

Introduction

Pyridoxine is a water-soluble vitamin. Man and other primates depend on external sources to cover their vitamin B₆ requirements. Vitamin B₆ was discovered in the 1930s almost as a by-product of the studies on pellagra, a deficiency disease caused by the absence in the body of the vitamin niacin. Negligible amounts of vitamin B₆ can be synthesised by intestinal bacteria. There are three different natural forms (vitamers) of vitamin B₆, namely pyridoxine, pyridoxamine, and pyridoxal, all of which are normally present in foods. For human metabolism the active derivative of the vitamin, pyridoxal 5'-phosphate (PLP), is of major importance as the metabolically active coenzyme form.

Functions

Vitamin B₆ serves as a coenzyme of approximately 100 enzymes that catalyse essential chemical reactions in the human body. It plays an important role in protein, carbohydrate and lipid metabolism. Its major function is the production of serotonin from the amino acid tryptophan in the brain and other neurotransmitters, and so it has a role in the regulation of mental processes and mood. Furthermore, it is involved in the conversion of tryptophan to the vitamin niacin, the formation of haemoglobin and the growth of red blood cells, the absorption of vitamin B₁₂, the production of prostaglandines and hydrochloric acid in the gastrointestinal tract, the sodium-potassium balance, and in histamine metabolism. As part of the vitamin B-complex it may also be involved in the downregulation of the homocysteine blood level. Vitamin B₆ also plays a role in the improvement of the immune system.

Main functions in a nutshell:

- Nervous system (neurotransmitter synthesis)
- Red blood cell formation
- Niacin formation
- Homocysteine downregulation (preventing atherosclerosis)
- Immune system (antibody production)
- Steroid hormones (inhibition of the binding of steroid hormones)

Dietary sources

Vitamin B₆ is widely distributed in foods, mainly in bound forms. Pyridoxine is found especially in plants, whereas pyridoxal and pyridoxamine are principally found in animal tissue, mainly in the form of PLP. Excellent sources of pyridoxine are chicken and the liver of beef, pork and veal. Good sources include fish (salmon, tuna, sardines, halibut, herring), nuts (walnuts, peanuts), bread, corn and whole grain cereals. Generally, vegetables and fruits are rather poor sources of vitamin B₆, although there are products in these food classes which contain considerable amounts of pyridoxine, such as lentils, courgettes and bananas.

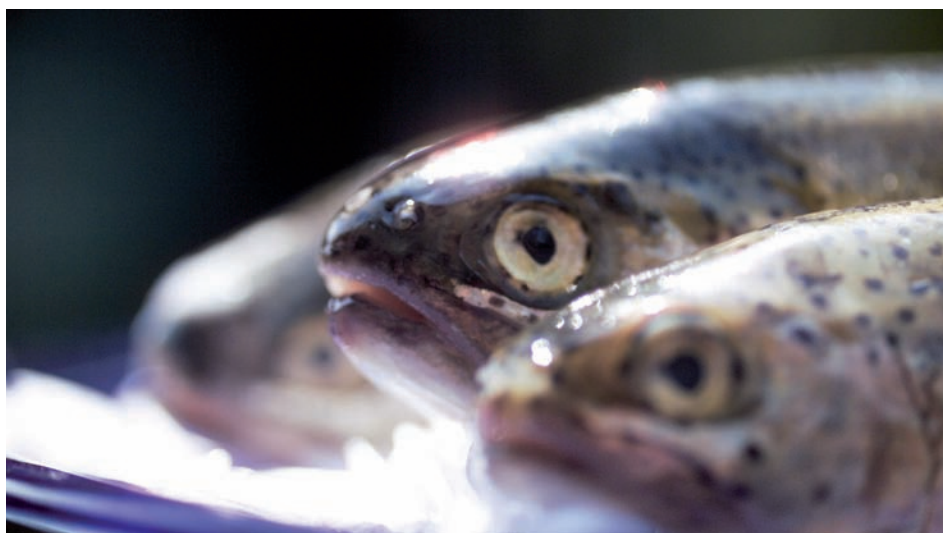
Vitamin B₆ content of foods

Food	Vitamin B ₆ (mg/100g)
Brewer's yeast	4.4
Salmon	0.98
Walnuts	0.87
Wheat germ	0.72
Pork liver	0.59
Lentils	0.57
Avocado	0.53
Chicken	0.5
Courgettes	0.46
Bananas	0.36

(Souci, Fachmann, Kraut)

Absorption and body stores

All three forms of vitamin B₆ (pyridoxine, pyridoxal and pyridoxamine) are readily absorbed in the small intestine by an energy dependent process. All three are converted to pyridoxal phosphate in the liver, a process which requires zinc and riboflavin. The bioavailability of plant-based foods varies considerably, ranging from 0% to 80%. Some plants contain pyridoxine glycosides that cannot be hydrolysed by intes-



tinal enzymes. Although these glycosides may be absorbed, they do not contribute to vitamin activity.

The storage capacity of water-soluble vitamins is generally low compared to that of fat-soluble ones. Small quantities of pyridoxine are widely distributed in body tissue, mainly as PLP in the liver and muscle. PLP is tightly bound to the proteins albumin and haemoglobin in plasma and red blood cells. Because the half-life of pyridoxine is 15-20 days and it is not significantly bound to plasma proteins, and the limited stores may be depleted within two to six weeks on a pyridoxine-free diet, a daily supply is required. Excess pyridoxine is excreted in the urine.



determination of urinary excretion of 4-pyridoxic acid (4-PA). The method of choice for quantification of both compounds is high performance liquid chromatography. Whole blood concentrations usually 35-110 nmol/L PLP. Concentrations of PLP have been found to correlate well with the pyridoxine status determined by indirect methods. Indirect methods measure the stimulated activity of pyridoxine dependent enzymes in erythrocytes by addition of PLP. This mainly determines the erythrocyte alanine aminotransferase activation coefficient (EAST-AC) or the erythrocyte aspartate aminotransferase activation coefficient. The coefficient of activity with stimulation to activity without stimulation indicates the pyridoxine status. For EAST-AC, values > 1.8 are considered to show deficiency, 1.7-1.8 to be marginal, and < 1.7 to be adequate.

For large-scale population surveys there is another method of assessing a pyridoxine deficiency state: the tryptophan load test.

Vitamin B₆ participates in the conversion of tryptophan to the vitamin niacin. A pyridoxine deficiency

blocks this process, producing more xanthurenic acid. If the administration of tryptophan leads to an increased excretion of xanthurenic acid, a pyridoxine deficiency can be diagnosed.

Typical serum level of pyridoxine = 15-37 nmol/L.

Stability

Pyridoxine is relatively stable to heat, but pyridoxal and pyridoxamine are not. Pasteurisation therefore causes milk to lose up to 20% of its vitamin B₆ content. Vitamin B₆ is decomposed by oxidation and ultraviolet light, and by an alkaline environment. Because of this light sensitivity, vitamin B₆ will disappear (50% within a few hours) from milk kept in glass bottles exposed to the sun or bright daylight. Alkalis, such as baking soda, also destroy pyridoxine. Freezing of vegetables causes a reduction of up to 25%, while milling of cereals leads to wastes as high as 90%. Cooking losses of processed foods may range from a few percent to nearly half the vitamin B₆ originally present. Cooking and storage losses are greater with animal products.

Interactions

Positive interactions

Certain vitamins of the B-complex (niacin, riboflavin, biotin) may act synergistically with pyridoxine.

Negative interactions

Pyridoxine requires riboflavin, zinc and magnesium to fulfil its physiological function in humans. It has been claimed that women taking oral contraceptives may have an increased requirement for pyridoxine. There are more than 40 drugs that interfere with vitamin B₆, potentially causing decreased availability and poor vitamin B₆ status. Supplementation with the affected nutrient may be necessary. Principal antagonists include:

- Phenytoin (an antiepileptic drug)
- Theophylline (a drug for respiratory diseases)
- Phenobarbitone (a barbiturate mainly used for its antiepileptic properties)

Measurement

There are several direct and indirect methods that can be used for assessing a person's vitamin B₆ status. Direct methods include determination of PLP in whole blood, and

- Desoxypridoxine, an effective antimetabolite
- Isoniazid (a tuberculostatic drug)
- Hydralazine (an antihypertensive)
- Cycloserine (an antibiotic)
- Penicillamine (used in treatment of Wilson's disease)

Vitamin B₆, for its part, reduces the therapeutic effect of levodopa – a naturally occurring amino acid used to treat Parkinson's disease – by accelerating its metabolism.

Deficiency

A deficiency of vitamin B₆ alone is uncommon, because it usually occurs in combination with a deficit in other B-complex vitamins, especially with riboflavin deficiency, because riboflavin is needed for the formation of the coenzyme PLP. A dietary deficiency state showing definable clinical deficiency symptoms is rare, although recent diet surveys revealed that a significant part of the following population groups have B₆ intakes below the RDA:

- pregnant and lactating women (additional demands)
- most women in general, especially those taking oral contraceptives
- the elderly (due to lower food intake)
- underweight people
- chronic alcoholics (heavy drinking may severely impair the ability of the liver to synthesise PLP, low intake)
- people with a high protein intake

A pyridoxine depleted diet, an antagonist-induced deficiency or certain genetic errors of amino acid metabolism may result in various symptoms, such as:

- hypochromic anaemia (abnormal decrease in the haemoglobin content of erythrocytes)
- nervous system dysfunction (decrease in the metabolism of

- glutamate in the brain)
- impairment of the immune system (decrease in circulating lymphocytes)
- epileptiform convulsions in infants
- skin lesions, e.g. seborrheic dermatitis (similar to pellagra)
- abdominal distress, nausea, vomiting
- kidney stones
- electroencephalographic abnormalities
- peripheral neuritis, nerve degeneration
- poor growth
- depression, insomnia, lethargy, decreased alertness
- elevated homocysteine



Disease prevention and therapeutic use

Sideroblastic anaemias and pyridoxine-dependent abnormalities of metabolism

Pyridoxine is an approved treatment for sideroblastic anaemias and pyridoxine-dependent abnormalities of metabolism. In such cases, therapeutic doses of approximately 40-200 mg vitamin B₆ per day are indicated.

PMS (premenstrual syndrome)

Some studies suggest that vitamin B₆ doses of up to 100 mg/day may be of value for relieving the symptom complex of premenstrual syndrome. However, final conclusions are still limited and more research is needed.

Current recommendations in the USA

RDA*

Infants	< 6 months	0.1 mg (Adequate Intake, AI)
Infants	7-12 months	0.3mg (AI)
Children	1-3 years	0.5mg
Children	4-8 years	0.6mg
Children	9-13 years	1mg
Males	14-50 years	1.3mg
Females	14-18 years	1.2mg
Females	19-50 years	1.3mg
Males	> 51 years	1.7mg
Females	> 51 years	1.7mg
Pregnancy		1.9mg
Lactation		2mg

*The Dietary Reference Intakes (DRIs) are actually a set of four reference values: Estimated Average Requirements (EAR), Recommended Dietary Allowances (RDA), Adequate Intakes (AI), and Tolerable Upper Intake Levels, (UL) that have replaced the 1989 Recommended Dietary

Allowances (RDAs). The RDA was established as a nutritional norm for planning and assessing dietary intake, and represents intake levels of essential nutrients considered to meet adequately the known needs of practically all healthy people

Hyperemesis gravidarum

Pyridoxine is often administered in doses of up to 40 mg/day in the treatment of nausea and vomiting during pregnancy (hyperemesis gravidarum). However, as “morning sickness” improves even without treatment it is difficult to prove the therapeutic benefit.

Depression

Pyridoxine is also used to assist in the relief of depression (especially in women taking oral contraceptives). However, clinical trials have not yet provided evidence for its efficacy.

Carpal tunnel syndrome

Pyridoxine has also been claimed to alleviate the symptoms of carpal tunnel syndrome. Some studies report benefits while others do not.

Hyperhomocystinaemia / cardiovascular disease

Elevated homocysteine levels in the blood are considered a risk factor for atherosclerotic disease. Several studies have shown that vitamin B₆, vitamin B₁₂ and folic acid can lower critical homocysteine levels.

Immune function

The elderly are a group that often suffers from impaired immune function. Adequate B₆ intake is thus important, and it has been shown that the amount of vitamin B₆ required to improve the immune system is higher (2.4 mg/day for men; 1.9 mg/day for women) than the current RDA.

Asthma

Asthma patients taking vitamin B₆ supplements may have fewer and less severe attacks of wheezing, coughing and breathing difficulties.

Diabetes

Research has also suggested that certain patients with diabetes mellitus or gestational diabetes experience an improvement in glucose tolerance when given vitamin B₆ supplements.

Kidney stones

Glyoxylate can be oxidised to oxalic acid that may lead to calcium oxalate kidney stones. Pyridoxal phosphate is a cofactor for the degradation of glyoxylate to glycine. There is some evidence that high doses of vitamin B₆ (> 150 mg/day) may be useful for normalising the oxalic acid metabolism to reduce the formation of kidney stones. However, the relationship between B₆ and kidney stones must be studied further before any definite conclusions can be drawn.

Chinese restaurant syndrome

People who are sensitive to glutamate, which is often used for the preparation of Asiatic dishes, can react with headache, tachycardia (accelerated heart rate), and nausea. 50 to 100 mg of pyridoxine can be of therapeutic value.

Autism

High dose therapy with pyridoxine improves the status of autistics in about 30% of cases.

Recommended Dietary Allowance (RDA)

The recommended daily intake of vitamin B₆ varies according to age, sex, risk group (see ‘Groups at risk’) and criteria applied. The vitamin B₆ requirement is increased when high-protein diets are consumed, since protein metabolism can only function properly with the assistance of pyridoxine. Pregnant and lactating women need an additional 0.7 mg to compensate for increased demands made by the foetus or baby.

Safety

Vitamin B₆ in all its forms is well tolerated, but large excesses are toxic. Daily oral doses of pyridoxine of up to 50 times the RDA (ca. 100 mg) for periods of 3-4 years have been administered without adverse effects. Daily doses of 500 mg and more may cause sensory neuropathy after several years of ingestion, whereas the intake of amounts in excess of 1 gram daily may lead to reversible sensory neuropathy within a few months. Sensory neuropathy has been selected as a critical endpoint on which to base a tolerable upper intake level (UL) of 100 mg/day for adults, although supplements somewhat higher than this may be safe for most individuals. Fortunately these side-effects are largely reversible upon cessation of vitamin B₆ intake. Today, prolonged intake of doses exceeding 500 mg a day is considered to carry the risk of adverse side-effects.

Supplements and food fortification

The most commonly available form of vitamin B₆ is pyridoxine hydrochloride, which is used in food fortification, nutritional supplements and therapeutic products such as capsules, tablets and ampoules. Vitamins, mostly of the B-complex, are widely used in the enrichment of cereals. Dietetic foods such as infant formulas and slimming diets are often fortified with vitamins, including pyridoxine.

History

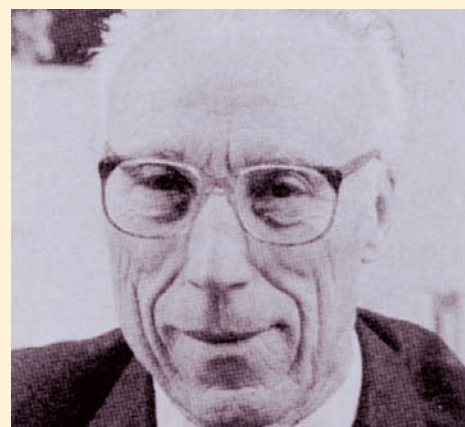
- 1926** Goldberger and coworkers feed rats a diet deficient in what is considered to be the pellagra-preventive factor; these animals develop skin lesions.
- 1934** György first identifies the factor as vitamin B₆ or adermin, a substance capable of curing a characteristic skin disease in rats (dermatitis acrodynia). The factor is then called the rat anti-acrodynia factor, deficiency of which causes so-called “rat-pellagra”
- 1935** Birch and György succeed in differentiating riboflavin and vitamin B₆ from the specific pellagra preventive factor (P-P) of Goldberger and his associates.
- 1938** Lepkovsky is the first to report the isolation of pure crystalline vitamin B₆. Independently, but slightly later, several other groups of researchers also report the isolation of crystallised vitamin B₆ from rice polishings (Keresztesy and Stevens; György; Kuhn and Wendt; Ichiba and Michi).
- 1939** Harris and Folkers determine the structure of pyridoxine and succeed in synthesising the vitamin. György proposes the name pyridoxine.
- 1945** Snell demonstrates that two other natural forms of the vitamin exist, namely pyridoxal and pyridoxamine.
- 1957** Snyderman determines the levels of vitamin B₆ required by humans.



Joseph Goldberger



Paul György



Esmond Emerson Snell