NAD+ and Liver Disease

Nicotinamide adenine dinucleotide (NAD+) is an essential cofactor and substrate for many cellular processes. This includes DNA damage repair, energy production and metabolism, intracellular calcium signaling, epigenetically modulated gene expression, and immunological functions.[1] NAD+ levels decrease with age and this decline has been associated with the development of metabolic concerns, such as non-alcoholic fatty liver disease (NAFLD).[2] If left unaddressed, NAFLD can progress to hepatic steatosis, hepatitis, liver cirrhosis, and ultimately, liver dysfunction. Individuals with NAFLD are also at increased risk for hepatocellular carcinoma relative to controls.[3] Pre-clinical studies suggest that low NAD+ levels, such as in the case of inhibition of de novo NAD+ synthesis, may lead to DNA damage, which increases the risk for hepatocellular carcinoma.[4]

The liver is the primary site of de novo biosynthesis of NAD+ from tryptophan, but intracellular NAD+ levels are largely maintained by the salvage pathway.[5] Whether created via de novo synthesis, the salvage pathway, or the Preiss-Handler pathway, our bodies' NAD+ stores decrease significantly over time. This age-related decline in NAD+ levels may lead to the liver becoming more susceptible to NAFLD and its complications. Replenishing the NAD+ stores by dietary and other means has been shown to mitigate these effects.

Research has not been able to demonstrate a significant elevation in plasma or tissue levels of NAD+ with oral supplementation of NAD+ or NADH. This may be the result of inefficient metabolism of NAD+ through the gut, which in turn results in poor bioavailability.[6] It may also be due to NADH not being oxidized to NAD+ in the body, not being efficiently absorbed in the gastrointestinal tract, and/or being converted to another product prior to being absorbed.[7-8]

Although the research is still in its infancy, researchers have been able to demonstrate an elevation in plasma NAD+ levels with oral supplementation using some NAD+ precursors, such as nicotinamide riboside (NR).[9-10] For example, although human randomized, controlled trials evaluating either NAD+ or its precursors in the treatment of liver disease are limited, pre-clinical studies demonstrate that NR may protect against ethanol-induced liver injury by replenishing NAD+[11] , may attenuate the development of liver fibrosis,[12] may protect against aging-induced NAFLD,[13] and may promote liver regeneration.[14]

While research regarding oral supplementation using NAD+ precursors appears promising, intravenous infusions of NAD+ are currently the only recognized, effective means of increasing systemic NAD+ levels.[1]

In a controlled trial that measured changes in urine and plasma levels of NAD+ and its metabolites during and after a six-hour 3 μmol/min NAD+ intravenous infusion, no change was noted in plasma NAD+ or its metabolites until after two hours,[15] demonstrating that NAD+ is rapidly and completely removed from the plasma for at least the first two hours when infused at an infusion rate of 3 μmol/min. At the six-hour mark, however, the continuous infusion resulted in a 398% increase in plasma NAD+ levels relative to baseline. NAD+ levels remained elevated at the 8-hour mark in the NAD+ group, but not in the saline-treated control group. The results of this study suggest that intravenous administration of NAD+ sufficiently raises plasma NAD+ levels and may be a highly efficacious means of preventing or addressing conditions associated with declines in NAD+, such as fatty liver disease and its complications.

No clinically significant adverse effects were noted during the six hour infusion of NAD+ or saline placebo.[15]

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