Vitamin B_{12}

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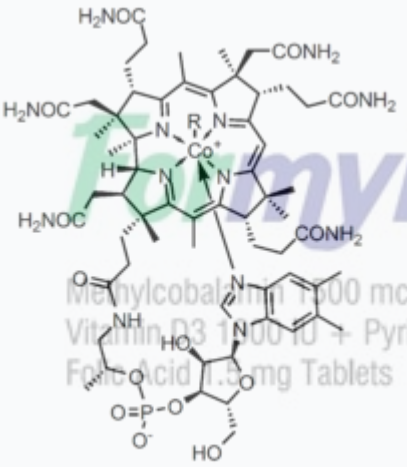
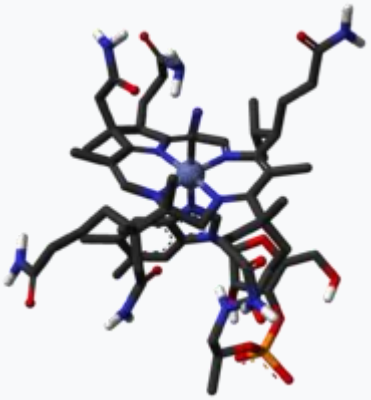
This article is about the family of vitamers. For individual forms, see hydroxocobalamin, cyanocobalamin, methylcobalamin, and adenosylcobalamin.

Vitamin B_{12}
(data for cyanocobalamin)



R = 5'-deoxyadenosyl, Me, OH, CN



Clinical data	
Synonyms	vitamin B12, vitamin B-12
AHFS/Drugs.com	Monograph

Routes of administration	by mouth, sublingual, IV, IM, intranasal
ATC code	B03BA01 (WHO)
Legal status	
Legal status	UK: POM (Prescription only) US: OTC
Pharmacokinetic data	
Bioavailability	Readily absorbed in distal half of the ileum
Protein binding	Very high to specific transcobalamins plasma proteins Binding of hydroxocobalamin is slightly higher than cyanocobalamin.
Metabolism	liver
Elimination half-life	Approximately 6 days (400 days in the liver)
Excretion	kidney
Identifiers	
IUPAC name[show]	
CAS Number	68-19-9✓
PubChem CID	184933
DrugBank	DB00115✗
ChemSpider	10469504✓
KEGG	D00166✓
ChEMBL	ChEMBL2110563✗
Chemical and physical data	
Formula	$C_{63}H_{88}CoN_{14}O_{14}P$
Molar mass	1355.388 g·mol^{-1}
3D model (JSmol)	Interactive image

SMILES[show]

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✗✓ (what is this?) (verify)

Vitamin B_{12}, also known as **cobalamin**, is a water-soluble vitamin that is involved in the metabolism of every cell of the human body: it is a cofactor in DNA synthesis, and in both fatty acid and amino acid metabolism.[1] It is particularly important in the normal functioning of the nervous system via its role in the synthesis of myelin,[2][3] and in the maturation of developing red blood cells in the bone marrow.[4]

Vitamin B_{12} is one of eight B vitamins; it is the largest and most structurally complex vitamin. It consists of a class of chemically related compounds (vitamers), all of which show physiological activity. It contains the biochemically rare element cobalt (chemical symbol **Co**) positioned in the center of a corrin ring. The only organisms to produce vitamin B_{12} are certain bacteria, and archaea. Some of these bacteria are found in the soil around the grasses that ruminants eat; they are taken into the animal, proliferate, form part of their gut flora, and continue to produce vitamin B_{12}.

Because there are few common vegetable sources of the vitamin, vegans must use a supplement or fortified foods for B_{12} intake or risk serious health consequences.[3][5] Otherwise, most omnivorous people in developed countries obtain enough vitamin B_{12} from consuming animal products including meat, milk, eggs, and fish.[6] Staple foods, especially those that form part of a vegan diet, are often fortified by having the vitamin added to them. Vitamin B_{12} supplements are available in single agent or multivitamin tablets; and pharmaceutical preparations may be given by intramuscular injection.[3][7]

The most common cause of vitamin B_{12} deficiency in developed countries is impaired absorption due to a loss of gastric intrinsic factor, which must be bound to food-source B_{12} in order for absorption to occur.[3] Another group affected are those on long term antacid therapy,[8] using proton pump inhibitors, H2 blockers or other antacids. This condition may be characterised by limb neuropathy or a blood disorder called pernicious anemia, a type of megaloblastic anemia. Folate levels in the individual may affect the course of pathological changes and symptomatology. Deficiency is more likely after age 60, and increases in incidence with advancing age.[3] Dietary deficiency is very rare in developed countries due to access to dietary meat and fortified foods, but children in some regions of developing countries are at particular risk due to increased requirements during growth coupled with lack of access to dietary B_{12}; adults in these regions are also at risk. Other causes of vitamin B_{12} deficiency are much less frequent.[9]

Contents

Deficiency[edit]

Main article: Vitamin B_{12} deficiency

Vitamin B_{12} deficiency can potentially cause severe and irreversible damage, especially to the brain and nervous system.[3][10] At levels only slightly lower than normal, a range of symptoms such as fatigue, lethargy, difficulty walking (staggering balance problems)[11] depression, poor memory, breathlessness, headaches, and pale skin, among others, may be experienced, especially in elderly people (over age 60)[3][12] who produce less stomach acid as they age, thereby increasing their probability of B_{12} deficiencies.[9] Vitamin B_{12} deficiency can also cause symptoms of mania and psychosis.[13]

Vitamin B_{12} deficiency is most commonly caused by low intakes, but can also result from malabsorption, certain intestinal disorders, low presence of binding proteins, and use of certain medications.[3] Vitamin B_{12} is rare from plant sources, so vegetarians are more likely to suffer from vitamin B_{12} deficiency. Infants are at a higher risk of vitamin B_{12}deficiency if they were born to vegetarian mothers. The elderly who have diets with limited meat or animal products are vulnerable populations as well. Vitamin B_{12} deficiency may occur in between 40% to 80% of the vegetarian population who are not also consuming a vitamin B_{12} supplement.[14] In Hong Kong and India, vitamin B_{12} deficiency has been found in roughly 80% of the vegan population as well. Vegans can avoid this by eating B12 fortified foods like cereals, plant-based milks, and nutritional yeast as a regular part of their diet.[15] In addition to worries concerning those following a vegetarian or vegan diet, research has found that approximately 39 percent of the general population may have possible B12 deficiencies or difficulty with the absorption of this nutrient. Taking a B12 supplement could be beneficial to most people.[16]

B_{12} is a co-substrate of various cell reactions involved in methylation synthesis of nucleic acid and neurotransmitters. Synthesis of the trimonoamine neurotransmitters can enhance the effects of a traditional antidepressant.[17] The intracellular concentrations of vitamin B_{12} can be inferred through the total plasma concentration of homocysteine, which can be converted to methionine through an enzymatic reaction that uses 5-methyltetrahydrofolate as the methyl donor group. Consequently, the plasma concentration of homocysteine falls as the intracellular concentration of vitamin B_{12} rises. The

active metabolite of vitamin B_{12} is required for the methylation of homocysteine in the production of methionine, which is involved in a number of biochemical processes including the monoamine neurotransmitters metabolism. Thus, a deficiency in vitamin B_{12} may impact the production and function of those neurotransmitters.[18]

Medical uses[edit]

A vitamin B_{12} solution (hydroxycobalamin) in a multi-dose bottle, with a single dose drawn up into a syringe for injection. Preparations are usually bright red.

Repletion of deficiency[edit]

Severe vitamin B_{12} deficiency is corrected with frequent intramuscular injections of large doses of the vitamin, followed by maintenance doses at longer intervals. Tablets are sometimes used for repletion in mild deficiency; and for maintenance regardless of severity. Vitamin B12 supplementation sometimes leads to acneiform eruptions (acne-like rashes).[19]

Cyanide poisoning[edit]

For cyanide poisoning, a large amount of hydroxocobalamin may be given intravenously and sometimes in combination with sodium thiosulfate.[20] The mechanism of action is straightforward: the hydroxycobalamin hydroxide ligand is displaced by the toxic cyanide ion, and the resulting harmless B_{12} complex is excreted in urine. In the United States, the Food and Drug Administration approved the use of hydroxocobalamin for acute treatment of cyanide poisoning.[21]

Dietary recommendations[edit]

The U.S. Institute of Medicine (renamed National Academy of Medicine in 2015) updated Estimated Average Requirements (EARs) and Recommended Dietary Allowances (RDAs) for vitamin B_{12} in 1998.[3] The EAR for vitamin B_{12} for women and men ages 14 and up is 2.0 µg/day; the RDA is 2.4 µg/day. RDAs are higher than EARs so as to identify amounts that will cover people with higher than average requirements. RDA for pregnancy equals 2.6 µg/day. RDA for lactation equals 2.8 µg/day. For infants up to 12 months the Adequate Intake (AI) is 0.4–0.5 µg/day. (AIs are established when there is insufficient information to determine EARs and RDAs.) For children ages 1–13 years the RDA increases with age from 0.9 to 1.8 µg/day. Because 10 to 30 percent of older people may be unable to effectively absorb vitamin B_{12} naturally occurring in foods, it is advisable for those older than 50 years to meet their RDA mainly by consuming foods fortified with vitamin B_{12} or a

supplement containing vitamin B_{12}. As for safety, Tolerable Upper Intake Levels (known as ULs) are set for vitamins and minerals when evidence is sufficient. In the case of vitamin B_{12} there is no UL, as there is no human data for adverse effects from high doses. Collectively the EARs, RDAs, AIs and ULs are referred to as Dietary Reference Intakes (DRIs).[22]

The European Food Safety Authority (EFSA) refers to the collective set of information as Dietary Reference Values, with Population Reference Intake (PRI) instead of RDA, and Average Requirement instead of EAR. AI and UL defined the same as in United States. For women and men over age 18 the Adequate Intake (AI) is set at 4.0 µg/day. AI for pregnancy is 4.5 µg/day, for lactation 5.0 µg/day. For children aged 1–17 years the AIs increase with age from 1.5 to 3.5 µg/day. These AIs are higher than the U.S. RDAs.[23] The EFSA also reviewed the safety question and reached the same conclusion as in United States - that there was not sufficient evidence to set a UL for vitamin B_{12}.[24]

For U.S. food and dietary supplement labeling purposes the amount in a serving is expressed as a percent of Daily Value (%DV). For vitamin B_{12} labeling purposes 100% of the Daily Value was 6.0 µg, but as of May 27, 2016, was revised downward to 2.4 µg.[25] A table of the old and new adult Daily Values is provided at Reference Daily Intake. The original deadline to be in compliance was July 28, 2018, but on September 29, 2017, the Food and Drug Administration (FDA) released a proposed rule that extended the deadline to January 1, 2020, for large companies and January 1, 2021, for small companies.[26] Manufacturers of single-ingredient sugars such as honey and maple syrup and certain cranberry products have until July 1, 2021, to make the changes.[26]

Sources[edit]

Most omnivorous people in developed countries obtain enough vitamin B_{12} from consuming animal products including, meat, fish, eggs, and milk.[3][6] Vegan sources in the common food supply are rare.[27]

Bacteria and archaea[edit]

B_{12} is only produced in nature by certain bacteria, and archaea.[3][28][29][30] It is synthesized by some bacteria in the gut flora in humans and other animals, but humans cannot absorb this as it is made in the colon, downstream from the small intestine, where the absorption of most nutrients occurs.[31] Ruminants, such as cows and sheep, absorb B_{12}produced by bacteria in their guts.[31] For gut bacteria of ruminants to produce B_{12} the animal must consume sufficient amounts of cobalt.[32] These grazing animals acquire the bacteria that produce vitamin B_{12}, and the vitamin itself.

Feces are a rich source of vitamin B_{12}, and are eaten by many animals, including dogs and cats.[33][34] Lagomorpha species, including rabbits and hares, form fecal pellets in their cecum called cecotropes, which consist of chewed plant material that has been metabolized by cecal bacteria; cecotropes contain digestible carbohydrates and B vitamins synthesized by the resident bacteria.[*citation needed*] These animals ingest cecotropes which have been expelled in their feces.[*citation needed*]

Animals[edit]

Animals store vitamin B_{12} in the liver and muscles and some pass the vitamin into their eggs and milk; meat, liver, eggs and milk are therefore sources of the vitamin for other animals as well as humans.[7][9][33] For humans, the bioavailability from eggs is less than 9%, compared to 40% to 60% from fish, fowl and meat.[35] Insects are a source of B_{12} for animals (including other insects and humans).[33][36]

Food sources with a high concentration of vitamin B_{12}—50 to 99 µg B_{12} per 100 grams of food[37]—include clams; liver and other organ meats from lamb, veal, beef, and turkey; mackerel; and crab meat.[3][7]

Plants and algae[edit]

Natural sources of B_{12} include fermented plant foods, such as tempeh,[38][39][40] nori[27] and laver, a seaweed.[27][41][42] Many other types of algae are rich in vitamin B_{12}, with some species, such as *Porphyra yezoensis*,[27] containing as much cobalamin as liver.[43] Methylcobalamin has been identified in *Chlorella vulgaris*.[44] In all cases of plant foods which contain B_{12}, the vitamin is produced by bacterial fermentation or by bacterial symbiosis with various species of algae.

Fortified foods[edit]

The UK Vegan Society, the Vegetarian Resource Group, and the Physicians Committee for Responsible Medicine, among others, recommend that every vegan who is not consuming adequate B_{12} from fortified foods take supplements.[35][45][46][47]

Foods for which B_{12}-fortified versions are widely available include breakfast cereals, soy products, energy bars, and nutritional yeast.[37]

Supplements[edit]

A blister pack of 500 µg methylcobalamin tablets

Vitamin B_{12} is included in multivitamin pills; and in some countries grain-based foods such as bread and pasta are fortified with B_{12}. In the U.S. non-prescription products can be purchased providing up to 5,000 µg per serving, and it is a common ingredient in energy drinks and energy shots, usually at many times the recommended dietary allowance of B_{12}. The vitamin can also be a prescription product via injection or other means. Tablets have sufficiently large quantities of the vitamin such that 1% to 5% of the free crystalline B_{12} is absorbed along the entire intestine by passive diffusion.[*citation needed*]

Sublingual methylcobalamin, which contains no cyanide, is available in 5-mg tablets. The metabolic fate and biological distribution of methylcobalamin are expected to be similar to that of other sources of vitamin B_{12} in the diet.,[48] but the amount of cyanide in cyanocobalamin even in the largest available dose—20 µg of cyanide in a 1,000-µg cyanocobalamin tablet—is less than the daily consumption of cyanide from food, and so cyanocobalamin is not considered a health risk.[48]

Parenteral administration[edit]

Injection and patches are sometimes used if digestive absorption is impaired, but this course of action may not be necessary with high-potency oral supplements (such as 0.5–1 mg or more).[49][50] A person with cobalamin C disease combined with methylmalonic aciduria and homocystinuria) may require treatment with intravenous, intramuscular hydroxocobalamin or transdermal B_{12}.[51]

Pseudovitamin-B_{12}[edit]

Pseudovitamin-B_{12} refers to B_{12}-like analogues that are biologically inactive in humans and yet found to be present alongside B_{12} in humans,[52] many food sources (including animals[53][54]), and possibly supplements and fortified foods.[55] Most cyanobacteria, including *Spirulina*, and some algae, such as dried Asakusa-nori (*Porphyra tenera*), have been found to contain mostly pseudovitamin-B_{12} instead of biologically active B_{12}.[56][57] In one common form of pseudo-B_{12} available to *Salmonella enterica* serovar *Typhimurium*, the α-axial ligand is changed from dimethylbenzimidazole to adenine.[58]

Drug interactions[edit]

H_2-receptor antagonists and proton-pump inhibitors[edit]

Gastric acid is needed to release vitamin B_{12} from protein for absorption. Reduced secretion of gastric acid and pepsin produced by H_2 blocker or proton-pump inhibitor (PPI) drugs can reduce absorption of protein-bound (dietary) vitamin B_{12}, although not of supplemental vitamin B_{12}. H_2-receptor antagonist examples include cimetidine, famotidine, nizatidine, and ranitidine. PPIs examples include omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole. Clinically significant vitamin B_{12} deficiency and megaloblastic anemia are unlikely, unless these drug therapies are prolonged for two or more years, or if in addition the person's diet is below recommended intakes. Symptomatic vitamin deficiency is more likely if the person is rendered achlorhydric (complete absence of gastric acid secretion), which occurs more frequently with proton pump inhibitors than H_2 blockers.[59]

Metformin[edit]

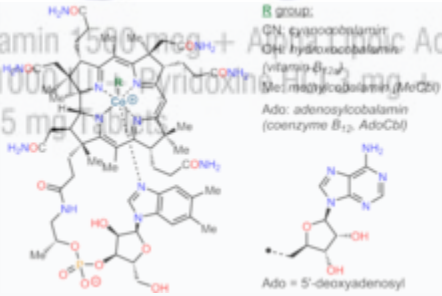
Reduced serum levels of vitamin B_{12} occur in up to 30% of people taking long-term anti-diabetic metformin.[60][61][62] Deficiency does not develop if dietary intake of vitamin B_{12} is adequate or prophylactic B_{12} supplementation is given. If the deficiency is detected, metformin can be continued while the deficiency is corrected with B_{12} supplements.[63]

Chemistry[edit]

Methylcobalamin (shown) is a form of vitamin B_{12}. Physically it resembles the other forms of vitamin B_{12}, occurring as dark red crystals that freely form cherry-colored transparent solutions in water.

B_{12} is the most chemically complex of all the vitamins.[3] The structure of B_{12} is based on a corrin ring, which is similar to the porphyrin ring found in heme. The central metal ion is cobalt. Four of the six coordination sites are provided by the corrin ring, and a fifth by a dimethylbenzimidazole group. The sixth coordination site, the reactive center, is variable, being a cyano group (–CN), a hydroxyl group (–OH), a methyl group ($–CH_3$) or a 5′-deoxyadenosyl group (here the C5′ atom of the deoxyribose forms the covalent bond with cobalt respectively, to yield the four vitamers (forms) of B_{12}. Historically, the covalent C-Co bond is one of the first examples of carbon-metal bonds to be discovered in biology. The hydrogenases and, by necessity, enzymes associated with cobalt utilization, involve metal-carbon bonds.[64]

Vitamin B_{12} is a generic descriptor name referring to a collection of cobalt and corrin ring molecules which are defined by their particular vitamin function in the body. All of the substrate cobalt-corrin molecules from which B_{12} is made must be synthesized by bacteria. After this synthesis is complete, the human body has the ability (except in rare cases) to convert any form of B_{12} to an active form, by means of enzymatically removing certain prosthetic chemical groups from the cobalt atom and replacing them with others.



The structures of the four most common vitamers of cobalamin, together with some synonyms. The structure of the 5'-deoxyadenosyl group, which forms the R group of adensoylcobalamin is also shown.

Vitamers[edit]

The four vitamers of B_{12} are all deeply red-colored crystals and water solutions, due to the color of the cobalt-corrin complex.

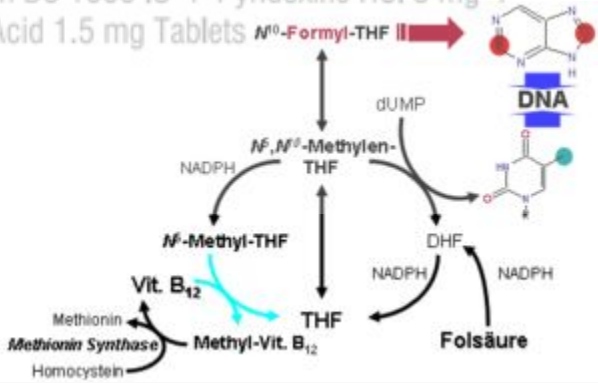
- **Cyanocobalamin** is one form of B_{12} because it can be metabolized in the body to an active coenzyme form.[3] The cyanocobalamin form of B_{12} does not occur in nature normally, but is a byproduct of the fact that other forms of B_{12} are avid binders of cyanide (–CN) which they pick up in the process of activated charcoal purification of the vitamin after it is made by bacteria in the commercial process. Since the cyanocobalamin form of B_{12} is easy to crystallize and is not sensitive to air-oxidation, it is typically used as a form of B_{12} for food additives and in many common multivitamins. Pure cyanocobalamin possesses the deep pink color associated with most octahedral cobalt(II) complexes and the crystals are well formed and easily grown up to millimeter size.
- **Hydroxocobalamin** is another vitamer of B_{12} commonly encountered in pharmacology, but is not normally present in the human body. Hydroxocobalamin is sometimes denoted B_{12a}. This is the form of B_{12} produced by bacteria, and which is converted to cyanocobalmin in the commercial charcoal filtration step of production. Hydroxocobalamin has an avid affinity for cyanide ions and has been used as an antidote to cyanide poisoning. It is supplied typically in water solution for injection. Hydroxocobalamin is thought to be converted to the active enzymic forms of B_{12} more easily than cyanocobalamin, and since it is little more expensive than

cyanocobalamin, and has longer retention times in the body, has been used for vitamin replacement in situations where added reassurance of activity is desired. Intramuscular administration of hydroxocobalamin is also the preferred treatment for pediatric patients with intrinsic cobalamin metabolic diseases, for vitamin B_{12} deficient patients with tobacco amblyopia (which is thought to perhaps have a component of cyanide poisoning from cyanide in cigarette smoke); and for treatment of patients with pernicious anemia who have optic neuropathy.

- **Adenosylcobalamin** (adoB_{12} or AdoCbl) and **methylcobalamin** (MeB_{12} or MeCbl) are the two enzymatically active cofactor forms of B_{12} that naturally occur in the body. Most of the body's reserves are stored as adoB_{12} in the liver. These are converted to the other methylcobalamin form as needed.

A review of what is reported in the literature about cobalamin chemistry, transport, and processing suggests that despite the increased cost, there is unlikely to be any advantage to the use of adensoylcobalamin or methylcobalamin for treatment of vitamin B_{12} deficiency over the other two forms except possibly in very rare circumstances in which an inborn metabolic disorder reduces the efficiency of the conversion of cyanocobalamin to MeCbl or AdoCbl. The use of parenteral hydroxocobalamin has been suggested in these cases. However, due to its excellent shelf-life and stability, cyanocobalamin is still considered the best choice for oral administration.[65] (For the treatment of cyanide poisoning, hydroxocobalamin is the required form.)

Biochemistry[edit]



Metabolism of vitamin B_{12} is seen at bottom left.

Coenzyme function[edit]

Vitamin B_{12} functions as a coenzyme, meaning that its presence is required for enzyme-catalyzed reactions.[3][66][67] Three types of enzymes:

1. Isomerases

   Rearrangements in which a hydrogen atom is directly transferred between two adjacent atoms with concomitant exchange of the second substituent, X, which may be a carbon atom with substituents, an oxygen atom of an alcohol, or an amine. These use the adoB_{12} (adenosylcobalamin) form of the vitamin.
2. Methyltransferases

   Methyl ($–CH_3$) group transfers between two molecules. These use MeB_{12} (methylcobalamin) form of the vitamin.
3. Dehalogenases

   Reactions in which a halogen atom is removed from an organic molecule. Enzymes in this class have not been identified in humans.

In humans, two major coenzyme B_{12}-dependent enzyme families corresponding to the first two reaction types, are known. These are typified by the following two enzymes:

1. MUT is an isomerase which uses the $AdoB_{12}$ form and reaction type 1 to catalyze a carbon skeleton rearrangement (the X group is -COSCoA). MUT's reaction converts MMl-CoA to Su-CoA, an important step in the extraction of energy from proteins and fats. This functionality is lost in vitamin B_{12} deficiency, and can be measured clinically as an increased methylmalonic acid (MMA) level. Unfortunately, an elevated MMA is a sensitive but not specific test, and not all who have it actually have B_{12} deficiency. For example, MMA is elevated in 90–98% of patients with B_{12} deficiency; 20–25% of patients over the age of 70 have elevated levels of MMA, yet 25–33% of them do not have B_{12} deficiency. For this reason, assessment of MMA levels is not routinely recommended in the elderly. There is no "gold standard" test for B_{12} deficiency because as a B_{12} deficiency occurs, serum values may be maintained while tissue B_{12} stores become depleted. Therefore, serum B_{12} values above the cut-off point of deficiency do not necessarily indicate adequate B_{12} status. The MUT function is necessary for proper myelin synthesis and is not affected by folate supplementation.
2. MTR, also known as methionine synthase, is a methyltransferase enzyme, which uses the MeB_{12} and reaction type 2 to transfer a methyl group from 5-methyltetrahydrofolate to homocysteine, thereby generating tetrahydrofolate (THF) and methionine.[68] This functionality is lost in vitamin B_{12} deficiency, resulting in an increased homocysteine level and the trapping of folate as 5-methyl-tetrahydrofolate, from which THF (the active form of folate) cannot be recovered. THF plays an important role in DNA synthesis so reduced availability of THF results in ineffective production of cells with rapid turnover, in particular red blood cells, and also intestinal wall cells which are responsible for absorption. THF may be regenerated via MTR or may be obtained from fresh folate in the diet. Thus all of the DNA synthetic effects of B_{12} deficiency, including the megaloblastic anemia of pernicious anemia, resolve if sufficient dietary folate is present. Thus the best-known "function" of B_{12} (that which is involved with DNA synthesis, cell-division, and anemia) is actually a facultative function which is mediated by B_{12}-conservation of an active form of folate which is needed for efficient DNA production.[69] Other cobalamin-requiring methyltransferase enzymes are also known in bacteria, such as Me-H_4-MPT, coenzyme M methyltransferase.

Enzyme function[edit]

If folate is present in quantity, then of the two absolutely vitamin B_{12}-dependent enzyme-family reactions in humans, the MUT-family reactions show the most direct and characteristic secondary effects, focusing on the nervous system (see below). This is because the MTR (methyltransferase-type) reactions are involved in regenerating folate, and thus are less evident when folate is in good supply.

Since the late 1990s, folic acid has begun to be added to fortify flour in many countries, so folate deficiency is now more rare. At the same time, since DNA synthetic-sensitive tests for anemia and erythrocyte size are routinely done in even simple medical test clinics (so that these folate-mediated biochemical effects are more often directly detected), the MTR-dependent effects of B_{12} deficiency are becoming apparent not as anemia due to DNA-synthetic problems (as they were classically), but now mainly as a simple and less obvious elevation of homocysteine in the blood and urine (homocysteinuria). This condition may result in long-term damage to arteries and in clotting (stroke and heart attack), but this effect is difficult to separate from other common processes associated with atherosclerosis and aging.

The specific myelin damage resulting from B_{12} deficiency, even in the presence of adequate folate and methionine, is more specifically and clearly a vitamin deficiency problem.[3]It has been connected to B_{12} most directly by reactions related to MUT, which is absolutely required to convert

methylmalonyl coenzyme A into succinyl coenzyme A. Failure of this second reaction to occur results in elevated levels of MMA, a myelin destabilizer. Excessive MMA will prevent normal fatty acid synthesis, or it will be incorporated into fatty acidsitself rather than normal malonic acid. If this abnormal fatty acid subsequently is incorporated into myelin, the resulting myelin will be too fragile, and demyelination will occur. Although the precise mechanism or mechanisms are not known with certainty, the result is subacute combined degeneration of spinal cord.[70] Whatever the cause, it is known that B_{12} deficiency causes neuropathies, even if folic acid is present in good supply, and therefore anemia is not present.

Vitamin B_{12}-dependent MTR reactions may also have neurological effects, through an indirect mechanism. Adequate methionine (which, like folate, must otherwise be obtained in the diet, if it is not regenerated from homocysteine by a B_{12} dependent reaction) is needed to make *S*-adenosyl methionine (SAMe), which is in turn necessary for methylation of myelin sheath phospholipids. Although production of SAMe is not B_{12} dependent, help in recycling for provision of one adequate substrate for it (the essential amino acidmethionine) is assisted by B_{12}. In addition, SAMe is involved in the manufacture of certain neurotransmitters, catecholamines and in brain metabolism. These neurotransmitters are important for maintaining mood, possibly explaining why depression is associated with B_{12} deficiency. Methylation of the myelin sheath phospholipids may also depend on adequate folate, which in turn is dependent on MTR recycling, unless ingested in relatively high amounts.

Physiology[edit]

Absorption[edit]

Methyl-B_{12} is absorbed by two processes. The first is an intestinal mechanism using intrinsic factor through which 1–2 micrograms can be absorbed every few hours. The second is a diffusion process by which approximately 1% of the remainder is absorbed.[71] The human physiology of vitamin B_{12} is complex, and therefore is prone to mishaps leading to vitamin B_{12} deficiency. Protein-bound vitamin B_{12} must be released from the proteins by the action of digestive proteases in both the stomach and small intestine.[72] Gastric acidreleases the vitamin from food particles; therefore antacid and acid-blocking medications (especially proton-pump inhibitors) may inhibit absorption of B_{12}.

B_{12} taken in a low-solubility, non-chewable supplement pill form may bypass the mouth and stomach and not mix with gastric acids, but acids are not necessary for the absorption of free B_{12} not bound to protein; acid is necessary only to recover naturally-occurring vitamin B_{12} from foods.

R-protein (also known as haptocorrin and cobalophilin) is a B_{12} binding protein that is produced in the salivary glands. It must wait to bind food-B_{12} until B_{12} has been freed from proteins in food by pepsin in the stomach. B_{12} then binds to the R-protein to avoid degradation of it in the acidic environment of the stomach.[73]

This pattern of B_{12} transfer to a special binding protein secreted in a previous digestive step, is repeated once more before absorption. The next binding protein for B_{12} is intrinsic factor (IF), a protein synthesized by gastric parietal cells that is secreted in response to histamine, gastrin and pentagastrin, as well as the presence of food. In the duodenum, proteases digest R-proteins and release their bound B_{12}, which then binds to IF, to form a complex (IF/B_{12}). B_{12} must be attached to IF for it to be efficiently absorbed, as receptors on the enterocytes in the terminal ileum of the small bowel only recognize the B_{12}-IF complex; in addition, intrinsic factor protects the vitamin from catabolism by intestinal bacteria.

Absorption of food vitamin B_{12} thus requires an intact and functioning stomach, exocrine pancreas, intrinsic factor, and small bowel.[3] Problems with any one of these organs makes a vitamin B_{12} deficiency possible. Individuals who lack intrinsic factor have a decreased ability to absorb B_{12}. In pernicious anemia, there is a lack of IF due to autoimmune atrophic gastritis, in which antibodies

form against parietal cells. Antibodies may alternately form against and bind to IF, inhibiting it from carrying out its B_{12} protective function. Due to the complexity of B_{12} absorption, geriatric patients, many of whom are hypoacidic due to reduced parietal cell function, have an increased risk of B_{12} deficiency.[74] This results in 80–100% excretion of oral doses in the feces versus 30–60% excretion in feces as seen in individuals with adequate IF.[74]

Once the IF/B_{12} complex is recognized by specialized ileal receptors, it is transported into the portal circulation. The vitamin is then transferred to transcobalamin II (TC-II/B_{12}), which serves as the plasma transporter. Hereditary defects in production of the transcobalamins and their receptors may produce functional deficiencies in B_{12} and infantile megaloblastic anemia, and abnormal B_{12} related biochemistry, even in some cases with normal blood B_{12} levels. For the vitamin to serve inside cells, the TC-II/B_{12} complex must bind to a cell receptor, and be endocytosed. The transcobalamin-II is degraded within a lysosome, and free B_{12} is finally released into the cytoplasm, where it may be transformed into the proper coenzyme, by certain cellular enzymes (see above).

Investigations into the intestinal absorption of B_{12} point out that the upper limit of absorption per single oral dose, under normal conditions, is about 1.5 µg: "Studies in normal persons indicated that about 1.5 µg is assimilated when a single dose varying from 5 to 50 µg is administered by mouth. In a similar study Swendseid *et al.* stated that the average maximum absorption was 1.6 µg [...]"[75] The bulk diffusion process of B_{12} absorption noted in the first paragraph above, may overwhelm the complex R-factor and IGF-factor dependent absorption, when oral doses of B_{12} are very large (a thousand or more µg per dose) as commonly happens in dedicated-pill oral B_{12} supplementation. It is this last fact which allows pernicious anemia and certain other defects in B_{12} absorption to be treated with oral megadoses of B_{12}, even without any correction of the underlying absorption defects.[76] See the section on supplements above.

Storage and excretion[edit]

The total amount of vitamin B_{12} stored in body is about 2–5 mg in adults. Around 50% of this is stored in the liver. Approximately 0.1% of this is lost per day by secretions into the gut, as not all these secretions are reabsorbed. Bile is the main form of B_{12} excretion; most of the B_{12} secreted in the bile is recycled via enterohepatic circulation. Excess B_{12}beyond the blood's binding capacity is typically excreted in urine. Owing to the extremely efficient enterohepatic circulation of B_{12}, the liver can store 3 to 5 years' worth of vitamin B_{12};[77] therefore, nutritional deficiency of this vitamin is rare. How fast B_{12} levels change depends on the balance between how much B_{12} is obtained from the diet, how much is secreted and how much is absorbed. B_{12} deficiency may arise in a year if initial stores are low and genetic factors unfavourable, or may not appear for decades. In infants, B_{12}deficiency can appear much more quickly.[78]

Production[edit]

Industrial[edit]

Industrial production of B_{12} is achieved through fermentation of selected microorganisms.[79] *Streptomyces griseus*, a bacterium once thought to be a fungus, was the commercial source of vitamin B_{12} for many years.[80][81] The species *Pseudomonas denitrificans* and *Propionibacterium freudenreichii* subsp. *shermanii* are more commonly used today.[82]These are frequently grown under special conditions to enhance yield, and at least one company uses genetically engineered versions of one or both of these species.[*citation needed*] Since a number of species of Propionibacterium produce no exotoxins or endotoxins and are generally recognized as safe (have been granted GRAS status) by the Food and Drug Administration of the United States, they are presently the FDA-preferred bacterial fermentation organisms for vitamin B_{12} production.[83]

The total world production of vitamin B_{12}, by four companies (the French Sanofi-Aventis and three Chinese companies) in 2008 was 35 tonnes.[84]

Laboratory[edit]

No eukaryotic organisms (including plants, animals, and fungi) are independently capable of constructing vitamin B_{12}.[85] Only bacteria and archaea[86] have the enzymes required for its biosynthesis. Like all tetrapyrroles, it is derived from uroporphyrinogen III. This porphyrinogen is methylated at two pyrrole rings to give dihydrosirohydrochlorin, which is oxidized to sirohydrochlorin, which undergoes further reactions, notably a ring contraction, to give the corrin ring.

The complete laboratory synthesis of B_{12} was achieved by Robert Burns Woodward[87] and Albert Eschenmoser in 1972,[88][89] and remains one of the classic feats of organic synthesis, requiring the effort of 91 postdoctoral fellows (mostly at Harvard) and 12 PhD students (at ETH Zurich) from 19 nations. The synthesis constitutes a formal total synthesis, since the research groups only prepared the known intermediate cobyric acid, whose chemical conversion to vitamin B_{12} was previously reported. Though it constitutes an intellectual achievement of the highest caliber, the Eschenmoser–Woodward synthesis of vitamin B_{12} is of no practical consequence due to its length, taking 72 chemical steps and giving an overall chemical yield well under 0.01%.[90] And although there have been sporadic synthetic efforts since 1972,[91] the Eschenmoser–Woodward synthesis remains the only completed (formal) total synthesis. Bacterial (or, perhaps archaeal) fermentation remains the only industrially viable source of the vitamin for food production and medicine.

Species from the following genera and species are known to synthesize B_{12}: *Propionibacterium shermanii*, *Pseudomonas denitrificans*, *Streptomyces griseus*,[92] *Acetobacterium*, *Aerobacter*, *Agrobacterium*, *Alcaligenes*, *Azotobacter*, *Bacillus*, *Clostridium*, *Corynebacterium*, *Flavobacterium*, *Lactobacillus*, *Micromonospora*, *Mycobacterium*, *Nocardia*, *Protaminobacter*, *Proteus*, *Rhizobium*, *Salmonella*, *Serratia*, *Streptococcus* and *Xanthomonas*.[93][94]

History[edit]

- 1849 - Thomas Addison first described a case of pernicious anemia.[4]
- 1877 - William Osler and William Gardner first described a case of neuropathy in this condition.[4]
- 1878 - Hayem first described large red cells in the peripheral blood in this condition, which he called "giant blood corpuscles", now called macrocytes.[4]
- 1880 - Paul Ehrlich first identified megaloblasts in the bone marrow in this condition.[4]
- 1887 - Ludwig Lichtheim first described a case of myelopathy in this condition.[4]
- 1920 - George Whipple discovered that ingesting large amounts of liver seemed to most rapidly cure the anemia of blood loss in dogs, and hypothesized that eating liver might treat pernicious anemia.[*citation needed*]
- 1926 - George Minot shared the 1934 Nobel Prize with William Murphy and George Whipple, for discovery of an effective treatment for pernicious anemia using liver concentrate, later found to contain a large amount of vitamin B_{12}.[4]
- 1928 - Edwin Cohn prepared a liver extract that was 50 to 100 times more potent in treating pernicious anema than the natural liver products. Whipple, Minot, and Murphy shared the 1934 Nobel Prize in Physiology or Medicine.[95]
- 1929 - William Castle demonstrated that gastric juice contained an "intrinsic factor" which when combined with meat ingestion resulted in absorption of the vitamin in this condition.[4]
- 1947 - Mary Shaw Shorb, in a collaborative project with Karl Folkers, was provided with a US$400 grant to develop the so-called "LLD assay" for B_{12}. LLD stood for *Lactobacillus lactis* Dorner,[96] a strain of bacterium which required "LLD factor" for growth, which was eventually identified as B_{12}.
- 1948 - Shorb and colleagues Karl A. Folkers and Alexander R. Todd used the LLD assay to rapidly extract the anti-pernicious anemia factor from liver extracts, and pure $B_{12}$was isolated.[97]

- 1949 - Shorb and Folkers received the Mead Johnson Award from the American Society of Nutritional Sciences for their discovery.[97]
- 1956 - The chemical structure of the molecule was determined by Dorothy Hodgkin, based on crystallographic data.[98] She was awarded the 1964 Nobel Prize in Chemistry for determining the structure of vitamin B_{12} and other complex molecules.
- 1959 - methods of producing the vitamin in large quantities from bacteria cultures were developed.
- 1981 - Observations of stereospecificity encountered by R. B. Woodward during the synthesis of vitamin B_{12} led to the formulation of the principle of the conservation of orbital symmetry, which would result in a Nobel Prize in Chemistry by R. Hoffmann and K. Fukui.

Six Nobel Prizes have been awarded for direct and indirect studies of vitamin B_{12}.[99]

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Vitamin D

From Wikipedia, the free encyclopedia
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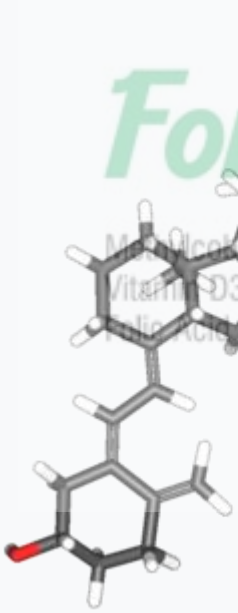
For other uses, see Vitamin D (disambiguation).

Vitamin D	
Drug class	
	
Cholecalciferol (D_3)	
Class identifiers	
Use	Rickets, osteoporosis, vitamin D deficiency
ATC code	A11CC
Biological target	vitamin D receptor
Clinical data	
Drugs.com	MedFacts Natural Products

External links	
MeSH	D014807
In Wikidata	

Vitamin D is a group of fat-soluble secosteroids responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, and multiple other biological effects.[1] In humans, the most important compounds in this group are vitamin D_3 (also known as cholecalciferol) and vitamin D_2 (ergocalciferol).[2]

The major natural source of the vitamin is synthesis of cholecalciferol in the skin from cholesterol through a chemical reaction that is dependent on sun exposure (specifically UVB radiation).[3][4] Cholecalciferol and ergocalciferol can be ingested from the diet and from supplements.[2][5][6] Only a few foods, such as the flesh of fatty fish, contain significant amounts of vitamin D, and fish does not contain enough vitamin D to achieve optimal Vitamin D status without sunlight or supplements.[7][8] Dietary recommendations typically assume that all of a person's vitamin D is taken by mouth, as sun exposure in the population is variable and recommendations about the amount of sun exposure that is safe are uncertain in view of the skin cancer risk.[7]

Vitamin D from the diet, or from skin synthesis, is biologically inactive. A protein enzyme must hydroxylate it to convert it to the active form. This is done in the liver and in the kidneys. As vitamin D can be synthesized in adequate amounts by most mammals exposed to sufficient sunlight, it is not an essential dietary factor, and so not technically a vitamin.[6] Instead it could be considered a hormone, with activation of the vitamin D pro-hormone resulting in the active form, calcitriol, which then produces effects via a nuclear receptor in multiple locations.[6]

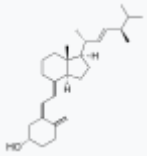
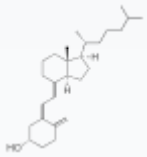
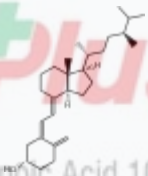
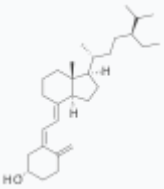
Cholecalciferol is converted in the liver to calcifediol (25-hydroxycholecalciferol); ergocalciferol is converted to 25-hydroxyergocalciferol. These two vitamin D metabolites (called 25-hydroxyvitamin D or 25(OH)D) are measured in serum to determine a person's vitamin D status.[9][10] Calcifediol is further hydroxylated by the kidneys to form calcitriol (also known as 1,25-dihydroxycholecalciferol), the biologically active form of vitamin D.[11] Calcitriol circulates as a hormone in the blood, having a major role regulating the concentration of calcium and phosphate, and promoting the healthy growth and remodeling of bone. Calcitriol also has other effects, including some on cell growth, neuromuscular and immune functions, and reduction of inflammation.[7]

Vitamin D has a significant role in calcium homeostasis and metabolism. Its discovery was due to effort to find the dietary substance lacking in children with rickets (the childhood form of osteomalacia).[12] Vitamin D supplements are given to treat or to prevent osteomalacia and rickets, but the evidence for other health effects of vitamin D supplementation in the general population is inconsistent.[13][14] The effect of vitamin D supplementation on mortality is not clear, with one meta-analysis finding a small decrease in mortality in elderly people,[15] and another concluding no clear justification exists for recommending supplementation for preventing many diseases, and that further research of similar design is unneeded in these areas.[16]

Contents

Types[edit]

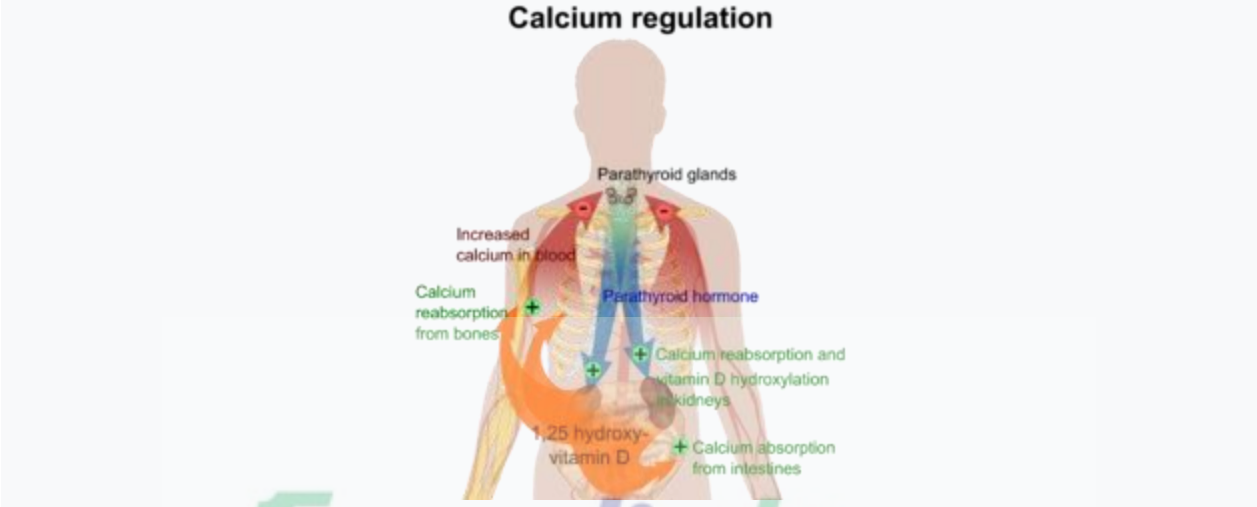
Name	Chemical composition	Structure
Vitamin D_1	Mixture of molecular compounds of ergocalciferol with lumisterol, 1:1	

Vitamin D_2	ergocalciferol (made from ergosterol)	
Vitamin D_3	cholecalciferol (made from 7-dehydrocholesterol in the skin).	
Vitamin D_4	22-dihydroergocalciferol	
Vitamin D_5	sitocalciferol (made from 7-dehydrositosterol)	

Several forms (vitamers) of vitamin D exist. The two major forms are vitamin D_2 or ergocalciferol, and vitamin D_3 or cholecalciferol; vitamin D without a subscript refers to either D_2 or D_3 or both. These are known collectively as calciferol.[17] Vitamin D_2 was chemically characterized in 1931. In 1935, the chemical structure of vitamin D_3 was established and proven to result from the ultraviolet irradiation of 7-dehydrocholesterol.[18]

Chemically, the various forms of vitamin D are secosteroids, i.e., steroids in which one of the bonds in the steroid rings is broken.[18] The structural difference between vitamin D_2 and vitamin D_3 is the side chain of D_2 contains a double bond between carbons 22 and 23, and a methyl group on carbon 24.

Biology[edit]



Calcium regulation in the human body.[19] The role of active vitamin D (1,25-dihydroxyvitamin D, calcitriol) is shown in orange.

The active vitamin D metabolite calcitriol mediates its biological effects by binding to the vitamin D receptor (VDR), which is principally located in the nuclei of target cells.[18] The binding of calcitriol to the VDR allows the VDR to act as a transcription factor that modulates the gene expression of transport proteins (such as TRPV6 and calbindin), which are involved in calcium absorption in the intestine.[20] The vitamin D receptor belongs to the nuclear receptor superfamily of steroid/thyroid hormone receptors, and VDRs are expressed by cells in most organs, including the brain, heart, skin, gonads, prostate, and breast.

VDR activation in the intestine, bone, kidney, and parathyroid gland cells leads to the maintenance of calcium and phosphorus levels in the blood (with the assistance of parathyroid hormone and calcitonin) and to the maintenance of bone content.[1]

One of the most important roles of vitamin D is to maintain skeletal calcium balance by promoting calcium absorption in the intestines, promoting bone resorption by increasing osteoclast number, maintaining calcium and phosphate levels for bone formation, and allowing proper functioning of parathyroid hormone to maintain serum calcium levels. Vitamin D deficiency can result in lower bone mineral densityand an increased risk of reduced bone density (osteoporosis) or bone fracture because a lack of vitamin D alters mineral metabolism in the body.[21] Thus, vitamin D is also critical for bone remodeling through its role as a potent stimulator of bone resorption.[21]

The VDR regulates cell proliferation and differentiation. Vitamin D also affects the immune system, and VDRs are expressed in several white blood cells, including monocytes and activated T and B cells.[22] In vitro, vitamin D increases expression of the tyrosine hydroxylasegene in adrenal medullary cells, and affects the synthesis of neurotrophic factors, nitric oxide synthase, and glutathione.[23]

Deficiency[edit]

Main article: Vitamin D deficiency

A diet deficient in vitamin D in conjunction with inadequate sun exposure causes osteomalacia (or rickets when it occurs in children), which is a softening of the bones. In the developed world, this is a rare disease.[24][25] However, vitamin D deficiency has become a worldwide problem in the elderly and remains common in children and adults.[26][27] Low blood calcifediol (25-hydroxy-vitamin D) can result from avoiding the sun.[28] Deficiency results in impaired bone mineralization and bone damage which

leads to bone-softening diseases,[29][30] including rickets and osteomalacia. Being deficient in vitamin D can cause intestinal absorption of dietary calcium to fall to 15%.[1] When not deficient, an individual usually absorbs between 60-80%.[1]

Bone health[edit]

Rickets[edit]

Main article: Rickets

Rickets, a childhood disease, is characterized by impeded growth and soft, weak, deformed long bones that bend and bow under their weight as children start to walk. This condition is characterized by bow legs,[30] which can be caused by calcium or phosphorus deficiency, as well as a lack of vitamin D; today, it is largely found in low-income countries in Africa, Asia, or the Middle East[31] and in those with genetic disorders such as pseudovitamin D deficiency rickets.[32]

Maternal vitamin D deficiency may cause overt bone disease from before birth and impairment of bone quality after birth.[33][34] Nutritional rickets exists in countries with intense year-round sunlight such as Nigeria and can occur without vitamin D deficiency.[35][36]

Although rickets and osteomalacia are now rare in the UK, outbreaks have happened in some immigrant communities in which osteomalacia sufferers included women with seemingly adequate daylight outdoor exposure wearing Western clothing.[37] Having darker skin and reduced exposure to sunshine did not produce rickets unless the diet deviated from a Western omnivore pattern characterized by high intakes of meat, fish, and eggs, and low intakes of high-extraction cereals.[38][39][40] The dietary risk factors for rickets include abstaining from animal foods.[37][41]

Vitamin D deficiency remains the main cause of rickets among young infants in most countries, because breast milk is low in vitamin D and social customs and climatic conditions can prevent adequate sun exposure. In sunny countries such as Nigeria, South Africa, and Bangladesh, where rickets occurs among older toddlers and children, it has been attributed to low dietary calcium intakes, which are characteristic of cereal-based diets with limited access to dairy products.[40]

Rickets was formerly a major public health problem among the US population; in Denver, where ultraviolet rays are about 20% stronger than at sea level on the same latitude,[42] almost two-thirds of 500 children had mild rickets in the late 1920s.[43] An increase in the proportion of animal protein[41][44] in the 20th century American diet coupled with increased consumption of milk[45][46] fortified with relatively small quantities of vitamin D coincided with a dramatic decline in the number of rickets cases.[1] Also, in the United States and Canada, vitamin D-fortified milk, infant vitamin supplements, and vitamin supplements have helped to eradicate the majority of cases of rickets for children with fat malabsorption conditions.[30]

Osteoporosis and osteomalacia[edit]

Main article: Osteoporosis

Main article: Osteomalacia

Osteomalacia is a disease in adults that results from vitamin D deficiency. Characteristics of this disease are softening of the bones, leading to bending of the spine, bowing of the legs, proximal muscle weakness, bone fragility, and increased risk for fractures.[47] Osteomalacia reduces calcium absorption and increases calcium loss from bone, which increases the risk for bone fractures. Osteomalacia is usually present when 25-hydroxyvitamin D levels are less than about 10 ng/mL.[2] Although the effects of osteomalacia are thought to contribute to chronic musculoskeletal pain,[48] there is no persuasive evidence of lower vitamin D levels in chronic pain sufferers[49] or that supplementation alleviates chronic nonspecific musculoskeletal pain.[50]

Skin pigmentation[edit]

Dark-skinned people living in temperate climates have been shown to have low vitamin D levels but the significance of this is not certain.[51][52][53] Dark-skinned people are less efficient at making vitamin D because melanin in the skin hinders vitamin D synthesis.[54]

Non-bone diseases[edit]

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Mortality, all cause[edit]

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Use of supplements[edit]

The effects of vitamin D supplementation on health are uncertain.[14][55] A 2013 review did not find any effect from supplementation on the rates of disease, other than a tentative decrease in mortality in the elderly.[56] Vitamin D supplements do not alter the outcomes for myocardial infarction, stroke or cerebrovascular disease, cancer, bone fractures or knee osteoarthritis.[16][57] Low vitamin D levels may result from disease rather than cause disease.[56]

A United States Institute of Medicine report states: "Outcomes related to cancer, cardiovascular disease and hypertension, and diabetes and metabolic syndrome, falls and physical performance, immune functioning and autoimmune disorders, infections, neuropsychological functioning, and preeclampsia could not be linked reliably with calcium or vitamin D intake and were often conflicting."[58]:5 Some researchers claim the IOM was too definitive in its recommendations and made a mathematical mistake when calculating the blood level of vitamin D associated with bone health.[59] Members of the IOM panel maintain that they used a "standard procedure for dietary recommendations" and that the report is solidly based on the data. Research on vitamin D supplements, including large-scale clinical trials, is continuing.[59]

Mortality, all-cause[edit]

Vitamin D_3 supplementation has been tentatively found to lead to a reduced risk of death in the elderly,[15][56] but the effect has not been deemed pronounced, or certain enough, to make taking supplements recommendable.[16] Other forms (vitamin D_2, alfacalcidol, and calcitriol) do not appear to have any beneficial effects with regard to the risk of death.[15]High blood levels appear to be associated with a lower risk of death, but it is unclear if supplementation can result in this benefit.[60] Both an excess and a deficiency in vitamin D appear to cause abnormal functioning and premature aging.[61][62][63] The relationship between serum calcifediol level and all-cause mortality is parabolic.[58] Harm from vitamin D appears to occur at a lower vitamin D level in the black population than in the white population.[58]:435

Bone health[edit]

In general, no good evidence supports the commonly held belief that vitamin D supplements can help prevent osteoporosis.[16] Its general use for prevention of this disease in those without vitamin D deficiency is thus likely not needed.[64] For older people with osteoporosis, taking vitamin D with calcium may help prevent hip fractures, but it also slightly increases the risk of stomach and kidney problems.[65] Supplementation with higher doses of vitamin D, in those older than 65 years, may decrease fracture risk.[66] The effect is small or none for people living independently.[67][68] Low serum vitamin D levels have been associated with falls, and low bone mineral density.[69] Taking extra vitamin D, however, does not appear to change the risk.[70] Athletes who are vitamin D deficient are at an increased risk of stress fractures and/or major breaks, particularly those engaging in contact

sports. The greatest benefit with supplementation is seen in athletes who are deficient (25(OH)D serum levels <30 ng/mL), or severely deficient (25(OH)D serum levels <25 ng/mL). Incremental decreases in risks are observed with rising serum 25(OH)D concentrations plateauing at 50 ng/mL with no additional benefits seen in levels beyond this point.[71]

The examples and perspective in this article **may not represent a worldwide view of the subject**. You may improve this article, discuss the issue on the talk page, or create a new article, as appropriate. *(February 2019) (Learn how and when to remove this template message)*

Because it found mounting evidence for a benefit to bone health, though it had not found good evidence of other benefits, the US Food and Drug Administration (FDA) has required manufacturers to declare the amount of vitamin D on nutrition facts labels, as "nutrients of public health significance", since May 2016. By a proposed deadline extension, small manufacturers with less than $10 million in annual food sales will have to comply by January 1, 2021, while larger ones have to comply by January 1, 2020.[72] Manufacturers of single-ingredient sugars such as honey and maple syrup and certain cranberry products have until July 1, 2021, to make the changes.[72]

Cancer[edit]

Vitamin D supplements have been widely marketed for their claimed anticancer properties.[73] Associations have been shown in observational studies between low vitamin D levels and the risk of development of certain cancers.[74] It is unclear, however, if taking additional vitamin D in the diet or as supplements affects the risk of cancer. Reviews have described the evidence as being "inconsistent, inconclusive as to causality, and insufficient to inform nutritional requirements"[58] and "not sufficiently robust to draw conclusions".[67] One 2014 review found that supplements had no significant effect on cancer risk.[16]

Another 2014 review concluded that vitamin D_3 may decrease the risk of death from cancer (one fewer death in 150 people treated over 5 years), but concerns with the quality of the data were noted.[15] Insufficient evidence exists to recommend vitamin D supplements for people with cancer, although some evidence suggests that low vitamin D may be associated with a worse outcome for some cancers,[75] and that higher 25-hydroxy vitamin D levels at the time of diagnosis are associated with better outcomes.[76]

Cardiovascular disease[edit]

Taking vitamin D supplements does not meaningfully reduce the risk of stroke, cerebrovascular disease, cardial infarction, or ischemic heart disease.[16][77] Supplementation may have no effect on blood pressure.[78]

Immune system[edit]

Infectious diseases[edit]

In general, vitamin D functions to activate the innate and dampen the adaptive immune systems.[79] Deficiency has been linked to increased risk or severity of viral infections, including HIV.[80][81] Low levels of vitamin D appear to be a risk factor for tuberculosis,[82] and historically it was used as a treatment.[83] Supplementation slightly decreases the risk of acute respiratory tract infections and the exacerbation of asthma.[84][85][86] Evidence is lacking on whether it does so in children under five years of age.[87] No clinical trials have been done to assess its effect on preventing other infections, such as malaria.

Autoimmune diseases[edit]

Although tentative data link low levels of vitamin D to asthma, evidence to support a beneficial effect on asthmatics from supplementation is inconclusive.[88] Accordingly, supplementation is not currently recommended for treatment or prevention of asthma.[89] Vitamin D and multiple sclerosis incidence

have been linked, but it is not clear what the nature of any causal relationship might be.[90] Two systemic reviews concluded that the evidence for vitamin D supplementation being helpful for treating people with multiple sclerosis is inconclusive.[91][92]

Inflammatory bowel disease[edit]

Low levels of vitamin D are associated with two major forms of human Inflammatory bowel disease (IBD): Crohn's disease and ulcerative colitis.[93] However, further studies are required to determine its significance and the potential role of vitamin D axis in IBD.[93][94]

Other conditions[edit]

Diabetes -- A systematic review of 2014 concluded that the available studies show no evidence of vitamin D3 supplementation having an effect on glucose homeostasis or diabetes prevention.[95] A review article of 2016 reported that while there is increasing evidence that vitamin D deficiency may be a risk factor for diabetes, over-all evidence regarding vitamin D levels and diabetes mellitus is contradictory, requiring further studies.[96]

Depression -- Clinical trials of vitamin D supplementation for depressive symptoms have generally been of low quality and show no overall effect, although subgroup analysis showed supplementation for participants with clinically significant depressive symptoms or depressive disorder had a moderate effect.[97]

Cognition and dementia -- A systematic review of clinical studies found an association between low vitamin D levels with cognitive impairment and a higher risk of developing Alzheimer's disease. However, lower vitamin D concentrations are also associated with poor nutrition and spending less time outdoors. Therefore, alternative explanations for the increase in cognitive impairment exist and hence a direct causal relationship between vitamin D levels and cognition could not be established.[98]

Pregnancy -- Low levels of vitamin D in pregnancy are associated with gestational diabetes, pre-eclampsia, and small (for gestational age) infants.[99] Although taking vitamin D supplements during pregnancy raises blood levels of vitamin D in the mother at term,[100] the extent of benefits for the mother or baby is unclear.[99][100][101] Pregnant women who take an adequate amount of vitamin D during gestation may experience a lower risk of pre-eclampsia[100] and positive immune effects.[102] A 2018 review found that supplements may reduce the risk of undersized babies and of their poor rate of growth.[103] Pregnant women often do not take the recommended amount of vitamin D.[102]

Weight loss -- Though hypothesized that vitamin D supplementation may be an effective treatment for obesity apart from calorie restriction, one systematic review found no association of supplementation with body weight or fat mass.[104] A 2016 meta-analysis found that circulating vitamin D status was improved by weight loss, indicating that fat mass may be inversely associated with blood levels of vitamin D.[105]

Allowable health claims[edit]

Governmental regulatory agencies stipulate for the food and dietary supplement industries certain health claims as allowable as statements on packaging.

European Food Safety Authority

- normal function of the immune system[106]
- normal inflammatory response[106]
- normal muscle function[106]
- reduced risk of falling in people over age 60[107]

US Food and Drug Administration (FDA)

- "Adequate calcium and vitamin D, as part of a well balanced diet, along with physical activity, may reduce the risk of osteoporosis."[108]

Health Canada

- Adequate calcium and regular exercise may help to achieve strong bones in children and adolescents and may reduce the risk of osteoporosis in older adults. An adequate intake of vitamin D is also necessary[109]

Other possible agencies with claim guidance: Japan FOSHU[110] and Australia-New Zealand.[111]

Dietary intake[edit]

Recommended levels[edit]

	United States	
Age group	**RDA (IU/day)**	**(µg/day)**[58]
Infants 0–6 months	400*	10
Infants 6–12 months	400*	10
1–70 years	600	15
71+ years	800	20
Pregnant/Lactating	600	15
Age group	**Tolerable upper intake level (IU/day)**	**(µg/day)**
Infants 0–6 months	1,000	25
Infants 6–12 months	1,500	37.5
1–3 years	2,500	62.5
4–8 years	3,000	75

9+ years	4,000	100
Pregnant/lactating	4,000	100 [58]
Canada		
Age group	**RDA (IU)**	**Tolerable upper intake (IU)**[112]
Infants 0–6 months	400*	1,000
Infants 7–12 months	400*	1,500
Children 1–3 years	600	2,500
Children 4–8 years	600	3,000
Children and Adults 9–70 years	600	4,000
Adults > 70 years	800	4,000
Pregnancy & Lactation	600	4,000
Australia and New Zealand		
Age group	**Adequate Intake (µg)**	**Upper Level of Intake (µg)**[113]
Infants 0–12 months	5*	25
Children 1–18 years	5*	80
Adults 19–50 years	5*	80

Adults 51–70 years	10*	80
Adults > 70 years	15*	80
European Food Safety Authority		
Age group	**Adequate Intake (µg)**[114]	**Tolerable upper limit (µg)**[115]
Infants 0–12 months	10	25
Children 1–10 years	15	50
Children 11–17 years	15	100
Adults	15	100
Pregnancy & Lactation	15	100
* Adequate intake, no RDA/RDI yet established		

Conversion: 1 µg = 40 IU.

Various institutions have proposed different recommendations for the amount of daily intake of vitamin D. These vary according to precise definition, age, pregnancy or lactation, and the extent assumptions are made regarding skin synthesis of vitamin D.[58][112][113][114]

United States[edit]

The dietary reference intake for vitamin D issued in 2010 by the Institute of Medicine (IoM) (renamed National Academy of Medicine in 2015), superseded previous recommendations which were expressed in terms of Adequate Intake. The recommendations were formed assuming the individual has no skin synthesis of vitamin D because of inadequate sun exposure. The reference intake for vitamin D refers to total intake from food, beverages and supplements, and assumes that calcium requirements are being met.[58]:5 The tolerable upper intake level (UL) is defined as "the highest average daily intake of a nutrient that is likely to pose no risk of adverse health effects for nearly all persons in the general population."[58]:403 Although ULs are believed to be safe, information on the long-term effects is incomplete and these levels of intake are not recommended for long-term consumption.[58]:403:433

For U.S food and dietary supplement labeling purposes, the amount in a serving is expressed as a percent of Daily Value (%DV). For vitamin D labeling purposes, 100% of the Daily Value was 400 IU (10 µg), but on May 27, 2016, it was revised to 800 IU (20 µg) to bring it into agreement with the

RDA.[116] The deadline to be in compliance was extended to January 1, 2020 for large companies and January 1, 2021 for small companies.[72]

Canada[edit]

Health Canada published recommended dietary allowances (RDA) and tolerable upper intake levels for vitamin D in 2012[112] based on the Institute of Medicine report.[58]

Australia and New Zealand[edit]

Australia and New Zealand published nutrient reference values including guidelines for dietary vitamin D intake in 2005.[113] About a third of Australians have vitamin D deficiency.[117]

European Union[edit]

The European Food Safety Authority (EFSA) in 2016[114] reviewed the current evidence, finding the relationship between serum 25(OH)D concentration and musculoskeletal health outcomes is widely variable. They considered that average requirements and population reference intakes values for vitamin D cannot be derived, and that a serum 25(OH)D concentration of 50 nmol/L was a suitable target value. For all people over the age of 1, including women who are pregnant or lactating, they set an adequate intake of 15 µg/day (600 IU).[114]

The EFSA reviewed safe levels of intake in 2012,[115] setting the tolerable upper limit for adults at 100 µg/day (4000 IU), a similar conclusion as the IOM.

The UK National Health Service recommends babies and young children aged six months to five years, pregnant or breastfeeding women, and sun-deprived elderly people should take daily vitamin supplements to ensure sufficient vitamin D intake.[118] In July 2016, Public Health England recommended that everyone consider taking a daily supplement containing 10 µg of vitamin D during autumn and winter because of inadequate sunlight for vitamin D synthesis.[119]

The Swedish National Food Agency recommends a daily intake of 10 µg (400 IU) of vitamin D3 for children and adults up to 75 years, and 20 µg (800 IU) for adults 75 and older.[120]

Non-government organisations in Europe have made their own recommendations. The German Society for Nutrition recommends 20 µg.[121] The European Menopause and Andropause Society recommends postmenopausal women consume15 µg (600 IU) until age 70, and 20 µg (800 IU) from age 71. This dose should be increased to 100 µg (4,000 IU) in some patients with very low vitamin D status or in case of co-morbid conditions.[122]

Sources[edit]

Although vitamin D is not present naturally in most foods,[2][6] it is commonly added as a fortification in manufactured foods. In some countries, staple foods are artificially fortifiedwith vitamin D.[123]

Natural sources[edit]

Main article: Ergocalciferol § Biosynthesis

In general, vitamin D_2 is found in fungi and vitamin D_3 is found in animals.[124][125] Vitamin D_2 is produced by ultraviolet irradiation of ergosterol found in many fungi. The vitamin D_2content in mushrooms and *Cladina arbuscula*, a lichen, increase with exposure to ultraviolet light.[126][127] This process is emulated by industrial ultraviolet lamps, concentrating vitamin D_2 levels to higher levels.[125]

The United States Department of Agriculture reports D_2 and D_3 content combined in one value.

Fungal sources

Source		µg/g	IU/g
C. arbuscula (lichen), thalli, dry[126]	**vitamin D_3**	0.67–2.04	27–82
	vitamin D_2	0.22–0.55	8.8–22
Agaricus bisporus (common mushroom): D_2 + D_3			
Portobello	Raw	0.003	0.1
	Exposed to ultraviolet light	0.112	4.46
Crimini	Raw	0.001	0.03
	Exposed to ultraviolet light	0.319	12.76

Animal sources[128]

Source	IU/g	Irregular
Cooked egg yolk	0.7	44 IU for a 61g egg
Beef liver, cooked, braised	0.5	
Fish liver oils, such as cod liver oil	100	450 IU per teaspoon (4.5 g)
Fatty fish species		
Salmon, pink, cooked, dry heat	5.2	

Mackerel, Pacific and jack, mixed species, cooked, dry heat	4.6	
Tuna, canned in oil	2.7	
Sardines, canned in oil, drained	1.9	

Food fortification[edit]

Manufactured foods fortified with vitamin D include some fruit juices and fruit juice drinks, meal replacement energy bars, soy protein-based beverages, certain cheese and cheese products, flour products, infant formulas, many breakfast cereals, and milk.[129][130]

In 2016 in the United States, the Food and Drug Administration (FDA) amended food additive regulations for milk fortification,[131] stating that vitamin D_3 levels not exceed 42 IU vitamin D per 100 g (400 IU per US quart) of dairy milk, 84 IU of vitamin D_2 per 100 g (800 IU per quart) of plant milks, and 89 IU per 100 g (800 IU per quart) in plant-based yogurts or in soy beverage products.[132][133][134] Plant milks are defined as beverages made from soy, almond, rice, among other plant sources intended as alternatives to dairy milk.[*citation needed*]

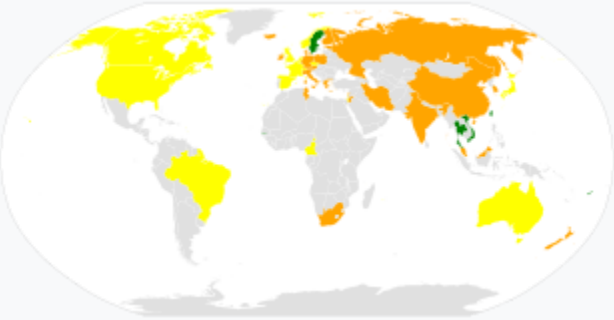
While some studies have found that vitamin D_3 raises 25(OH)D blood levels faster and remains active in the body longer,[135][136] others contend that vitamin D_2 sources are equally bioavailable and effective as D_3 for raising and sustaining 25(OH)D.[125][137][138]

Food preparation[edit]

Vitamin D content in typical foods is reduced variably by cooking. Boiled, fried and baked foods retained 69–89% of original vitamin D.[139]

Recommended serum levels[edit]

See also: Reference ranges for blood tests § Vitamins, and Hypervitaminosis D § Ethnic differences



Global vitamin D serum levels among adults (nmol/L).[140][141]

- > 75
- 50-74
- 25-49

Recommendations on recommended 25(OH)D serum levels vary across authorities, and vary based on factors like age.[7]US labs generally report 25(OH)D levels in ng/mL.[*citation needed*] Other countries often use nmol/L.[*citation needed*] One ng/mL is approximately equal to 2.5 nmol/L.[*citation needed*]

A 2014 review concluded that the most advantageous serum levels for 25(OH)D for all outcomes appeared to be close to 30 ng/mL (75 nmol/L).[142] The optimal vitamin D levels are still controversial and another review concluded that ranges from 30 to 40 ng/mL (75 to 100 nmol/L) were to be recommended for athletes.[143] Part of the controversy is because numerous studies have found differences in serum levels of 25(OH)D between ethnic groups; studies point to genetic as well as environmental reasons behind these variations.[144] Supplementation to achieve these standard levels could cause harmful vascular calcification.[53]

A 2012 meta-analysis showed that the risk of cardiovascular diseases increases when blood levels of vitamin D are lowest in a range of 8 to 24 ng/mL (20 to 60 nmol/L), although results among the studies analyzed were inconsistent.[145]

In 2011 an IOM committee concluded a serum 25(OH)D level of 20 ng/mL (50 nmol/L) is needed for bone and overall health. The dietary reference intakes for vitamin D are chosen with a margin of safety and 'overshoot' the targeted serum value to ensure the specified levels of intake achieve the desired serum 25(OH)D levels in almost all persons. No contributions to serum 25(OH)D level are assumed from sun exposure and the recommendations are fully applicable to people with dark skin or negligible exposure to sunlight. The Institute found serum 25(OH)D concentrations above 30 ng/mL (75 nmol/L) are "not consistently associated with increased benefit". Serum 25(OH)D levels above 50 ng/mL (125 nmol/L) may be cause for concern. However, some people with serum 25(OH)D between 30 and 50 ng/mL (75 nmol/L-125 nmol/L) will also have inadequate vitamin D.[58]

Excess[edit]

Further information: hypervitaminosis D

Vitamin D toxicity is rare.[27] It is caused by supplementing with high doses of vitamin D rather than sunlight. The threshold for vitamin D toxicity has not been established; however, according to some research, the tolerable upper intake level (UL) is 4,000 IU/day for ages 9–71[146] (100 µg/day), while other research concludes that, in healthy adults, sustained intake of more than 1250 µg/day (50,000 IU) can produce overt toxicity after several months and can increase serum 25-hydroxyvitamin D levels to 150 ng/mL and greater.[27][147]Those with certain medical conditions, such as primary hyperparathyroidism,[148] are far more sensitive to vitamin D and develop hypercalcemia in response to any increase in vitamin D nutrition, while maternal hypercalcemia during pregnancy may increase fetal sensitivity to effects of vitamin D and lead to a syndrome of mental retardation and facial deformities.[148][149]

A review published in 2015 noted that adverse effects have been reported only at 25(OH)D serum concentrations above 200 nmol/L.[143]

Published cases of toxicity involving hypercalcemia in which the vitamin D dose and the 25-hydroxy-vitamin D levels are known all involve an intake of ≥40,000 IU (1,000 µg) per day.[148]

Pregnant or breastfeeding women should consult a doctor before taking a vitamin D supplement. The FDA advised manufacturers of liquid vitamin D supplements that droppers accompanying these products should be clearly and accurately marked for 400 international units (1 IU is the biological equivalent of 25 ng cholecalciferol/ergocalciferol). In addition, for products intended for infants, the FDA recommends the dropper hold no more than 400 IU.[150] For infants (birth to 12 months), the tolerable upper limit (maximum amount that can be tolerated without harm) is set at 25 µg/day (1,000 IU). One thousand micrograms per day in infants has produced toxicity within one month.[147] After being commissioned by the Canadian and American governments, the Institute of Medicine (IOM) as of 30 November 2010, has increased the tolerable upper limit (UL) to 2,500 IU per day for ages 1–3 years, 3,000 IU per day for ages 4–8 years and 4,000 IU per day for ages 9–71+ years (including pregnant or lactating women).[146]

Calcitriol itself is auto-regulated in a negative feedback cycle, and is also affected by parathyroid hormone, fibroblast growth factor 23, cytokines, calcium, and phosphate.[151]

Effect of excess[edit]

Vitamin D overdose causes hypercalcemia, which is a strong indication of vitamin D toxicity – this can be noted with an increase in urination and thirst. If hypercalcemia is not treated, it results in excess deposits of calcium in soft tissues and organs such as the kidneys, liver, and heart, resulting in pain and organ damage.[27][30][47]

The main symptoms of vitamin D overdose which are those of hypercalcemia including anorexia, nausea, and vomiting. These may be followed by polyuria, polydipsia, weakness, insomnia, nervousness, pruritus and ultimately renal failure. Furthermore, proteinuria, urinary casts, azotemia, and metastatic calcification (especially in the kidneys) may develop.[147] Other symptoms of vitamin D toxicity include mental retardation in young children, abnormal bone growth and formation, diarrhea, irritability, weight loss, and severe depression.[27][47]

Vitamin D toxicity is treated by discontinuing vitamin D supplementation and restricting calcium intake. Kidney damage may be irreversible. Exposure to sunlight for extended periods of time does not normally cause vitamin D toxicity. The concentrations of vitamin D precursors produced in the skin reach an equilibrium, and any further vitamin D produced is degraded.[148]

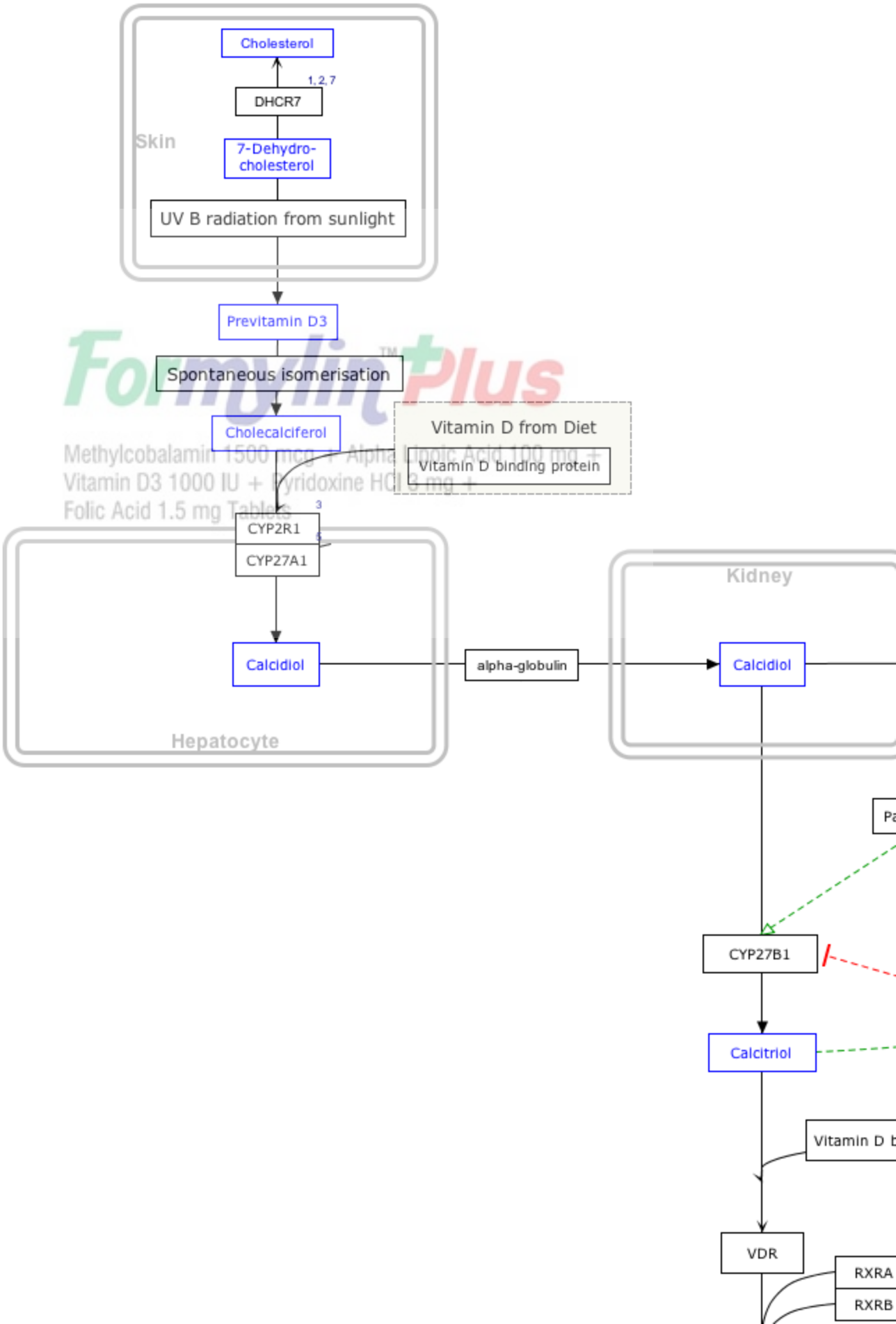
Biosynthesis[edit]

Synthesis of vitamin D in nature is dependent on the presence of UV radiation and subsequent activation in liver and in kidney. Many animals synthesize vitamin D_3 from 7-dehydrocholesterol, and many fungi synthesize vitamin D_2 from ergosterol.[124][125]

Interactive pathway[edit]

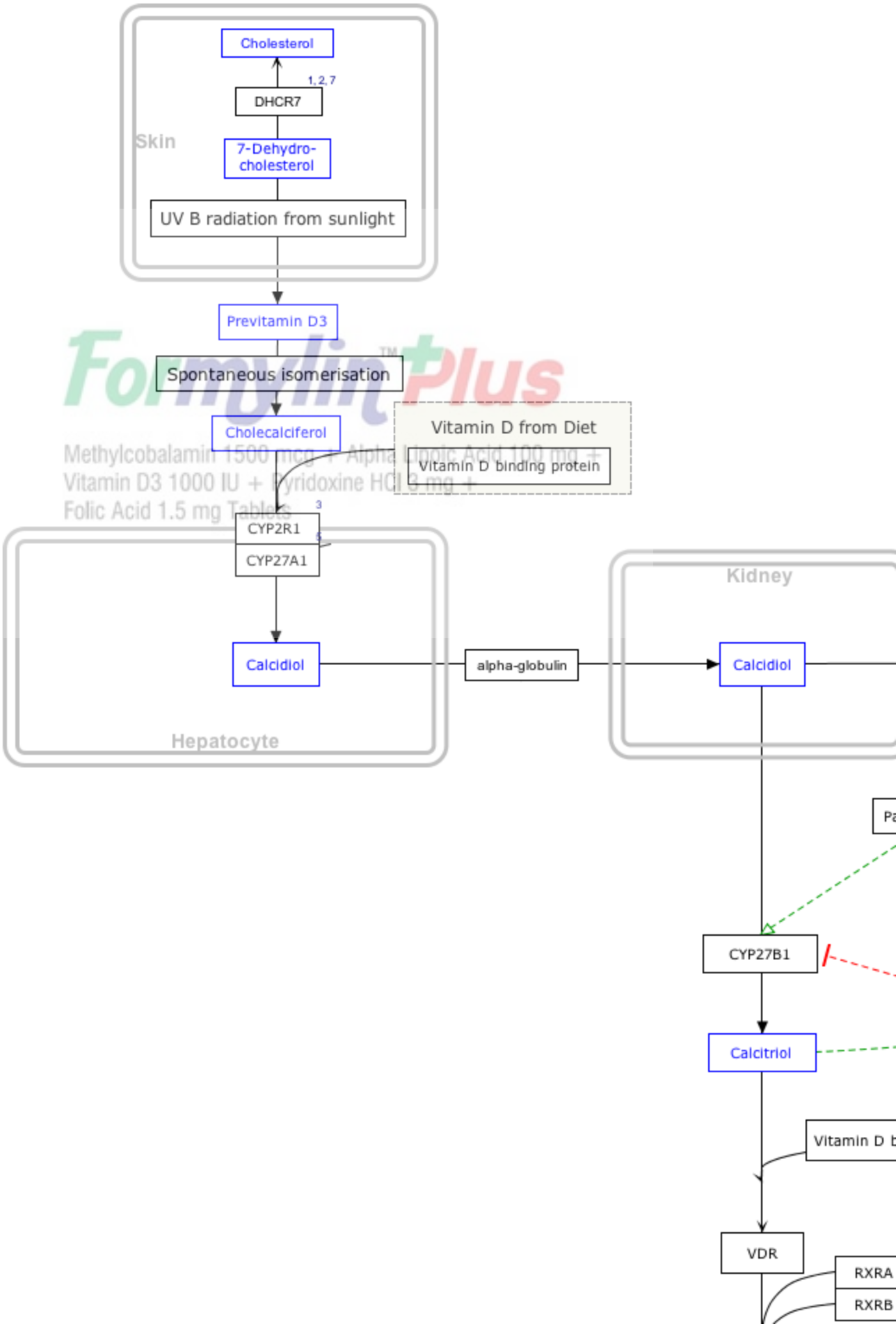
Click on icon in lower right corner to open. *Click on genes, proteins and metabolites below to link to respective articles.* [§ 1]

[[File:


Cholesterol
1,2,7
DHCR7
Skin
7-Dehydro-cholesterol
UV B radiation from sunlight
Previtamin D3
Spontaneous isomerisation
Cholecalciferol
Vitamin D from Diet
Vitamin D binding protein
3
CYP2R1
6
CYP27A1
Calcidiol
Hepatocyte
alpha-globulin
Kidney
Calcidiol
CYP27B1
Calcitriol
VDR
RXRA
RXRB

Formylin™ Plus

Methylcobalamin 1500 mcg + Alpha Lipoic Acid 100 mg +
Vitamin D3 1000 IU + Pyridoxine HCl 3 mg +
Folic Acid 1.5 mg Tablets

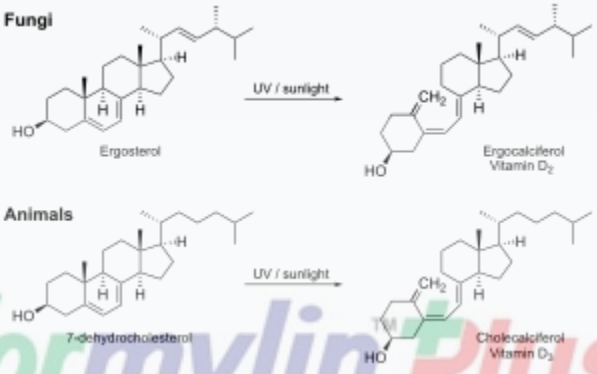

Cholesterol
1,2,7
DHCR7
Skin
7-Dehydro-cholesterol
UV B radiation from sunlight
Previtamin D3
Spontaneous isomerisation
Cholecalciferol
Vitamin D from Diet
Vitamin D binding protein
3
CYP2R1
6
CYP27A1
Calcidiol
Hepatocyte
alpha-globulin
Kidney
Calcidiol
CYP27B1
Calcitriol
VDR
RXRA
RXRB

|{{{bSize}}}px|alt=Vitamin D Synthesis Pathway (view / edit)]]

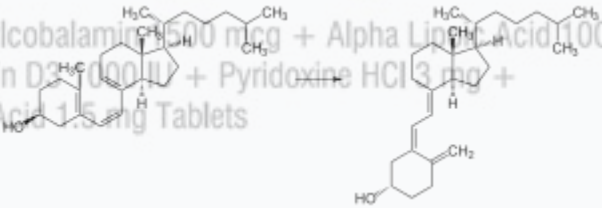
Vitamin D Synthesis Pathway (view / edit)

1. ^ The interactive pathway map can be edited at WikiPathways: *"VitaminDSynthesis_WP1531"*.

Photochemistry[edit]



The photochemistry of vitamin D biosynthesis in animal and fungi

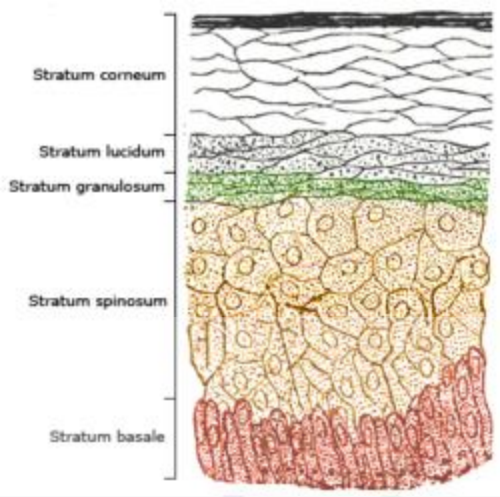


Thermal isomerization of previtamin D_3 to vitamin D_3

The transformation that converts 7-dehydrocholesterol to vitamin D_3 occurs in two steps.[152][153] First, 7-dehydrocholesterol is photolyzed by ultraviolet light in a 6-electron conrotatory ring-opening electrocyclic reaction; the product is previtamin D_3. Second, previtamin D_3 spontaneously isomerizes to vitamin D_3 (cholecalciferol) in an antarafacial sigmatropic [1,7] hydride shift. At room temperature, the transformation of previtamin D_3 to vitamin D_3 in an organic solvent takes about 12 days to complete. The conversion of previtamin D_3 to vitamin D_3 in the skin is about 10 times faster than in an organic solvent.[154]

The conversion from ergosterol to vitamin D_2 follows a similar procedure, forming previtamin D_2 by photolysis, which isomerizes to vitamin D_2.[155] The transformation of previtamin D_2 to vitamin D_2 in methanol has a rate comparable to that of previtamin D_3. The process is faster in white button mushrooms.[125](fig. 3)

Synthesis in the skin[edit]



In the epidermal strata of the skin, vitamin D production is greatest in the stratum basale (colored red in the illustration) and stratum spinosum (colored light brown).

Vitamin D_3 is produced photochemically from 7-dehydrocholesterol in the skin of most vertebrate animals, including humans.[156] The precursor of vitamin D_3, 7-dehydrocholesterol is produced in relatively large quantities. 7-Dehydrocholesterol reacts with UVB light at wavelengths of 290–315 nm.[157] These wavelengths are present in sunlight, as well as in the light emitted by the UV lamps in tanning beds (which produce ultraviolet primarily in the UVA spectrum, but typically produce 4% to 10% of the total UV emissions as UVB). Exposure to light through windows is insufficient because glass almost completely blocks UVB light.[158][159]

Adequate amounts of vitamin D can be produced with moderate sun exposure to the face, arms and legs, averaging 5–30 minutes twice per week, or approximately 25% of the time for minimal sunburn. The darker the skin, and the weaker the sunlight, the more minutes of exposure are needed. Vitamin D overdose is impossible from UV exposure; the skin reaches an equilibrium where the vitamin degrades as fast as it is created.[27][160][161]

Sunscreen absorbs or reflects ultraviolet light and prevents much of it from reaching the skin.[162] Sunscreen with a sun protection factor (SPF) of 8 based on the UVB spectrum decreases vitamin D synthetic capacity by 95%, and SPF 15 decreases it by 98%.[58]

The skin consists of two primary layers: the inner layer called the dermis, composed largely of connective tissue, and the outer, thinner epidermis.[163] Thick epidermis in the soles and palms consists of five strata; from outer to inner, they are: the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. Vitamin D is produced in the keratinocytes[164] of two innermost strata, the stratum basale and stratum spinosum.[162]

Evolution[edit]

Vitamin D can be synthesized only by a photochemical process. Phytoplankton in the ocean (such as coccolithophore and *Emiliania huxleyi*) have been photosynthesizing vitamin D for more than 500 million years. Primitive vertebrates in the ocean could absorb calcium from the ocean into their skeletons and eat plankton rich in vitamin D.

Land vertebrates required another source of vitamin D other than plants for their calcified skeletons. They had to either ingest it or be exposed to sunlight to photosynthesize it in their skin.[124][154] Land vertebrates have been photosynthesizing vitamin D for more than 350 million years.[165]

In birds and fur-bearing mammals, fur or feathers block UV rays from reaching the skin. Instead, vitamin D is created from oily secretions of the skin deposited onto the feathers or fur, and is

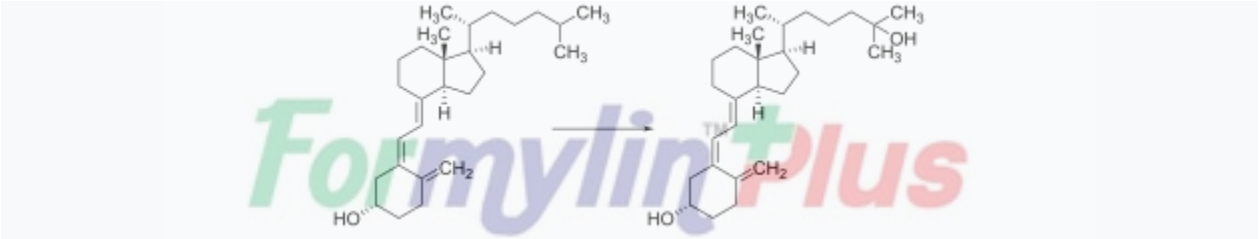
obtained orally during grooming.[166] However, some animals, such as the naked mole-rat, are naturally cholecalciferol-deficient, as serum 25-OH vitamin D levels are undetectable.[167]

Industrial synthesis[edit]

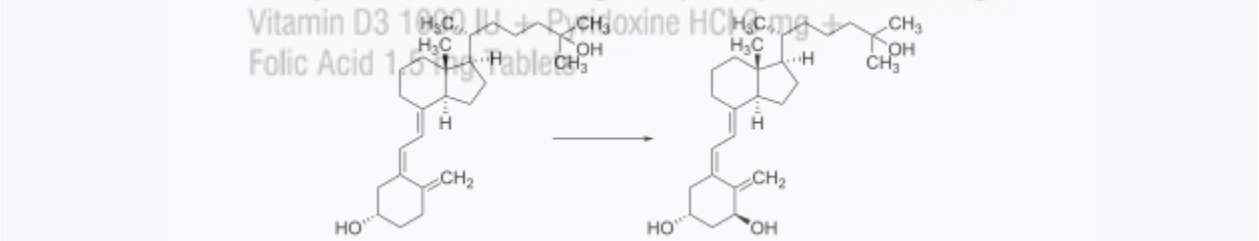
Vitamin D_3 (cholecalciferol) is produced industrially by exposing 7-dehydrocholesterol to UVB light, followed by purification.[168] The 7-dehydrocholesterol is a natural substance in fish organs, especially the liver,[169] or in wool grease (lanolin) from sheep. Vitamin D_2 (ergocalciferol) is produced in a similar way using ergosterol from yeast or mushrooms as a starting material.[168][125]

Mechanism of action[edit]

Metabolic activation[edit]



Liver hydroxylation of cholecalciferol to calcifediol



Kidney hydroxylation of calcifediol to calcitriol

Vitamin D is carried in the bloodstream to the liver, where it is converted into the prohormone calcifediol. Circulating calcifediol may then be converted into calcitriol, the biologically active form of vitamin D, in the kidneys.[170]

Whether it is made in the skin or ingested, vitamin D is hydroxylated in the liver at position 25 (upper right of the molecule) to form 25-hydroxycholecalciferol (calcifediol or 25(OH)D).[171] This reaction is catalyzed by the microsomal enzyme vitamin D 25-hydroxylase, the product of the *CYP2R1* human gene, and expressed by hepatocytes.[172] Once made, the product is released into the plasma, where it is bound to an α-globulin carrier protein named the vitamin D-binding protein.[173]

Calcifediol is transported to the proximal tubules of the kidneys, where it is hydroxylated at the 1-α position (lower right of the molecule) to form calcitriol (1,25-dihydroxycholecalciferol, $1,25(OH)_2D$). The conversion of calcifediol to calcitriol is catalyzed by the enzyme 25-hydroxyvitamin D_3 1-alpha-hydroxylase, which is the product of the *CYP27B1* human gene. The activity of CYP27B1 is increased by parathyroid hormone, and also by low calcium or phosphate.[6][170]

Following the final converting step in the kidney, calcitriol is released into the circulation. By binding to vitamin D-binding protein, calcitriol is transported throughout the body, including to the classical target organs of intestine, kidney and bone.[18]Calcitriol is the most potent natural ligand of the vitamin D receptor, which mediates most of the physiological actions of vitamin D.[6][170]

In addition to the kidneys, calcitriol is also synthesized by certain other cells including monocyte-macrophages in the immune system. When synthesized by monocyte-macrophages, calcitriol acts

locally as a cytokine, modulating body defenses against microbial invaders by stimulating the innate immune system.[170]

Inactivation[edit]

The activity of calcifediol and calcitriol can be reduced by hydroxylation at position 24 by vitamin D3 24-hydroxylase, forming secalciferol and calcitetrol, respectively.[171]

Difference between substrates[edit]

Vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecaliferol) share a similar mechanism of action as outlined above.[171] Metabolites produced by vitamin D_2 are sometimes named with an *er-* or *ergo* prefix to differentiate them from the D_3-based counterparts.[174]

- Metabolites produced from vitamin D_2 tend to bind less well to the vitamin D-binding protein.
- Vitamin D_3 can alternatively be hydroxylated to calcifediol by sterol 27-hydroxylase (CYP27A1), but vitamin D_2 cannot.
- Ergocalciferol can be directly hydroxylated at position 24. This hydroxylation also leads to a greater degree of inactivation: while calcitriol's activity decreases to 60% of original after 24-hydroxylation, [175] ercalcitriol suffers a 10-fold decrease in activity on conversion to ercalcitetrol.[176]

History[edit]

American researchers Elmer McCollum and Marguerite Davis in 1914[12] discovered a substance in cod liver oil which later was called "vitamin A". British doctor Edward Mellanbynoticed dogs that were fed cod liver oil did not develop rickets and concluded vitamin A, or a closely associated factor, could prevent the disease. In 1922, Elmer McCollum tested modified cod liver oil in which the vitamin A had been destroyed.[12] The modified oil cured the sick dogs, so McCollum concluded the factor in cod liver oil which cured rickets was distinct from vitamin A. He called it vitamin D because it was the fourth vitamin to be named.[177][178][179] It was not initially realized that, unlike other vitamins, vitamin D can be synthesised by humans through exposure to UV light.

In 1925,[12] it was established that when 7-dehydrocholesterol is irradiated with light, a form of a fat-soluble vitamin is produced (now known as D_3). Alfred Fabian Hess stated: "Light equals vitamin D."[180] Adolf Windaus, at the University of Göttingen in Germany, received the Nobel Prize in Chemistry in 1928 for his work on the constitution of sterols and their connection with vitamins.[181] In 1929, a group at NIMR in Hampstead, London, were working on the structure of vitamin D, which was still unknown, as well as the structure of steroids. A meeting took place with J.B.S. Haldane, J.D. Bernal, and Dorothy Crowfoot to discuss possible structures, which contributed to bringing a team together. X-ray crystallography demonstrated the sterol molecules were flat, not as proposed by the German team led by Windaus. In 1932, Otto Rosenheim and Harold King published a paper putting forward structures for sterols and bile acids which found immediate acceptance.[182] The informal academic collaboration between the team members Robert Benedict Bourdillon, Otto Rosenheim, Harold King, and Kenneth Callow was very productive and led to the isolation and characterization of vitamin D.[183] At this time, the policy of the Medical Research Council was not to patent discoveries, believing the results of medical research should be open to everybody. In the 1930s, Windaus clarified further the chemical structure of vitamin D.[184]

In 1923, American biochemist Harry Steenbock at the University of Wisconsin demonstrated that irradiation by ultraviolet light increased the vitamin D content of foods and other organic materials.[185] After irradiating rodent food, Steenbock discovered the rodents were cured of rickets. A vitamin D deficiency is a known cause of rickets. Using $300 of his own money, Steenbock patented his invention. His irradiation technique was used for foodstuffs, most memorably for milk. By the expiration of his patent in 1945, rickets had been all but eliminated in the US.[186]

In 1969, after studying nuclear fragments of intestinal cells, a specific binding protein for vitamin D called the vitamin D receptor was identified by Mark Haussler and Tony Norman.[187] In 1971–72, the further metabolism of vitamin D to active forms was discovered. In the liver, vitamin D was found to be converted to calcifediol. Calcifediol is then converted by the kidneys to calcitriol, the biologically active form of vitamin D.[11] Calcitriol circulates as a hormone in the blood, regulating the concentration of calcium and phosphate in the bloodstream and promoting the healthy growth and remodeling of bone. The vitamin D metabolites, calcifediol and calcitriol, were identified by competing teams led by Michael F. Holick in the laboratory of Hector DeLuca and by Tony Norman and colleagues.[188][189][190]

Research[edit]

There is considerable research activity looking at effects of vitamin D and its metabolites in animal models, cell systems, gene expression studies, epidemiology and clinical therapeutics. These different types of studies can produce conflicting evidence as to the benefits of interventions with vitamin D.[191] One school of thought contends the human physiology is fine-tuned to an intake of 4,000–12,000 IU/day from sun exposure with concomitant serum 25-hydroxyvitamin D levels of 40 to 80 ng/mL[192] and this is required for optimal health. Proponents of this view, who include some members of the panel that drafted a now-superseded 1997 report on vitamin D from the IOM, contend the IOM's warning about serum concentrations above 50 ng/mL lacks biological plausibility. They suggest, for some people, reducing the risk of preventable disease requires a higher level of vitamin D than that recommended by the IOM.[192][193]

The United States National Institutes of Health Office of Dietary Supplements established a Vitamin D Initiative in 2014 to track current research and provide education to consumers.[194] In their 2016 review, they recognize that a growing body of research suggests that vitamin D might play some role in the prevention and treatment of types 1 and 2 diabetes, glucose intolerance, hypertension, multiple sclerosis, and other medical conditions. They state further: "however, most evidence for these roles comes from in vitro, animal, and epidemiological studies, not the randomized clinical trials considered to be more definitive. Until such trials are conducted, the implications of the available evidence for public health and patient care will be debated".[7]

Some preliminary studies link low vitamin D levels with disease later in life.[195] Evidence as of 2013 is insufficient to determine whether vitamin D affects the risk of cancer.[196]One meta-analysis found a decrease in mortality in elderly people.[15] Another meta-analysis covering over 350,000 people concluded that vitamin D supplementation in unselected community-dwelling individuals does not reduce skeletal (total fracture) or non-skeletal outcomes (myocardial infarction, ischemic heart disease, stroke, cerebrovascular disease, cancer) by more than 15%, and that further research trials with similar design are unlikely to change these conclusions.[16] A 2019 meta-analysis found that there may be an increased risk of stroke when taking both calcium and vitamin D.[197]

Vitamin D deficiency is widespread in the European population.[198] European research is assessing vitamin D intake levels in association with disease rates and policies of dietary recommendations, food fortification, vitamin D supplementation, and small amounts of sun exposure.[130]

Apart from VDR activation, various alternative mechanisms of action are under study, such as inhibition of signal transduction by hedgehog, a hormone involved in morphogenesis.[199]

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Pyridoxine

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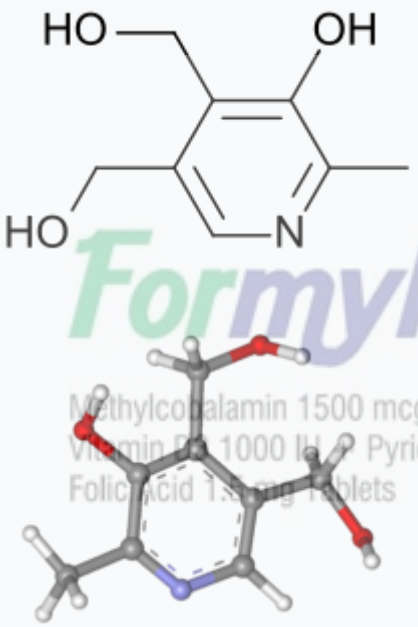
Pyridoxine	
 Pyridoxine	
Clinical data	
Synonyms	vitamin B_6,[1] pyridoxol[2]pyridoxine hydrochloride
AHFS/Drugs.com	Monograph
Pregnancy category	US: A (No risk in human studies) and C
Routes of administration	by mouth, IV, IM, subQ
ATC code	A11HA02 (WHO)
Legal status	
Legal status	US: OTC

Identifiers	
IUPAC name[show]	
CAS Number	65-23-6
DrugBank	DB00165
ChemSpider	1025
UNII	KV2JZ1BI6Z
KEGG	D08454
ChEBI	CHEBI:16709
ChEMBL	ChEMBL1364
CompTox Dashboard (EPA)	DTXSID4023541
ECHA InfoCard	100.000.548
Chemical and physical data	
Formula	$C_8H_{11}NO_3$
Molar mass	169.180 g·mol^{-1}
3D model (JSmol)	Interactive image
Melting point	159 to 162 °C (318 to 324 °F)
SMILES[show]	
InChI[show]	

Pyridoxine, also known as **vitamin B$_6$**, is a form of vitamin B$_6$ found commonly in food and used as dietary supplement.[1] As a supplement it is used to treat and prevent pyridoxine deficiency, sideroblastic anaemia, pyridoxine-dependent epilepsy, certain metabolic disorders, problems from isoniazid, and certain types of mushroom poisoning.[3][1] It is used by mouth or by injection.[3]

It is usually well tolerated.[3] Occasionally side effects include headache, numbness, and sleepiness.[3] Normal doses are safe during pregnancy and breastfeeding.[3] Pyridoxine is in the vitamin B family of vitamins.[3] It is required by the body to make amino acids, carbohydrates, and lipids.[3] Sources in the diet include fruit, vegetables, and grain.[4]

Pyridoxine was discovered in 1934, isolated in 1938, and first made in 1939.[5][6] It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.[7] Pyridoxine is available as a generic medication and over the counter.[3] The wholesale cost in the developing world is about US$0.59–3.54 per month.[8] Foods, such as breakfast cereal have pyridoxine added in some countries.[4]

Contents

Medical uses[edit]

As a supplement it is used to treat and prevent pyridoxine deficiency, sideroblastic anaemia, pyridoxine-dependent epilepsy, certain metabolic disorders, problems from isoniazid, and certain types of mushroom poisoning.[3][1] Pyridoxine-dependent epilepsy is a type of rare epilepsy that does not improve with typical antiseizure medications.[9] Pyridoxine is used by mouth or by injection.[3]

Pyridoxine in combination with doxylamine is used as a treatment for morning sickness in pregnant women. It has been used in hydrazine exposure with unclear effect.[10]

Side effects[edit]

It is usually well tolerated.[3] Occasionally side effects include headache, numbness, and sleepiness.[3] Normal doses are safe during pregnancy and breastfeeding.[3]

Mechanism[edit]

Pyridoxine is in the vitamin B family of vitamins.[3] It is required by the body to make amino acids, carbohydrates, and lipids.[3]Sources in the diet include fruit, vegetables, and grain.[4] It is also required for muscle phosphorylase activity associated with glycogen metabolism.

History and culture[edit]

Pyridoxine was discovered in 1934, isolated in 1938, and first made in 1939.[5][6] It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.[7] Pyridoxine is available as a generic medication and over the counter.[3] The wholesale cost in the developing world is about US$0.59–3.54 per month.[8] Foods, such as breakfast cereal have pyridoxine added in some countries.[4]

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2. ^ *Dryhurst, Glenn (2012). Electrochemistry of Biological Molecules. Elsevier. p. 562. ISBN 9780323144520. Archived from the original on 2016-12-30.*
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5. ^ Jump up to:[a] [b] *Squires, Victor R. (2011). The Role of Food, Agriculture, Forestry and Fisheries in Human Nutrition - Volume IV. EOLSS Publications. p. 121. ISBN 9781848261952.*

6. ^ Jump up to:[a] [b] *Harris, Harry (2012). Advances in Human Genetics 6. Springer Science & Business Media. p. 39. ISBN 9781461582649.*
7. ^ Jump up to:[a] [b] *"WHO Model List of Essential Medicines (19th List)" (PDF). World Health Organization. April 2015. Archived (PDF) from the original on 13 December 2016. Retrieved 8 December2016.*
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External links[edit]

- Media related to Pyridoxine at Wikimedia Commons
- Pyridoxine mass spectrum

Folate

From Wikipedia, the free encyclopedia

(Redirected from Folic acid)

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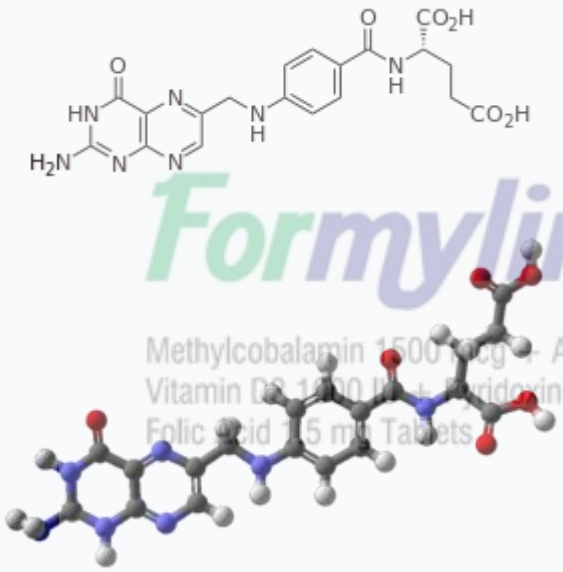
Folic acid



Clinical data	
Pronunciation	/ˈfoʊlɪk, ˈfɒlɪk/
Synonyms	FA, *N*-(4-{[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]amino}benzoyl)-L-glutamic acid, pteroyl-L-glutamic acid, vitamin B_9,[1] vitamin B_c,[2] vitamin M,[3] folacin, pteroyl-L-glutamate
AHFS/Drugs.com	Monograph
MedlinePlus	a682591
Pregnancy category	US: A (No risk in human studies)
Routes of	By mouth, IM, IV, sub-Q

administration	
ATC code	B03BB01 (WHO)
Legal status	
Legal status	US: OTC
Pharmacokinetic data	
Bioavailability	50–100%[4]
Metabolism	Liver[4]
Excretion	Urine[4]
Identifiers	
IUPAC name[show]	
CAS Number	59-30-3
PubChem CID	6037
IUPHAR/BPS	4563
DrugBank	DB00158✓
ChemSpider	5815
UNII	935E97BOY8
KEGG	C00504
ChEBI	CHEBI:27470
ChEMBL	ChEMBL1622
CompTox Dashboard (EPA)	DTXSID0022519
ECHA InfoCard	100.000.381
Chemical and physical data	
Formula	$C_{19}H_{19}N_7O_6$
Molar mass	441.404 g·mol^{-1}
3D model (JSmol)	Interactive image
Density	1.6±0.1[6] g/cm^3
Melting point	250 °C (482 °F) (decomposition)

Solubility in water	1.6 mg/L (25 °C) mg/mL (20 °C)
SMILES[show]	
InChI[show]	

Folate, distinct forms of which are known as **folic acid**, **folacin**, and **vitamin B_9**,[7] is one of the B vitamins.[4] It may be taken by mouth or by injection.[4] The recommended adult daily intake of folate in the U.S. is 400 micrograms from foods or dietary supplements.[8] Folate in the form of folic acid is used to treat anemia caused by folate deficiency.[4] Folic acid is also used as a supplement by women during pregnancy to reduce the risk of neural tube defects (NTDs) in the baby.[4][9] Low levels in early pregnancy are believed to be the cause of more than half of babies born with NTDs.[8] More than 80 countries use fortification of certain foods with folic acid as a measure to decrease the rate of NTDs.[10] Long-term supplementation is also associated with small reductions in the risk of stroke and cardiovascular disease.[11]

No common side effects are known.[4] There are concerns that large amounts of folic acid might hide vitamin B_{12} deficiency.[8]Folate is essential for the body to make DNA, RNA, and metabolise amino acids, which are required for cell division.[8] As humans cannot make folate, it is required from the diet, making it an essential vitamin.[12]

Not consuming enough folate can lead to folate deficiency.[8] This may result in a type of anemia in which low numbers of large red blood cells occur.[8] Symptoms may include feeling tired, heart palpitations, shortness of breath, open sores on the tongue, and changes in the color of the skin or hair.[8] Folate deficiency in children may develop within a month of poor dietary intake.[13]In adults, normal total body folate is between 10 and 30 mg with blood levels of greater than 7 nmol/L (3 ng/mL).[8]

Folic acid was discovered between 1931 and 1943.[14] It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.[15] The wholesale cost of supplements in the developing world is between US$0.001 and 0.005 per dose as of 2014.[16] The term "folic" is from the Latin word *folium* (which means leaf) because it was found in dark-green leafy vegetables.[17] Folates occur naturally in many foods.[7][8] In 2016, it was the 96th most prescribed medication in the United States, with more than 8 million prescriptions.[18]

Contents

Definition[edit]

"Folate" is the term used to name the many forms of the vitamin—namely folic acid and its congeners, including tetrahydrofolic acid (the activated form of the vitamin), methyltetrahydrofolate (the primary form found in the serum), methenyltetrahydrofolate, folinic acid, and folacin.[7][19][20][21] Other names include vitamin B_9,[1] vitamin B_c,[2] vitamin M,[3] and pteroyl-L-glutamate.

Health effects[edit]

Folate is necessary for the production and maintenance of new cells, for DNA synthesis and RNA synthesis through methylation, and for preventing changes to DNA.[22] It is especially important during periods of frequent cell division and growth, such as infancy and pregnancy. Folate deficiency hinders DNA synthesis and cell division, affecting hematopoietic cells and neoplasms the most because of their greater frequency of cell division. RNA transcription and subsequent protein synthesis are less affected by folate deficiency, as the mRNA can be recycled and used again (as opposed to DNA synthesis, where a new genomic copy must be created). Since folate deficiency limits cell division, erythropoiesis (production of red blood cells) is hindered. This leads to megaloblastic anemia, which is characterized by large, immature red blood cells. This pathology results from persistently thwarted attempts at normal DNA replication, DNA repair, and cell division, and produces abnormally large red cells called megaloblasts (and hypersegmented neutrophils) with abundant cytoplasm capable of RNA and protein synthesis, but with clumping and fragmentation of nuclear chromatin. Some of these large cells, although immature (reticulocytes), are released early from the marrow in an attempt to compensate for the anemia.[23] Both adults and children need folate to make normal red and white blood cells and prevent anemia.[24] Deficiency of folate in pregnant women has been implicated in NTDs; therefore, many developed countries have implemented mandatory folic acid fortification in cereals, etc. NTDs occur early in pregnancy (first month), therefore women must have abundant folate upon conception. Folate is required to make red blood cells and white blood cells and folate deficiency may lead to anemia, which causes fatigue, weakness, and inability to concentrate.[25]

Pregnancy[edit]

Folate intake during pregnancy has been linked to a lessened risk of neural tube defects (NTDs), and for this reason there is a recommendation that any woman planning to become pregnant consume a folate-containing dietary supplement before and during pregnancy.[26] Compliance with

this recommendation is not complete, and many women become pregnant without this being a planned pregnancy, or may not realize that they are pregnant until well into the first trimester, which is the critical period for reducing risk of NTDs. Countries have implemented either mandatory or voluntary food fortification of wheat flour and other grains, or else have no such program and depend on public health and healthcare practitioner advice to women of childbearing age. A meta-analysis of global birth prevalence of spina bifida showed that when mandatory fortification was compared to countries with voluntary fortification or no fortification program, there was a 30% reduction in live births with spina bifida.[27] The United States Preventive Services Task Forcerecommends folic acid as the supplement or fortification ingredient, as forms of folate other than folic acid have not been studied.[20]

A meta-analysis of folate supplementation during pregnancy reported a 28% lower risk of newborn congenital heart defects.[28] Prenatal supplementation with folic acid did not appear to reduce the risk of preterm births.[29][30] One systematic review indicated no effect of folic acid on mortality, growth, body composition, respiratory, or cognitive outcomes of children from birth to 9 years old.[31] There was no correlation between maternal folic acid supplementation and an increased risk for childhood asthma.[32]

Fertility[edit]

Folate is necessary for fertility in both men and women. It contributes to spermatogenesis. Therefore, receiving sufficient amounts through the diet is necessary to avoid low fertility.[33] Also, polymorphisms in genes of enzymes involved in folate metabolism could be one reason for fertility complications in some women with unexplained infertility.[34]

Heart disease[edit]

Taking folic acid over years reduced the risk of cardiovascular disease by 4%,[11] where another study found it did not affect cardiovascular disease, even while reducing homocysteine levels.[35] Several studies provided preliminary evidence that folate-rich diets were associated with reduced risk of cardiovascular diseases by lowering blood levels of homocysteine.[7]

Stroke[edit]

Long-term supplementation with folic acid reduced the risk of stroke by 10%, which may be due to the role folate plays in regulating homocysteine concentration.[11] A meta-analysis indicated the risk of stroke appeared to be reduced only in some individuals, so a definite recommendation regarding supplementation beyond the current RDA has not been established.[36] Asian populations had greater protection against stroke with folate supplementation than did European or North American subjects.[11] Observed stroke reduction is consistent with the reduction in pulse pressure produced by folate supplementation of 5 mg per day, since hypertension is a key risk factor for stroke. Folic supplements are inexpensive and relatively safe to use, which is why people who have had strokes or who have hyperhomocysteinemia are encouraged to consume daily B vitamins including folic acid.[37]

Cancer[edit]

Studies on folic acid intake from food and folate supplementation with regards to cancer risk are based on the adequacy of chronic intake. Chronically insufficient intake of folate may increase the risk of colorectal, breast, ovarian, pancreas, brain, lung, cervical, and prostate cancers.[7][38][39] Other studies showed that excessive dietary supplementation with folic acid may modestly increase the risk of certain cancers, but only prostate cancer was significant.[40][41] A subsequent meta-analysis found no relationship between taking folate supplements and cancer risk of any type.[42]

Antifolate chemotherapy[edit]

Folate is important for cells and tissues that divide rapidly.[22] Cancer cells divide rapidly, and drugs that interfere with folate metabolism are used to treat cancer. The antifolate drug methotrexate is often used to treat cancer because it inhibits the production of the active form of THF from the inactive dihydrofolate (DHF). However, methotrexate can be toxic,[43][44][45] producing side effects, such as inflammation in the digestive tract that make eating normally more difficult. Also, bone marrow depression (inducing leukopenia and thrombocytopenia) and acute kidney and liver failure have been reported.

Folinic acid, under the drug name leucovorin, a form of folate (formyl-THF), can help "rescue" or reverse the toxic effects of methotrexate.[46] Folinic acid is *not* the same as folic acid. Folic acid supplements have little established role in cancer chemotherapy.[47][48] Cases of severe adverse effects of accidental substitution of folic acid for folinic acid have been reported in people receiving methotrexate cancer chemotherapy. Anyone receiving methotrexate should follow medical advice on the use of folic or folinic acid supplements. The supplement of folinic acid in people undergoing methotrexate treatment is to give cells dividing less rapidly enough folate to maintain normal cell functions. The amount of folate given is depleted by rapidly dividing cells (cancer) quickly, so does not negate the effects of methotrexate.

Neurological[edit]

Some evidence links a shortage of folate with clinical depression.[49] Limited evidence from randomized controlled trials showed using folic acid in addition to selective serotonin reuptake inhibitors (SSRIs) may have benefits.[50] Research found a link between depression and low levels of folate.[51][52] Folate may reduce homocysteine levels, which are associated with cognitive functions.[7]

The exact mechanisms involved in the development of schizophrenia and depression are not entirely clear, but the bioactive folate, methyltetrahydrofolate (5-MTHF), a direct target of methyl donors such as S-adenosyl methionine (SAMe), recycles the inactive dihydrobiopterin (BH_2) into tetrahydrobiopterin (BH_4), the necessary cofactor in various steps of monoamine synthesis, including that of dopamine. BH_4 serves a regulatory role in monoamine neurotransmission and is required to mediate the actions of most antidepressants. 5-MTHF also plays both direct & indirect roles in DNA methylation, NO_2 synthesis, and one-carbon metabolism.[53]

Age-related macular degeneration[edit]

A sub-study of the *Women's Antioxidant and Folic Acid Cardiovascular Study* published in 2009 reported use of a nutritional supplement containing folic acid at 2,500 µg/day, pyridoxine at 50 mg/day, and vitamin B_{12} at 1,000 µg/day decreased the risk of developing age-related macular degeneration by 34.7%. The amount of folic acid used in this clinical trial – 2,500 µg/day – was higher than the tolerable upper intake level of 1,000 µg.[54]

Folic acid, B_{12} and iron[edit]

A complex interaction occurs between folic acid, vitamin B_{12}, and iron. A deficiency of one may be "masked" by excess of another, so the three must always be in balance.[55][56][57]

Folate deficiency[edit]

Main article: Folate deficiency

Folate deficiency can be caused by unhealthy diets that do not include enough vegetables and other folate-rich foods; diseases in which folates are not well absorbed in the digestive system (such as Crohn's disease or celiac disease); some genetic disorders that affect levels of folate; and certain medicines (such as phenytoin, sulfasalazine, or trimethoprim-sulfamethoxazole).[58] Folate deficiency is accelerated by alcohol consumption, possibly by interference with folate transport.[59]

Folate deficiency may lead to glossitis, diarrhea, depression, confusion, anemia, and fetal neural tube and brain defects.[60] Other symptoms include fatigue, gray hair, mouth sores, poor growth, and swollen tongue.[58] Folate deficiency is diagnosed by analyzing a Complete blood count (CBC) and

plasma vitamin B_{12} and folate levels. A serum folate of 3 µg/L or lower indicates deficiency.[60] Serum folate level reflects folate status, but erythrocyte folate level better reflects tissue stores after intake. An erythrocyte folate level of 140 µg/L or lower indicates inadequate folate status. Serum folate reacts more rapidly to folate intake than erythrocyte folate.[61]

Increased homocysteine levels suggest tissue folate deficiency, but homocysteine is also affected by vitamin B_{12} and vitamin B_6, renal function, and genetics. One way to differentiate between folate (vitamin B_9) deficiency from vitamin B_{12} deficiency is by testing for methylmalonic acid (MMA) levels. Normal MMA levels indicate folate deficiency and elevated MMA levels indicate vitamin B_{12} deficiency.[60] Folate deficiency is treated with supplemental oral folic acid of 400 to 1000 µg per day. This treatment is very successful in replenishing tissues, even if deficiency was caused by malabsorption. People with megaloblastic anemia need to be tested for vitamin B_{12} deficiency before treatment with folic acid, because if the person has vitamin B_{12} deficiency, folic acid supplementation can remove the anemia, but can also worsen neurologic problems.[60] Cobalamin deficiency may lead to folate deficiency, which, in turn, increases homocysteine levels and may result in the development of cardiovascular disease or birth defects.[62]

Malaria[edit]

Some studies show iron–folic acid supplementation in children under five may result in increased mortality due to malaria; this has prompted the World Health Organization to alter their iron–folic acid supplementation policies for children in malaria-prone areas, such as India.[63]

Dietary recommendations[edit]

Because of the difference in bioavailability between supplemented folic acid and the different forms of folate found in food, the dietary folate equivalent (DFE) system was established. One DFE is defined as 1 µg of dietary folate. One µg of folic acid supplement counts as 1.7 µg DFE. The reason for the difference is that at least 85% of folic acid is estimated to be bioavailable when taken with food, whereas only about 50% of folate naturally present in food is bioavailable.[8]

National Institutes of Health (U.S.) nutritional recommendations[8]
(µg DFE per day for RDA, µg folic acid for UL)

Age	Infants		Children and adults		Pregnant women		Lactating women	
	(AI)	(UL)	(RDA)	(UL)	(RDA)	(UL)	(RDA)	(UL)
0–6 months	65	None set	–	–	–	–	–	–
7–12 months	80	None set	–	–	–	–	–	–
1–3 years	–	–	150	300	–	–	–	–

4–8 years	–	–	200	400	–	–	–	–
9–13 years	–	–	300	600	–	–	–	–
14–18	–	–	400	800	600	800	500	800
19+	–	–	400	1000	600	1000	500	1000

The U.S. Institute of Medicine (IOM) updated Recommended Dietary Allowances (RDAs) and Tolerable upper intake levels (ULs) for folate in 2001. Collectively the EARs, RDAs, AIs, and ULs are referred to as Dietary Reference Intakes (DRIs).[8][60] The European Food Safety Authority (EFSA) refers to the collective set of information as Dietary Reference Values, with Population Reference Intake (PRI) instead of RDA, and Average Requirement instead of EAR. AI and UL defined the same as in United States. For women and men over age 18 the PRI is set at 330 µg/day. PRI for pregnancy is 600 µg/day, for lactation 500 µg/day. For children ages 1–17 years the PRIs increase with age from 120 to 270 µg/day. These values differ somewhat from the U.S. RDAs.[64] The United Kingdom's Dietary Reference Value for folate, set by the Committee on Medical Aspects of Food and Nutrition Policy (COMA) in 1991, is 200 µg/day for adults.[65]

Safety[edit]

The risk of toxicity from folic acid is low, because folate is a water-soluble vitamin and is regularly removed from the body through urine. One potential issue associated with high doses of folic acid is that it has a masking effect on the diagnosis of pernicious anaemia due to vitamin B_{12} deficiency.[60] An additional concern raised was that low vitamin B_{12} status in combination with high folic acid intake appeared to increase the risk of cognitive impairment in the elderly.[66] The IOM sets ULs for vitamins and minerals when evidence is sufficient. The adult UL of 1000 µg for folate (and lower for children) refers to folic acid used as a supplement, as no health risks have been associated with high intake of folate from food sources. The EFSA reviewed the safety question and agreed with United States that the UL be set at 1000 µg.[67] The Japan National Institute of Health and Nutrition set the adult UL at 1,300 or 1,400 µg depending on age.[68]

Food labeling[edit]

For U.S. food and dietary supplement labeling purposes the amount in a serving is expressed as a percent of Daily Value (%DV). For folate labeling purposes 100% of the Daily Value was 400 µg. As of the 27 May 2016 update, it was kept unchanged at 400 µg. [69] A table of the old and new adult Daily Values is provided at Reference Daily Intake. The original deadline to be in compliance was 28 July 2018, but on 29 September 2017 the FDA released a proposed rule that extended the deadline to 1 January 2020 for large companies and 1 January 2021 for small companies.[70] European Union regulations require that labels declare energy, protein, fat, saturated fat, carbohydrates, sugars, and salt. Voluntary nutrients may be shown if present in significant amounts. Instead of Daily Values, amounts are shown as percent of Reference Intakes (RIs). For folate, 100% RI was set at 200 µg in 2011.[71]

Sources[edit]

The United States Department of Agriculture (USDA), Agricultural Research Service, maintains a food composition database from which folate content in hundreds of foods can be searched as

shown in the table.[72] The Food Fortification Initiative lists all countries in the world that conduct fortification programs,[73] and within each country, what nutrients are added to which foods, and whether those programs are voluntary or mandatory. In the US, mandatory fortification of enriched breads, cereals, flours, corn meal, pastas, rice, and other grain products began in January 1998. As of December 21, 2018, 81 countries required food fortification with one or more vitamins.[74] The most commonly fortified vitamin – as used in 62 countries – is folate; the most commonly fortified food is wheat flour, followed by maize flour and rice. From country to country, added folic acid amounts range from 0.4 to 5.1 µg/100 g, but the great majority are in a more narrow range of 1.5 to 2.5 µg/100 g.[74] Folate naturally found in food is susceptible to destruction from high heat cooking, especially in the presence of acidic foods and sauces. It is soluble in water, and so may be lost from foods boiled in water.[75] For foods that are normally consumed cooked, values in the table are for folate naturally occurring in cooked foods.

Plant sources[72]	Amount as Folate (µg / 100g)
Peanuts	246
Sunflower seed kernels	238
Lentils	181
Chickpeas	172
Asparagus	149
Spinach	146
Lettuce	136
Peanuts (oil-roasted)	125
Soybeans	111
Broccoli	108

Walnuts	98
Plant sources[72]	**Amount as Folate (µg / 100g)**
Peanut butter	92
Hazelnuts	88
Avocados	81
Beets	80
Kale	65
Bread (not fortified)	65
Cabbage	46
Red bell peppers	46
Cauliflower	44
Tofu	29
Potatoes	28

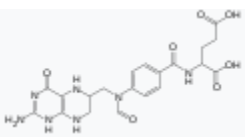
Animal sources[72]	**Amount as Folate (µg / 100g)**

Chicken liver	578
Calf liver	331
Cheese	20-60
Chicken eggs	44
Salmon	35
Chicken	12
Beef	12
Pork	8
Yogurt	8-11
Milk, whole	5
Butter, salted	3

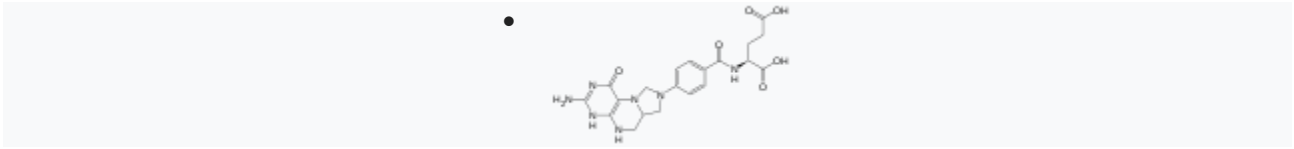
Biological roles[edit]

The formation of tetrahydrofolate (FH_4, also THF) begins when folic acid (F) is reduced to dihydrofolate (DHF) (FH_2), which is then reduced to THF. Dihydrofolate reductasecatalyses the last step.[76] Vitamin B_3 in the form of NADPH is a cofactor for both steps. Thus, hydride is transferred from NADPH to the C6 position of the pteridine ring.[77]

C1-derivatives of folate[edit]



10-Formyl-THF

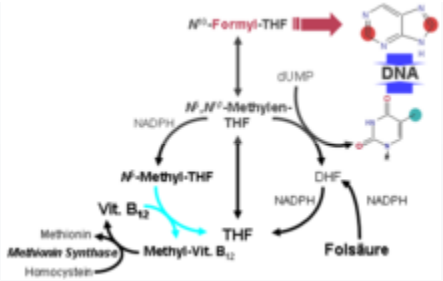


5,10-methylenetetrahydrofolic acid

Folate is a carrier of C1 groups (methyl, methylene, formyl). Methylene-THF (CH_2FH_4) is formed from THF by the addition of a methylene bridge from one of three carbon donors: formate, serine, or glycine. For example, serine hydroxymethyltransferase catalyzes the conversion of THF to CH_2-THF, extracting the C1 unit from L-serine giving glycine. This reaction provides the largest part of the one-carbon units available to the cell.[78] Methyl tetrahydrofolate (CH_3-THF, or methyl-THF) forms by reduction of methylene-THF by NADPH. Also, histidine can donate a single carbon to THF to form methenyl-THF. 10-Formyl-THF forms from two pathways. It results from oxidation of methylene-THF. It also forms from formate donating formyl group to THF.

DNA production[edit]

Folate derivatives participate in the biosynthesis of both purines and pyrimidines. Formyl folate is required for two of the steps in the biosynthesis of inosine monophosphate, the precursor to GMP and AMP. Methylenetetrahydrofolate donates the C1 center required for the biosynthesis of dTMP (2′-deoxythymidine-5′-phosphate) from dUMP (2′-deoxyuridine-5′-phosphate). The conversion is catalyzed by thymidylate synthase.

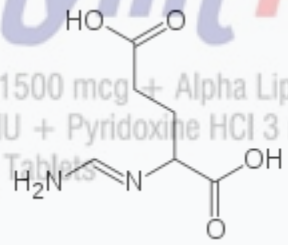


Metabolism of folic acid to recycle homocysteine into methionine

Amino acid processing[edit]

Methyl-THF converts vitamin B_{12} to methyl-B_{12} (methylcobalamin). Methyl-B_{12} converts homocysteine, in a reaction catalyzed by homocysteine methyltransferase, to methionine. A defect in homocysteine methyltransferase or a deficiency of B_{12} may lead to a so-called "methyl-trap" of THF, in which THF converts to methyl-THF, causing a deficiency in folate.[79] Thus, a deficiency in B_{12} can cause accumulation of methyl-THF, mimicking folate deficiency. Methionyl-tRNA formyltransferase catalyzes the conversion of L-methionyl-tRNA^{fMet} into *N*-formylmethionyl-tRNA^{fMet}.

Folate metabolism



Formiminoglutamic acid is an intermediate in the conversion of histidine to glutamic acid, catalyzed by THF.

Conversion to biologically active derivatives[edit]

All the biological functions of folic acid are performed by tetrahydrofolate and other derivatives. Their biological availability to the body depends upon dihydrofolate reductase action in the liver. This action is unusually slow in humans, being less than 2% of that in rats (and with an almost-5-fold variation in enzymatic activity), leading to the accumulation of unmetabolized folic acid.[80] It has been suggested this low activity limits the conversion of folic acid into its biologically active forms "when folic acid is consumed at levels higher than the Tolerable Upper Intake Level (1 mg/d for adults)."[80]

Drugs that interfere with folate reactions[edit]

A number of drugs interfere with the biosynthesis of folic acid and THF. Among them are the dihydrofolate reductase inhibitors such as trimethoprim, pyrimethamine, and methotrexate; the sulfonamides (competitive inhibitors of 4-aminobenzoic acid in the reactions of dihydropteroate synthetase). Valproic acid, one of the most commonly prescribed anticonvulsants that is also used to treat certain psychological conditions, is a known inhibitor of folic acid, and as such, has been shown to cause neural tube defects and cases of spina bifida and cognitive impairment in the newborn. Because of this considerable risk, those mothers who must continue to use valproic acid or its derivatives during pregnancy to control their condition (as opposed to stopping the drug or switching to another drug or to a lesser dose) should take folic acid supplements under the direction and guidance of their health care providers.

Food fortification[edit]

See also: Food fortification

Folic acid fortification is a process where folic acid is added to flour with the intention of promoting public health through increasing blood folate levels in the populace. In the U.S., food is fortified with folic acid, only one of the many naturally occurring forms of folate, and a substance contributing only a minor amount to the folates in natural foods.[66] After the discovery of the link between insufficient folic acid and neural tube defects, governments and health organizations worldwide made recommendations concerning folic acid *supplementation* for women intending to become pregnant. Because the neural tube closes in the first four weeks of gestation, often before many women even know they are pregnant, many countries in time decided to implement mandatory food fortification programs. A meta-analysis of global birth prevalence of spina bifida showed that when mandatory fortification was compared to countries with voluntary fortification or no fortification program, there was a 30% reduction in live births with spina bifida.[27] Folic acid is added to grain products in more than 80 countries,[10] and these fortified products make up a significant source of the population's folate intake.[81]Fortification is controversial, with issues having been raised concerning individual liberty,[66] as well as the health concerns described in the Toxicity section. In the U.S., there is concern that the federal government mandates fortification but does not provide monitoring of potential undesirable effects of fortification.[66] The Food Fortification Initiative lists all countries in the world that conduct fortification programs,[73] and within each country, what nutrients are added to which foods. As of December 21, 2018, 81 countries required food fortification with one or more vitamins.[74] The most commonly fortified vitamin – as used in 62 countries – is folate; the most commonly fortified food is wheat flour.[74]

Australia and New Zealand[edit]

Australia and New Zealand jointly agreed to wheat flour fortification through the Food Standards Australia New Zealand in 2007. The requirement was set at 135 µg of folate per 100 g of bread. Australia implemented the program in 2009.[82] New Zealand was also planning to fortify bread (excluding organic and unleavened varieties) starting in 2009, but then opted to wait until more research was done. The Association of Bakers and the Green Party had opposed mandatory fortification, describing it as "mass medication."[83][84]Food Safety Minister Kate Wilkinson reviewed the decision to fortify in July 2009, citing as reasons to oppose claims for links between over consumption of folate with increased risk of cancer.[85] In 2012 the delayed mandatory fortification program was revoked and replaced by a voluntary program, with the hope of achieving a 50% bread fortification target.[86]

Canada[edit]

According to a Canadian survey, 58% of women said they took a folic acid containing multivitamin or a folic acid supplement as early as three months before becoming pregnant. Women in higher income households and with more years of school education were more likely to use folic acid supplements before pregnancy, as were women with planned pregnancies and those over the age of 25. Canadian public health efforts focused on promoting awareness of the importance of folic acid supplementation for all women of childbearing age and decreasing socio-economic inequalities by providing practical folic acid support to vulnerable groups of women.[87] Folic acid food fortification became mandatory in 1998, with the fortification of 150 µg of folic acid per 100 grams of enriched flour and uncooked cereal grains.[88] The results of folic acid fortification on the rate of neural tube defects in Canada have been positive, showing a 46% reduction in prevalence of NTDs; the magnitude of reduction was proportional to the prefortification rate of NTDs, essentially removing geographical variations in rates of NTDs seen in Canada before fortification.[89]

United Kingdom[edit]

While the Food Standards Agency recommended folic acid fortification,[90][91][92] and wheat flour is fortified with iron,[93] folic acid fortification of wheat flour is allowed voluntarily rather than required. A 2018 review by authors based in the United Kingdom strongly recommended that mandatory fortification be reconsidered as a means of reducing the risk of neural tube defects.[10]

United States[edit]

In the United States many grain products are fortified with folic acid.

In 1996, the United States Food and Drug Administration (FDA) published regulations requiring the addition of folic acid to enriched breads, cereals, flours, corn meals, pastas, rice, and other grain products.[94][95] This ruling took effect on 1 January 1998, and was specifically targeted to reduce the risk of neural tube birth defects in newborns.[96] There were concerns expressed that the amount of folate added was insufficient.[97]

The fortification program was expected to raise a person's folic acid intake level by 70–130 µg/day;[98] however, an increase of almost double that amount was actually observed.[99] This could be from the fact that many foods are over-fortified by 160–175% over the required amount.[99] Much of the elder population take supplements that add 400 µg to their daily folic acid intake. This is a concern because 70–80% of the population have detectable levels of unmetabolized folic acid in their blood, a consequence of folic acid supplementation and fortification, and high intakes are thought to accelerate the growth of preneoplastic lesions that could lead to cancer.[100]

The U.S. National Center for Health Statistics conducts biannual National Health and Nutrition Examination Survey (NHANES) to assess the health and nutritional status of adults and children in the United States. Some results are reported as What We Eat In America. The 2013–2014 survey reported that for adults ages 20 years and older, men consumed on average of 249 µg/d folate from food plus 207/d µg of folic acid from consumption of fortified foods, for a combined total of 601 µg/d of dietary folate equivalents (DFEs; because each microgram of folic acid counts as 1.7 µg of food folate). For women, the values are 199, 153 and 459 µg/d, respectively. This means that fortification led to a bigger increase in folic acid intake than first projected, and that more than half the adults are consuming more than the RDA of 400 µg (as DFEs)> Even so, fewer than half of pregnant women are exceeding the pregnancy RDA of 600 µg/d.[101]

The Centers for Disease Control and Prevention in Atlanta, Georgia used data from 23 birth defect registries covering about half of United States births, and extrapolated their findings to the rest of the country. These data indicate that since the addition of folic acid in grain-based foods as mandated by the FDA, the rate of neural tube defects dropped by 25% in the United States.[102] Before folic acid fortification, about 4,100 pregnancies were affected by a neural tube defect each year in the United States. After fortification, this number declined to around 3,000.[103]

History[edit]

In the 1920s, scientists believed folate deficiency and anemia were the same condition.[104] In 1931, researcher Lucy Wills made a key observation that led to the identification of folate as the nutrient required to prevent anemia during pregnancy. Wills demonstrated that anemia could be reversed with brewer's yeast.[14][105] In the late 1930s, folate was identified as the corrective substance in brewer's yeast. It was first isolated via extraction from spinach leaves by Herschel K. Mitchell, Esmond E. Snell, and Roger J. Williams in 1941.[106] Bob Stokstad isolated the pure crystalline form in 1943, and was able to determine its chemical structure while working at the Lederle Laboratories of the American Cyanamid Company.[79] This historical research project, of obtaining folic acid in a pure crystalline form in 1945, was done by the team called the "folic acid boys," under the supervision and guidance of Director of Research Dr. Yellapragada Subbarow, at the Lederle Lab, Pearl River, NY.[107]

This research subsequently led to the synthesis of the antifolate aminopterin, the first-ever anticancer drug, the clinical efficacy was proven by Sidney Farber in 1948. In the 1950s and 1960s, scientists began to discover the biochemical mechanisms of action for folate.[104] In 1960, experts first linked folate deficiency to neural tube defects.[104] In the late 1990s, U.S. scientists realized, despite the availability of folate in foods and in supplements, there was still a challenge for people to meet their daily folate requirements, which is when the US implemented the folate fortification program.[104]

See also[edit]

- Levomefolic acid
- Pteridine: Substituted pteridines are intermediates in the biosynthesis of dihydrofolic acid in many microorganisms.

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