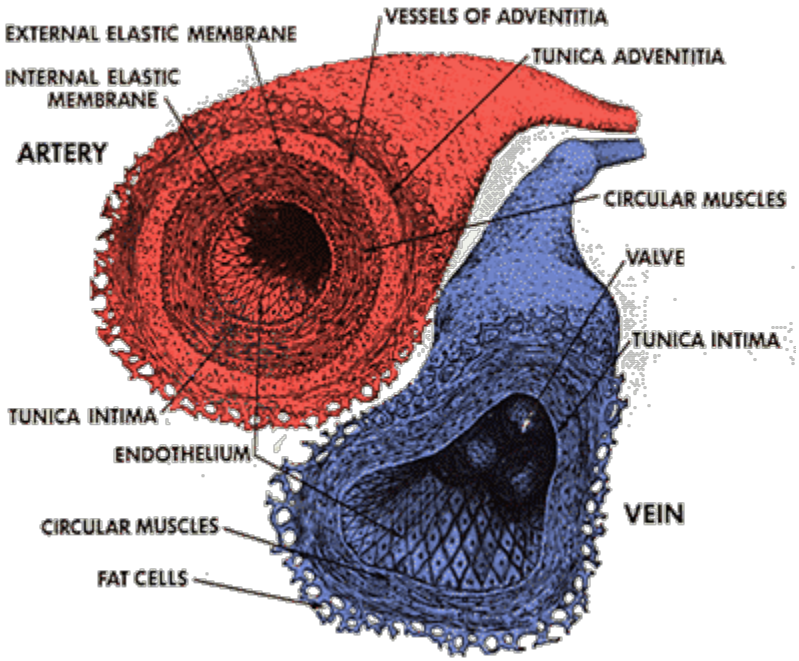
vitamin K3

- Required for normal process of blood clotting to occur. Thus, vitamin K1 is essential for the synthesis of clotting factors II, VII, IX and X and of the anticoagulant proteins C and S. The reduced form of vitamin K1 (formed through the action of a reductase on phylloquinone) is necessary for the post-translational modification of coagulation factors II, VII, IX and X. The modified protein (contains g-carboxyglutamic acid residues) is able to bind calcium, an essential property of the coagulation factors.
- Plays an important role in bone and teeth metabolism, i.e. the conversion of osteocalcin (a major non-collagen protein) to its active form, which appears to regulate bone's shape by depositing calcium in a certain way. This way the mineralization of the bone is not impaired (2, 3). Besides osteocalcin there is another protein called matrix Gla protein (MGP), which is involved more directly in mineralization of bones (4). It's interesting to note that onions contain the co-called g-glutamyl peptides, which were shown to increase bone density by inhibiting the activity of osteoclasts. The structure of such a peptide is shown below:



γ -L-glutamyl trans-S-1-propenyl-L-cysteine sulfoxide

- Involved in the protection against cardiovascular disease. In healthy arteries the vitamin K2-dependent MGP surrounds the elastic fibers of the tunica media (the anatomy of an arterial wall vessel is shown below) and prevents the formation of calcium salts crystals.



In early atherosclerosis most MGP occurs in an inert form because there is not enough vitamin K2 around to activate it. As a result, MGP associates with calcified structures

containing oxidized lipids, macrophages and debris of smooth muscle cells. Patients with severe calcification have high a high percentage of inactive osteocalcin, indicating a deficiency of vitamin K2 (5).

- Vitamin K2 can induce apoptosis in myeloma and B-cell lymphoma cell lines as recent experimental data have demonstrated (6).
- Involved in brain metabolism and cognitive function. The brain contains the highest concentration of vitamin K2 after pancreas, salivary glands and the cartilaginous tissue of the sternum. Vitamin K2 supports enzymes that produce the sulfatides (an important group of brain lipids). The decline of sulfatides and vitamin K2 levels are associated with aging and neurodegeneration (7).
- Synergysm: Vitamin K2 acts synergically with vitamins A and D. Vitamin K2 activates the Ca-binding proteins that were synthesized after vitamin A and D-triggered expression of the genes coding these proteins. Vitamins A and D regulate the expression of matrix Gla protein (this protein has five to six residues of the vitamin K-dependent amino acid, g-carboxyglutamic acid), which is responsible for mineralizing bone and protecting the arteries from calcification; like osteocalcin, however, matrix Gla protein can only fulfill its function once it has been activated by vitamin K2. While vitamins A and D contribute to growth by stimulating growth factors and promoting the absorption of minerals, vitamin K2 makes its own essential contribution to growth by preventing the premature calcification of the cartilaginous growth zones of bones.
- Interactions: Aspirin, warfarin (a synthetic anticoagulant agent, which inhibits the synthesis of vitamin K-dependent clotting factors), certain antibiotics and higher dosages of vitamin E (over 800 I.U.) may interfere with the biological function of vitamin K.
- Therapeutic uses: Epidemiological studies in the last 10 years showed that a large portion of the population is vitamin K2 deficient. Although colon bacteria produce this vitamin it is not absorbed by that segment of the GI tract so supplementation may be required for the prevention and treatment of osteoporosis, dental cavities, cardiovascular disease and excessive menstrual bleeding.
- Best food sources: Dark green leafy vegetables, kale, broccoli, lettuce, spinach, green tea, dairy products especially the fermented ones such as cheese (rich in menaquinone species).

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