

A NARRATIVE REVIEW ON SYNERGISTIC ACTION OF VITAMIN D, GLUTAMINE AND ONCOTHRAD IMMUNOMODULATORS IN INTERFERON SIGNALLING AND COVID 19

SYNERGISTIC ACTION OF VITAMIN D, GLUTAMINE AND ONCOTHRAD IMMUNOMODULATORS IN INTERFERON SIGNALLING AND COVID 19

Dr Sunayna Juneja^{1*}, Dr Yeshwant Lamture², Dr Shubhi Gupta³, Dr Chetan Agrawal⁴

¹MBBS Intern, Department of Orthopaedics, Jawaharlal Nehru medical college, Datta Meghe Institute of Medical Sciences (Deemed to be University), Wardha, Maharashtra, India.

²HOD & Prof, Department of Surgery, Jawaharlal Nehru medical college, Datta Meghe Institute of Medical Sciences (Deemed to be University), Wardha, Maharashtra, India.

³MBBS Intern, Department of Orthopaedics, Jawaharlal Nehru medical college, Datta Meghe Institute of Medical Sciences (Deemed to be University), Wardha, Maharashtra, India.

⁴ Junior Resident, Department of Emergency Medicine, Index Medical College and Research Centre, Indore, Madhya Pradesh, India.

***Corresponding Author:**

Abstract

The reason behind the Novel Coronavirus disorder 2019 (COVID-19) is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was found in Wuhan, China, in December 2019. The investigation into the best pharmacotherapy continues as it makes rapid progress in covering a wide range of nations. It is known that coronaviruses, such as SARS-CoV-19, can mask Associate in Nursing stand back from the host organism's antiviral responses. Antiviral (IFN), a family of cytokines that plays a critical role in antiviral resistance concerning the body's defense mechanism and has been used therapeutically for persistent viral infections, mediates these responses. OncoTherad, a reliable and effective adoptive immunotherapy for the treatment of non-muscle invasive bladder cancer (N.M.I.B.C.), will increase IFN signaling and be shown to be a promising recovery strategy for COVID-19 in a trial that reflected the rapid recovery of a 78-year-old NMIBC patient with comorbidities. This takes into account targets to determine the viable synergistic motion of OncoTherad with vitamins like zinc and glutamine, vitamin d. These microelements play a crucial role in strengthening the body's defenses and fighting off pathogens through various mechanisms. For example, vitamin d is anti-inflammatory and also helps in the prevention of tissue injury by inhibiting cytokines. Zinc is essential for the development and proper functioning of immune cells, as well as for preventing viral replication. Glutamine acts as a fuel reservoir for immune cells and also possesses antioxidant properties. Therefore, providing adequate nutritional support from micronutrients can have a positive impact on the outcome of COVID19. have been validated to facilitate immune responses mediated with the aid of using I.F.N. signaling, in addition to the ability of this mixture in regulating immune characteristic within the remedy of COVID-19. This article briefly focuses on how micronutrients like zinc, vitamin D, and glutamine interact with the synergistic presence of interferons and oncotherad in the therapy regimen for COVID-19.

Keywords: COVID-19, SARS-CoV-2, Interferon, Immunity, zinc, glutamine, vitamin D, OncoTherad

INTRODUCTION

Coronavirus named 'covid-19' or '2019 novel coronavirus' via way of means of the World Health Organization (WHO) is going for walks the display for the continued outbreak of pneumonia which were given opened up at the start of December 2019 close to in Wuhan City, Hubei Province, China. (1)

A near communion among the coronavirus and the body's defence machine of a person consequences in variegated miscellaneous medical manifestations of the SARS-CoV-2 sickness. While antibody production after antigen exposure either from pathogen or vaccination are considered necessary against coronavirus, the cells of the natural immune system, including macrophages, might also additionally lead to the sickness development in a few cases. Macrophages have proven a superb manufacturing of IL-6, advocating they will make contributions to the immoderate infection in COVID-19 sickness. Macrophage Activation Syndrome might also additionally, in addition, elucidate the excessive serum stages of C.R.P., which might usually be missing in viral disease. In adaptive immunological reaction, it is indicated that cytotoxic CD8+ T cells display operative expenditure patterns, which includes the expression of NKG2A, PD-1, and TIM-3. As coronavirus limits pathogen presentation with the aid of using negative regulating MHC elegance I and II molecules with, consequently obstructs the T cell-mediated antibody reaction, B cell-mediated antibody reaction additionally act as widespread catalyst. Particularly IgA reaction seems to be higher and greater enduring over IgM reaction. In addition, IgM and IgG antibodies exhibit kinetics likewise in coronavirus disease. (2)

Several vitamins possess the quality of harmonizing the natural immune system along with the acquired immune system, and act as a critical component against viral disease. The discovery regarding dependable, collaborative moves amongst vitamins, in addition to among vitamins and drugs, might also additionally supply the improvement of complicated formulations that capabilities incredibly from the man or woman components. In this context, positive atypical vitamins, specifically zinc, vitamin D and glutamine, were scrutinized. These vitamins are referred to as ability adjuvants in the treatment and prevention of viral disease. (3)

VITAMIN D

Vitamin D is one of the fat-soluble nutrition which performs diverse crucial functions in your body, Sunlight is the key source of VITAMIN D, human body utilizes ultraviolet rays of the sun to convert cholesterol into vitamin d(4)

It is a key nutrient your body demands to invigorate and strengthen your bones, furthermore, it is require for the appropriate and effective Functioning of your immune system — that is body's first line of defence towards contamination and disease.(5)

vitamin D deficiency is also mentioned to hike a process named the "cytokine storm" (6). These cytokines result in intense tissue injury and promote disease intensity as well as severity. A cytokine storm denotes the unrestrained exposure of pro-inflammatory cytokines that occur as a result of infection. This imbalance in the level of cytokines cause massive tissue injury and progression of disease and severity. (7)

These cytokine storm also occurs in covid 19 infection if left untreated and worsen the condition of the patient by immunopathogenic damage that leads to ARDS(acute respiratory distress syndrome) also, tissue degeneration, multiple organ failure and eventually death. Many research have been published and postulated that vitamin D supplementation is able to minimize complexity and hindrance, which is resulted due to cytokine storms and uncontrolled inflammation in patients with COVID-19(8)

Thus, it's far more important to encompass diet d in covid-19 treatment after testing its level.

ZINC (Zn)

Zinc is a micronutrient which is an essential element needed by the body in small quantities. It is necessary since many constitutional activities, especially growth and proper functioning of immune cells like t-cells, white blood cells, specially neutrophils, immune gadget relies upon the enough accessibility of this micronutrient. In past few long time, lots of researches have done to persuade the prognosis of diverse sicknesses by means of supplementing zinc, together with diarrhoea, continual hepatitis C, Shigellosis, leprosy, tuberculosis, pneumonia, acute decreased respiration infections, as well as recently for covid-19 also (9) the participation zinc (Zn) in heterogeneously influencing direct and indirect antiviral properties, is also well established which can be obtrusive through distinctive mechanisms. A regime of zinc adjuncts has the capability to strengthen resistance against viral infection, each innate in addition to humoral, and to regenerate exhausted immune cellular characteristics or to decorate common immune mobile property, particularly in immunodeficient or immunocompromise sufferers. Zinc can perform distinctly and is very effective when administered in combination with the conventional remedies against the virus. Zinc can additionally secure or balance the cellular surface that prevent the access of viruses into the cellular. Except this, it became revealed that Zn can also suppress viral replication through alteration in the processing of proteolysis replications polypeptides by its misfolding,(10) further Zn can impact numerous capabilities of transduction by monocyte signalling furthermore by launching cytokine-induced seasoned-anti-inflammatory response and interrupt the bond of white blood cells feature-related antigen I to Intercellular

adhesion molecule1, therefore control inflammation. this could explain the reduction in infection skilled by means of humans taking zinc gluconate / glycine (Z.G.G.) capsules to deal with CHD. Rhinitis caused by allergy and Chronic cough have numerous general signs and symptoms, and zinc, gluconate/glycine additionally reduces the signs and symptoms of allergic rhinitis (R.A.). Focal stimulation multiplied ICAM1 expression, and leukocyte recruitment to lesions of epithelium is a usual components. Zn ions perhaps be a critical element due to the fact they could block the coupling of H.R.V. and LFA1 with ICAM1. (11)

Thus including zinc in covid19 treatment regimens is an effective and wise measure as it helps in decreasing severity as well as mortality.

INTERFERONS

When cells are diseased through a virulent disease, viral pathogen-related molecular patterns (PAMPs) could be outstanding via diverse intracellular T.L.R. reputation receptors (P.R.R.s), such as T.L.R.s. Like T.L.R. 2, T.L.R. 3, T.L.R. 4, T.L.R. 7, T.L.R. 8 and T.L.R. 9 play a huge element in the identity of chromosomes (R.N.A. and D.N.A.) precise to the viral genome. Sure viruses are able to steer clear of TLRs and can be preferred through a few other intracellular PRRs present withinside the cytosol. in spite of the diverse sort of P.R.R.s that may be induced, the antiviral immune reaction after the PAMP-PRR interaction embodies similar signalling pathways. normal, the popularity of viral antigen is accompanying the release of severe inflammatory cytokines, particularly IFNs, that have a massive antiviral and antiproliferative movement (12) specifically type 1 interferon.

interferons (I.F.N.I.s) were primary found 60 years before a classic study with lindenman and Isaacs that found IFNIs have antiviral activity in great detail of the body's first line of defense. Human interferons1 include thirteen Comparable IFN α with eighty percent lower homology and single IFN ω , κ , ϵ and β , with less homology (30-50%). Type I interferons (I.F.N.I.) are a separate member of the cytokines family that combines with the type I interferon receptor and are made from the IFNAR1 and IFNAR2 transmembrane subunits. Receptors originate from an in vitro zone that combines I.F.N.I., a transmembrane helix, and an intracellular unstructured region (ICD) which combine J.A.K. and STAT(13)

with respect to immunological factors , Interferons are capable of 3 predominant features: 1. To spark off against viral country at inflamed region and also at surrounding tissue which helps in prevention of viral disease. 2. Regulate the body's natural immune system, including presentation of pathogens and also have pathogen killing capabilities which limit the cause of inflammation. 3. stimulating the body's antibody response mechanism in order to improve the affinity against antigen, specifically T lymphocytic and B lymphocytic response (14). considering interferons as an energetic cell, their antigen-presenting and monitoring efficiency is highly essential. IFN-Is speak among cells towards pathogens and feature a crucial position withinside the body's defence mechanism, consisting of stimulating macrophages and herbal killer (NK) cells. Opposing augmenting and suppressive indicators are triggered with the aid of using host factors. (15)

IFN-Is purpose flu-like signs, which can be determined in diverse diseases. These signs might also additionally have a position in alerting someone of his/her sickness, which allows you to restrict ailment-unfold to different individuals. Coronavirus infection has been proven to inhibit interferon mechanisms withinside the infected individual via more than one pathway. A restrained interferon reaction minimizes the presentation of antigen; thus, it also decreases the adaptive immunological response against the virus. Coronavirus infection enforces techniques to avoid the defence response with the aid of using antagonizing IFN-I brought on signalling pathways. This dampening technique is surprisingly related to the ailment severeness and elevated death rate. (16) Across the deadly instances of Covid-19 infections, it is observed that the entry of inflammatory cells is increased. In a small version of Covid-19 infection, disbalance between inflammatory molecules and interferon had been proven as a primary reason for deadly lung inflammation. (17)

ONCOTHEAD

Onco Therad compound is made up of steel salts and phosphate in nanometric form and is related to a glycosylation of protein with a size of 420-530 nm. This new therapy by nanomaterial encourages the body's defence system to eradicate malignant tumours and might be a favourable approach in opposition to coronavirus infection. It is a new therapy via an intravesical approach of immunizing along with antineoplastic qualities in favour of medical care of N.M.I.B.C. However, surgical transurethral resection is the essential remedy for N.M.I.B.C., which is observed by intravesical B.C.G. immunotherapy to prevent tumour development and reduce recurrence. More precisely, the induction of the body's defence system caused by OncoTherad by Toll-like receptor 2 and 4 occurs via phosphorylation of hydroxylated amino acids like tyrosine, threonine and serine through compounds containing salts of phosphate, which leads to the actuation of stimulator of interferon genes, along with subsequent enhance in the production of IFN α and IFN γ . The enhancement inside the generation of I.F.N.s encourages the actuation of T lymphocytes, antigen-presenting cells along with phagocytic cells, concluding to the prime efficacy of OncoTherad inside the medical management of bladder, majority of malignant tumours whenever correlated to B.C.G. On experimenting on rodents and puppies it highlighted that it is capable of lower

the appearance of receptor activator of nuclear element κ B (RANK) and receptor activator of nuclear element κ B ligand (R.A.N.K.L.) reaction and, consequently preventing the spread of cancer and neutralize its development.

.A case report was made to detect the action of this immunotherapy on a covid19 positive 78 year old patient with nmibc. The patient received oncotherad prior to hospitalization. It was observed that that symptoms improved after 6 days, and on the 8th day, there was significant improvement and the on the 10th day, the patient was discharged. It was observed that the patient showed progressive and rapid recovery in a shorter time as compared to the previous study. In a Chinese language, look out of 100 sufferers, 86 sufferers have been discharged after sixteen days of hospitalization, with a maximum of the person on the 7th day showing radiologic deterioration and development on the 14th day.

according the record file of immunological remedy along oncotherad, 33 molecules associated with the metabolic kingdom have been diagnosed with the aid of delafori et al at e entrance and 39 on improving the hospital circumstance and after the hospital stay. Thinking about patents having coexisting morbid conditions along with thier age means that immunological therapy with oncotherad exhibit a protecting position on the affected person, stopping the development of disease to its maximum excessive level and encouraging rapid recuperation with no use of intensive care.

(18)

GLUTAMINE

Glutamine is the principal aminoalkanoic acid withinside humans, which encompasses sixty per cent of the general collection of unfastened aminoalkanoic acids. The main synthetic sources of (Levo)glutamine distributed in protoplasm are stratified muscle, fat-storing tissue, and the respiratory unit. (levo)glutamine perform the majority of nitrogen transportation out of stratified muscle towards internal organ. (Levo)glutamide serves as a number one gasoline for lots hastily dividing cells, such as R.B.C.s, colonocytes, lymphocytes, and fibroblasts. (19) Glutamine performs a position in basilar stability vis the manufacturing of ammonium withinside the excretory. Their oxidated shape NH_2O affords the raw material for the production of pyrimidines and purines vital in manufacturing genetic material. Likewise, it is a pioneer of an effective antioxidant that is glutathione which is endogenously manufactured. It belongs to the most investigated aminoalkanoic on a couple of factors of scientific dietary care, such as situations inclusive of G.I.T. diseases, observe of tumours, burned trauma, HIV/ AIDS, and persistent lesion control and covid 19. (20) furthermore, (Levo)glutamide has proved to be frequent as a reservoir of fuel for the body's defence mechanism, inclusive phagocytic cell and white blood cells, which might be required to supply unique immunostimulatory results. Newly, (Levo)glutamide and glutamate-derivative aminoalkanoic biogenesis was tested as an essential element to be necessary for the production collagen tissue in fibroblastic cell along with demarcation of myofibroblastic cell inside the respiratory system, As formerly stated in several breathing viruses, coronavirus is mentioned presently to intention the infected body, consisting of myofibroblastic, showing ACE2 receptors and induction of ARDS, Nutritional dietary supplements along with L- Glutamine improve immunological device particularly through inhibition of inflammatory responses. Our outcomes propose including intestinal L-glutamine to the everyday nutrients withinside the onset duration of Covid-19 contamination can also additionally result in a discounted medical institution life and result in uncommon want for ICU. This look at estimate the results of L-Glutamine usage on administrated duration, sizable medical attention, along with deaths due to coronavirus sufferers at the side of decrease respiration tract involvement. In contrast sufferers provided with L-Glutamine confirmed shorter period of hospitalization and want for extensive care than people who did now no longer use L-Glutamine. This become the primary examine withinside the literature analyzing the consequences of immune dietary supplements along with L-glutamine brought to traditional contemporary remedies at the route of Covid

-19.

(21)

Conclusion

Along with the development of the SARS-CoV-2 outburst, there's a pressing want in recognition of techniques which could participate in a fight against coronavirus infection. OncoTherad With Immunotherapy has turned out to be a secure as well as a powerful withinside the remedy of Non muscle invasive bladder cancer via way of means of growing the signaling related to Interferons and cytokines which has a crucial ability withinside of stimulation of the body's natural defence against any pathogen including virus.(22) Zinc, nutrition D and glutamine vitamins, and the OncoTherad immunomodulator act as activators of interferon manufacturing and, therefore, display big synergistic capability withinside the remedy of COVID-19, they're necessary against viral response, with emphasizing in the involvement of those vitamins which take part in interferon signaling, prompting an adjunctive and synergic healing capability with OncoTherad to modulate the defence mechanism withinside the remedy of coronavirus infection. Hence, the capability useful function of those compounds at some stage in contamination via way of means of SARS-Cov-2 justifies the want for pre-medical and medical research that validate their mixture and standardize the dosages that offer the best advantage to the patient."

This evaluation examined the position of elements like zinc, vitamin C, also vitamin D in body's defence system, as these micronutrients have the strongest grounds in favour of natural immunity boosting process.(23) In this situation, the research cited above shows that zinc and vitamins C and D are significant elements of the body's defence machine and exhibit synergic talents in numerous levels in immune system, including assuring the fundamentals of organ boundaries and properties of immune cells that built body's immune systems. Thus, any inadequacy or shortage of these fundamental elements, which are found synergistically in adherent and tight-junction proteins, can lead to deterioration of upper mucosal lining, making them in all likelihood particularly vulnerable to invasion by compound pathogens. by coronavirus. Universally, the scientific research shows that adjunct therapy with nutrients zinc, vitamin D, along with vitamin C can reduce viral respiratory tract infection. For this reason, supplementation with such nutrients with respect to SARS-CoV-2 outbreak can be described as an easily accessible, convenient, coffee fee diploma that can be helpful in meeting the growing need for vitamins in the event of contact with the virus and That initiation of immune responses similar to those that reduce the risk of excessive development and the outcome of this coronavirus contamination..(24)

REFERENCE

- Hanaei S, Rezaei N. COVID-19: Developing from an Outbreak to A Pandemic. Arch Med Res. 2020 Aug;51(6):582–4.
- Paces J, Strizova Z, Smrz D, Cerny J. COVID-19 and the Immune System. Physiol Res. 2020 Jun 30;379–88.
- Read SA, Obeid S, Ahlenstiel C, Ahlenstiel G. The Role of Zinc in Antiviral Immunity. Adv Nutr Bethesda Md. 2019 Jul 1;10(4):696–710.
- Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection [Internet]. [cited 2021 Aug 29]. Available from: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0239799>
- Bivona G, Agnello L, Ciaccio M. The immunological implication of the new vitamin D metabolism. Cent-Eur J Immunol. 2018;43(3):331–4.
- Marik PE, Kory P, Varon J. Does vitamin D status impact mortality from SARS-CoV-2 infection? Med Drug Discov. 2020 Jun;6:100041.
- Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. J Infect. 2020 Jun;80(6):607–13.
- Vitamin D, zinc and glutamine: Synergistic action with OncoTherad immunomodulator in interferon signaling and COVID-19 (Review) [Internet]. [cited 2021 Aug 29]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7834962/>
- Overbeck S, Rink L, Haase H. Modulating the immune response by oral zinc supplementation: a single approach for multiple diseases. Arch Immunol Ther Exp (Warsz). 2008 Feb;56(1):15–30.
- Kumar A, Kubota Y, Chernov M, Kasuya H. Potential role of zinc supplementation in prophylaxis and treatment of COVID-19. Med Hypotheses. 2020 Nov;144:109848.
- Novick SG, Godfrey JC, Pollack RL, Wilder HR. Zinc-induced suppression of inflammation in the respiratory tract, caused by infection with human rhinovirus and other irritants. Med Hypotheses. 1997 Oct;49(4):347–57.
- Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. Nutrients. 2015 May 29;7(6):4240–70.
- Thomas C, Moraga I, Levin D, Krutzik PO, Podoplelova Y, Trejo A, et al. Structural linkage between ligand discrimination and receptor activation by type I interferons. Cell. 2011 Aug 19;146(4):621–32.
- Linossi EM, Nicholson SE. Kinase inhibition, competitive binding and proteasomal degradation: resolving the molecular function of the suppressor of cytokine signaling (SOCS) proteins. Immunol Rev. 2015;266(1):123–33.
- Receptor dimerization dynamics as a regulatory valve for plasticity of type I interferon signaling | Journal of Cell Biology | Rockefeller University Press [Internet]. [cited 2021 Aug 29]. Available from: <https://rupress.org/jcb/article/209/4/579/38129/Receptor-dimerization-dynamics-as-a-regulatory>
- Perlman S, Dandekar AA. Immunopathogenesis of coronavirus infections: implications for SARS. Nat Rev Immunol. 2005 Dec;5(12):917–27.
- Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017 Jul;39(5):529–39.
- Name JJ, Vasconcelos AR, Souza ACR, Fávoro WJ. Vitamin D, zinc and glutamine: Synergistic action with OncoTherad immunomodulator in interferon signaling and COVID-19 (Review). Int J Mol Med. 2021 Mar;47(3):11.
- Bergström J, Fürst P, Norée LO, Vinnars E. Intracellular free amino acid concentration in human muscle tissue. J Appl Physiol. 1974 Jun;36(6):693–7.
- Savy GK. Glutamine supplementation. Heal the gut, help the patient. J Infus Nurs Off Publ Infus Nurses Soc. 2002 Feb;25(1):65–9.

21. Cengiz M, Borku Uysal B, Ikitimur H, Ozcan E, Islamoğlu MS, Aktepe E, et al. Effect of oral L-Glutamine supplementation on Covid-19 treatment. *Clin Nutr Exp*. 2020 Oct;33:24–31.
22. Name J, Vasconcelos A, Souza A, Fávaro W. Vitamin D, zinc and glutamine: Synergistic action with OncoTherad immunomodulator in interferon signaling and COVID-19 (Review). *Int J Mol Med*. 2021 Jan 4;47(3):11.
23. Gombart AF, Pierre A, Maggini S. A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection. *Nutrients*. 2020 Jan 16;12(1):E236.
24. Name JJ, Souza ACR, Vasconcelos AR, Prado PS, Pereira CPM. Zinc, Vitamin D and Vitamin C: Perspectives for COVID-19 With a Focus on Physical Tissue Barrier Integrity. *Front Nutr*. 2020;7:295.