

Niacin^{1,2}

Metabolic Roles of Niacin

To fulfill its metabolic roles, niacin is initially incorporated into NAD⁺, which may be subsequently phosphorylated to form NAD(P)⁺, allowing enzyme selectivity (1). Both pools undergo 2-electron redox reactions and generate distinct redox couples in metabolism [NAD⁺/NAD(H), NAD(P)⁺/NAD(P)H]. In healthy cells, the NAD pool is maintained in a highly oxidized state (~90% NAD⁺) mainly by the action of the electron transport chain. Conversely, the NAD(P) pool is maintained in a highly reduced state mainly by the action of the pentose phosphate pathway. The result is that other enzymes linked to the NAD redox couple become strongly oxidizing, whereas those linked to the NAD(P) redox couple become strongly reducing. Remarkably, the NAD redox couple participates in ~400 reactions, predominantly in catabolic metabolism, as seen in glycolysis, the Krebs cycle, ethanol oxidation, etc. The NAD(P) redox couple participates in ~30 reactions, largely in anabolic metabolism, oxidant defense, and cytochrome P450 metabolism of endobiotics and xenobiotics. In addition to these, there are ~50 ADP-ribosyl transferases that use NAD⁺ as a substrate, leading to its degradation. Some of these enzymes add mono(ADP-ribose) units to G proteins or poly(ADP-ribose) chains to DNA repair enzymes to regulate their activity. The NAD-dependent deacetylases use ADP-ribose as an acceptor when deacetylating substrates, such as sirtuin proteins (involved in lifespan extension). Last, cADP-ribose and nicotinic acid ADP act to control intracellular calcium signaling, which is critical to nervous system function. Many of these roles will be reflected by the pathologies of niacin deficiency.

Niacin Deficiencies

Severe niacin deficiency presents in humans as the disease pellagra, which is characterized by the “4 Ds” (dermatitis, dementia, diarrhea, and death) (1). The dermatitis is unique in that it results from sun exposure, suggesting a defect in DNA repair. This defect is now thought to be caused by the impaired synthesis of poly(ADP-ribose) in response to UV radiation-induced DNA damage. Experimental models have demonstrated genomic instability in response to niacin deficiency (2). Although understudied, human epidemiology suggests that niacin deficiency enhances cancer risk. The dementia is also unique in that it presents like schizophrenia with hallucinations and delusions and responds within hours of niacin therapy. The symptoms are thought to be caused by impaired formation of cADP-ribose and nicotinic acid ADP, leading to altered neural calcium signaling. Pellagra has been largely eliminated in developed countries by niacin fortification of flour, but subclinical deficiencies of niacin persist, and their relation to disease susceptibility is understudied. Benefits of niacin supplementation have been observed in experimental

models of cancer, cardiovascular disease, skin health, mental health, and oxidant lung injury.

Food Sources

Epidemics of pellagra have presented in corn-eating populations for centuries (1). Corn has a low tryptophan content, and the niacin is tightly bound, requiring alkaline food processing to make it bioavailable. Food-processing traditions were lost when corn was discovered in the Americas and distributed to the rest of the world. Tryptophan can be converted to NAD at a low efficiency, leading to the concept of niacin equivalents (NEs),³ where the total food NE = mg niacin + 1/60 mg tryptophan. Grains (other than corn), nuts, and legumes are good sources of NEs because of a combination of nicotinic acid and tryptophan along with their high dietary intakes. Fish and meats are excellent sources of NEs because of high concentrations of tryptophan and nicotinamide [derived from NAD/NAD(P) during digestion]. Last, fortification of flour and cereal products occurs in most developed countries and adds 1–50 mg/200 kcal per serving. See [Table 1](#) for RDAs and tolerable upper intake concentrations for niacin (3).

Clinical Trials and Niacin

Pharmacological doses of nicotinic acid (1–3 g/d) reduce serum LDL cholesterol and increase serum HDL cholesterol, suggesting potential clinical benefits for the prevention and treatment of cardiovascular diseases (CVDs) (4). Niacin intake, both in monotherapy or in combinations with statins and/or bile acid sequestrants, was found to correct the HDL:LDL cholesterol ratio in patients with dyslipidemia and to greatly improve markers for atherosclerosis, such as carotid intima-media thickening and stenosis incidence. However, recent clinical trials that analyzed long-term niacin-supplemented statin therapy did not find reduced frequencies of cardiovascular incidents in patients with optimally statin-controlled blood lipids (4). They did find increased risks for serious adverse effects and new-onset diabetes, however. The disagreement between short-term biomarkers and long-term outcomes is likely caused in part by the high statin use in the long-term trial design, and niacin may still be an important therapy for patients with intolerance to statins or sequestrants who are struggling to reach their target HDL and LDL cholesterol values. The adverse effects observed in clinical trials included the typical skin flushing and itching but also more serious conditions, including gastrointestinal and musculoskeletal problems, heart failure, diabetic complications, and new-onset diabetes (4). These effects will be expanded upon in the following section.

³Abbreviations used: CVD, cardiovascular disease; FFA, free FA; NE, niacin equivalent; PARP, poly(ADP-ribose) polymerase; UL, upper limit.

TABLE 1 RDAs and tolerable upper intake concentrations for niacin¹

	Age, y						Pregnancy	Lactation
	0–0.5	>0.5–1	>1–3	>3–8	>8–13	>13		
RDA (or AI if an RDA is not established) (mg niacin for ages 0–0.5 y; mg NE for other age groups)	2 (AI)	4 (AI)	6	8	12	Women: 14; men: 16	18	17
UL (mg supplemental and fortified niacin)	ND	ND	10	15	20	30–35	30–35	30–35

¹Data from (3). AI, adequate intake; ND, not defined; NE, niacin equivalent; UL, upper limit.

Toxicity

The upper limit (UL) for niacin (35 mg/d in adults) is based on the excessive intake of nicotinic acid in the form of supplements and food fortification. It does not apply to natural-food niacin or tryptophan. The UL is based on the flushed reaction of the skin to a large dose of nicotinic acid. Nicotinic acid seems to be an unphysiological ligand for a receptor that normally responds to lactate and ketone bodies. The natural responses are thought to regulate FA release during fasting and control ketoacidosis. The niacin-induced skin flushing generates uncomfortable heat and itching and is a major reason for the failure of niacin compliance in CVD patients. However, it is not thought to present a long-term risk or lead to pathologies. The flushing diminishes with habituation and can be controlled with prostaglandin inhibitors. Of interest, pure niacin supplements are generally given in 500-mg doses, and B-50, B-75, and B-100 vitamin combinations all exceed the UL for niacin, which is a regulatory anomaly. The serious complications observed with niacin therapy in populations with CVD seem to be legitimate concerns within the context of that population (4). It is uncertain whether any of these risks are present in younger and/or healthier populations taking niacin supplements. This may be of interest in the future because niacin is being further promoted as an antiaging supplement (see following section). Some weak epidemiological links have been drawn between increasing niacin status in the United States during the recent decades of increasing obesity and type 2 diabetes.

Recent Research

On the clinical side, current research on niacin is focused on the adverse effects observed with pharmacological doses of nicotinic acid used in clinical trials. There are particular concerns about glycemic control in patients with dyslipidemia undergoing niacin therapy. Although niacin ameliorated dyslipidemia, increased fasting glycemia and the development of new-onset diabetes were observed in these randomized trials (4). This led to the recommendation of avoiding niacin therapies in patients with diabetes or metabolic syndrome. Current preclinical research in cells and laboratory animals is being directed at understanding the underlying cause of this phenomenon. Recent findings point toward roles of plasma free FAs (FFAs) and of the niacin-responsive G protein-coupled receptor GPR109a. Niacin-mediated stimulation of GPR109a increases local glucose uptake in intestinal cells in vivo and could thereby directly contribute to the observed loss of glycemic control. In addition, lipid overload in the form of high FFA concentrations in nonadipose

tissues has been linked to insulin resistance in muscles, but details of the mechanism are still controversial. Acute niacin administration results in a rapid reduction of plasma FFA concentrations and reverses insulin resistance induced by lipid overload. Unfortunately, a continuous high dose of niacin exposure, e.g., as expected from extended-release niacin formulations, induces tolerance against this FFA reduction, causing rebound lipid overload and associated insulin resistance. Intermittent niacin infusion prevented rebound lipid overload and preserved FFA reduction in animal models, indicating that the timing of niacin administration seems to be a critical factor. Adjusted timing of dosing regimens could thus potentially preserve insulin sensitivity in niacin therapies.

Current research is also being directed at the basic role of niacin in aging-related processes. The rationale of these studies is based on the intimate connection between dietary niacin intake and resulting NAD concentrations. The observation that NAD concentrations decline with age has led to the idea that lower NAD concentrations contribute to or cause human aging-associated pathologies by impairing NAD-dependent nuclear and mitochondrial functions. Cell biological experiments recently demonstrated that reduced intracellular NAD concentrations induced senescence at a cellular level (5). Mediators of such aging-related pathologies are NAD-dependent enzymes, e.g., poly(ADP-ribose) polymerase (PARP) and sirtuin proteins (5). PARP activity is required for DNA damage repair and normally provides ongoing protection of the genome. Reduced PARP activity, as it may occur when NAD concentrations are insufficient, causes an increase in reactive oxygen species and cancer incidence. Sirtuins mediate metabolic responses to nutrient availability and are required for the lifespan-extending effects of caloric restriction. Defects of sirtuin activity in laboratory animals were associated with premature aging and age-associated neurological disorders such as Parkinson, Huntington, and Alzheimer disease; amyotrophic lateral sclerosis; and muscular atrophy. On the other hand, supplementation with dietary precursors of NAD⁺ was able to counteract many age-associated diseases, including neurodegenerative diseases, in experimental settings. These results indicate that a therapeutic increase of NAD concentrations might prevent age-associated health decline and that dietary supplementation with niacin as the major nutritional NAD precursor could provide antiaging properties.

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