Rationale for Nicotinamide Adenine Dinucleotide (NAD+) Metabolome Disruption as a Pathogenic Mechanism of Post-Acute COVID-19 Syndrome

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ABSTRACT: Many acute COVID-19 convalescents experience a persistent sequelae of infection, called post-acute COVID-19 syndrome (PACS). With incidence ranging between 31% and 69%, PACS is becoming increasingly acknowledged as a new disease state in the context of SARS-CoV-2 infection. As SARS-CoV-2 infection can affect several organ systems to varying degrees and durations, the cellular and molecular abnormalities contributing to PACS pathogenesis remain unclear. Despite our limited understanding of how SARS-CoV-2 infection promotes this persistent disease state, mitochondrial dysfunction has been increasingly recognized as a contributing factor to acute SARS-CoV-2 infection and, more recently, to PACS pathogenesis. The biological mechanisms contributing to this phenomena have not been well established in previous literature; however, in this review, we summarize the evidence that NAD+ metabolome disruption and subsequent mitochondrial dysfunction following SARS-CoV-2 genome integration may contribute to PACS biological pathogenesis. We also briefly examine the coordinated and complex relationship between increased oxidative stress, inflammation, and mitochondrial dysfunction and speculate as to how SARS-CoV-2-mediated NAD+ depletion may be causing these abnormalities in PACS. As such, we present evidence supporting the therapeutic potential of intravenous administration of NAD+ as a novel treatment intervention for PACS symptom management.

KEYWORDS: SARS virus, NAD, oxidative stress, mitochondria, metabolome, Coronavirus infections

Introduction

Post-acute COVID-19 syndrome (PACS), also known as long COVID or post COVID, is a variety of persistent symptoms that affects patients who have recovered from acute infection by the SARS-CoV-2 virus. PACS patients present with a combination of symptoms that may include dyspnea, chronic fatigue, post-exertional malaise, neurocognitive issues such as difficulty concentrating (“brain fog”), persistent cough, chest pain, headache, palpitations, joint or muscle pain, diarrhea, insomnia, fever, dizziness, rash, anosmia, or ageusia.1 Clinical presentation of varies person-to-person, and the diverse symptoms associated with this syndrome indicate the involvement of multiple organ systems in its pathogenesis. The heterogeneity of persisting symptoms contributes to the complex diagnosis of PACS, so categorizing PACS into subsets based on the predominant organ systems involved may help identify the etiology of this condition: (1) post-acute COVID cardiovascular syndrome, (2) post-acute COVID pulmonary syndrome, (3) post-acute COVID neuropsychiatric syndrome, and (4) post-acute COVID multi-system syndrome.1-3

The risk factors for PACS development remain ill-defined, but the severity of initial SARS-CoV-2 infection, extent of organ damage, time required for organ recovery, persistence of chronic inflammation, and some psychological conditions such as post-traumatic stress may contribute to the risk of persistent symptoms associated with this condition.2-5 Unfortunately, PACS can affect any individual who has been infected with the SARS-CoV-2 virus, despite a mild or asymptomatic initial symptom presentation. Notably, PACS symptoms in patients who experienced severe initial COVID-19 symptoms may be secondary to COVID-19–induced organ damage, but PACS patients can experience severe and persistent symptoms following acute infection without apparent organ damage.6 As PACS is a new disease, real-world data continues to inform known risk factors, disease incidence, prevention and treatments. Su et al7 recently revealed 4 quantifiable risk-factors for PACS at the time of initial COVID-19 diagnosis: (1) type 2 diabetes, (2) SARS-CoV-2 RNAemia, (3) Epstein-Barr virus viremia, and (4) specific autoantibodies. Though this study provides significant insight into specific biological factors that contribute to the heterogeneity of PACS, the cellular mechanisms contributing to PACS pathogenesis and potential PACS treatment options remain unknown. Furthermore, results from numerous systematic prospective follow-up studies after hospitalization due to COVID-19 indicate that approximately 87% of people recovered and discharged from hospitals showed persistence of at least one symptom at 60 days, and about 35% of outpatient COVID-19 patients experience residual symptoms consistent with PACS.4,8-10 Altogether, approximately 31% to 69% of COVID-19 patients suffer from PACS.31 As such, the development of novel treatment options for PACS remains critical in the wake of the COVID-19 pandemic.

Recent studies and hypotheses have suggested myriad cellular and molecular abnormalities which may contribute to PACS pathogenesis. As previously mentioned, Su et al7 suggested 4 unique risk factors for PACS development. Among
these, the finding that there is an association of cortisol deficiency in patients with respiratory viral PACS is particularly relevant. Stefano et al. hypothesized that neuropsychiatric PACS symptoms may potentially develop as a result of an aberrant immune response to SARS-CoV-2 infection that permits the virus to seize control of neuronal mitochondria in the central nervous system, effectively driving neuronal apoptosis. Fogarty et al. hypothesized that sustained endotheliopathy at 10 weeks observed following recovery of acute SARS-CoV-2 infection may contribute to the increased risk of thrombotic events in PACS patients. Alternatively, Oronsky et al. suggests that some symptoms associated with PACS, such as persistent immunosuppression and fibrosis, may be attributed to SARS-CoV-2-induced overexpression of transforming growth factor beta. These findings represent only a handful of publications discussing the physiological disturbances contributing to PACS pathogenesis, and the heterogeneity of this condition complicates the process of understanding its progression.

At present, the approach to PACS treatment is typically multi-disciplinary, focusing on symptomatic management and addressing underlying health problems. For example, antiviral administration in acute COVID-19 infection may reduce the risk of PACS development and utilizing therapies that target hyperinflammation may influence PACS severity. Some symptoms of PACS can be effectively managed using such therapies, but other symptoms are difficult to treat with existing protocols. Of the many PACS symptoms that persist following unsuccessful treatment interventions, neuropsychiatric PACS symptoms, such as chronic fatigue, are the most common and are particularly difficult to treat.

The SARS-CoV-2 virus interferes with numerous cellular and molecular processes involved in PACS pathogenesis. In particular, it has been hypothesized that SARS-CoV-2-mediated disruption of the NAD+ metabolome contributes to PACS pathogenesis because viral genome integration reduces NAD+ available for host metabolism, resulting in subsequent mitochondrial dysfunction, inflammation, and ultimately cell death. This commentary discusses the evidence substantiating this hypothesis and discusses the rationale supporting intravenous NAD+ to restore normal functioning of the NAD+ metabolome as a novel therapeutic intervention for managing PACS symptoms, specifically chronic fatigue.

The Role of NAD+ in Metabolic Stress
NAD+ is the abbreviation for the oxidized form of a compound called nicotinamide adenine dinucleotide, which is well-known for its critical role in cellular energy production. As both a substrate for NAD(+) dependent and NAD(+) consuming enzymes and a cofactor for hydride-transfer enzymes, NAD+ is essential to energy production, regulation of gene expression, DNA repair mechanisms and immune function. During the natural aging process, DNA damage from toxin accumulation, ultraviolet light exposure and other environmental or physiological stressors cause NAD+ levels to decline. In addition, many disease states associated with increased oxidative stress cause a reduction of NAD+ levels. Under normal conditions, reactive oxygen species (ROS) are produced by many cellular processes, including cellular respiration and antimicrobial activities, and are typically cleared or counteracted by antioxidant enzymes or compounds. If these antioxidant mechanisms are impaired, ROS can accumulate causing DNA damage and subsequent reduction in NAD+ levels and increased inflammation. Elevated levels of ROS are linked to chronic inflammatory lung conditions, such as chronic obstructive pulmonary disease, and to neurological diseases, such as Parkinson’s disease, Alzheimer’s disease, depression, and memory loss. In the context of chronic inflammatory lung conditions, oxidative stress has been shown to activate pro-inflammatory transcription factors, such as NF-kappa B, enhancing the activity of inflammatory pathways associated with the development of these conditions. Elevated levels of ROS and subsequent oxidative stress are also known to have deleterious effects on neuronal health by initiating intracellular signaling cascades that promote pro-inflammatory gene expression.

Consequences of SARS-CoV-2-Mediated Oxidative Stress on Immunometabolism
Since the first reports of persistent COVID-19 symptoms, many researchers have focused on examining the cellular and molecular mechanisms by which SARS-CoV-2 infection can lead to PACS. Recent research has illuminated how SARS-CoV-2-mediated alterations of key physiological processes, such as NAD+ depletion and mitochondrial dysfunction, may contribute to the development of persistent symptoms consistent with PACS.

During SARS-CoV-2 infection, it has been hypothesized that mitochondria greatly increase ROS production in response to virally-mediated stimulation of NADPH oxidases (NOX) in the cytosol. As mitochondrial production of ROS increases during SARS-CoV-2 infection, the oxidative stress placed on the mitochondria is exacerbated and can lead to mitochondrial dysfunction. Depending on the tissue infected with SARS-CoV-2, mitochondrial dysfunction can induce aberrant functioning of a wide range of molecular pathways. For example, in the central nervous system, SARS-CoV-2 stimulates cytosolic NOX activity to promote microglial activation. Sustained microglial activation facilitates viral entry through the blood brain barrier (BBB) by destroying the structural integrity of the BBB, effectively manipulating host physiology to promote continuation of SARS-CoV-2 infection. Microglial activation has been demonstrated to elicit a potent neuroinflammatory response and may potentially relate to inflammatory neurological symptoms associated with PACS.

When elevated, ROS act as signaling molecules to activate oxidative stress mechanisms, such as DNA oxidation or
activation of pro-inflammatory kinases, which induce DNA damage and tissue damage.\textsuperscript{20} DNA damage caused by ROS accumulation is detected by repair-associated enzymes, such as poly(ADP-ribose) polymerase (PARP).\textsuperscript{26} The activity of PARP1, one of 17 human PARP proteins, is predominantly responsible for initiating antiviral pathways in response to virally-mediated DNA damage. NAD\textsuperscript{+} is the sole donor of ADP-ribose required for PARP1 activity, and hyperactivation of PARP1 in response to virally-mediated elevation of ROS and subsequent DNA damage may lead to NAD\textsuperscript{+} depletion.\textsuperscript{26} Some RNA viruses, including SARS-CoV-2, have been shown to modulate PARP1 activity to enhance processes that favor viral replication, effectively depleting intracellular NAD\textsuperscript{+} levels.\textsuperscript{27,28} Similarly, increased oxidative stress and DNA oxidation in numerous pathologies, such as neurodegeneration and cancer, are hypothesized to reduce the activity of enzymes involved in the salvage pathway of NAD\textsuperscript{+} synthesis.\textsuperscript{29} Inefficiency of the NAD\textsuperscript{+} synthesis salvage pathway can result in intracellular NAD\textsuperscript{+} depletion and subsequent disruption of energy homeostasis.\textsuperscript{29}

**SARS-CoV-2 Infection Induces NAD\textsuperscript{+} Metabolome Disruption**

Reduced levels of NAD\textsuperscript{+} have been shown to cause altered metabolic states and increased disease susceptibility. The consequences of insufficient levels of NAD\textsuperscript{+} have been widely studied in the context of age-related disorders and neurodegenerative diseases.\textsuperscript{19,30,31} Dysregulation of NAD\textsuperscript{+} metabolism can have a range of health implications from compromised cardiac function to hyperinflammation and DNA damage due to increased oxidative stress.\textsuperscript{31-33} More recently, however, research suggests the consequences of NAD\textsuperscript{+} metabolome disruption may contribute to the extensive biological abnormalities seen across the SARS-CoV-2 disease spectrum.\textsuperscript{34}

Many NAD\textsuperscript{+}-dependent enzymes are required for the antiviral activity of the interferon system, a branch of the immune system that responds to viral infection.\textsuperscript{16} Activation of the interferon system is therefore contingent on NAD\textsuperscript{+} availability to carry out antiviral responses.\textsuperscript{16-18} In many viral infections, enzymes responsible for initiating transcription of interferon stimulating genes (ISGs) have undisrupted access to NAD\textsuperscript{+} and permit for an adequate and appropriate immune response required for viral elimination.\textsuperscript{16-18} During acute infection with SARS-CoV-2, viral integration into the host genome of infected cells facilitates viral replication by interfering with normal activation of ISGs.\textsuperscript{16-18} Some of these modifications significantly alter the activity of enzymes involved in the biosynthesis, metabolism and consumption of NAD\textsuperscript{+} and ultimately divert this substrate away from enzymes required for ISG activation and toward enzymes that support viral replication.\textsuperscript{16,18}

As previously mentioned, there is a strong link between overstimulation of PARP1 activity and NAD\textsuperscript{+} depletion.\textsuperscript{27,28} To execute its antiviral activity, PARP1 utilizes ADP-ribose derived from NAD\textsuperscript{+} to tag the viral genome, which, in turn, stimulates the expression of several antiviral ISGs, functionally restricting viral replication.\textsuperscript{25,28} SARS-CoV-2 harbors the molecular machinery to remove the ADP-ribose molecular tag placed by PARP1, effectively preventing PARP1 antiviral activity.\textsuperscript{29} SARS-CoV-2-infected cells respond by overstimulating PARP1 to attempt to promote the antiviral activity of PARP1 and inhibit viral replication.\textsuperscript{16-18,27,28} While normal PARP1 signaling can effectively restrict viral replication by increasing NAD\textsuperscript{+} biosynthesis to ensure the NAD\textsuperscript{+} supply required for antiviral ISG activation, PARP1 hyperactivity in SARS-CoV-2 infection instead promotes viral replication by depleting NAD\textsuperscript{+} levels available for antiviral responses and by downregulating host NAD\textsuperscript{+} utilizing biosynthetic pathways.\textsuperscript{16-18} SARS-CoV-2-infected cells divert NAD\textsuperscript{+} towards processes that favor viral replication. SARS-CoV-2-mediated NAD\textsuperscript{+} depletion severely impairs redox balance and ultimately results in depletion of intracellular ATP, mitochondrial dysfunction and subsequent cellular apoptosis.\textsuperscript{18} Recent research has also indicated NAD\textsuperscript{+} depletion caused by PARP1 hyperactivity leads to dysregulation of the inflammatory response via increased NF-kappa B signaling, which suggests a close link between the NAD\textsuperscript{+} metabolome and dysregulated immune function in SARS-CoV-2 infection.\textsuperscript{26}

The hypothesis on the involvement of PARP1 in NAD\textsuperscript{+} depletion pathology is not limited to the scope of SARS-CoV-2 infection. Studies have demonstrated that this model may contribute to human immunodeficiency virus (HIV) pathogenesis and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) pathogenesis.\textsuperscript{25-27,29} Research has demonstrated that in both HIV and ME/CFS, the oxidative stress that occurs during active viral infection can leave mitochondria in a dysfunctional state, which may contribute to impaired recovery and secondary pathologies.\textsuperscript{24-27,29}

**NAD\textsuperscript{+} Metabolome Dysfunction Contributes to PACS-Related Biological Abnormalities**

VIRALLY-MEDIATED NAD\textsuperscript{+} depletion is associated with excessive mitochondrial stress, aberrant immune response activation and apoptosis.\textsuperscript{26} Recent studies propose that NAD\textsuperscript{+} deficiency may predispose certain populations to severe COVID-19 outcomes and COVID-related mortality because these populations are in a pre-existent NAD\textsuperscript{+}-depleted state.\textsuperscript{35} It is hypothesized that, in these NAD\textsuperscript{+}-depleted populations, the hyperactivity of PARP1 during SARS-CoV-2 infection causes further depletion of NAD\textsuperscript{+} and exacerbates mitochondrial dysfunction (ie, energy loss, ATP deficiency, increased pro-inflammatory signaling), and eventually increased cell death.\textsuperscript{35} Research also suggests that there is an association of cortisol deficiency in patients with respiratory viral PACS.\textsuperscript{7} The first and last steps in cortisol synthesis occur in the mitochondria and require functional cytochrome P450
for catalysis. The expression of mitochondrial steroidogenic P450 is thought to be regulated by the activity of NAD(+) dependent SIRT deacetylases. Enzymes involved in mitochondrial cortisol synthesis are highly dependent on NAD+ to carry out their respective functions. Thus, cortisol production requires sufficient mitochondrial NAD+ levels. As such, NAD+ depletion following SARS-CoV-2 infection may prove to be a contributing biological factor to the association between cortisol deficiency and increased risk of PACS. Altogether, it would be reasonable to infer that the consequences of NAD+ depletion may play a pivotal role not only in the pathogenesis of SARS-CoV-2, but also in the development of PACS following acute SARS-CoV-2 infection.

**SARS-CoV-2-Mediated NAD+ Metabolome Disruption Facilitates Mitochondrial Dysfunction**

With involvement in processes ranging from energy metabolism to ROS production to apoptosis, aberrant mitochondrial health has been widely recognized as a component of disease progression in the context of numerous pathologies, including Parkinson’s disease, neuropathic pain, diabetes, and chronic fatigue syndrome. As both a substrate for many mitochondrial enzymes, sufficient NAD+ levels are essential for maintaining mitochondrial health (ie, normal energy production, gene expression, DNA repair mechanisms, immunomodulation). Regarding PACS, research suggests that some PACS symptoms, such as chronic fatigue, may be associated with NAD+ depletion and mitochondrial dysfunction. Further, SARS-CoV-2 has been shown to inhibit complex I of the mitochondrial electron transport chain, obstructing a key enzyme in energy biosynthesis. Disruption of mitochondrial energy production in SARS-CoV-2-infected cells and subsequent ATP deficiency may represent a metabolic consequence of NAD+ metabolome dysregulation. As such, SARS-CoV-2-mediated disruption of the NAD+ metabolome may, at least in part, explain a potential biological factor contributing to PACS pathogenesis. Supplemental Table 1 provides key findings of the highlighted studies in relation to NAD+ metabolome disruption and mitochondrial dysfunction following SARS-CoV-2 infection.

**Rationale for NAD+ Intravenous Administration Therapy for PACS Symptom Management**

As SARS-CoV-2 infection severely depletes host cell NAD+ levels primarily via PAPR1 overactivation, it would be reasonable to consider NAD+ supplementation as a potential therapeutic intervention aimed at avoiding the downstream consequences of NAD+ metabolome disruption (ie, increased oxidative stress, mitochondrial dysfunction and apoptosis). Indeed, studies have demonstrated that NAD+ boosting via supplementation may mitigate symptoms of chronic fatigue syndrome, many of which closely resemble symptoms associated with PACS (ie, prolonged fatigue, neurocognitive dysfunction, myalgia, headache, low-grade fever). In murine models, NAD+ supplementation has been shown to effectively extend both lifespan and healthspan, a term used to describe the period of life time in which an organism is healthy. Mitochondrial health is often used as a cellular marker of healthspan, and these models suggest NAD+ supplementation can significantly improve mitochondrial function, reduce levels of pro-inflammatory cytokines, and restore aberrant DNA repair mechanisms, ultimately delaying the potential onset of multiple pathologies. Based on animal models and preclinical findings and the hypothesis that NAD+ depletion may contribute to PACS pathogenesis, NAD+ supplementation may represent a promising therapeutic option for clinical management of PACS symptoms. The key findings from the highlighted clinical studies with evidence supporting NAD+ supplementation are summarized in Supplemental Table 2.
Although further studies are needed to conclusively determine the impact of SARS-CoV-2-mediated NAD+ depletion in PACS pathogenesis, preclinical and clinical data has suggested that supplementation with NAD+ or its analogs may accelerate PACS recovery.\textsuperscript{55-59} Moreover, there is one ongoing pilot study with NAD+ investigating its effect on reducing fatigue in PACS.\textsuperscript{60} Despite the evidence supporting NAD+ supplementation as potential PACS therapy, considerably more information about the safety, efficacy and potential long-term sequel of IV NAD+ administration is required to claim a therapeutic effect in PACS patients. Further, such evidence is a prerequisite to definitively determine the impact of SARS-CoV-2-mediated NAD+ depletion in PACS pathogenesis and is hinged upon future clinical investigations. As such, the appropriate dosing and other clinical indicators, and potential secondary outcomes need to be critically evaluated and carefully considered prior to designing clinical trials investigating IV NAD+ administration as a potential therapeutic for PACS.

Conclusion

The multifactorial nature of PACS pathogenesis poses marked challenges in determining the risk factors, safe and effective treatments, and preventive measures for this group of disease states. Although recent research has significantly improved our understanding of PACS pathogenesis, this commentary presents a novel perspective on PACS pathogenesis focused on the consequences of SARS-CoV-2-mediated NAD+ metabolome disruption and mitochondrial dysfunction. While additional studies are needed to discern the exact molecular mechanisms involved in SARS-CoV-2-mediated NAD+ metabolome disruption and the clinical implications of this abnormality in PACS patients, this commentary serves as a preliminary advancement in addressing the limitations of current views on PACS pathogenesis and provides evidence for a potential targeted PACS treatment utilizing intravenous NAD+ therapy.

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Author Contributions

TB drafted the manuscript and incorporated revisions. JK devised the study and reviewed the manuscript. Both authors reviewed and approved the final submission.

Supplemental Material

Supplemental material for this article is available online.

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