

Nicotinamide (niacin)

Introduction

Niacin (also known as vitamin B3) is one of the water-soluble B vitamins. Niacin is the generic name for nicotinic acid (pyridine-3-carboxylic acid), nicotinamide (niacinamide or pyridine-3-carboxamide), and related derivatives, such as nicotinamide riboside. Niacin is naturally present in many foods, added to some food products, and available as a dietary supplement.

All tissues in the body convert absorbed niacin into its main metabolically active form, the coenzyme nicotinamide adenine dinucleotide (NAD). More than 400 enzymes require NAD to catalyze reactions in the body, which is more than for any other vitamin-derived coenzyme. NAD is also converted into another active form, the coenzyme nicotinamide adenine dinucleotide phosphate (NADP), in all tissues except skeletal muscle.

NAD and NADP are required in most metabolic redox processes in cells where substrates are oxidized or reduced. NAD is primarily involved in catabolic reactions that transfer the potential energy in carbohydrates, fats, and proteins to adenosine triphosphate (ATP), the cell's primary energy currency. NAD is also required for enzymes involved in critical cellular functions, such as the maintenance of genome integrity, control of gene expression, and cellular communication]. NADP, in contrast, enables anabolic reactions, such as the synthesis of cholesterol and fatty acids, and plays a critical role in maintaining cellular antioxidant function.

Most dietary niacin is in the form of nicotinic acid and nicotinamide, but some foods contain small amounts of NAD and NADP. The body also converts some tryptophan, an amino acid in protein, to NAD, so tryptophan is considered a dietary source of niacin.

When NAD and NADP are consumed in foods, they are converted to nicotinamide in the gut and then absorbed. Ingested niacin is absorbed primarily in the small intestine, but some is absorbed in the stomach.

Even when taken in very high doses of 3–4 g, niacin is almost completely absorbed. Once absorbed, physiologic amounts of niacin are metabolized to NAD. Some excess niacin is taken up by red blood cells to form a circulating reserve pool. The liver methylates any remaining excess to N1-methyl-nicotinamide, N1-methyl-2-pyridone-5-carboxamide, and other pyridone oxidation products, which are then excreted in the urine. Unmetabolized nicotinic acid and nicotinamide might be present in the urine as well when niacin intakes are very high.

Levels of niacin in the blood are not reliable indicators of niacin status. The most sensitive and reliable measure of niacin status is the urinary excretion of its two major methylated metabolites, N1-methyl-nicotinamide and N1-methyl-2-pyridone-5-carboxamide. Excretion rates in adults of more than 17.5 micromol/day of these two metabolites reflect adequate niacin status, while excretion rates between 5.8 and 17.5 micromol/day reflect low niacin status. An adult has deficient niacin status when urinary-excretion rates are less than 5.8 micromol/day. Indicators of inadequacy such as this and other biochemical signs (e.g., a 2-pyridone oxidation product of N1-methyl-nicotinamide below detection limits in plasma or low erythrocyte NAD concentrations) occur well before overt clinical signs of deficiency. Another measure of niacin status takes into account the fact that NAD levels decline as niacin status deteriorates, whereas NADP levels remain relatively constant. A “niacin number” (the ratio of NAD to NADP concentrations in whole blood x 100) below 130 suggests niacin deficiency. A “niacin index” (the ratio of erythrocyte NAD to NADP concentrations) below 1 suggests that an individual is at risk of developing niacin deficiency. No functional biochemical tests that reflect total body stores of niacin are available.

Recommended Intakes

Intake recommendations for niacin and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by an expert committee of the Food and Nutrition Board (FNB) at the National Academies of Sciences, Engineering, and Medicine. DRI is the general term for a set of reference values used for planning and assessing nutrient intakes of healthy people. These values, which vary by age and sex, include:

- Recommended Dietary Allowance (RDA): Average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals; often used to plan nutritionally adequate diets for individuals.
- Adequate Intake (AI): Intake at this level is assumed to ensure nutritional adequacy; established when evidence is insufficient to develop an RDA.
- Estimated Average Requirement (EAR): Average daily level of intake estimated to meet the requirements of 50% of healthy individuals; usually used to assess the nutrient intakes of groups of people and to plan nutritionally adequate diets for them; can also be used to assess the nutrient intakes of individuals.
- Tolerable Upper Intake Level (UL): Maximum daily intake unlikely to cause adverse health effects.

Table 1 lists the current RDAs for niacin as mg of niacin equivalents (NE). The FNB defines 1 NE as 1 mg niacin or 60 mg of the amino acid tryptophan (which the body can convert to niacin). Niacin RDAs for adults are based on niacin metabolite excretion data. For children and adolescents, niacin RDAs are extrapolated from adult values on the basis of body weight. The AI for infants from birth to 6 months is for niacin alone, as young infants use almost all the protein they consume for growth and development; it is equivalent to the mean intake of niacin in

healthy, breastfed infants. For infants aged 7-12 months, the AI for niacin is in mg NE and is based on amounts consumed from breast milk and solid foods.

Sources of Niacin

Food

Niacin is present in a wide variety of foods. Many animal-based foods—including poultry, beef, and fish—provide about 5-10 mg niacin per serving, primarily in the highly bioavailable forms of NAD and NADP. Plant-based foods, such as nuts, legumes, and grains, provide about 2-5 mg niacin per serving, mainly as nicotinic acid. In some grain products, however, naturally present niacin is largely bound to polysaccharides and glycopeptides that make it only about 30% bioavailable. Many breads, cereals, and infant formulas in the United States and many other countries contain added niacin. Niacin that is added to enriched and fortified foods is in its free form and therefore highly bioavailable.

Tryptophan is another food source of niacin because this amino acid—when present in amounts beyond that required for protein synthesis—can be converted to NAD, mainly in the liver. The most commonly used estimate of efficiency for tryptophan conversion to NAD is 1:60 (i.e., 1 mg niacin [NAD] from 60 mg tryptophan). Turkey is an example of a food high in tryptophan; a 3-oz portion of turkey breast meat provides about 180 mg tryptophan, which could be equivalent to 3 mg niacin. However, the efficiency of the conversion of tryptophan to NAD varies considerably in different people.

Dietary supplements

Niacin is available in multivitamin-mineral products, in supplements containing other B-complex vitamins, and in supplements containing niacin only. Nicotinic acid and nicotinamide are the two most common forms of niacin in supplements. Some niacin-only supplements contain 500 mg or more per serving, which is much higher than the RDA for this nutrient.

Nicotinic acid in supplemental amounts beyond nutritional needs can cause skin flushing, so some formulations are manufactured and labeled as prolonged, sustained, extended, or timed release to minimize this unpleasant side effect. Nicotinamide does not produce skin flushing because of its slightly different chemical structure. Niacin supplements are also available in the form of inositol hexanicotinate, and these supplements are frequently labeled as being “flush free” because they do not cause flushing. The absorption of niacin from inositol hexanicotinate varies widely but on average is 30% lower than from nicotinic acid or nicotinamide, which are almost completely absorbed. A niacin-like compound, nicotinamide riboside, is also available as a dietary supplement, but it is not marketed or labelled as a source of niacin.

Niacin Intakes and Status

Most people in the United States consume more than the RDA for niacin. An analysis of data from the 2015–2016 National Health and Nutrition Examination Survey (NHANES) found that the average daily niacin intake from foods and beverages was 21.4 mg for ages 2–19. In adults, the average daily niacin intake from foods and beverages was 31.4 mg in men and 21.3 mg in women. An analysis of data from the 2009-2012 NHANES found that only 1% of adults had intakes of niacin from foods and beverages below the EAR. Among all racial and ethnic groups, Hispanics had the greatest prevalence, 1.3%, of niacin intakes below the EAR.

According to self-reported data from the 2013-2014 NHANES, 21% of all individuals aged 2 and older took a dietary supplement containing niacin. The proportion of users increased with age from 8% of those aged 12-19 years to 39% of men and 40% of women aged 60 and older. Supplement use doubled or tripled total niacin intakes compared with intakes from diet alone. According to data from the 2003-2006 NHANES, 10% of all individuals aged 2 and older who took dietary supplements had total niacin intakes that reached or exceeded the UL.

Niacin Deficiency

Severe niacin deficiency leads to pellagra, a disease characterized by a pigmented rash or brown discoloration on skin exposed to sunlight; the skin also develops a roughened, sunburned-like appearance. In addition, pellagra can cause a bright red tongue and changes in the digestive tract that lead to vomiting, constipation, or diarrhea. The neurological symptoms of pellagra can include depression; apathy; headache; fatigue; loss of memory that can progress to aggressive, paranoid, and suicidal behaviors; and auditory and visual hallucinations. As pellagra progresses, anorexia develops, and the affected individual eventually dies.

Pellagra is uncommon in industrialized populations and is mostly limited to people living in poverty, such as refugees and displaced people who eat very limited diets low in niacin and protein. Pellagra was not uncommon in the early 20th century among individuals living in poverty in the southern United States and parts of Europe whose limited diets consisted mainly of corn. The World Health Organization recommends treating pellagra with 300 mg/day nicotinamide in divided doses for 3-4 weeks along with a B-complex or yeast product to treat likely deficiencies in other B vitamins.

Although frank niacin deficiencies leading to pellagra are very rare in the United States, some individuals have marginal or low niacin status.

Groups at Risk of Niacin Inadequacy

Niacin inadequacy usually arises from insufficient intakes of foods containing niacin and tryptophan. It can also be caused by factors that reduce the conversion of tryptophan to niacin, such as low intakes of other nutrients. The following groups are among those most likely to have inadequate niacin status.

People with undernutrition

People who are undernourished because they live in poverty or have anorexia, alcohol use disorder, AIDS, inflammatory bowel disease, or liver cirrhosis often have inadequate intakes of niacin and other nutrients.

People with inadequate riboflavin, pyridoxine, and/or iron intakes

People who do not consume enough riboflavin (vitamin B2), pyridoxine (vitamin B6), or iron convert less tryptophan to niacin because enzymes in the metabolic pathway for this conversion depend on these nutrients to function.

People with Hartnup disease

Hartnup disease is a rare genetic disorder involving the renal, intestinal, and cellular transport processes for several amino acids, including tryptophan. The disease interferes with the absorption of tryptophan in the small intestine and increases its loss in the urine via the kidneys. As a result, the body has less available tryptophan to convert to niacin.

People with carcinoid syndrome

Carcinoid syndrome is caused by slow-growing tumors in the gastrointestinal tract that release serotonin and other substances. It is characterized by facial flushing, diarrhea, and other symptoms. In those with carcinoid syndrome, tryptophan is preferentially oxidized to serotonin and not metabolized to niacin. As a result, the body has less available tryptophan to convert to niacin.

Niacin and Health

Cardiovascular disease

Very high doses of nicotinic acid—more than 100 times the RDA—taken for months or years are effective treatments for dyslipidemias. Nicotinamide does not have this effect because, unlike nicotinic acid, it does not bind to the receptors that mediate nicotinic acid's effects on lipid profiles. Studies conducted since the late 1950s show that these doses can increase high-density lipoprotein (HDL; “good”) cholesterol levels by 10-30% and reduce low-density lipoprotein (LDL; “bad”) cholesterol levels by 10-25%, triglyceride levels by 20-50%, and lipoprotein(a) levels by 10-30%. Together, these changes in lipid parameters might be expected to reduce the risk of first-time or subsequent cardiac events, such as heart attacks and strokes, in adults with atherosclerotic cardiovascular disease. However, despite dozens of published clinical trials, experts do not agree on the value of nicotinic acid to treat cardiovascular disease, especially given its side effects, safety concerns, and poor patient compliance.

In one large clinical trial from the 1970s, 8,341 participants aged 30 to 64 years who had had one or more heart attacks were randomized to take one of five lipid-lowering medications, including 3,000 mg/day nicotinic acid, or a placebo for an average of 6.2 years. Those taking nicotinic acid

lowered their serum cholesterol levels by an average of 9.9% and triglyceride levels by 26.1% over 5 years of treatment. During 5 to 8.5 years of treatment, these participants had significantly fewer nonfatal myocardial infarctions but more cardiac arrhythmias than those in the placebo group. Their overall rates of mortality and cause-specific mortality, including from coronary heart disease, did not decline. But 9 years after the study ended, participants who had taken the nicotinic acid experienced significantly fewer (11%) deaths from all causes than those who had taken the placebo.

In the largest international, multicenter, clinical trial of nicotinic acid to date, 25,673 adults aged 50-80 years (83% men) with cardiovascular disease who were taking a statin were randomized to take 2 g/day extended-release nicotinic acid with a medication to reduce nicotinic acid's flushing effect and therefore improve treatment compliance or a matching placebo for a median of 4 years. The nicotinic acid group had a mean reduction in LDL cholesterol (of 10 mg/dl) and triglycerides (of 33 mg/dl) and an increase in HDL cholesterol (of 6 mg/dl), but this group had no significant reduction in rates of major vascular events compared with the placebo (statin-only) group. Furthermore, the nicotinic acid group had a significantly greater risk of diabetes, gastrointestinal dyspepsia, diarrhea, ulceration, bleeding events in the gut and brain, and skin rashes and ulcerations. An earlier randomized clinical trial of 3,414 patients with established cardiovascular disease was stopped after 3 years when the researchers found that patients taking niacin (1,500-2,000 mg/day extended release) in addition to their cholesterol-reduction medications did not have fewer cardiovascular events than those taking medication alone, even though the niacin reduced triglyceride and LDL-cholesterol levels further and raised HDL cholesterol levels further. The results also showed that patients taking niacin had an increased risk of ischemic stroke.

The authors of two 2017 systematic reviews examining the clinical trial data concluded that nicotinic acid therapy provides little if any protection from atherosclerotic heart disease, even though the therapy raises HDL cholesterol levels and lowers total cholesterol, LDL cholesterol, and triglyceride levels. One of these reviews examined 23 randomized controlled trials of moderate to high quality in 39,195 participants aged 33-71 years (average 65 years; majority were male). Some had experienced a heart attack, and most were taking a statin. The doses used and treatment duration in these studies varied widely; the median dose of nicotinic acid was 2 g/day (range 0.5 to 4 g/day) for a median of 11.5 months (range 6 months to 6 years). Overall, use of nicotinic acid did not reduce overall mortality or cardiovascular mortality rates or the number of fatal or nonfatal myocardial infarctions or strokes. Eighteen percent of participants taking nicotinic acid discontinued treatment because of side effects. The second review examined 13 randomized controlled trials with 35,206 participants with, or at risk of, atherosclerotic cardiovascular disease. Overall, the addition of nicotinic acid supplementation (dose range not specified) to statin therapy taken for a mean of 33 months (with a broad range of 6 to 60 months) did not lead to significant reductions in rates of all-cause or cardiovascular mortality, myocardial infarction, or stroke. Nicotinic acid treatment was associated with a

significantly higher risk of gastrointestinal and musculoskeletal adverse events. In addition, four of the studies that examined diabetes as an outcome found that the patients taking niacin had a significantly higher risk of developing the disease.

A 2018 review of three randomized controlled trials with 29,195 patients found that all-cause mortality increased by 10% more in those who took 1 to 3 g/day extended release nicotinic acid in addition to a statin medication than patients taking the statin alone.

In their guidelines for lowering blood cholesterol levels, the American College of Cardiology and the American Heart Association advise that nonstatin therapies, compared with or in addition to statin therapy, do not provide atherosclerotic cardiovascular disease risk-reduction benefits that outweigh the potential harms of their adverse effects. When discussing the use of nicotinic acid supplements to reduce the risk of hyperlipidemia (for example, in patients unable to tolerate statin medications), the two professional societies recommend that patients take 500 mg/day extended-release nicotinic acid supplements and increase the dose to a maximum of 2,000 mg/day over 4 to 8 weeks or take 100 mg immediate-release nicotinic acid three times a day and increase the dose to 3,000 mg/day divided into two or three doses. (Their joint statement about monitoring supplement users who take niacin to reduce hyperlipidemia risk for adverse effects is described in the Health Risks from Excessive Niacin section below.) In their 2018 report, these two professional societies stated that although niacin may be useful in some cases of severe hypertriglyceridemia, it has only mild LDL-lowering effects. The societies therefore do not recommend using it as an add-on drug to statin therapy.

Overall, the evidence indicates that nicotinic acid supplementation improves blood lipid profiles but has no significant effects on risk of cardiovascular events. Although nicotinic acid is a nutrient, if very high doses (thousands of mg) are taken to treat hyperlipidemias, the supplement is being used as a drug. Such doses should only be taken with medical approval and supervision.

Health Risks from Excessive Niacin

No adverse effects have been reported from the consumption of naturally occurring niacin in foods. However, high intakes of both nicotinic acid and nicotinamide taken as a dietary supplement or medication can cause adverse effects, although their toxicity profiles are not the same.

Thirty to 50 mg nicotinic acid or more typically causes flushing; the skin on the patient's face, arms, and chest turns a reddish color because of vasodilation of small subcutaneous blood vessels. The flushing is accompanied by burning, tingling, and itching sensations. These signs and symptoms are typically transient and can occur within 30 minutes of intake or over days or weeks with repeated dosing; they are considered an unpleasant, rather than a toxic, side effect. However, the flushing can be accompanied by more serious signs and symptoms, such as

headache, rash, dizziness, and/or a decrease in blood pressure. Supplement users can reduce the flushing effects by taking nicotinic acid supplements with food, slowly increasing the dose over time, or simply waiting for the body to develop a natural tolerance.

When taken in pharmacologic doses of 1,000 to 3,000 mg/day, nicotinic acid can also cause more serious adverse effects. Many of these effects have occurred in patients taking high-dose nicotinic acid supplements to treat hyperlipidemias. These adverse effects can include hypotension severe enough to increase the risk of falls; fatigue; impaired glucose tolerance and insulin resistance; gastrointestinal effects, such as nausea, heartburn, and abdominal pain; and ocular effects, such as blurred or impaired vision and macular edema (a buildup of fluid at the center of the retina). High doses of nicotinic acid taken over months or years can also be hepatotoxic; effects can include increased levels of liver enzymes; hepatic dysfunction resulting in fatigue, nausea, and anorexia; hepatitis; and acute liver failure. Hepatotoxicity is more likely to occur with the use of extended-release forms of nicotinic acid.

To minimize the risk of adverse effects from nicotinic acid supplementation or to identify them before they become serious, the American College of Cardiology and the American Heart Association recommend measuring hepatic transaminase, fasting blood glucose or hemoglobin A1C, and uric acid levels in all supplement users before they start therapy, while the dose is being increased to a maintenance level, and every 6 months thereafter. The societies also recommend that patients not use nicotinic acid supplements or stop using them if their hepatic transaminase levels are more than two or three times the upper limits of normal; if they develop persistent hyperglycemia, acute gout, unexplained abdominal pain, gastrointestinal symptoms, new-onset atrial fibrillation, or weight loss; or if they have persistent and severe skin reactions, such as flushing or rashes.

Nicotinamide does not cause skin flushing and has fewer adverse effects than nicotinic acid, and these effects typically begin with much higher doses. Nausea, vomiting, and signs of liver toxicity can occur with nicotinamide intakes of 3,000 mg/day. In several small studies of participants undergoing hemodialysis, the most common adverse effects from 500-1,500 mg/day nicotinamide supplementation for several months were diarrhea and thrombocytopenia (low platelet count).

The FNB has established ULs for niacin that apply only to supplemental niacin for healthy infants, children, and adults. These ULs are based on the levels associated with skin flushing. The FNB acknowledges that although excess nicotinamide does not cause flushing, a UL for nicotinic acid based on flushing can prevent the potential adverse effects of nicotinamide. The UL, therefore, applies to both forms of supplemental niacin. However, the UL does not apply to individuals who are receiving supplemental niacin under medical supervision.

* Breast milk, formula, and food should be the only sources of niacin for infants.

Interactions with Medications

Niacin can interact with certain medications, and several types of medications might adversely affect niacin levels. A few examples are provided below. Individuals taking these and other medications on a regular basis should discuss their niacin status with their healthcare providers.

Isoniazid and pyrazinamide

Isoniazid and pyrazinamide (together in Rifater®), used to treat tuberculosis, are structural analogs of niacin and interrupt the production of niacin from tryptophan by competing with a vitamin B6-dependent enzyme required for this process. In addition, isoniazid can interfere with niacin's conversion to NAD. Although pellagra can occur in patients with tuberculosis treated with isoniazid, it can be prevented with increased intakes of niacin.

Antidiabetes medications

Large doses of nicotinic acid can raise blood glucose levels by causing or aggravating insulin resistance and increasing hepatic production of glucose. Some studies have found that nicotinic acid doses of 1.5 g/day or more are most likely to increase blood glucose levels in individuals with or without diabetes. People who take any antidiabetes medications should have their blood glucose levels monitored if they take high-dose nicotinic acid supplements concomitantly because they might require dose adjustments.