Vitamin A and Viral Infection: A systematic review

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Abstract
Vitamin A is fat-soluble compounds of retinoid derivate, consisting of retinol, retinal, and retinyl esters. Vitamin A also affects cell growth and differentiation, playing a critical role in the normal formation and function of the heart, lungs, kidneys, and other organs. According to the role of vitamin A in enhancing immune function, it is known as an anti-inflammatory agent. Also, vitamin A supplementation by reducing morbidity and mortality in different infectious diseases, such as measles, diarrheal disease, measles-related pneumonia, human immunodeficiency virus infection, and malaria considered as a crucial factor against infection. So vitamin A deficiency can be life-threatening, because of impairing the response to infection and significant risk of development of severe respiratory infections in infants and young children. In this paper, we have discussed the effects of vitamin A in modulating immune responses in viral infections and the direct effects of this vitamin on viral replication by comparing its role during different types of viral infections.

Keywords: Vitamin A [MeSH], COVID-19 [MeSH], DNA viruses [MeSH], RNA viruses [MeSH]

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Introduction

Vitamin A (VA) has been known as a critical fat-soluble vitamin that is needed for human health (1, 2). It is a micronutrient in diet, which is necessary for the immune system and facilitates modulation of Retinoic acid (RA) (3, 4). Also this vitamin plays a key role in growth and fertility mechanisms (5). Its functional form in the body has been recognized as All Trans’ Retinoic Acid (ATRA)(5-7). Uptaking vitamin A from meat occurs as retinyl esters of fatty acids in membranous lipid and fat cells. Carotenoids are Pro-vitamin A in vegetables that are connected with cellular lipids. However, they are located in cellular complex structures like the chloroplasts cellulose-consisting matrix. Studies on vitamin A and carotenoid absorption in digestion procedure from embedding food has shown that better absorption of micronutrients occurs from meat toward vegetable tissues (2, 5, 8-11). Various metabolites of vitamin A regulate proliferation, differentiation, cell death of epithelial cells, penetrability of the intestinal epithelium, and immunity tasks of the gastrointestinal epithelium(12-14). The vitamin A supplements decreases rate of morbidity and mortality in measles (15, 16), diarrhea (17, 18), respiratory tract infections (17, 19, 20), malaria (21, 22), HIV infection (23, 24) and some other infections (25, 26). Furthermore, some impacts of vitamin A on immune system elements toward pathogens have been recognized by medical scientists in clinical studies. Numerous reports, have shown the extensive effect of vitamin A and its other metabolites on the expansion and function of the immunity agents in children, consisting of its special effects on T (27) and B-cells, antigen-presenting cells (APCs), dendritic cells (DCs) (28), and other immune system elements (26-28).

On the other hand, vitamin A deficiency (VAD) is linked with decreased immunogenicity of various vaccines (29) including diphtheria, measles (26, 30) and tetanus toxoid (31). Retinoic acid has known to facilitate IgA production and gut homing of IgA+ plasma cells (32) and T-cells (33). Besides mediating these responses, vitamin A is also crucial for regular T-cell responses in the intestinal mucosa (29, 33-35). Therefore, vitamin A is involved in modulation of intestinal immunity. Vitamin A deficiency shifts cytokine responses as polarization to amplified T-helper cell type 1 (Th1) cytokine responses in children (36). Some studies revealed that treatment of T cells with RA enhances Th2 development and decreases Th1 production (37, 38). These comparisons suggest that the modulation of immune function by vitamin A is complex and involves many different arms of the immune system (5, 39). Interestingly, retinol upregulates IgA production (1) in vitro when solenocyte B cells are triggered in the presence of a respiratory epithelial cell line (LETs) (40), in an IL-6 dependent manner (25, 41). Despite its clear positive influences on IgA induction, modulation of immune responses through vitamin A and its active metabolites has been shown to occur via nuclear retinoic acid receptors at the level of the genome as well as via a pathway involving retinoid (42, 43). Even though vitamin A and its metabolites have been demonstrated to have key unspecific effects on host immunity, the therapeutic property of vitamin A intake in improving differentiation to various types of viral agents differ significantly (26, 42). The purpose of the present paper is to gain an insight into the effects of vitamin A in modulating immune responses in viral infections and direct effects of this vitamin on viral reproduction by comparing its function during different types of viral infections.
Materials and Methods

**Literature search strategy**

This systematic review explored the advantages of vitamin A administration in different viral infections. The Embase, PubMed, and Scopus databases were searched up to July 22 keywords single and combinations of the following key words: (Vitamin A and Viral and infection and viruses) and (Vitamin A OR Viral OR infection OR viruses). The search strategy for this review was conducted as the (Fig-1. Flowchart).

**Study selection**

Briefly, the extracted articles were screened by two independent reviewers and based on the titles and abstracts, some of articles were excluded. Then articles without full text were excluded.

Diagram1. Flowchart of systematic review

1. **SARS-CoV-2**

Coronavirus Disease 2019 (COVID-19) is a pandemic disease with severe pulmonary damage and hyper inflammation sign (44). Vitamin A considered as an important factor in the development of immune system responses and the regulation of acute inflammation. Vitamin A by the development of normal lung tissue and tissue repair after injury due to infection (45) may play a key role in the recovery after severe COVID-19 pneumonia (46). Vitamin A has the ability in

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immune regulatory functions by affecting the innate and adaptive immune cell response (47, 48). The deficiency in Vitamin A may disrupt vaccine-induced plasma cells and affect immunoglobulin development in the respiratory tracts (49, 50). Normally, Vitamin A (VA) has benefits in physiological functions, such as promoting growth and reproduction and maintaining bone, epithelial tissue, vision, and normal secretion of mucosal epithelium. Also, derivatives of VA can suppress precancerous lesions. This factor is necessary for the maintenance of immune cells count and it can be affected in immune cell differentiation and proliferation (51, 52). Vitamin A considered as the factor for minimization of COVID-19 adverse effects on the angiotensin system and medication-related adverse effects by improving respiratory health and diminishing inflammation and fibrosis (53). Therefore, according to COVID-19 inflammatory response/cytokine storm, especially the involvement of the liver, lung, and kidney, which further increase the risk of death in patients, vitamin A can combat the life-threatening disease (54).

2. HSV

Today the prevalence of genital herpes simplex virus (HSV) infections through HSV-1 and HSV-2 are increasing in population and as a result the incidence of neonatal herpes with its undeniable problems resulting in neurologic disabilities or perhaps death (55). Usually, HSV-1 and HSV-2 infection in newborns happens through the birth process, while the neonate is exposed to HSV shedding in the cervical or vaginal excretions (55, 56). The earlier studies have reported reduction in HSV infectivity through treatment with RA. But, the consequence of several mechanisms leads to fewer virus proliferation or the production of noninfectious viruses. Both of these options could be caused by the effect of RA nuclear receptors on various elements such as the transcription factors or host or HSV genomes or even the effect on viral proteins which are not responsible for replication (57). Studies have reported much evidence that suppression of N-glycosylation in HSV-1 glycoproteins with tunicamycin or any drugs that prevent N-linked glycosylation results in the proliferation of noninfectious HSV particles (58, 59). These studies have shown that RA treatment of HSV-1 infected Vero cells is capable to decrease the proliferation of infectious particles through producing viral glycoproteins with lower molecular weights. Based on previous examinations it has been revealed that RA can cause accumulation of gB, gC and gD viral ligands in variable molecular weights suggesting that RA can interfere in protein glycosylation (60).

3. HCV

Several studies have been revealed that VAD is common in cirrhosis patients and its occurrence is higher in individuals with Hepatitis C virus (HCV) induced cirrhosis than other patients with the same sex, age and economic situation (61-63). In previous studies HCV positive cirrhosis Patients have been tested for vitamin A and these reports that the majority of inadequate vitamin A intake is common in them. Furthermore, in addition to VAD, they had higher serum bilirubin and serum albumin toward people with normal vitamin. VAD is related to Child-Pugh class (64). Outcomes of all studies are similar in high incidence of VAD in individuals with HCV-induced cirrhosis (65). Cirrhosis is linked to a series of biological happenings such as a hypermetabolic situation, more protein catabolism, induced lipid oxidation, reduced glycogen storage and glucose oxidation, and other factors of poor nutritional status (66). It has been shown that triggered lipid oxidation product including hydroxynonenal and malondialdehyde (67) can stimulate hepatic stellate cells (HSCs) in HCV-infected patients. In a healthy liver, HSCs are known as the main storage spots of vitamin A. HSCs in liver damaged conditions miss their retinol and excrete a noticeable measure of extracellular matrix with more collagen I, resulting in liver fibrosis (68, 69). In HSCs, retinyl esters carried in lipid particles hydrolyze and subsequently excrete from cells as retinol (70). The retinyl ester amount in the cells depends on the synthesis of lecithin retacyltransferaseerase, the single hepatic enzyme
able to retinyl ester production in vivo\(^{(71)}\). Other effectors related to decreasing of serum retinol measure in chronic liver disease have been revealed as a dietary lacking vitamin A supplement and decreased synthesis of retinol-binding protein in hepatocytes, because of liver disorder protein-energy starvation \(^{(63,72)}\). Besides, triggered expression of Cytochrome P4502E1 (CYP2E1) in hepatic disorders \(^{(73)}\) has been revealed to play a key role in the reduction of hepatic retinoic acid stores through simplifying deprivation of retinoic acid into other metabolites \(^{(64)}\).

4. **Noroviruses**

One of the common reasons of acute gastroenteritis is Norovirus. The main symptoms related to this infectious disease consist of vomiting, diarrhea, nausea, abdominal pain, and fever for 3 days \(^{(74)}\). Norovirus infection is one of the most important public health problems because of the absence of effective treatment or vaccine for this infection \(^{(74,75)}\). According to the latest studies, Norovirus infection has no significant effect on gut microbiota so this is not one of issues related to viral pathogenesis \(^{(76)}\). Based on epidemiological studies using of sufficient vitamin A ultimate reduction in this viral infection and clinical symptoms \(^{(77)}\). One of the metabolites of vitamin A dietary is Retinoic acid that can be useful in stimulation of innate immune response against viral infection. During researching it has been confirmed that sufficient vitamin A supplementation influenced mortality and morbidity rate and with reduction of this factors, it can be affect viral gastrointestinal diseases \(^{(78)}\). In other word during in vitro and in vivo studies, it has been shown that vitamin A interferes with human Norovirus 1 replication and antiviral effect of vitamin A on Norovirus has been identified. As one of effects of vitamin A on immune response, it is recognized that IFN-b expression plays a key role in immune responses during vitamin A treatment \(^{(79)}\). Therefore, besides vitamin A effect on antiviral immune responses, RIG-1 signaling was stimulated against human Norovirus \(^{(79-81)}\).

5. **HIV**

Regarding to clinical studies used vitamin A as a therapeutic component in child survived from acute measles, it has been suggested that this method of treatment can be useful against human immunodeficiency virus (HIV) infection \(^{(82,83)}\). During Epidemiological studies, it has been shown that vitamin A deficiency between HIV-infected pregnant women is a common problem \(^{(84-86)}\), as well as drug users and addicts populations \(^{(83)}\). In poor countries like African countries that using antiretroviral and prophylactic therapies are expensive, treatment with micronutrients like vitamin A can be best strategy to improve survival rate and reducing vertical transmission of HIV \(^{(87,88)}\). According clinical trials about effectiveness of vitamin A therapy for HIV-infected children, it was observed that using vitamin A as a therapeutic component can reduces diarrhea morbidity \(^{(24,89)}\) and increases the host's immunity \(^{(90)}\). Almost Four clinical trial have been done in different countries such as Tanzania \(^{(87,91)}\), South Africa \(^{(92)}\), Malawi \(^{(93)}\), and Zimbabwe \(^{(94)}\) to figure out that whether vertical transmission and mortality rate of infant can be reduced by antenatal vitamin A supplementation \(^{(95)}\). In other study periodic vitamin A supplementation have been investigated in one clinical trial in Uganda to study whether this periodic supplementation can be useful in improvement of survival of HIV infected children \(^{(96)}\). By World Bank (1993) analysis between forty-seven major health interventions studies using vitamin A it has been shown that vitamin A has the second-highest cost-benefit effect in patients. There are some aspects of study on vitamin A's effects as a beneficial supplementation in reduction of vertical transmission in HIV infection \(^{(97)}\), and infant mortality that remained unknown and needs more studies \(^{(84,98,99)}\).

6. **Entroviruses**\(^{(71)}\)

One of the common viral infections in under four years’ children is Hand, foot, and mouth disease (HFMD) related \(^{t3o} Entroviruses\). Skin and mucous membranes are major regions that get
influenced by this viruses (100, 101). Based on the recent data of in-vitro studies (28, 102, 103) which revealed that retinoic acid receptor (RAR)-a is critical for the antiviral outcome of ATRA, current studies assessed the influences of variation of RAR-a expression through ATRA in EV71-infected cells (104). The quantitative PCR has discovered that ATRA may be efficient in up-regulation of RAR-a expression in either infected U937 (monocytes progenitor cell line) cells and non-infected cells (105). Nevertheless, by adding arotinoid ethyl ester (Ro) to the cell culture get understood that adding this factor prevents increasing the expression of RAR-a mRNA. So it can be concluded that, expression of RAR-a mRNA not affected by EV71 infection itself (106-108). RIG-I is a main IFN triggering gene that in response to EV71 can induce excretion of IFN-a (109, 110). For investigation of the antiviral effect of ATRA on IFN-a signaling, estimating the measure of RIG-I mRNA and genes in the downstream of signaling pathway carried out (100). Previous studies showed that in the lacking vitamin A treatment condition of U937 cells, RIG-I mRNA expression is in low levels. Also through ATRA treatment alone without other factors moderate increase in the expression of RIG-I mRNA was observed, but in EV71 infection alone, expression of RIG-I mRNA in this cell line not found. When the U937 cells get infected with EV71, for treatment of these cells ATRA was used as an effective factor to exhibited higher levels of RIG-I mRNA expression than cells that get treated with ATRA alone. In addition to modifications by effect of ATRA-treated and EV71-infected U937 cell model, it was understood that increase of expression of several downstream genes (IFN promoter-stimulating factor 1 (IPS-1), TRAF family member-associated NF-kB activator-binding kinase 1 (TBK1) TNF receptor-associated factor 3 (TRAF3) and interferon regulatory factor 3 (IRF3) in the RIG-I signaling pathway can be influence by this factor (104, 111). Thus, it can be mentioned that treatment with ATRA can activate RIG-I signaling in EV71-infected cells. Ro is the factor that can block the induction of RIG-I mRNA expression in EV71-infected cells that get treated with ATRA, so it means that up-regulation of the expression of this gene is mediated by RAR-a (104).

7. HPV

Cervical lesions are common pathological damages in women (112). One of the most important causes of these lesions is human papillomaviruses (HPV) infection, and during expression of viral transforming genes, neoplastic modification can be seen in these lesions (113). It has been revealed that DNA of HPV types 16 and 18 that are oncogenic HPVs can immortalize cultured human keratinocytes (HKc) and human cervical cells so this cell line can be a model to study molecular mechanisms of cervical carcinogenesis(114-119).

HKc infected with HPV16 primarily undergo to malignancy developments with a chain of identified phenotypic occurrences in vitro, such as growth factor independence and differentiation resistance.(117, 120) but HKc are consequently vulnerable to malignancy transformations after transfection with a viral or host cell Ras oncogene (121, 122). Based on the previous studies it can be concluded that HKc cells infected with HPV16 are more sensitive to growth and differentiation control by managing with all-trans-retinoic acid (RA), an active metabolite of vitamin A (123).

Additionally, when RA uses as a treatment for HKc cells infected with HPV16, it can reduce steadily the levels of the HPV16 oncogenes E6 and E7 mRNA and protein (124-126). Also physiologic levels of RA (1 nM) influenced immortalized situation of cells, as an inhibitor factor of HPV16-mediated immortalization of normal HKc approximately 95% (124, 125). Previous studies revealed that RA treatment can be an activator factor for triggering of the production of the growth suppressor transforming growth factor-β (TGF-β) (127, 128) in normal HKc and HKc/HPV16, suggested that RA suppression of growth is mediated via the TGF-β (129). This result is the same as findings of Woodworth et al. (1990) that considered, TGF- β as an inhibitor for E6 (130) and E7 (131) .
Table 1. Viral infections and role of vitamin A

<table>
<thead>
<tr>
<th>Viral infection</th>
<th>Common complicated associated</th>
<th>Role of vitamin A</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-2</td>
<td>Severe pulmonary damage &amp; hyper activation of immune response &amp; cytokine storm</td>
<td>Repair of damaged pulmonary pneumocysts &amp; airway epithelium</td>
</tr>
<tr>
<td>HSV</td>
<td>incidence of neonatal herpes &amp; neurologic disabilities</td>
<td>decrease the proliferation of infectious particles through producing viral glycoproteins with lower molecular weights</td>
</tr>
<tr>
<td>HCV</td>
<td>cirrhosis occurrence in individuals with Hepatitis C virus</td>
<td>increased expression of genes that store retinol as retinyl ester (RE) and oxidize RA to metabolites</td>
</tr>
<tr>
<td>Noroviruses</td>
<td>common reasons of acute gastroenteritis</td>
<td>Increase IgA response</td>
</tr>
<tr>
<td>HIV</td>
<td>Immune response dysfunction &amp; cytokine storm</td>
<td>Increase protective immunity</td>
</tr>
<tr>
<td>Entrovirus71</td>
<td>common viral infections in under four years’ children is Hand, foot, and mouth disease (HFMD) related to Enteroviruses</td>
<td>ATRA affect IFN-a signaling, estimating the measure of RIG-I mRNA and genes in the downstream of signaling pathway carried out</td>
</tr>
<tr>
<td>HPV</td>
<td>Cervical lesions as pathological damages in women</td>
<td>RA reduce the levels of the oncogenes E6 and E7 mRNA and protein</td>
</tr>
<tr>
<td>Mumps</td>
<td>Swelling of salivary gland &amp; loss of hearing</td>
<td>Retinoids inhibit MuV replication in uninfected bystander cells through a retinoid inducible gene I (RIG-I), retinoic acid receptor (RAR) and IFN dependent manner making them refractory to subsequent rounds of viral replication</td>
</tr>
</tbody>
</table>

8. Mumps

U937 cells are considered as neoplastic and histiocytic progenitors of monocytes that in many times during immunological studies have been used (132). These cells specially are an important case during Mumps virus (MuV) infection to studying of interferon pathways (133-131). During studies get understood that increasing doses of retinol in these cells act as an inhibitor for MuV replication and the quantity of process measured by TCID50. It was observed that concentrations as low as 1 μM, act as suitable inhibitor and also with this dose increased expression of the retinoid responsive gene RARβ was observed. Increasing doses of ATRA during treatment of U937 cells have efficient operation as inhibitor of MuV output and are effective in the induction of RARβ mRNA expression (132). Several studies reported ATRA at a dose of 1 μM have antiviral effect on MuV. Also IFN signaling increases during the Retinoid treatment. As a primary control of infection, the innate immune response thought to be responsible for immunity and it is mentioned that up-regulation of the type I IFN response functions have an important role in antiviral responses. When MuV infection alone occurred in the U937 model, it causes induction in expression of IFNα1 mRNA. Also, using ATRA as a treatment of MuV infected cells act as a cofactor and its operation has a synergism action to increase the expression of IFNα1 mRNA and its protein levels. So with these concepts it can be assumed that expression of IFNβ mRNA and its protein levels, during treatment of ATRA in MuV infection will get increased. The expression of ISGs will be influenced by increasing in type I IFN production. Also, over the treatment by ATRA in the U937 model, (106) IRF-1 mRNA expression get increased, and this result is favorable in some previous studies and literatures (108, 133, 134). So for expression of RIG-I mRNA, treatment with ATRA is required (Table1) (132).

Conclusion

The promising role of vitamin A in different viral infections is well-described by several epidemiological studies, supporting the notion
that higher level of vitamin A is associated with better prognosis and improved outcomes. Although the mechanisms responsible for vitamin A function in the host immune system have been widely described, the interplay between viral infections and vitamin A status remains an intriguing area, and the potential interactions between viral infections and vitamin A appears to be more complex than our previous knowledge. Induction of antimicrobial peptides, immunoregulatory function, interaction with cellular and viral factors are the main underlying mechanisms by which vitamin A insufficiency could contribute to viral disease development. These Data demonstrate that retinoid can inhibit viral replication commonly through a retinoid inducible gene I (RIG-I), Retinoic Acid Receptor (RAR) and IFN dependent manner making them refractory to subsequent rounds of viral replication. These observations raise the possibility that pharmacological doses of retinoids might have clinical benefit in different viral infections.

Declaration

This study has been conducted in Microbiology Department of the School of Medicine Golestan University of Medical Sciences.

Conflict of interest

The authors declare no conflicts of interests.

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