The MOSS NUTRITION REPORT

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Product Review

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SUPPLEMENTAL SUPPORT FOR THOSE ANTICIPATING POSSIBLE SARS-CoV-2 ENCOUNTERS

INTRODUCTION

At the time of the writing of this newsletter, the third week of January 2021, prevalence of COVID-19 is very high or at an all-time high in several locales. Despite this, I rarely am contacted by individuals who are experiencing active COVID-19 and are seeking supplemental and/or lifestyle supportive suggestions. Instead, most inquiries during the last month or so involve requests for preventive measures. As you probably know, there is no shortage of publications making different supplemental recommendations concerning prevention. Unfortunately, many of these recommendations are so cumbersome in terms of the amounts of products and pills that they are not practical for many individuals for many reasons that range from cost to inconvenience. Therefore, with a focus on cost effectiveness and practicality, I have been considering of late, based on my ongoing examination of the large volume of literature that has been and continues to be published on supplemental and lifestyle approaches to SARS-CoV-2 and COVID-19, the one supplement I would recommend on a general basis for those who would like to reduce the risk of adverse health consequences of a SARS-CoV-2 encounter.

Based on a very large body of research, one recommendation of which you are probably aware is vitamin D. However, that is not the one I am going to be recommending. Why? As indicated by the paper "Increased risk for COVID-19 in patients with vitamin D deficiency" by Katz et al (Katz J et al. *Nutrition*, Vol 84, 111106, 2021), the vast majority of the literature on the subject discusses the relationship between deficiency of vitamin D and risk for COVID-19. The authors state:

"In conclusion, the present study has demonstrated that vitamin D deficiency is strongly associated with COVID-19 infection (*P* < 0.001), even after controlling for sex, malabsorption, dental diseases, race, diabetes, and obesity. Perhaps the most important finding was that vitamin D deficiency increased the risk of developing COVID-19 by a factor of 5 after adjusting for age."

The study did not conclude that vitamin D supplementation, based on these findings, would prevent COVID-19 infection. Therefore, Katz et al recommend that studies should be performed on this very issue:

"Prospective interventional studies are required to validate the hypothesis that vitamin D supplementation can be helpful for the prevention and treatment of COVID-19."

Because of this, I would suggest, in the seemingly very possible likelihood that vitamin D supplementation would be helpful for prevention and treatment, it would only apply to individuals who are vitamin D deficient at the time of a SARS-CoV-2 encounter. A similar but lesser known scenario is the relationship between potassium status and COVID-19, which I have addressed in the *Moss Nutrition Report* and will address in much more detail based on current research in future editions of the *Moss Nutrition Report.*

Does research exist that suggests there are supplements that might provide a neutraceutical preventive effect for a wide range of individuals under varying health and lifestyle

circumstances? While many supplements might fit this criterion, based on my objective stated above to consider both cost and practicality in addition to efficacy, I have, based on my examination of the published literature, narrowed my recommendation to one supplement:

- **N-acetylcysteine**

MY RATIONALE FOR RECOMMENDING N-ACETYLCYSTEINE (NAC)

While I have read several papers on the relationship between N-acetylcysteine and COVID-19, the one that influenced me the most in terms of making N-acetylcysteine one of my two recommendations is "Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19" by De Flora et al (De Flora S et al. *The FASEB Journal*, published online July 24, 2020). There are two reasons why this paper influenced me so much. First, and most important, is the information presented, which I am about to review. The second is that it was published in one of the world's leading and most respected peer-reviewed journals, *The FASEB Journal*.

The first quote I would like to feature from this paper provides the primary rationale for routine N-acetylcysteine (NAC) supplementation for COVID-19 patients or those susceptible to COVID-19, glutathione (GSH) depletion. In this quote De Flora et al point out that due to oxidative stress, significant imbalances exist with one of the key enzymes involved in GSH metabolism, glutathione reductase:

"A significant elevation in blood serum glutathione reductase (GR), resulting from oxidative stress imbalance, was detected in COVID-19 patients, especially when admitted to ICU. From an accumulation of literature data, an endogenous deficiency in GSH may underlie the serious manifestations and death from COVID-19."

In addition:

"…NAC is used in a broad range of conditions to restore or protect against GSH depletion and has a wide safety margin."

The impact of NAC on ACE2

As you might expect by now if you have been following my newsletters on COVID-19, no matter what topic is being discussed in relationship to COVID-19, inevitably, all roads seem to lead back to ACE2, so to speak. As you will see in the following quotes, the impact of NAC on COVID-19 is no exception. The connection, in this case, is the relationship between the ACE2 receptors and the SARS-CoV-2 virus, which involves cysteine residues:

"The receptor binding domain of the viral spike proteins and ACE2 has several cysteine residues."

As you will see in the following quote, the ability of the virus to bind to the ACE2 receptor is significantly impaired if the sulfur bonds in both the SARS-CoV-2 spike proteins and the ACE2 receptor are in unoxidized (reduced) state:

"Molecular dynamic simulations showed that the binding affinity was significantly impaired when all the disulfide bonds of both ACE2 and SARS-CoV-2 spike proteins were reduced to thiol groups. These findings are consistent with the view that the reduction of disulfides into sulfhydryl groups completely impairs the binding of SARS-CoV-2 spike protein to ACE2 and provide a molecular basis for the severity of COVID-19 infection due to oxidative stress."

Could this impact of NAC on binding affinity between SARS-CoV-2 and ACE2 be significant in terms of infectivity of the recently discovered, highly publicized, SARS-CoV-2 variant, SARS-CoV-2 B.1.1.7? Based on the following quote from the recently published paper "The high infectivity of SARS-CoV-2 B.1.1.7 is associated with increased interaction force between spike-ACE2 caused by the viral N501& mutation" by Santos and Passos (Santos JC & Passos GA. *bioRxiv*, published online January 1, 2021), it is an interesting thought to ponder:

"This finding shows that the increased infectivity of SARS-CoV-2 lineage B.1.1.7 is associated with the interaction force between Spike RBD Y501 mutant residue with the ACE2 receptor, which in this strain is increased."

Getting back to the De Flora et al paper, NAC has been demonstrated to inhibit the proinflammatory, vasoconstrictive opposite of ACE2 in the renin angiotensin system, ACE/ACE1:

"Furthermore, both animal studies and clinical studies suggested that supplementation of NAC, which is known to attenuate the tolerance to nitrates, modifies the function of the renin/angiotensin system in vivo. Such as effect is probably mediated by inhibition of ACE activity. By blocking ACE, NAC may provide protection from the deleterious effects of angiotensin II, a potentially useful activity in SARS-CoV-2 infection."

Why is NAC so effective in increasing GSH production?

De Flora et al state:

"NAC easily penetrates cells where it is deacetylated to yield L-cysteine thereby promoting GSH synthesis. Therefore, NAC works per se in the extracellular environment and as a precursor of GSH inside cells. Accordingly, all its intracellular effects are mediated by GSH replenishment."

Why is increased GSH production so important with COVID-19?

As I mentioned above, the oxidative stress seen with COVID-19 inhibits the recycling of oxidized glutathione back to reduced GSH, thereby necessitating a GSH production enhancer such as NAC:

"Recycling of GSH increases but cannot match the high consumption in COVID-19 lung disease. This requires new GSH synthesis…"

The authors go on to point out that new GSH synthesis is largely mediated by the enzyme glutamate-cysteine ligase (GCL), activity of which is completely dependent on the availability of intracellular L-cysteine. As noted above, supplemental NAC is an excellent tool to increase intracellular L-cysteine levels.

More on why is GSH so important with COVID-19

Another reason why GSH is so important in terms of COVID-19 is that GSH is essential for optimal immune activity. De Flora et al point out:

"Reactive oxygen species (ROS) and thiol antioxidants, including GSH, regulate innate immunity at various levels, as documented by a broad literature."

More specifically:

"It is noteworthy that GSH not only affects certain factors involved in immunological processes, but it also modifies complex immune reactions such as fever, and there are data suggesting that fever induction is associated with oxidative stress."

One particularly important aspect of the increased immune activity seen with COVID-19 is upregulation of a key part of the immune system known as "complement." The authors begin their discussion of the role of complement in COVID-19 by discussing the general role of complement in innate immune activity:

"Although the complement system is a key mediator of the innate immune response that protects against infectious agents, it also plays a critical role in promoting the inflammatory process that leads to tissue injury."

With the latter aspect of the above quote in mind, it should come as no surprise that complement can be involved in SARS-CoV-2 pathogenesis:

"In particular, complement may be involved in coronavirus pathogenesis, as inferred from the finding that C3 knockout mice infected with SARS-CoV have less lung disease than wild-type mice."

To clarify, C3 is a specific complement fraction that is highly pro-inflammatory. "C3 knockout" means that the mice were genetically bred to produce no C3.

What other complement fractions might be involved with COVID-19? De Flora et al continue:

"Preliminary data provide evidence for activation of complement (sC5b-9 and C5a) in patients with COVID-19, with significantly higher plasma levels in the patients with severe disease than those with moderate disease. Hence, complement activation has been suggested as a novel therapeutic target in COVID-19."

Can NAC supplementation have an impact on complement levels? The authors state:

"In this context, it is noteworthy that administration of NAC (2 x 600 mg/day for 8 weeks) in a placebo-controlled study has been shown to reduce the plasma levels of inflammatory markers, including complement (C3), in peritoneal dialysis patients."

More information on why NAC can be helpful with COVID-19 patients

In addition to what was stated above, why might NAC be effective with COVID-19? De Flora et al point out one way that may be quite significant. First, even though it was stated before, the authors again emphasize:

"NAC works via a broad variety of mechanisms, which inside cells are mediated by GSH replenishment."

With this in mind, consider the impact of NAC on acute respiratory distress syndrome (ARDS), a common finding with moderate to severe COVID-19 patients:

"…NAC has been shown to have protective effects in ARDS. It is well established that reactive oxygen species play a key role in the pathogenesis of the acute lung injury and that the alveolar epithelial lining fluid of patients with ARDS is deficient in GSH, which may predispose these patients to that disease."

The impact of NAC on other viral ailments

Can previous research on the use of NAC with other viral ailments assist us on the use of NAC with COVID-19 patients? To answer that question, consider the following quotes. First, De Flora et al state:

"NAC has been demonstrated to attenuate the incidence and severity of influenza and influenza-like illnesses. It was tested in a double-blind trial, involving 20 Italian Centers, which enrolled 262 subjects of both sexes randomized to receive either placebo or NAC tablets (600 mg) twice daily for 6 months. Both local and systemic symptoms were sharply and significantly reduced in the NAC group. Moreover, only 25% of A/H1N1 influenza virus-infected subjects under NAC treatment developed a symptomatic form vs 79% in the placebo group."

What is the possible reason that NAC supplementation was helpful in the above instance? Again, GSH appears to be the key:

"Infection by RNA viruses induces oxidative stress in host cells, and growing evidence indicates that viral replication is regulated by the redox state of the host cell and that the GSH content contributes to downregulate influenza virus replication."

Another reason is the following:

"It has also been demonstrated that NAC inhibits virus replication and expression of pro-inflammatory molecules in adenocarcinoma human alveolar basal epithelial (A549) cells infected by the highly pathogenic H5N1 influenza virus."

Could efforts to raise GSH levels via NAC supplementation be helpful for smokers in relation to COVID-19 risk?

Several papers have suggested, as you probably would guess, that smokers are at increased risk for COVID-19 related complications. Could GSH levels be part of the picture? De Flora et al point out:

"An analysis of the literature suggests that smoking is most likely associated with the negative progression and adverse outcomes of COVID-19. Exposure to cigarette smoke increases ROS levels and causes a drop in GSH intracellular concentrations. Aldehydes in cigarette smoke deplete the total available GSH pool by reacting to form nonreducible GSH-aldehyde derivatives. GSH depletion accelerates cigarette smoke-induced inflammation and airspace enlargement, and the GSH adaptive response declines with age."

How might NAC supplementation help?

"By increasing GSH production, NAC has the ability to modulate a large variety of smoking-

related end-points and cancer in experimental test systems due to many interconnected mechanisms and properties. In addition, NAC was shown to attenuate several biomarker alterations in a randomized, double-blind, placebo-controlled, Phase II chemoprevention trial in heavy smokers who received NAC tablets (600 mg) twice daily for 6 months."

<u>Some final conclusions from De Flora et al</u>

First, consider the following:

"Almost 60 years of experience in the prophylaxis and therapy of a variety of clinical conditions have established the safety of this drug, even at very high doses and for long-term treatments. Drug repurposing is the fastest strategy toward an effective and accessible treatment against COVID-19 before a vaccine is available, and molecules working via multiple mechanisms of action, such as NAC, are more likely to be effective as compared with drugs having a single target."

With the above in mind, the authors state:

"Based on the herein discussed mechanistic premises, NAC may be proposed both in the prevention and in the therapy of COVID-19, In particular, the oral administration of NAC, at the dose of 600 mg twice daily, may be proposed for preventive purposes aimed at attenuating the risk of developing COVID-19 and its severity during epidemic periods, as we previously demonstrated in the case of influenza and influenza-like illnesses, especially in elderly people and in individuals who suffer from chronic conditions that predispose them to this kind of diseases and increase their severity. Persons who have been in proximity of infected SARS-CoV-2 carriers, including those detected by means of smartphone contact tracing apps, may be an additional target for taking oral NAC in order to decrease the risk of developing COVID-19."

The N-acetylcysteine product from Moss Nutrition, <u>N-Acetyl Cysteine - 120 Vegetarian Capsules</u>, contains 700 mg per capsule. Therefore, based on the recommendations above by De Flora et al, a basic preventive protocol would be 2 caps per day. Because NAC can sometimes cause GI distress, it is recommended that the product be taken with meals in divided doses.