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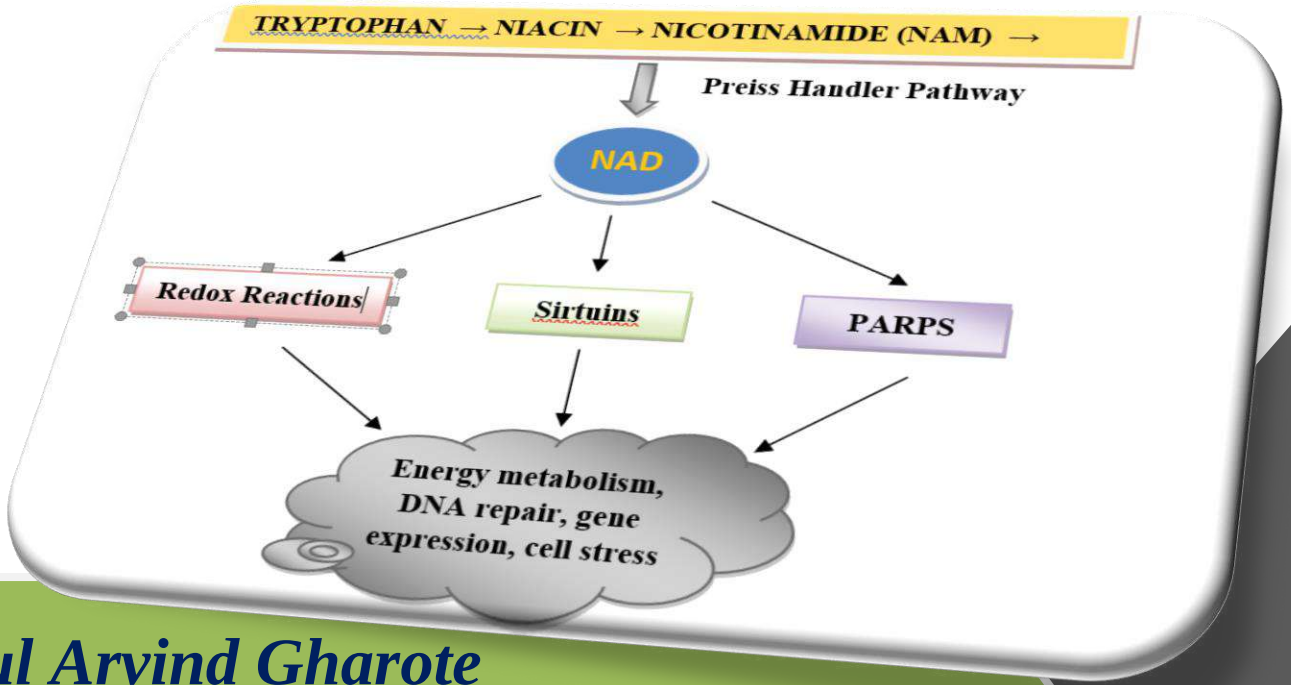

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Potential Role of Nicotinamide Supplementation in Prevention of Global Covid-19 Transmission

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Abstract

Worldwide COVID crisis is deepening; administrative measures such as lockdown have been imposed to check chain of transmission. Yet this pandemic is not getting over, Virus keeps on mutating making vaccine induced immunity ineffective. We need to boost innate immunity so as to prevent viral transmission. Nicotinamide riboside, a vitamin B3 derivative, can be helpful in boosting innate immunity. Recent trials on high dose Nicotinamide have claimed its role in COVID-19 as supportive treatment. The recent Phase II clinical study found that the combination of a nutritional supplementation which included Nicotinamide, along with the standard of care, reduced COVID-19 patient recovery time by nearly 30% compared to standard of care alone. Nicotinamide supplementation in patients suffering from Coronavirus infection may prevent transmission by inhibiting Cytokine production.

Thus, it may be useful in breaking the chain of transmission helping in controlling the pandemic. This is a perspective we need to discuss in detail.

Keywords: Nicotinamide; NAD+; COVID-19; Innate immunity

Introduction

Since its initial outbreak, novel corona virus COVID-19, has and continues to significantly permeate and impact most all aspects of human existence. Subsequent waves of infection and adapting variants-leaves the world grappling in its wake. Regardless of concerted attempts to eliminate this chimeric entity through engineered and administrative controls, such as strict and aggressive vaccination and compulsory lockdown (to name but some), the COVID-19 crisis remains. This paper represents a differing approach.

Herein, we suggest the mass scale distribution and use of Nicotinamide (NAM) supplementation to decrease COVID-19 prevalence. The underlying aim of ubiquitous administration of NAM is twofold: to decrease viral replication and, consequently, reduce the incidence of human-to-human transmission of COVID-19, thus breaking the chain of transmission. There is considerable scientific support for nicotinamide as a potent immunomodulator [1]. The potential of nicotinamide as an antiviral agent, beneficially augmenting the Preiss-Handler Pathway (PHP), may represent a critical component to immunocompetence relative COVID-19: infection, transmission, repair and antibody response [2].

Role of Nicotinamide in Innate Immunity against COVID-19

In the fight against COVID-19, the body's first line of defense is at a cellular level. Upon entry, COVID-19 replicates by utilizing and exhausting cell resources-such as the consequential depletion of the cellular NAD+ reserve. COVID-19 infected cells, control viral replication by activating NAD+ dependent Sirtuin 1 (SIRT-1) (Figure 1).

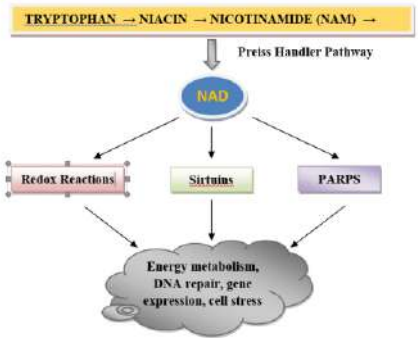

Figure 1: Simple diagrammatic of NAD metabolism and its effect on energy metabolism, gene expression. As illustrated, nicotinamide (NAM) is essential to homeostasis, energy balance, DNA repair; impact on Sirtuins and PARP help reduce viral replication, and consequently - transmission.

SIRT1 activation reduces the NAD+ reserve. Significant NAD+ consumption can result in depletion and a failure of SIRT-1 to control viral replication. This is similar for PARP (Poly ADP- Ribose Polymerase), which is activated by viral entry and controls replication. PARP also utilizes NAD+, the hyperactivation of which lends to further NAD+ depletion and SIRT inactivation, priming cells for subsequent viral replication and pro-inflammatory cytokine release.

An imbalance in NAD+ supply and NAD consuming enzymes have been specifically reflected by clinical features of lymphocytopenia [3]. This feature is unique as viral infection leads to lymphocytosis. A plausible theory for same is extensive activation of PARP during innate immune responses and consequent depletion of cellular NAD+ further leading to depletion of adaptive immune system response; lymphocytosis is tell-tale sign of adaptive immune response [4]. Such observation prompted suggestions to supplement vitamin B3 (niacin, nicotinamide) in-order to boost innate and adaptive responses to SARS-COV-2 infection [5-7]. It is of note also, that elderly, obese and diabetics are deficient in NAD+, and prone to suffer from severe COVID-19 [7].

In a recent Phase II clinical study combination of various nutritional supplementations which included nicotinamide, along with the standard of care, reduced COVID-19 patient recovery time significantly [8]. The medical literature contains much research on the conferred health impacts and safety of nicotinamide. However, the initial findings from this Phase II trial and previous preclinical studies, serve as justification for future, larger studies of B3 vitamins. The protective and strengthening capacity of nicotinamide on lung, gastro-intestinal and immunity, suggests nicotinamide could be used as an adjunct treatment for COVID-19 patients [5,9].

How Can Nicotinamide (NAM) Prevent/ Reduce Transmission?

COVID-19 is transmitted mainly *via* droplet (aerosol) generation: sneezing, coughing and talking [10]. Binding of SARS-CoV-2 to ACE-2 receptor and accumulation of ang2 depletes NAD+ further [11]. Nicotinamide supplementation replenishes cellular NAD+ stores (optimizing PHP), metabolically rescuing infected, depleted cells. NAM administration was observed to reduce viral replication and chemokine secretion in human islet cells infected with Enterovirus, HIV and herpes virus [12]. Conferred benefit is likely in COVID-19, given overlapping mechanisms of viral replication. Mass scale NAM use would ultimately equate to a new reality of decreased viral replication, load and transmission.

As proxy, analyzing the epidemiology of the second wave of COVID-19 in India may serve reference. The state of Maharashtra, India contributes almost 50% of the active national case load. Notably, the staple food of Maharashtra is Jowar (sorghum)-which due to its high leucine concentration [13] inhibits tryptophan and causes metabolically inefficient conversion to niacin (60 mg of tryptophan gets converted in 1 mg of niacin [14] leading to prevalent niacin deficiency. Rather than a slow progression toward overt pellagra, the Maharashtra population is predisposed, in the immediate, to heavy viral infection and susceptibility. Maize, also rich in leucine can lead to niacin deficiency; maize is a staple food in Africa, China, Europe and Mexico. Is it a coincidence that the United States, the highest producer of maize world wide-currently nurses the highest number of COVID-19 cases?

Beyond complexity and difficulties inherent analysis-dietary interplay, NAM (PHP) and COVID-19, may represent a plausible explanation of a modifiable, if not detrimental, risk factor regarding regional distributions in incidence and prevalence. Adapting to COVID-19 by substituting maladaptive behavior's and adopting appropriate practices conducive to cellular and immunological competence is paramount to break the chain of infection. This is important, given that COVID-19 cases continue to accrue regardless of societal habituation, complacent disinterest and fatigue. But, even here, however, it is noteworthy that nicotinamide (and niacin) benefits mental and overall health (mood, stress, addictions, sleep, MSC etc.) beyond lowering COVID-19 predisposition. Further, NAM can promote post COVID-19 recovery [15]; is the return to health a function of NAM repletion?

Sometimes history repeats, imparting wisdom. In the 1700s, pellagra (niacin deficiency) first appeared in Italy [17]. Centuries later, in 2020, during the first wave of COVID-19 Italy were the European epicenter of a coronavirus influenced and, perhaps, predicated upon niacin insufficiency. In the early 1900s, pellagra was rampant in Southern States of USA, due to the deficiency of niacin; as main dietary component was corn. Corn or maize is rich in leucine, which leads to deficient conversion of tryptophan-niacin. Pellagra is now a rare and clinically forgotten entity [18]. China has few reported cases of pellagra [17]. Pellagra and niacin deficiency are diagnosed clinically using the ratio of two urinary metabolites of niacin i.e., N-methyl pyridone and N-methyl niacinamide [18]. Though classical or fulminant niacin deficiency may represent anomaly, subclinical insufficiency may pervade, with the manifestation of tissue specific NAM deficiency greatly misunderstood and underappreciated-individually and globally. Refined wheat flour is low in NAM, although wheat germ and wheat bran contain Nicotinic acid and nicotinamide [19].

It's difficult to prove human susceptibility based on dietary predisposition as result of any deficiency. But supplementation of nicotinamide even if dietary supply is adequate may help in boosting innate immunity and reduced transmission.

Nicotinamide (particularly: 1-methyl-nicotinamide) has been suggested for reducing inflammation in COVID-19 [20]. NAM suppresses MHC class II and ICAM-1 expression and modifies pro-inflammatory cytokine expression, such as: IL-1β, IL-8, IL-6, IL-2. As well, TNFα suppression-which plays a key role in the damaging effect of cellular respiratory burst during Coronavirus infection is attenuated in COVID-19 with NAM administration [5,21] (Table 1).

Table 1: Possible role of Nicotinamide and its role in COVID-19 virus

Mechanism of action
Boost innate immunity [5,6,7]
Prevents PARP hyper activation and
Promotes Sirtuin (Sirt1) function
during viral replication [3]
Destruction of viral proteins [12]
Prevention of transmission [5,21]

Altered NAD+ in Elderly / Diabetes / Metabolic Diseases

Numerous studies have shown an altered NAD+ metabolism with advanced age, diabetes and various metabolic disorders [22]. NAD+ levels are depleted in such persons who are concomitantly at a higher risk of contracting COVID-19 and infection severity. In particular, the elderly population has a slower metabolism due to aging leading to NAD+ deficiency and is at risk of severe COVID-19 infection, only made worst by comorbid conditions of NAD+ reduction such as hypertension, diabetes etc. Administration of nicotinamide supplementation, at high concentration may serve particularly valuable in elderly patients and beckons large scale study. Such study can gauge and provide insight on the prevalence and manifestation of subclinical nicotinamide deficiency. Presently, the role of nicotinamide supplementation relative COVID-19 represents perspective, only. If studied, given its potential benefits, NAM may represent a primary, pragmatic and prudent solution to COVID-19 [23].

Trials of nicotinamide on COVID-19 are also ongoing, including: a Turkish trial gave a nutritional cocktail with nicotinamide in the post COVID-19 recovery phase and monitored the response telephonically. Reported was a 3.5 days lesser time to recovery with nicotinamide compared to placebo. Two trials are, also, currently registered administering 1 gm of nicotinamide for a 14-day study period within an elderly population. Nicotinamide is well tolerated upto 2 gm /day in human trials done before. Nicotinamide improves exercise performance in elderly, thus has a role in reducing COVID induced fatigue as well (Figure 1).

Conclusion

The current and continuous state of the COVID-19 pandemic warrants boosting the innate immunity of the global population at large. Vaccinations are helpful in preventing mortality and reducing morbidity yet, are not efficacious in preventing human-to-human transmission. Further, mutating variants can decrease vaccine effectiveness. Resource burden, including: cost, production, logistics, stability and side effects are but some impediments to expediting COVID-19 vaccinations. Given this precarious reality, the approach of mass scale nicotinamide supplementation to bolster host immune response and compliment other therapies, vaccines especially during lapses in availability, and given the immediacy of NAM's effect may be food for thought. NAM may represent a path forward amidst the cytokine storm, as we sail the waves of COVID-19 toward a clearer horizon.

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