The Role of Vitamin B3 in the Immune Response to COVID-19: New Observations and New Insights

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Introduction – What is vitamin B3?

The term Vitamin B3 is currently used to refer to a vitamin family that includes three forms or vitamers:

- **niacin** (nicotinic acid),
- **nicotinammide** (niacinammide),
- **nicotinammide riboside** (identified as a form of vitamin B3 in 2004).

B3 family vitamins are essential nutrients that must be consumed at adequate levels in the diet. At the beginning of the 20th century, vitamin B3 deficiency was first identified in the southern United States as the cause of the so-called 'Pellagra', a frequent pathology among populations that made exclusive use of sorghum or corn polenta as a staple food.

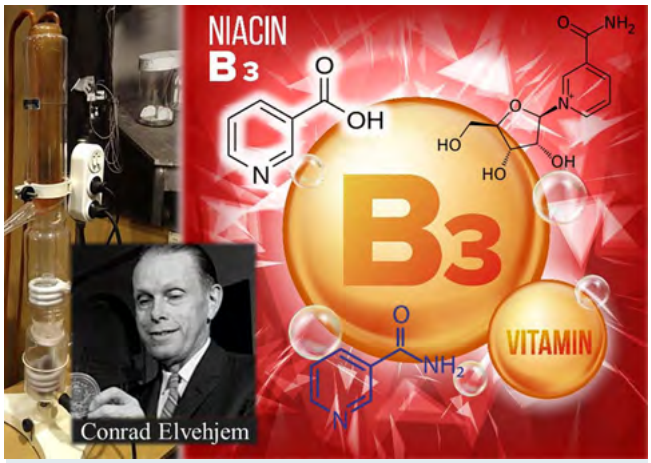
All three forms of vitamin B3 are converted within the body to **nicotinammide adenine dinucleotide** (NAD^+).

NAD^+ is a coenzyme that is found in all kinds of living cells, ranging from bacteria to man. Present both in the cytoplasm and in the nucleus. This special molecule plays an important role in the biochemical pathways that convert nutrients into energy within the mitochondria.

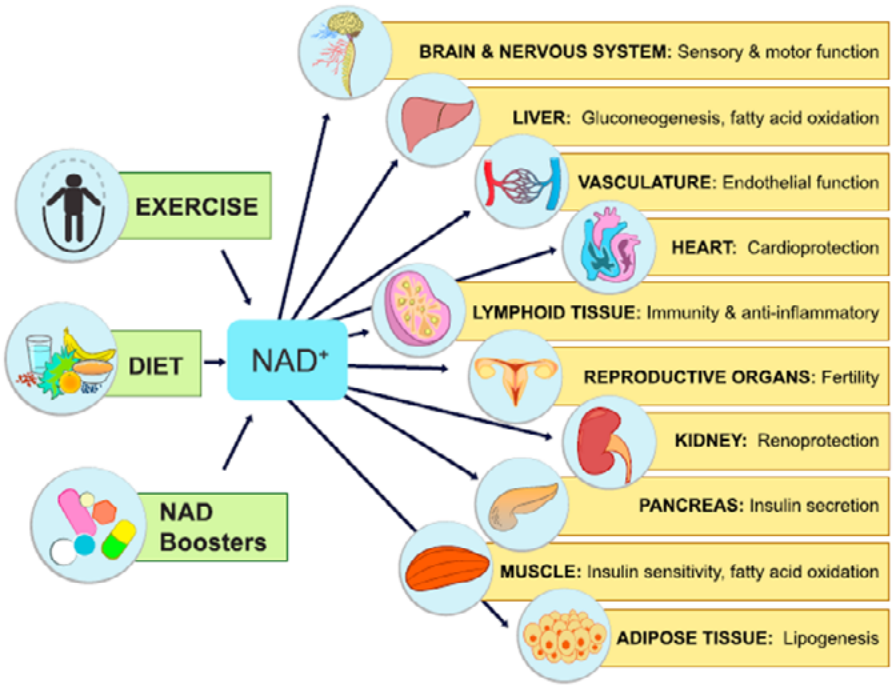
Additionally, NAD^+ protects tissues from free radicals, supports innate immune function, participates in DNA repair reactions, and extends life span.[1]

The human body manufactures NAD^+ from vitamin B3 delivered in our diet, but the majority of the NAD^+ in the body (total quantity of about 3 grams in the average person) is in a constant state of synthesis, degradation, and recycling.

NAD^+ is one of the most important and essential molecules in cellular energetic metabolism. It is required



Conrad Arnold Elvehjem (May 27, 1901 – July 27, 1962), American biochemist, known for having discovered Vitamin B3, whose deficiency is the cause of pellagra.



Therapeutic Potential of NAD-Boosting Molecules: The In Vivo Evidence
Luis Rajman, Karolina Chwalek, and David A. Sinclair
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for over 500 enzymatic reactions and plays a key role in the regulation of almost all major biological processes, including our immune responses and DNA repair against damage caused by aggressive chemicals or radiation.

In the article "*NAD^+ metabolism: pathophysiologic mechanisms and therapeutic potential*"[2] by Na Xie et al., published online by *Nature*, on October 7, 2020, one can read:

- *"**Prolonged disequilibrium of NAD^+ metabolism disturbs the physiological functions, resulting in diseases including metabolic diseases, cancer, aging and neurodegeneration disorder**..."* (bold added)
- *"**NAD^+ precursors can be used as a nutritional supplement to improve a broad spectrum of physiological functions and pathological processes**... The therapeutic and preventive efficacy of NAD^+ boosters, especially the soluble and orally bioavailable endogenous molecules NR [nicotinamide riboside], NAM [nicotinamide] and Niacin, have been assessed in a series of clinical trials in humans"* (bold added)
- *"**A healthy lifestyle and exercise are nonpharmacologic strategies to improve the body's resilience and extend healthy lifespan through enhancing NAD^+ levels. NAD^+ booster can be applied for a broad spectrum of NAD^+, deficiency related pathologies, such as infection, cancer, metabolic diseases, acute injury, aging and aging-related neurodegenerative disorders**."* (bold added)

Role of vitamin B3 and NAD^+ in the prophilaxys and in experimental anti COVID-19 therapies

The global COVID-19 epidemic has spread rapidly around the world and has already caused the death of several millions people.

As already well known, this disease is caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and started in China around December 2019. Patients with critical COVID-19 develop severe respiratory distress, and death (Pan et al., 2020).

Many researchers around the world have been and are still investigating, with very promising results, the effect of treating COVID-19 patients with NAD^+ or its precursors and found that the pneumonia, including excessive inflammatory cell infiltration (the so called "cytokine storm"[3]) and blockage of arteries in SARS-CoV-2 infected lungs, were significantly rescued by boosting NAD+ levels NAD^+. See, to this regards, the scientific article "*Treatment of SARS-CoV-2 induced pneumonia with NAD^+ in a mouse model*"[4] by Yisheng Jiang et al., published on October 30, 2020 – by *Research Square*, where you read:

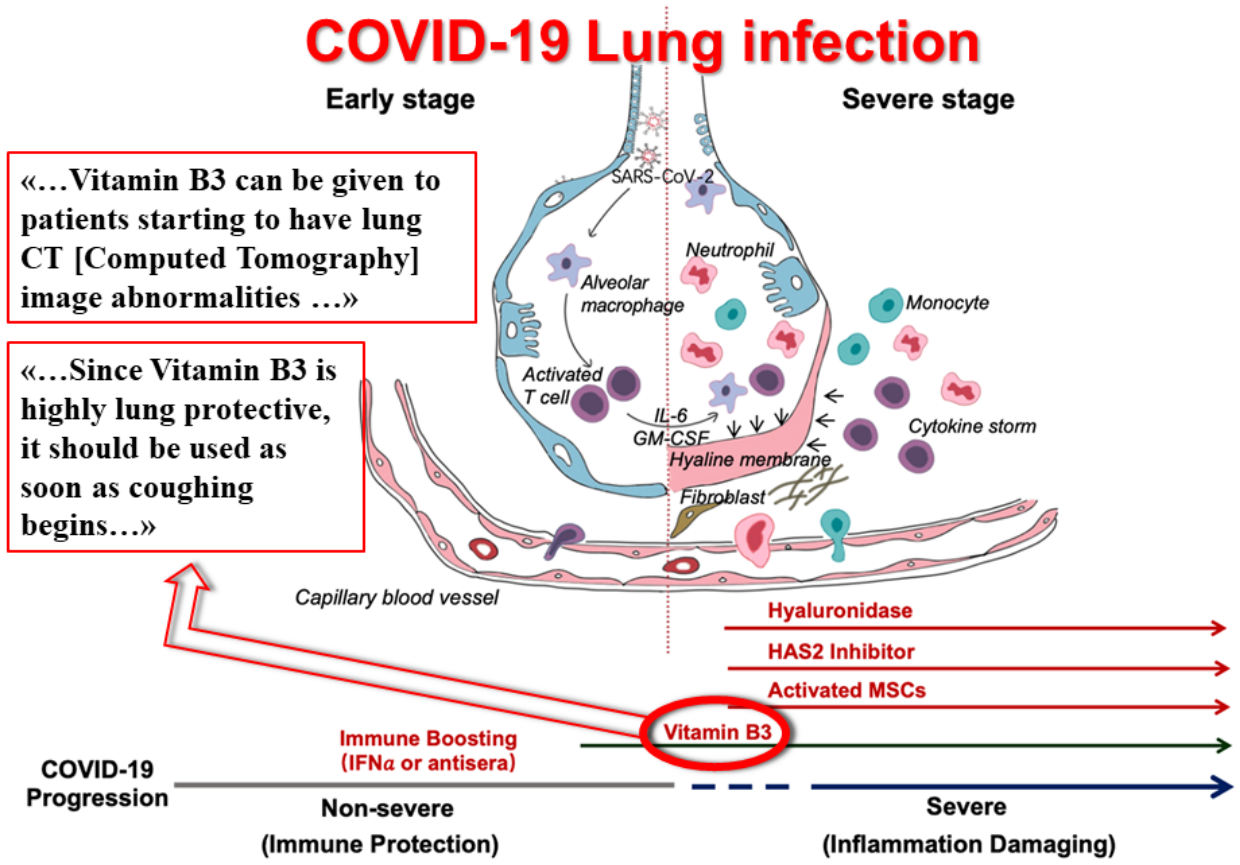
- *"...These results indicate that **NAD^+ supplementation can protect the lung from infiammatory injury, including cell death, caused by SARS-Cov-2 infection in both old and young mice**...."* (bold added)
- *"...Therefore, our study is in strong support of initiating a trial for treating COVID-19 patients with NAD^+ or its precursors..."*

On March 23, 2020, the prestigious scientific journal *Nature* published an article entitled "*COVID-19 infection: the perspectives on immune responses*"[5], co-signed by scientific representatives of prestigious Italian academic institutions, such as the *Spallanzani Institute* and the *Tor Vergata University* of Rome (authors: Yufang Shi, Ying Wang, Changshun Shao, Jianan Huang, Jianhe Gan, Xiaoping Huang, Enrico Bucci, Mauro Piacentini[6], Giuseppe Ippolito[7], Gerry Melino[8]), where you can read the following:

- *"...**vitamin B3 (niacin or nicotinamide) is highly effective in preventing lung tissue damage**. It might be a wise approach to supply this food supplement to the COVID-19 patients..."* (bold added)
- *"...Vitamin B3 can be given to patients starting to have lung CT image abnormalities..."*
- *"We propose some simple, but largely ignored, approaches to the treatment of COVID-19 patients... **Since Vitamin B3 is highly lung protective, it should be used as soon as coughing begins**..."* (bold added)

In another scientific study, dated April 29, 2020, entitled "*Why does COVID-19 disproportionately affect older people?*"[9] (authors: Amber L. Mueller, Maeve S. McNamara, David A. Sinclair)[10], we can read:

- *"The severity and outcome of coronavirus disease 2019 **(COVID-19)** largely depends on a patient's age. **Adults over 65 years of age represent 80% of hospitalizations** and have a **23-fold greater risk of death than those under 65**."* (bold added)
- *"... Conversely, **individuals who live healthy lifestyles and consume geroprotectors such as ... NAD^+ boosters may have a decreased risk of fatality**"*. (bold added)
- *"**During aging, NAD^+ levels decline... Maintaining NAD^+ levels may therefore alleviate COVID-19***



Da: "COVID-19 infection: the perspectives on immune responses"
Shi, Y., Wang, Y., Shao, C. et al. COVID-19 infection: the perspectives on immune responses. Cell Death Differ 27, 1451–1454 (2020). https://doi.org/10.1038/s41418-020-0530-3

***symptoms**... Additionally, **NAD⁺ precursors lower inflammation in human subjects**..."* (bold added)

- *"...**NAD⁺ precursors... have been suggested as possible treatments for COVID-19, especially in older people**... Clinical studies are needed to determine if NAD⁺ supplementation would benefit in the early stages of SARS-CoV-2 to reduce replication or if NAD⁺ treatment during acute COVID-19 can hasten recovery"* (bold added)

Similarly, the article entitled "*Influence of NAD⁺ as an ageing-related immunomodulator on COVID19 infection: A hypothesis*"[11] by Huda M. Omran, Mohamed S. Almaliki, published on June 7, 2020 in the *Journal of Infection and Public Health*, reports that:

- *"**Elderly COVID-19 patients are at a real risk of complications** due to impaired immune function, cytokine storm and defective respiratory function. Administration of anti-ageing immunomodulation factors like **Nicotinamide Adenine Dinucleotide (NAD⁺) can minimize these changes through its potent immunomodulation and longevity effects**."* (bold added)
- *"...We suggested **the use of NAD⁺ is an immunomodulator for COVID-19 in older patients. Restoring normal NAD⁺ levels could decrease the severity of immune reaction in those patients and improve their clinical condition**..."* (bold added)

In the scientific article "*Covid-19, Coronavirus, SARS-CoV-2 and the small bowel*"[12], (authors: Klaus Mönkemüller, Lucia C. Fry and Steffen Rickes), published in *Revista Española de Enfermedades Digestivas* (26/04/2020), we read:

- *"...it would be important to evaluate whether there is **a tryptophan or B3 deficiency in Covid-19 patients**. If so, rapid substitution of tryptophan or niacinamide could help to prevent or ameliorate the vicious circle of the **malnutrition - inflammation - immunodeficiency cascade**."* (bold added)

Perhaps the most informative study on this topic is entitled: "*Understanding the immune response in COVID-19 – new opportunities and new insights*"[13], published in July 2021 in a South African medical journal (*DeNovo Medica*). His author, professor Guy Richards, from Charlotte Maxeke Academic Hospital, Johannesburg, is one of the founders of the intensive-care specialty in South Africa and was at the forefront of treatment for Covid-19 patients at the start of the pandemic.[14]

Here are some significant excerpts from his very interesting article, which, in addition to being widely documented and well articulated, summarizes synthetically and masterfully exposes, on a biochemical and immunological level, the full picture of the complex interactions and relationships existing between NAD^+ depletion and the devastating effects of COVID-19:

- *"...**NAD^+ levels decline with age and are also reduced in conditions associated with oxidative stress as occurs with hypertension, diabetes and obesity, all of which have been observed to have higher mortality following infection with SARS-CoV-2**."* (bold added)
- *"...New insights regarding the metabolic abnormalities and hyperinflammatory response that are associated with **COVID-19** suggest that **a deficiency in nicotinammide adenine dinucleotide (NAD^+)**, unmasked by a significant increase in oxidative stress, **may be a primary factor related to the disease spectrum and the risk for mortality**."* (bold added)
- *" ... A recent phase II clinical study has found that **the combination of a nutritional cocktail that included NR [Nicotinamide Riboside]** together with the standard of care, **reduced recovery time by nearly 30% compared to standard of care alone** (6.6 vs 9.3 days) in 304 patients with mild to moderate COVID-19..."* (bold added)
- *"... The cell has innate processes which serve as a first line of defence against virally mediated damage. **These defence mechanisms consume and deplete NAD^+** and in so doing, **intracellular immune defences may be compromised**."* (bold added)

Understanding the immune response in COVID-19 – new opportunities and new insights" published in July 2021 in DeNovo Medica. Author, professor Guy Richards, Wits University.

- *"...**NAD^+ has a vital role in controlling the ongoing inflammatory state, overactivation of the immune system, and even the cytokine storm**."* (bold added)
- *"**Those at higher risk of developing more serious COVID-19 disease may have a deficiency of NAD^+**, which declines with age and is also reduced in conditions associated with oxidative stress."* (bold added)
- *"NAD^+ is involved in multiple metabolic pathways including energy metabolism and **has several roles in immunological function**"* (bold added)
- *"Cellular NAD^+ levels may be enhanced by the **use of NAM [Nicotinamide], NR [Nicotinamide riboside] or NA [Nicotinic Acid] supplements**"* (bold added)

Conclusions

It is increasingly evident, from numerous and in-depth studies carried out in various countries, that, to avoid severe COVID-19 disease (and the potentially significant implications of Long Covid), if and when we do get infected, we must improve our physical resilience and immune system. Taking a vitamin B3 supplement, as discussed above, is an inexpensive, effective and risk-free way to strengthen all those biochemical mechanisms of resistance and immunization to infections caused by even more insidious pathogens than SARS-Cov-2.

Vitamin B3 is converted in the body to NAD^+, a compound that is currently being investigated mainly for its anti-aging promising properties, notably by Prof. John Sinclair at Harvard. According to a paper that he co-authored "*NAD^+ levels steadily decline with age, resulting in altered metabolism and increased disease susceptibility. Restoration of NAD^+ levels*

in old or diseased animals can promote health and extend lifespan, prompting a search for safe and efficacious NAD-boosting molecules that hold the promise of increasing the body's resilience, not just to one disease, but to many, thereby extending healthy human lifespan… It is exciting to imagine an NAD+ booster being tested in humans for the ability to increase vitality, reduce all causes of mortality, and extend healthy lifespan. If that happens, more than the discoverers of NAD+ could ever have imagined, NAD+ would truly be ***the molecule of life***."[15]

Vitamin B3, in addition to being the factor that eradicated in the last century the disease known as *Pellagra*, has a long history of significant therapeutic results in multiple areas of medicine, for example as an adjuvant in the treatment of arthritis, cardiovascular diseases, allergies, Alzheimer's, some tumors, detoxification from chemical agents, hypercholesterolemia, etc.[16]

However, despite the fact that it has generally been considered "only" a vitamin or a simple and harmless supplement of "marginal" support to the immune system, and not really an essential therapeutic factor (except in the case of *Pellagra*), it is no longer possible to ignore or underestimate the fact that numerous and clear-cut signs are increasingly emerging all over the world that would announce its glorious return to the scene of prophylaxis and therapy. And this time, not as a mere "supplement", but as an effective and indispensable weapon of defense in the fight against COVID-19 and Long COVID, obviously in pharmacological dosages and always under careful medical supervision.

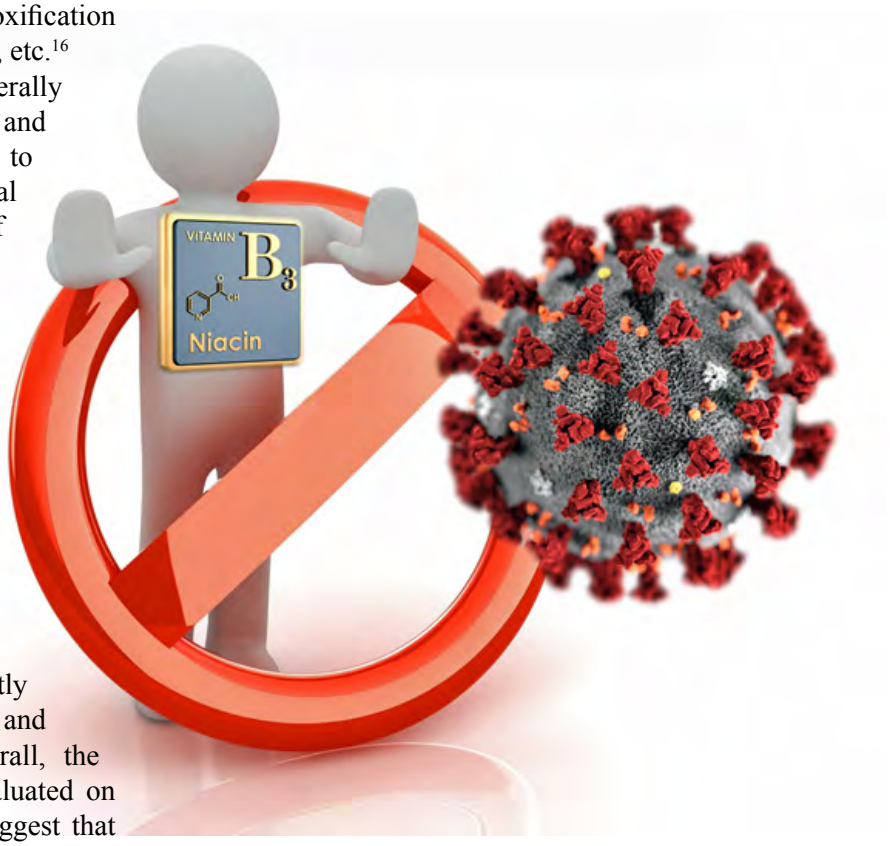
The evaluations and clinical trials currently underway will certainly provide further and valuable information in this regard. Overall, the promising results so far examined and evaluated on a biochemical and immunological level, suggest that the use of specific vitamin supplements may have a promising, if not decisive, impact on reducing the risk and / or severity of COVID-19:

"… Nutritional support to restore levels of NAD+ and associated enzymes could minimise disease severity if administered prophylactically and/or therapeutically – writes prof. Guy Richards – *The significance of this, if proven, has far-reaching consequences in the management of COVID-19 especially in third world countries, where resources and finances are limited…"*.[17]

Vitamin B3: A possible treatment for COVID-19?[18]

Is it "just" a scientifically too ambitious, too unlikely hypothesis?

Perhaps, but so was David's victory with his little slingshot, 3000 years ago…



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3 A cytokine storm is a physiological reaction in humans and other animals in which the innate immune system causes an uncontrolled and excessive release of pro-inflammatory signaling molecules called *cytokines*.

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