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REVIEW ARTICLE

The Valuable Role of Micronutrients in Improving the Potential for Vaccines to Mitigate Severe Viral Infections (COVID-19): A Perspective on Nutritional Therapy in Medicine

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ABSTRACT

Optimal nutritional status is considered to play an integral role in supporting and regulating immune functions for better resistance and recovery from severe viral infections. Nutrient inadequacies have been associated with poor vaccine responses to various targeted viruses, while improved nutritional status has generally resulted in improved vaccine responses and efficacy. It is plausible that better overall nutritional status may improve the therapeutic potentials of COVID-19 vaccines. This is especially relevant with the variant COVID-19 strains that are currently surfacing. Furthermore, micronutrient compounds, including polyphenols, may possibly offer better vaccine delivery systems, and may also limit the numerous adverse events associated with vaccination (Communicable Disease Control Manual Chapter 2., November 2016). Medical nutrition therapists should therefore be involved with assessing the overall nutritional status of individuals considering vaccination for COVID-19. The diagnosis of possible deficiencies and or inadequacies, and recommendation of appropriate dietary intervention or supplementation can correct for nutrient imbalances where warranted. In so doing, the therapeutic potentials for COVID-19 vaccination may be enhanced - while fortifying both the innate and adaptive immune responses to support improved outcomes in individuals who become infected.

INTRODUCTION

Balanced nutrition, with an emphasis on select nutrients including vitamins C, D and zinc, is considered to play an invaluable role in supporting immune physiology. For this reason, optimal nutrient status is considered by many researchers as an important strategy for preventing and treating many viral infections. Extensive peer-reviewed literature suggests that deficiencies and or sub optimal levels of select essential nutrients are common throughout many demographics of the population, thus elevating the risks for a compromised immune response to viruses, and the potential for severe virus associated complications. Further supporting the valuable role of nutrition, preliminary studies are demonstrating that optimal nutrition may even enhance the therapeutic potential of vaccines to prevent viral infection.

The investigators of a recent clinical trial found that seniors vaccinated for influenza who consumed a nutrient-dense liquid support supplement (rich in vitamins, minerals, protein calories, and enhanced antioxidants) had significantly higher HINI antibody titers, and influenza-activated lymphocytes compared with those seniors that consumed the regular liquid supplement. Additionally, the intervention group who consumed the nutrient-dense liquid supplement required less medical treatment for fever and were prescribed less antibiotics. The authors concluded that the extra nutrient support enhanced immune response to the influenza vaccine and resulted in more favorable outcomes (Langkamp-Henken B et al., 2006). Wouters-

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Wesseling W et al. (2002) found similar benefits and concluded that a complete liquid nutrition supplement rich in antioxidants demonstrated a positive flu vaccine immunization antibody effect, as indicated by significant increase in the antibody titers for influenza strains A/Sydney/5/97. The authors recommended that larger clinical trials on nutrition and vaccines be explored.

A relatively recent double-blinded clinical trial looked at the effects of vitamins A and D supplementation on influenza vaccine response in children ages 2 to 8 years. The children with low baseline vitamin A and D status showed significant improvements in flu vaccination response when supplemented with oral bolus of vitamins A and D (20 000 IU retinyl palmitate, and 2000IU of cholecalciferol) along with vaccination; as evidenced by increased hemagglutination inhibition antibody response. The authors concluded that supplementation with vitamins A and D improves influenza vaccine response in children that are deficient in these nutrients, warranting future clinical trials (Patel N et al,.2019).

Iron deficiency anemia is common in many third world countries, and it is understood that iron deficiency impairs adaptive immunity, which is known to be common with African infants at time of vaccination. A recent randomized clinical trial follow-up study evaluated the effects of iron supplementation on iron deficient Kenyan infants. The main findings showed that Kenyan infants that were anemic and iron deficient experienced a reduced response to diphtheria, pertussis, and pneumococcal vaccines, while the primary response to measles vaccine may be increased by iron supplementation (higher anti measles IgG, seroconversion and IgG avidity with iron supplemented infants) at the time of vaccination. The authors concluded that correction of iron deficiency anemia in Kenyan infants during early infancy may improve vaccination response (Stoffel NU et al,.2020).

Interestingly, other vaccine targets including those utilized in cancer treatment have been suggested to perform better with lifestyle modifications including nutrition, calorie restrictions and physical activity. Hance KW et al. (2010), postulate that many protective lifestyle factors in the primary cancer prevention setting may pose as important adjuvants for cancer vaccines. They observed that modulation of energy balance through exercise and nutrient metabolism in the tumor microenvironment represent the most promising partner for therapeutic cancer vaccines. They also noted that vitamin E succinate holds strong promise for potentiating vaccine effectiveness. Vitamin E succinate appears to mediate some of its chemopreventive and immunomodulatory effects via the inhibition of COX-2 activity and PGE2 production in target tissues. Three preclinical trials have evaluated vitamin E succinate in combination with dendritic cell based (DC-based) cancer vaccines. In one of the studies by the same authors, a vitamin E succinate formulation, that was shown to be more soluble in aqueous solutions, enhanced the anti-tumor efficacy of DC-based vaccines against 4T1 breast and Lewis lung carcinomas. The authors concluded that adjuvant properties of vitamin E succinate is a promising candidate for future complimentary cancer vaccine research (Hance KW et al,. 2010).

The extent of evidence showing potential synergistic effects of micronutrient supplementation on vaccine efficacy warrents knowledge translation to clinical applications of COVID-19 vaccines. To ensure optimal COVID-19 vaccine response, strong consideration should be undertaken to improve the nutritional status of those receiving COVID-19 vaccines. There is ample evidence showing that select nutrient inadequacies and or deficiencies compromise various vaccine responses.

With reference to a risky population group, a systematic review and meta-analysis of 2367 participants was associated with reduced seroprotection to both influenza A and B virus for those that were vitamin D deficient (Rayman MP et al,. Jan 28 2021).

It is highly plausible that poor COVID-19 vaccine response may occur in population groups that are experiencing varying levels of nutrient deficiencies. This is especially the case with many elderly, particularly those residing in care facilities where a considerable percentage of seniors are presenting with known deficiencies in vitamins C, D, and zinc (Ziccarelli V,. 2020). These particular nutrients have been shown to not only improve immunity against viruses, while regulating immune reactions to prevent severe viral complications; but they have been shown to improve influenza vaccination immune response in the elderly population. A systematic review and meta-analysis of 2367 participants (Rayman MP et al,. Jan 28 2021) was associated with reduced seroprotection to both influenza A and B virus for those that were vitamin D deficient. Vitamin D status has been associated with improved COVID-19 ICU patient status. Patients with higher vitamin D levels experience significantly less severe complications and mortality rates (Munshi R,. 2020).

Micronutrient inadequacies and or deficiencies are not exclusive to the senior population. For instance, many adults at varying ages may be at risk for sub-clinical and

or low intake of essential nutrients that influence immune functions and adaptive immunity. According to a national survey, up to 31% of the American population have been reported to be consuming dietary vitamin C below the recommended levels for adequate intake (National Nutrition Survey,. 2016). Poor intake patterns of fruit and vegetables, the primary dietary source for many antioxidant nutrients, have also been reported in Canada. A study analysis using information from the Canadian Community Health Survey showed that among the 77% of those Canadian adults surveyed – the intake of fruit and vegetable servings were less than 5 times daily, demonstrating amounts well below the recommended levels for health protection. The authors recommended more educational strategies tailored at the community and individual level, to promote better fruit and vegetable intake behaviors for Canadians (Dehghan M, et al,. 2011).

People with sub-optimal nutrient status may be at an elevated risk for severe complications associated with the COVID-19 virus. It is therefore prudent that health care professionals look closely at dietary intake patterns of individuals, assess for potential nutrient inadequacies, and under the guidance of qualified medical nutrition therapists, correct nutrient deficiencies with appropriate dietary intervention, including supplementation when warranted. Correcting nutritional inadequacies will likely potentiate the therapeutic effects of the COVID-19 vaccines for those individuals that are at risk for nutrient deficiencies or sub-optimal intake – or at minimum improve overall nutritional status and consequently enhance innate and adaptive immunity.

CAUTION IS WARRANTED WITH IRON STATUS

Although adequate iron nutritional status may be important for immune functions and potentially better vaccination response – it is important to note that recent studies with COVID-19 have shown associations between altered iron homeostasis and hyper-inflammation leading to possible disease progression. For this reason, some researchers have suggested to evaluate iron parameters in COVID-19 patients including transferrin saturation, plasma iron levels, hepcidin, and non-transferrin bound iron. This will help to evaluate for possible iron overload. In those cases of excess iron levels, future clinical trials should look at evaluating the potentials for iron chelators and hepcidin modulators to help mitigate the hyper-ferritinemia to limit the excessive viral inflammatory response (Edeas M,. 2020) . In contrast, other researchers state that the ferritin surge characteristic for severe COVID-19 does not indicate iron overload, it is likely a marker for acute infection. Recommendations to use iron chelators or limit iron deficiency anemia therapy may in fact increase hypoxia and ultimately harm the health of patients, particularly infected pregnant women (Gromova OA,. 2020).

Thus with reference to iron, caution is recommended to ensure adequate intake primarily from dietary sources, and when supplementing, to maintain well within the DRI recommendations to prevent excessive intake while supporting adequate serum iron levels. Indeed, a recent retrospective study has shown that COVID-19 patients with low serum iron levels are associated with greater severity and mortality of the disease. There may be some merit to correcting low iron levels, as other studies on pulmonary function have shown low iron status to increase allergic asthma symptoms, whereas supplementing with iron helped to reduce chronic cough and inflammation in the lungs. The authors concluded that low serum iron may be an independent risk factor for death with COVID-19 patients (Zhao K,. 2020). Iron is therefore a nutrient that should be closely monitored – to promote normal serum levels while limiting risks for both deficiency and or excess. Until more conclusive evidence is available, the latter may be a more logical medical nutrition approach supporting better vaccination response and or recovery if infected.

NUTRIENTS HAVE POTENTIAL FOR LIMITING VACCINATION-INDUCED ADVERSE EFFECTS

It is noteworthy to also look for therapeutic strategies to help not only improve vaccine host response, but also reduce vaccination induced adverse effects. Some researchers suggest that nutrition may play a valuable role accordingly. For instance, it has been suggested that vitamins, flavonoids, and plant oils may offer immune-modulating effects favoring vaccine response while reducing adverse events (Vlajdy M,. 2011).

Over the centuries vaccinologists have researched the development of life saving vaccines based on live attenuated viruses, bacteria and toxoids – with current research emphasizing vaccine adjuvant discovery using less risky viral and bacterial vectors. In order to further lessen the risks for adverse reactions to vaccinations; vitamins, flavonoids and plant oils are suggested to possess immune-modulating properties that may potentiate vaccines and also serve as safe and effective delivery systems for vaccines – with possibilities to reduce adverse reactions to vaccines (Vlajdy M,. 2011).

It has been reported in the literature that there are those groups of people within the population that are at elevated risk for adverse reaction to the COVID-19 vaccine, such as those people with a history of severe allergies. There have also been reports of mild to moderate short term adverse reactions by some adults (3 months post vaccination) including mild pain, swelling, redness, or fever at the vaccination injection site; or mild headache or fatigue (Al-Worafi Y et al,. 2021). As suggested for other vaccines, perhaps nutrients such as vitamin D, polyphenols, and plant oils may help with modulating immune reactions to mitigate adverse reactions. These are important areas to consider, as there may be potentials for synergetic effects with nutraceutical and or functional food components to work with COVID-19 vaccines for better therapeutic outcomes.

Beyond the essential nutrients there are thousands of antinutrients and nutrient compounds found in foods, especially of plant origin. An example of a particularly health protective group of antinutrients are the polyphenols. Polyphenols include catechins found in green tea, quercetin found in many fruit and vegetables such as onions and apples, gallates and proanthocyanidins found in red grapes. Preliminary studies are showing that polyphenols may offer potent antiviral properties limiting viral replication through mechanisms such as coronavirus enzyme (protease) inhibition, showing potentials as novel therapeutic treatments for COVID-19. Authors suggested that new processing and formulation technologies may provide for optimized solubility and delivery systems of naturally derived antiviral bioactive compounds to adapt them as antiviral drugs and functional foods; as potential preventative and treatment options against COVID-19 (Chojnaka K et al,. 2020).

Other preliminary polyphenolic work shows chemo-preventative effects against various cancer lines, with cancer vaccine potentiating properties (Giffoni de Carvalho JT et al,. 2020). These vaccine potentials may apply to vaccines for COVID-19.

CONCLUSION

Researchers should further evaluate all available opportunities to overcome the continued challenges resuting from viral infections. As the COVID-19 virus continues to evolve, genetic variants may pose even greater risks for controlling transmission and managing outcomes in those individuals who become infected. In cases where patients or population groups are at risk for micronutrient deficiencies, emerging evidence suggests that optimizing nutritional status is advisable for a more effective COVID-19 vaccine response. Engaging health care professionals with expertise in medical nutrition to implement strategies for assessment, and determine the most appropriate nutritional interventions, should be an integral part of public health strategy. Vaccine researchers should consider micronutrients and nutritional compounds (a-nutrients) as potential adjuvants for supporting efficacy and reducing adverse reactions to COVID-19 vaccines.

REFERENCES

Al-Worafi Y, et al.(2021) Adverse reactions of COVID-19 vaccine among frontline workers in Fujairah, UAE. https://doi.org/10.21203/rs.3.rs-137445/v1

BC Centre for Disease Control (2016) Communicable Disease Control Manual Chapter 2: Immunization Part 5 – Adverse events following immunization – http://www.bccdc.ca/resource-gallery/

Cahill L, Corey PN & El-Sohemy A (2009) Vitamin C deficiency in a population of young Canadian adults. *American Journal of Epidemiology*, 170(4) – https://doi.org/10.1093/aje/kwp156

Chojnaka K, et al. (2020) Phytochemicals containing biologically active polyphenols as an effective agent against COVID-19 inducing Coronavirus. *Journal of Functional Foods*, 73 – https://doi.org/10.1016/j.jff.2020.104146

Dehghan M, Akhtar-Danesh N & Merchant AT (2011) Factors associated with fruit and vegetable consumption among adults. *Journal of Human Nutrition and Dietetics*, 24(2) – https://doi.org/10.1111/j.1365-277X.2010.01142.x

Edeas M, Saleh J & Peyssonnaux C (2020) Iron innocent bystander or vicious Culprit in COVID-19 pathogenesis? *International Journal of Infectious Diseases*, 97 – . https://doi.org/10.1016/j.ijid.2020.05.110

Giffoni de Carvalho JT, et al. (2020) The immunoregulatory functions of polyphenols: Implications in cancer immunity. *The Journal of Nutritional Biochemistry*, 85 – https://doi.org/10.1016/j.jnutbio.2020.108428

Gromova OA, et al. (2020) COVID-19 and iron deficiency anemia: Relationships of pathogenesis and therapy, obstetrics, gynecology and reproduction. 14(5) – https://doi.org/10.17749/2313-7347/ob.gyn.rep.2020.179

Hance KW, et al. (2010) Combination of physical activity, nutrition, or other metabolic factors and vaccine response. *Front Biosc*, 12 – https://doi.org/10.2741/2444

Kang Zhao, et al. (2020) Serum iron level as a potential predictor of Coronavirus disease 2019 severity and mortality: A retrospective study. *Open Forum Infectious Disease*, 7(7) – https://doi.org/10.1093/ofid/ofaa250

Langkamp-Henken B, et al. (2006) Nutritional formula improved immune profiles of seniors living in nursing homes. *Journal of the American Geriatrics Society*. 54(12) – https://doi.org/10.1111/j.1532-5415.2006.00982.x

Munshi R, et al. (2020) Vitamin D insufficiency as a potential culprit in critical COVID-19 patients. *Journal of Medical Virology*, 93 – https://doi.org/10.1002/jmv.26360

National Nutrition Survey- US: NHANES. Nutri-Facts Understanding Vitamins and More 2016 (March 30). https://www.nutri-facts.org/en_US/news/u-s—nhanes.html

Patel N, et al. (2019) Baseline serum vitamin A and D levels determine benefit of oral vitamin A & D supplements to humoral immune responses following pediatric influenza vaccination. *Viruses*. 11(907) – https://doi.org/10.3390/v11100907

Rayman MP & Calder PC (2021) Optimising COVID 19 vaccine efficacy by ensuring nutritional adequacy. *British Journal of Nutrition*, 1-2 – https://doi.org/10.1017/S0007114521000386

Stoffel NU, et al. (2020) Iron deficiency anemia at time of vaccination predicts decreased vaccine response and iron supplementation at time of vaccination increases humoral vaccine response: A birth cohort study and a randomized trial follow-up study in Kenyan infants. *Frontiers in Immunology*, 11(1313)- https://doi.org/10.3389/fimmu.2020.01313

Vlajdy M (2011) Immunomodulatory properties of vitamins, flavonoids, and plant oils and their potential as vaccine adjuvants and delivery systems. *Expert Opinion on Biology Therapy*, 11(11) – https://doi.org/10.1517/14712598.2011.623695

Wouters-Wesseling W, et al. (2002) Effect of a complete nutritional supplement on antibody response to influenza vaccine in elderly people. *Journal of Gerontology: Medical Sciences*, 57A(9) – https://www.researchgate.net/profile/Wendeline-Wouters-Wesseling

Zhao K, et al. (2020) Serum iron levels as a potential predictor of Coronavirus disease 2019 severity and mortality: A retrospective study. *Open Forum Infectious Diseases*, 7(7) – https://doi.org/10.1093/ofid/ofaa250

Ziccarelli V (2020) Nutrition therapy for severe viral infections (COVID-19): Recommendations and considerations for integrative medical treatments. *Journal of Orthomolecular Medicine*, 35(1) – https://isom.ca/article/nutrition-therapy-for-severe-viral-infections-covid-19/