State of the Science: Clinical & Preclinical NAD+ & NR Research (COVID-19 & Long COVID)

"The elderly are at increased risk of mortality and morbidity of the COVID-19 infection, and pharmacological enhancement of NAD levels, which might have a beneficial effect on the biological processes of aging, might be particularly useful in this context." Radenkovic & Verdin (2020) [1]

Executive Summary

Nicotinamide adenine dinucleotide (NAD+) is an essential molecule found in all living cells, crucial for various cellular processes, including energy production, mitochondrial function, and cellular repair. As research into NAD+ continues to expand, its importance in supporting overall cellular health has become increasingly evident, particularly in the context of viral infections and immune health.

The immune system relies heavily on efficient cellular metabolism and robust energy production to fight off infections. Disruptions in NAD+ metabolism can compromise these processes, impairing the body's ability to mount an effective defense against pathogens which may lead to prolonged illness or increased disease severity [2–5]. This is relevant in the case of COVID-19, where the SARS-CoV-2 virus triggers widespread systemic inflammation and disrupts normal cellular metabolic pathways [6,7] .

Since the occurrence and severity of COVID-19 are disproportionately affected by age—and NAD+ levels naturally decline with age—maintaining adequate NAD+ levels becomes increasingly important to support immune health in the face of acute infection [8] .

Beyond the acute phase of infection, a significant subset of individuals experience prolonged and often impairing symptoms—a condition recognized as long COVID or post-acute sequelae of SARS-CoV-2 infection [9]. Symptoms include chronic fatigue, cognitive dysfunction, persistent inflammation, and shortness of breath, all of which are closely linked to mitochondrial dysfunction and immune system dysregulation [10,11]. However, it is important to recognize that long COVID is diagnosed subjectively—based on self-reported symptoms—rather than through objective clinical tests, which may contribute to greater variability in both the presence and severity of symptoms across patients.

Studies have revealed that COVID-19 patients exhibit disrupted NAD+ metabolism and altered SIRT1 activity, suggesting impaired immune regulation [12,13]. Additionally, clinical research in long COVID patients has demonstrated that oral supplementation with the NAD+ precursor, **nicotinamide riboside (NR)**, is safe and effectively increases NAD+ levels, and improves executive functioning, fatigue, sleep quality, and mood—addressing some of the most debilitating symptoms of long COVD [14].

Preclinical studies in animal models of COVID-19 and related coronaviruses have further underscored the potential benefits of NR supplementation. In mice, COVID-19 infection was shown to reduce NAD+ levels, increase NAD+ turnover, and cause dysfunction in endothelial cells. Notably, NR treatment mitigated viral replication, protected endothelial cell function, and helped maintain body weight during infection and recovery [15–18]. This promising data has paved the way for ongoing clinical trials exploring the therapeutic potential of NR in COVID-19, including its impact on long COVID.

In summary, NAD+ is essential for a healthy immune system and effective viral defense, with emerging evidence suggesting that boosting NAD+ levels—particularly through NR supplementation—may offer substantial benefits for individuals suffering from COVID-19, although its effects on long COVID remain uncertain. As research advances, NAD+ supplementation may emerge as a novel approach to improving outcomes in COVID-19 patients. However, additional clinical studies are needed to clarify the effects of NR in individuals with long COVID.

Clinical Studies

Publication	Intervention	Objective	Key Outcomes
Wu et al., 2025 [14] Effects of nicotinamide riboside on NAD+ levels, cognition, and symptom recovery in long-COVID: a	**Niagen NR**	To investigate the effects of Niagen NR supplementation on symptoms of Long COVID in non-hospitalized patients.	• Niagen NR significantly boosted NAD+ levels by up to 210% after 5 weeks of supplementation and remained significantly elevated by 110% by the end of the 20-week intervention.

randomized controlled trial CERP ChromaDex External Research Program			• While primary outcomes were not significant between Niagen NR and placebo, participants taking Niagen NR showed significant improvements from baseline to week 10 in executive functioning, fatigue severity, sleep quality, and symptoms of depression.
Valderrabano et al., 2024 [13] Dysregulated Nicotinamide Adenine Dinucleotide Metabolome in Patients Hospitalized with COVID-19	**None**	To investigate the relationship between NAD+ and its metabolites with disease severity in patients with COVID-19.	• Compared to healthy individuals, patients with COVID-19 had altered NAD+ metabolism, marked by slightly lower levels of NAD+ and increased NAD+ turnover—the process of NAD+ being produced, then consumed in the body.
Lonati et al., 2023 [12] Urinary Phenotyping of SARS-CoV-2 Infection Connects Clinical Diagnostics with Metabolomics and Uncovers Impaired NAD+ Pathway and SIRT1 Activation	**None**	To investigate how SARS-CoV-2 infection causes metabolic changes in the urine of COVID-19 patients, with a focus on NAD+ metabolism and SIRT1 activation.	• In patients with COVID-19, NAD+ metabolism was disrupted and SIRT1 activity was altered. Notably, these changes were more pronounced in patients with greater disease severity.
Altay et al., 2021 [19] Combined Metabolic Activators Accelerates Recovery in Mild-to-Moderate COVID-19 CERP ChromaDex External Research Program	**Niagen NR**	To investigate supplementation of combined metabolic activators (CMA), consisting of Niagen NR, L-carnitine tartrate, N-acetyl-L-cysteine (NAC), and L-serine for the treatment of patients with COVID-19.	• CMA, when administered alongside the standard of care, led to faster recovery in COVID-19 patients compared to placebo groups in both the phase-2 and phase-3 trials (6.6 vs 9.3 days and 5.7 vs. 9.2 days, respectively).

Preclinical Studies			
Publication	**Intervention**	**Objective**	**Key Outcomes**
Freeberg et al., 2023 [15] NAD+-Boosting Compounds Enhance Nitric Oxide Production and Prevent Oxidative Stress in Endothelial Cells Exposed to Plasma from Patients with COVID-19 CERP ChromaDex External Research Program	**Niagen NR**	To investigate the effects of exposing human aortic endothelial cells (HAECs) to plasma from COVID-19 patients and assess the protective effects of Niagen NR.	• HAECs exposed to plasma from COVID-19 patients experienced depleted NAD+ levels and endothelial dysfunction. • Niagen NR prevented the COVID-19 plasma-induced endothelial dysfunction by protecting against the depletion of nitric oxide levels and accumulation of reactive oxygen species in HAECs.
Izadpanah et al., 2023 [17] SARS-CoV-2 Infection Dysregulates NAD Metabolism	**Niagen NR**	To investigate the impact of COVID-19 infection on NAD+ metabolism and determine whether Niagen NR	• In the lungs of patients and mice with COVID-19, NAD+ turnover was increased as evidenced by the increased expression of enzymes involved in both NAD+ synthesis and

CERP ChromaDex External Research Program		treatment affects disease progression.	consumption, suggesting that COVID-19 infection increases NAD+ demand. • Hindering NAD+ production by inhibiting the NAMPT enzyme decreased mouse body weight, while concomitant Niagen NR treatment helped mitigate this effect. Additionally, Niagen NR-treated mice had higher body weights during the recovery phase.
Lee et al., 2022 [18] Activation of TCA Cycle Restrains Virus-Metabolic Hijacking and Viral Replication in Mouse Hepatitis Virus-Infected Cells	**NR**	To investigate the potential therapeutic effects of NR in SARS-CoV-2 by using a closely related coronavirus in mice—MHV.	• NR suppressed viral replication in mouse MHV-infected cells by activating the TCA cycle, a key process in carbohydrate and fat metabolism. This effect was amplified when NR was treated in combination with a TCA cycle activator.
Heer et al., 2020 [16] Coronavirus Infection and PARP Expression Dysregulate the NAD Metabolome: An Actionable Component of Innate Immunity CERP ChromaDex External Research Program	**Niagen NR**	To investigate how COVID-19 infection affects NAD+ metabolism and to explore whether boosting NAD+ with Niagen NR or related compounds can limit viral replication in models of coronavirus infection, including murine hepatitis virus (MHV), a virus closely related to SARS-CoV-2—the virus that causes COVID-19.	• In a mouse model of COVID-19, NAD+ levels were reduced by over 3-fold in primary bone marrow-derived macrophages (BMDMs). • In MHV-infected mouse fibroblasts, Niagen NR decreased replication of the MHV virus by 6.4-fold. In BMDMs, Niagen NR further reduced replication by 2.7-fold.

CERP ChromaDex External Research Program *The **ChromaDex External Research Program (CERP)** is an essential component of Niagen Bioscience's R&D Program. Through CERP, Niagen Bioscience material, such as the company's patented nicotinamide riboside (NR) ingredient, Niagen®, and technical expertise is freely provided for exceptional preclinical and clinical, investigator-initiated research projects. Additionally, CERP funds research studies supporting Niagen Bioscience's business needs. Please visit https://www.chromadex.com/research/cerp/ for more information.*

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