

Nicotinamide Riboside: A Supplement for Aging?

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Nicotinamide riboside is a form of vitamin B3 found in unprocessed plant and animal foods. It is relatively new to the supplement market, having made its debut in 2013.ⁱ Like the major forms of vitamin B3, nicotinamide and nicotinic acid, nicotinamide riboside is a precursor to nicotinamide adenine dinucleotide (NAD⁺) in the body.^{ii iii}

The Important Functions of NAD⁺

NAD⁺ is well known as a universal cofactor that plays a critical role in intracellular oxidative and reductive reactions, including the oxidative phosphorylation process that leads to production of ATP in mitochondria. In addition, NAD⁺ has recently been recognized as a regulator of enzymes such as poly(ADP-ribose) polymerases (PARPs), cyclic ADPribose synthetases, and sirtuins, which in turn govern an array of cell functions including gene expression, metabolism, DNA repair, apoptosis (programmed cell death), and aging.^{iv v vi} Importantly, while the structural backbone of NAD⁺ and its reduced form NADH is generally preserved in oxidative/reductive reactions, NAD⁺ is depleted in its role in these other cellular activities.^{vii} As a result, the prospect of promoting NAD⁺ production raises the hope of being able to prevent many age-related diseases and slow the aging process.^{viii ix x}

Calorie restriction and fasting have been noted to stimulate NAD⁺ synthesis in animal and in vitro studies. In fact, the increased availability of NAD⁺ that accompanies calorie restriction is thought to explain, at least in part, its association with extended lifespan. On the other hand, a high-fat diet appears to inhibit NAD⁺ synthesis. Aging itself is also associated with decreased NAD⁺ production, and decreased NAD⁺/NADH ratio has been correlated with mitochondrial dysfunction and age-related and metabolic disorders such as diabetes, obesity, non-alcoholic fatty liver disease, cardiovascular disease, neurodegenerative diseases, and some cancers.^{xi xii xiii xiv xv}

Evidence from Laboratory and Animal Studies

Laboratory research has shown that extracellular nicotinamide riboside can cross cell and mitochondrial membranes and increase intracellular NAD⁺ production.^{xvi xvii} Nicotinamide and nicotinic acid also increase production of NAD⁺ in some tissues,^{xviii} but nicotinamide riboside may have this effect in a broader array of tissues.^{xix} It may, for example, be the only form of vitamin B3 that can increase production of NAD⁺ in neurons.^{xx} In a comparison study in mice, oral nicotinamide riboside was found to be substantially more effective at raising hepatic NAD⁺ levels than nicotinamide, which was more effective than nicotinic acid.^{xxi}

In mice, administering oral nicotinamide riboside has been found to:

- increase cerebral NAD⁺ levels and improve cognitive function;^{xxii xxiii}
- prevent noise-induced nerve damage and hearing loss;^{xxiv}
- prevent high-fat diet-induced weight gain;^{xxv}
- prevent diabetes-induced weight gain, neuropathy, and fatty liver;^{xxvi}
- reverse age-related muscle loss and restore exercise tolerance;^{xxvii xxviii}
- improve mitochondrial function and number;^{xxix xxx}
- and, maintain the regenerative potential of stem cells and extend lifespan.^{xxxi}

Another B3 Derivative: Nicotinamide mononucleotide

The nicotinamide-derived compound, nicotinamide mononucleotide, is an intermediate in NAD⁺ synthesis. When administered to laboratory animals, nicotinamide mononucleotide displays similar benefits to nicotinamide riboside, and these benefits are attributed to elevation of intracellular NAD⁺ levels. Laboratory research suggests that nicotinamide mononucleotide does not cross cell membranes, but is instead converted to nicotinamide riboside, which is then taken up by cells and used to synthesize NAD⁺.^{xxxii}

Clinical Trials

In a pharmacokinetic study in healthy adults, single doses of 100 mg, 300 mg, and 1,000 mg of nicotinamide riboside were found to safely and dose-dependently elevate circulating levels of NAD⁺.^{xxxiii} A similar study confirmed the safety and efficacy of nicotinamide riboside at short-term doses up to 1,000 mg twice daily for increasing blood NAD⁺ levels in healthy volunteers.^{xxxiv}

In a placebo-controlled trial to observe pharmacokinetics and safety, 120 healthy subjects between 60 and 80 years old took 250 mg or 500 mg of nicotinamide riboside plus 50 mg or 100 mg, respectively, of the blueberry polyphenol pterostilbene daily for eight weeks. Pterostilbene is a naturally-occurring analog of another polyphenol (resveratrol); because it appears to activate sirtuins without increasing NAD⁺ levels, pterostilbene and nicotinamide riboside are postulated to have complementary may anti-aging effects.^{xxxv} At the end of the trial, serum NAD⁺ levels were found to have increased dose-dependently. No safety issues arose, although several people taking the higher dose had digestive symptoms that may have been related to the treatment.^{xxxvi}

A six-week double-blind placebo-controlled crossover trial in 30 healthy adults showed that nicotinamide riboside supplementation, at a dose of 500 mg twice daily, increased intracellular levels of NAD⁺ in circulating mononuclear cells. Interestingly, an average 9 mmHg drop in systolic blood pressure and a decrease in aortic stiffness, as determined by carotid pulse wave velocity, was noted in a subgroup of participants whose baseline blood pressures met the criteria for stage I hypertension.^{xxxvii}

A double-blind placebo-controlled trial enrolled 40 obese men with insulin resistance in order to assess the safety and effect of nicotinamide riboside on markers of metabolic health. The men received 1,000 mg nicotinamide riboside twice daily or placebo for 12 weeks. They underwent a series of tests at the beginning and end of the trial: blood tests measuring HgA1c and lipid, glucose, and insulin levels; whole body DXA and MRI scans to assess body composition and hepatic MR spectroscopy to determine hepatic fat content; and, tracers using labelled glucose and palmitate, indirect calorimetry, and hyperinsulinemic euglycemic clamp studies to measure insulin sensitivity. A 2% drop in hepatic lipid content was noted in those receiving the nicotinamide riboside, compared with a 0.2% drop in those receiving placebo; although this difference was not statistically significant, the authors deemed it an indicator of a potential benefit, warranting further studies with more participants over a longer time period. No other changes in markers of metabolic health were detected, and no serious adverse events were reported.^{xxxviii}

Closing Remarks

The notion of using nicotinamide riboside as a supplement to prevent age-related health problems has a firm basis in biochemical studies of aging and animal research. The somewhat disappointing findings from the only clinical trial to date in unhealthy men doesn't necessarily preclude the possibility of a benefit. Since no toxicity has been noted in animal or human studies, more research is certainly in order.

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