Review Article

Role of Vitamin A Supplementation in Prevention and Control of Coronavirus Disease-19: A Narrative Review

Abstract

Coronavirus disease-19 (COVID-19) caused by SARS-CoV-2 is a novel viral infectious disease, which broke out in the end of winter season 2019 in China and soon became a pandemic. Characteristically there was severe local and systemic immune-inflammatory response to the virus, damaging the respiratory system and other organ systems. The morbidity and mortality caused by the disease are producing tremendous impact on health. The understanding about pathogenesis and manifestations of the disease was obscure. To date, no classic treatment or preventive measure was available for COVID-19 other than symptomatic and supportive care or few drugs under trial. A possibility exists that maintaining vitamin A adequate levels can protect the affected respiratory mucosa, increase antimicrobial activity, produce better antibody response, and have antiinflammatory effects, thereby promoting repair and healing as well. It has been discussed in the review that by various mechanisms, immune regulation through vitamin A supplementation is beneficial to boost immunity in the current outbreak situation when the population is susceptible to the disease. There is a high possibility that vitamin A supplementation to cases as well as population at risk of COVID-19 has a key role in prevention and control. Hence, it is believed that along with other therapeutic and preventive measures, maintaining vitamin A sufficiency during and prior to the development of active disease may act as an adjuvant in population at risk and cases to prevent and control COVID-19.

Keywords: *Antiinflammatory, COVID-19, immunomodulation, SARS-CoV-2, vitamin A supplementation*

Nikita Singh, Harsh Vardhan Chawla, Arun Kumar[1], Sangeeta Singh[2]

Departments of Biochemistry, [1]Community Medicine, [2]Biochemistry, Shaheed Hasan Khan Mewati Govt Medical College Nalhar, Nuh, Mewat, Haryana, India

Introduction

Coronavirus disease-19 (COVID-19) is a novel viral disease and World Health Organization (WHO) has declared it a public health emergency of international concern.[1] The disease is contagious and, in affected individuals, has the risk of spreading rapidly from upper to lower respiratory tract, and has high morbidity and mortality.[1]

There was an urgent need to take appropriate preventive and control measures for the emerging disease. Also not much was known about the natural history of the novel viral disease.

Animal studies have shown that low levels of vitamin A are likely to increase the susceptibility to COVID-19 as in case of other infections including acute respiratory infections.[2-5] In an experiment conducted in 35-day-old hamsters, the findings had shown that vitamin A deprivation decreased the replication of basal cells and mucous cells in tracheal epithelium, which showed minimal morphologic change with the manifold reduction of the mitotic rates.[2] Similarly, findings of the experiments conducted in rats had shown that vitamin A was important for the maintenance and functional integrity of mucus-secreting goblet cells in the small intestine.[4] Moreover, in view of the findings of a review article published in 2018, vitamin A supplementation in its deficiency state has been shown to improve immune response in infectious diseases.[6]

Vitamin A also has a role in host defense and has been suggested to have potential importance in the prevention of respiratory tract infections by regulating and promoting local and systemic immune responses.[6] Thus, the immune-regulatory mechanisms with adequate vitamin A required extensive review of available literature. In this article, we attempted to explore different

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Address for correspondence:
Dr. Arun Kumar, Department of Community Medicine, Shaheed Hasan Khan Mewati Govt Medical College Nalhar, Mewat, Haryana. E-mail: arun.pgims@gmail.com

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mechanisms by which vitamin A can improve immune function to combat microbial infections and how the knowledge be applied in the prevention and control of COVID-19.

Hence, the authors made an attempt to review the available studies on various infectious/inflammatory diseases in order to explore the potential role of vitamin A supplementation in the prevention and control of COVID-19.

Methods

The current paper is a narrative review whereon a search was done for various relevant studies on PubMed, Medline, EMBASE, Google Scholar, and other databases. The search areas were mainly vitamin A deficiency, infectious diseases, infections, microbes, virus, immune cells, coronavirus respiratory infections, COVID-19, and SARS-CoV-2. The relevant studies in English were selected and reviewed while others were excluded. The findings were interpreted to explore whether or not and how vitamin A supplementation can be beneficial in efforts to control COVID-19.

Results and Discussion

Pathogenesis of COVID-19

According to an observational prospective study conducted in Wuhan, China and published in a reputed journal, the upper respiratory system including the nasal and oropharyngeal mucosae are the first to be affected by SARS-CoV-2. Thereafter the virus affects the lower respiratory tract producing symptoms like fever, dry cough, dyspnea, etc.[7] In another descriptive study conducted in Wuhan, the findings, however, also showed that presentations of respiratory symptoms in COVID-19 could be a bit varied,[8] which could confuse further the management of cases. The peculiarity of the disease was that it was fatal in elderly and those with comorbid conditions.[8]

In a study conducted in Texas, the cellular and molecular bases of the increased inflammatory responses and severe tissue destruction within the lungs of SARS patients were studied.[9] As stated in the paper findings, SARS coronavirus bound to host cell angiotensin-converting enzyme 2 receptors for the virus spike protein to enter the respiratory epithelial cells and thereafter multiplied inside the host cell. As the virus entered the host, cell innate immunity comprising mucus layer along with underneath macrophages and dendritic cell fought against to eliminate the virus till adaptive immunity was made to respond for further handling of the infective agent.[9] In a literature review, earlier coronaviruses had been shown to activate the adaptive immune system through T-cell mediated secretion of inflammatory chemicals, proteins, and antiinflammatory chemicals/proteins.[10] Observational and other study evidences to support the role of T-cells for clearing the infection indicated lymphopenia in patients with severe COVID-19.[11,12] A noteworthy finding published in a paper was that activated innate and adaptive immune systems produced inflammatory cytokines including IL-6, monocyte chemoattractant protein-1, tumor necrosis factor (TNF)-alpha, and macrophage inflammatory protein 1 alpha.[7,11,12] According to the findings of another molecular level study, though the activated cytotoxic T-cells, the CD8+ T-cells derived from CD4+ T-cells, contributed to killing the virus, this also contributed to lung tissue destruction.[13] The highly expressed inflammatory cytokines were likely to accelerate progression to cytokines storm. Most patients with COVID-19 predominantly had respiratory tract infections inoculated with SARS-CoV-2 infection, which was a milder form of the disease. However, a small proportion of cases could progress to more severe systemic disease characterized by acute respiratory distress syndrome, sepsis and shock, and multi-organ failure including kidney injury and cardiac injury. Autopsy findings in China and European countries showed endothelial damage of pulmonary vasculature and microvascular thrombosis in the findings of a review.[14]

The role of vitamin A in immunity is classified into action on the innate immune system and adaptive immune system, and its antiinflammatory effects.

Immunomodulatory effects of vitamin A on the innate and adaptive immune system:

In view of the findings of a comprehensive review article,[15] an effective immunity is critical to remove the pathogen and to limit the extent of injury. Humans have an elaborate innate and adaptive immune system, which play a vital role in eliminating injurious stimuli and promoting repair of the tissue.[15]

Host immune response to the pathogen also determines the severity of tissue damage, while immune deficiency is known to predispose to infectious diseases. It is recognized that the interplay of the immune system components in response to the pathogen is responsible for the pathophysiological effects and symptoms of the disease.

Recently, in the studies published in a reputed journal, vitamin A was reported as a nutrient having pleiotropic effects in the immune system through the molecular effects of its metabolites.[16,17] Vitamin A was required for optimum mucosal barrier function, appropriate functioning of neutrophils, macrophages, and natural killer (NK) cells, and also for the components of the adaptive immune system including T cells and B cells.[18]

Way back to 1925, researchers reported that in vitamin A deficiency states, various epithelia were changed to stratified squamous keratinizing epithelium.[19] Later in 1929–1930, before the advent of antibiotics, vitamin A was reported as an antiinfective agent.[20]

Findings of several randomized clinical trials of vitamin A supplementation suggested that maintaining vitamin A

sufficiency in the at-risk population decreased disease severity and reduced morbidity and mortality in many infectious diseases.[21,22] Also recent research showed that vitamin A supplementation had potential use in decreasing severity in measles, lower respiratory tract infections, and meningitis.[1] It was then reported that vitamin A deficiency caused epithelial cell shrinkage and predisposed to squamous keratinization in skin, digestive tract, respiratory tract, genitourinary tract, cornea, and surrounding soft tissue responsible for the symptoms of dry skin, diarrhea, coughing, keratomalacia, corneal opacity, dry eye, and urinary lithiasis.[23-26] Symptoms were relieved because of the key role of vitamin A in synthesis and maintenance of the integrity of the glycoprotein layer of the epithelium for its adequate function. Further, it was reported that keratinized epithelial tissue was not able to stop the foreign pathogen in its attack on the epithelial layer of the organ systems, promoting various infections.[27] The ability of vitamin A to regenerate damaged mucosa and at the same time promote phagocytosis by neutrophils and macrophages could reduce the incidence and duration of invasive disease like Shigella dysentery.[28,29] The protective effects of vitamin A were suggested due to the restoration of intestinal IgA secretion and T helper-2 cells (Th2) cytokine production. It is explained that the increase in IgA, which is a pathogen-specific antibody in the gut, improves recovery from primary infection and increases the ability to fight off secondary infection.[30]

Early evidence reported that vitamin A deficiency affected neutrophil development and compromised bacterial phagocytosis and microbial killing capacity.[31] Also as per the findings of some studies, vitamin A deficiency causes neutrophilia in rats in peripheral blood smear.[32,33] However, the development of neutrophilia was not seen in all mice strains during vitamin A deficiency.[34]

These studies indicate derangement of neutrophil function in vitamin A deficiency.

Vitamin A deficiency is also known to increase the transcription of interleukin-12 (IL-12) in macrophages.[35] However, retinoic acid inhibits IL-12 production by primary macrophages. Kim *et al*. demonstrated that the innate immune system through the transcellular metabolism activated dendritic cells and macrophages, and the immunomodulatory nutrient vitamin A produced antimicrobial response in tuberculosis.[36] Also low levels of serum vitamin A concentrations were found to be correlated with susceptibility to tuberculosis.[37-39] In another study, vitamin A deficiency was strongly suggested to have a role in viral disease—measles and diarrhea.[40]

In an extensive review, the antiviral responses of NK cells were demonstrated to be decreased in vitamin A deficiency.[41] Additionally in another study protective role of NK cells in the early stages of viral infections was notably decreased in cases with vitamin A insufficient levels.[42]

Researches have been conducted where in the effect of high dietary intake of vitamin A on recovery from influenza A viral pneumonia in mice was studied.[43] It has been seen in animal studies that vitamin A deficiency was found to cause alteration in T helper-1/T helper-2 (Th1/Th2) cytokine production. In vitamin A deficiency, secretion of Th2 cytokines was decreased while that of Th1 cytokines was increased. However, recently it was shown that high dietary vitamin A significantly increased antiinflammatory cytokines and improved secretory antibody IgA levels and decreased interferon (IFN)-gamma levels.[43]

Thus, the evidences discussed above irrefutably pointed to the immune-modulatory role of vitamin A, particularly in infectious disorders.

Antiinflammatory effects of vitamin A

Inflammatory reaction is part of immune response and is comprised of immune cells and chemicals at the local site of injury and in the systemic circulation. Literature exists in which vitamin A had been reported to be a physiological antiinflammatory agent.[44] Moreover, a supportive observational study suggested that vitamin A deficiency induced exaggerated inflammation to injurious stimuli which might result in severe tissue injury so that children with low levels of vitamin A during acute illness with viral respiratory pathogen were associated with increased severity of the illness.[45]

The increased severity of illness was attributed to increased rate of vitamin A consumption by the injured epithelial tissue suggesting adequate levels of vitamin A promoted epithelial regeneration and decreased severity of the symptoms,[45] and it was hypothesized that vitamin A supplementation may have a role in the management of infection with respiratory syncytial virus, an RNA virus.[45]

Evidences were available which showed that adequate vitamin A levels reduced proinflammatory cytokines secreted by macrophages and at the same time promoted antiinflammatory cytokine.[46] In addition, as per findings of some molecular level studies in animals, vitamin A was also suggested to induce macrophages toward antiinflammatory lineage.[47,48] Furthermore, in an available research, the effect of retinoic acid on human dendritic cells was studied, and findings showed that vitamin A metabolite retinoic acid also promoted antiinflammatory cytokine secretion IL-10 by dendritic cells thus favoring T-cell differentiation toward antiinflammatory effects.[49] Further in a trial conducted on mice, it was shown that retinoic acid treatment inhibited IL-12 production in lipopolysaccharide activated macrophages by inhibition of nuclear factor-kappa B-DNA interaction and competition between NF-KB and retinoic acid X receptor.[50] In an inquiry, researchers examined the effects of metabolites of vitamin A on different proinflammatory and immune-modulating cytokines produced by monocytes to

understand the mechanisms by which retinoids affect the immune response.

The findings of the study showed that retinoic acid inhibited the production of TNF-alpha and IL-12, the proinflammatory cytokines and at the same time potentiate IL-10 production in monocyte/macrophage cell lines and human cord blood mononuclear cells.[51] In an investigation on the molecular mechanisms, it was suggested that plasma factors such as transforming growth factor-β and prostaglandin E2 in presence of retinoic acid, acted synergistically to form IL-6 by basophils so that sensitivity of macrophages to Il-6 increased which resulted in M2 macrophage polarization thereby regulating inflammatory process in mice.[52]

As published in a review article, it had also been observed that macrophages in the tissue were highly adaptive in terms of their function to different microenvironments.[53] In addition to the role of vitamin A in the inflammatory phase, retinoic acid was witnessed to enhance wound healing primarily through promoting extracellular matrix components and decreasing levels of degrading matrix metalloproteinases.[54] This shows the role of vitamin A in multiple stages in the natural history of infectious disorders. In some surveys, vitamin A deficiency has been found to be highly prevalent in India.[55,56]

In an exhaustive literature review, vitamin A supplementation was substantiated to reduce morbidity and mortality in several randomized controlled trials in various infectious diseases.[6] In an observational study, lower levels of beta-carotene, which is a naturally occurring precursor of retinol (vitamin A), were also found to be related to tuberculosis morbidity and mortality.[57]

A spectrum of infections in which vitamin A supplementation has been presented/evidenced to have a role is shown in Table 1. Though the spectrum of these infections is large, a noteworthy finding is that many of the infections discussed above are acute respiratory infections. Similar to these instances, vitamin A supplementation was believed to benefit COVID-19 patients. This justifies at large for supplementation of vitamin A in SARS–CoV-2 as a preventive and control measure. Hence, the review has broadened knowledge regarding role of vitamin A in prevention and control of COVID-19.

Table 1: List of microbial infections showing improvement with vitamin A supplementation

Name of Infectious disease
Tuberculosis[57,58]
HIV/AIDS[18,54,59-61]
Upper respiratory infections[18,62]
Lower respiratory infections[18,62-65]
Diarrheal diseases[18,66,67]
Measles[18,68]
Mumps[69]
Malaria[18,70]

Conclusion and Recommendation

Pathological/cellular changes in COVID-19 resemble those of other infectious respiratory disorders. Vitamin A has a role in the prevention of infectious disorders particularly respiratory disorders including prevention of the complications by modulating immune response to favor antimicrobial actions as well as restoring epithelial mucosa thereby promoting healing as well. It is concluded and hypothesized that vitamin A may have a preventive role in COVID-19 similar to other infectious disorders. Hence, ensuring vitamin A sufficiency through vitamin A supplementation may be one of the key strategies in the prevention and control of the pandemic of a novel infectious respiratory disease, COVID-19.

It is recommended that for effective control of COVID-19, efforts to eliminate vitamin A deficiency should remain one of the priorities as a public health measure. It is, however, suggested that as a good public health practice, while the introduction of vitamin A supplementation as a prevention and control measure for COVID-19, prior opinion/consent of the custodians of the communities may be sought so that the intervention is informed and acceptability is maximum among the populations.

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Conflicts of interest

There are no conflicts of interest.

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References

1. World Health Organization. Novel Coronavirus (2019-nCoV): Situation report-11. c2020. [Last accessed on 2020 Apr 23]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
2. McDowell EM, Keenan KP, Huang M. Effects of vitamin A-deprivation on hamster tracheal epithelium: A quantitative morphologic study. Virchows Arch B Cell Pathol Incl Mol Pathol 1984;45:197-219.
3. Wong YC, Buck RC. An electron microscopic study of metaplasia of the rat tracheal epithelium in vitamin A deficiency. Lab Invest 1971;24:55-66.
4. Rojanapo W, Lamb AJ, Olson JA. The prevalence, metabolism and migration of goblet cells in rat intestine following the induction of rapid, synchronous vitamin A deficiency. J Nutr 1980;110:178-88.
5. Warden RA, Strazzari MJ, Dunkley PR, O'Loughlin EV. Vitamin A-deficient rats have only mild changes in jejunal structure and function. J Nutr 1996;126:1817-26.
6. Huang Z, Liu Y, Qi G, Brand D, Zheng SG. Role of vitamin A in the immune system. J Clin Med 2018;7:258.
7. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in

Wuhan, China. Lancet 2020;395:497-506.
8. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020;395:507-13.
9. Yoshikawa T, Hill T, Li K, Peters CJ, Tseng CT. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. J Virol 2009;83:3039-48.
10. Channappanavar R, Zhao J, Perlman S. T cell-mediated immune response to respiratory coronaviruses. Immunol Res 2014;59:118-28.
11. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, *et al*. Dysregulation of immune response in patients with Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis 2020;71:762-8.
12. Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Qi Y, *et al*. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. Natl Sci Rev 2020:nwaa041. Published online 2020. doi: 10.1093/nsr/nwaa041.
13. Small BA, Dressel SA, Lawrence CW, Drake 3rd DR, Stoler MH, Enelow RI, *et al*. CD8(+) T cell-mediated injury *in vivo* progresses in the absence of effector T cells. J Exp Med 2001;194:1835-46.
14. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol 2020;215:108427.
15. Ferrero-Miliani L, Nielsen OH, Andersen PS, Girardin SE. Chronic inflammation: Importance of NOD2 and NALP3 in interleukin-1beta generation. Clin Exp Immunol 2007;147:227-35.
16. Mangelsdorf DJ, Ong ES, Dyck JA, Evans RM. Nuclear receptor that identifies a novel retinoic acid response pathway. Nature 1990;345:224-9.
17. Petkovich M, Brand NJ, Krust A, Chambon P. A human retinoic acid receptor which belongs to the family of nuclear receptors. Nature 1987;330:444-50.
18. Stephensen CB. Vitamin A, infection, and immune function. Annu Rev Nutr 2001;21:167-92.
19. Wolbach SB, Howe PR. Tissue changes following deprivation of fat-soluble a vitamin. J Exp Med 1925;42:753-77.
20. Green HN, Mellanby E. Vitamin a as an anti-infective agent. Br Med J 1928;2:691-6.
21. Thorne-Lyman A, Fawzi WW. Vitamin A supplementation, infectious disease and child mortality: A summary of the evidence. Nestle Nutr Inst Workshop Ser 2012;70:79-90.
22. Semba RD. Vitamin A and immunity to viral, bacterial and protozoan infections. Proc Nutr Soc 1999;58:719-27.
23. Wilson JR, DuBOIS RO. Report of a fatal case of keratomalacia in an infant, with postmortem examination. Am J Dis Child 1923;26:431-46.
24. Blackfan KD, Wolbach SB. Vitamin a deficiency in infants: A clinical and pathological study. J Pediatr 1933;3:679-706.
25. Keenum DG, Semba RD, Wirasasmita S, Natadisastra G, Muhilal S, West Jr KP, *et al*. Assessment of vitamin A status by a disk applicator for conjunctival impression cytology. Arch Ophthalmol 1990;108:1436-41.
26. Natadisastra G, Wittpenn JR, West KP Jr, Muhilal, Sommer A. Impression cytology for detection of vitamin A deficiency. Arch Ophthalmol 1987;105:1224-8.
27. Qi YJ, Niu QL, Zhu XL, Zhao XZ, Yang WW, Wang XJ. Relationship between deficiencies in vitamin A and E and occurrence of infectious diseases among children. Eur Rev Med Pharmacol Sci 2016;20:5009-12.
28. Villamor E, Fawzi WW. Vitamin A supplementation: Implications for morbidity and mortality in children. J Infect Dis 2000;182(Suppl 1):S122-33.
29. Barreto ML, Santos LM, Assis AM, Araújo MP, Farenzena GG, Santos PA, *et al*. Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections in young children in Brazil. Lancet 1994;344:228-31.
30. Nikawa T, Odahara K, Koizumi H, Kido Y, Teshima S, Rokutan K, *et al*. Vitamin A prevents the decline in immunoglobulin A and Th2 cytokine levels in small intestinal mucosa of protein-malnourished mice. J Nutr 1999;129:934-41.
31. Twining SS, Schulte DP, Wilson PM, Fish BL, Moulder JE. Vitamin A deficiency alters rat neutrophil function. J Nutr 1997;127:558-65.
32. Nauss KM, Mark DA, Suskind RM. The effect of vitamin A deficiency on the *in vitro* cellular immune response of rats. J Nutr 1979;109:1815-23.
33. Zhao Z, Ross AC. Retinoic acid repletion restores the number of leukocytes and their subsets and stimulates natural cytotoxicity in vitamin A-deficient rats. J Nutr 1995;125:2064-73.
34. Miller SC, Kearney SL. Effect of *in vivo* administration of all trans-retinoic acid on the hemopoietic cell populations of the spleen and bone marrow: Profound strain differences between A/J and C57BL/6J mice. Lab Anim Sci 1998;48:74-80.
35. Cantorna MT, Nashold FE, Hayes CE. Vitamin A deficiency results in a priming environment conducive for Th1 cell development. Eur J Immunol 1995;25:1673-9.
36. Kim EW, De Leon A, Jiang Z, Radu RA, Martineau AR, Chan ED, *et al*. Vitamin A metabolism by dendritic cells triggers an antimicrobial response against mycobacterium tuberculosis. mSphere 2019;4:e00327-19.
37. Mugusi FM, Rusizoka O, Habib N, Fawzi W. Vitamin A status of patients presenting with pulmonary tuberculosis and asymptomatic HIV-infected individuals, Dar Es Salaam, Tanzania. Int J Tuberc Lung Dis 2003;7:804-7.
38. Ramachandran G, Santha T, Garg R, Baskaran D, Iliayas SA, Venkatesan P, *et al*. Vitamin A levels in sputum-positive pulmonary tuberculosis patients in comparison with household contacts and healthy 'Normals'. Int J Tuberc Lung Dis 2004;8:1130-3.
39. Wheelwright M, Kim EW, Inkeles MS, De Leon A, Pellegrini M, Krutzik SR, *et al*. All-*trans* retinoic acid triggered antimicrobial activity against *Mycobacterium tuberculosis* is dependent on NPC2. J Immunol 2014;192:2280-90.
40. Kańtoch M, Litwińska B, Szkoda M, Siennicka J. Importance of vitamin A deficiency in pathology and immunology of viral infections. Rocz Panstw Zakl Hig 2002;53:385-92.
41. Ross AC, Stephensen CB. Vitamin A and retinoids in antiviral responses. FASEB J 1996;10:979-85.
42. Dawson HD, Li NQ, DeCicco KL, Nibert JA, Ross AC. Chronic marginal vitamin A status reduces natural killer cell number and function in aging lewis rats. J Nutr 1999;129:1510-7.
43. Cui D, Moldoveanu Z, Stephensen CB. High-level dietary vitamin A enhances T-helper type 2 cytokine production and secretory immunoglobulin a response to influenza a virus infection in BALB/c mice. J Nutr 2000;130:1132-9.
44. Reifen R. Vitamin A as an anti-inflammatory agent. Proc Nutr Soc 2002;61:397-400.
45. Neuzil KM, Gruber WC, Chytil F, Stahlman MT, Engelhardt B, Graham BS. Serum vitamin A levels in respiratory syncytial virus infection. J Pediatr 1994;124:433-6.
46. Greiller CL, Martineau AR. Modulation of the immune response

to respiratory viruses by vitamin D. Nutrients 2015;7:4240-70.
47. Vellozo NS, Pereira-Marques ST, Cabral-Piccin MP, Filardy AA, Ribeiro-Gomes FL, Rigoni TS, *et al*. All-trans retinoic acid promotes an M1- to M2-phenotype shift and inhibits macrophage-mediated immunity to leishmania major. Front Immunol 2017;8:1560.
48. Pereira WF, Ribeiro-Gomes FL, Guillermo LVC, Vellozo NS, Montalvão F, Dosreis GA, *et al*. Myeloid-derived suppressor cells help protective immunity to leishmania major infection despite suppressed T cell responses. J Leukoc Biol 2011;90:1191-7.
49. Bakdash G, Vogelpoel LTC, van Capel TMM, Kapsenberg ML, de Jong EC. Retinoic acid primes human dendritic cells to induce gut-homing, IL-10-producing regulatory T cells. Mucosal Immunol 2015;8:265-78.
50. Kang BY, Chung SW, Kim SH, Kang SN, Choe YK, Kim TS. Retinoid-mediated inhibition of interleukin-12 production in mouse macrophages suppresses Th1 cytokine profile in CD4(+) T cells. Br J Pharmacol 2000;130:581-6.
51. Wang X, Allen C, Ballow M. Retinoic acid enhances the production of IL-10 while reducing the synthesis of IL-12 and TNF-alpha from LPS-stimulated monocytes/macrophages. J Clin Immunol 2007;27:193-200.
52. Ho VW, Hofs E, Elisia I, Lam V, Hsu BE, Lai J, *et al*. All trans retinoic acid, transforming growth factor β and prostaglandin E2 in mouse plasma synergize with basophil-secreted interleukin-4 to M2 polarize murine macrophages. PLoS One 2016;11:e0168072.
53. Davies LC, Jenkins SJ, Allen JE, Taylor PR. Tissue-resident macrophages. Nat Immunol 2013;14:986-95.
54. Polcz ME, Barbul A. The role of vitamin A in wound healing. Nutr Clin Pract 2019;34:695-700.
55. Akhtar S, Ahmed A, Randhawa MA, Atukorala S, Arlappa N, Ismail T, *et al*. Prevalence of vitamin A deficiency in South Asia: Causes, outcomes, and possible remedies. J Health Popul Nutr 2013;31:413-23.
56. Suri S, Kumar D, Das R. Dietary deficiency of vitamin A among rural children: A community-based survey using a food-frequency questionnaire. Natl Med J India 2017;30:61-4.
57. Campa A, Baum MK, Bussmann H, Martinez SS, Farahani M, van Widenfelt E, *et al*. The effect of micronutrient supplementation on active TB incidence early in HIV infection in Botswana. Nutr Diet Suppl 2017;2017:37-45.
58. Anand PK, Kaul D, Sharma M. Synergistic action of vitamin D and retinoic acid restricts invasion of macrophages by pathogenic mycobacteria. J Microbiol Immunol Infect 2008;41:17-25.
59. Mehta S, Fawzi W. Effects of vitamins, including vitamin A, on HIV/AIDS patients. Vitam Horm 2007;75:355-83.
60. Schreck R, Rieber P, Baeuerle PA. Reactive oxygen intermediates as apparently widely used messengers in the activation of the NF-kappa B transcription factor and HIV-1. EMBO J 1991;10:2247-58.
61. Shivakoti R, Christian P, Yang W-T, Gupte N, Mwelase N, Kanyama C, *et al*. Prevalence and risk factors of micronutrient deficiencies pre- and post-antiretroviral therapy (ART) among a diverse multicountry cohort of HIV-infected adults. Clin Nutr 2016;35:183-9.
62. Fawzi W. Micronutrients and human immunodeficiency virus type 1 disease progression among adults and children. Clin Infect Dis 2003;37(Suppl 2):S112-6.
63. Mayo-Wilson E, Imdad A, Herzer K, Yakoob MY, Bhutta ZA. Vitamin A supplements for preventing mortality, illness, and blindness in children aged under 5: Systematic review and meta-analysis. BMJ 2011;343:d5094.
64. Hu N, Li QB, Zou SY. [Effect of vitamin A as an adjuvant therapy for pneumonia in children: A meta analysis]. Zhongguo Dang Dai Er Ke Za Zhi 2018;20:146-53.
65. Bhandari N, Bhan MK, Sazawal S. Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity. BMJ 1994;309:1404-7.
66. Rahman MM, Vermund SH, Wahed MA, Fuchs GJ, Baqui AH, Alvarez JO. Simultaneous zinc and vitamin A supplementation in Bangladeshi children: Randomised double blind controlled trial. BMJ 2001;323:314-8.
67. Coutsoudis A, Bobat RA, Coovadia HM, Kuhn L, Tsai WY, Stein ZA. The effects of vitamin A supplementation on the morbidity of children born to HIV-infected women. Am J Public Health 1995;85:1076-81.
68. Ehrenpreis ED, Carlson SJ, Boorstein HL, Craig RM. Malabsorption and deficiency of vitamin B12 in HIV-infected patients with chronic diarrhea. Dig Dis Sci 1994;39:2159-62.
69. Soye KJ, Trottier C, Di Lenardo TZ, Restori KH, Reichman L, Miller Jr WH, *et al*. *In vitro* inhibition of mumps virus by retinoids. Virol J 2013;10:337.
70. Owusu-Agyei S, Newton S, Mahama E, Febir LG, Ali M, Adjei K, *et al*. Impact of vitamin A with zinc supplementation on malaria morbidity in Ghana. Nutr J 2013;12:131.