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Review Article

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Vitamin A and Immunity: A Review

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Abstract Vitamins are essential constituents of our diet that have long been known to influence the immune system. Vitamin A has received particular attention in recent years as this vitamin has been shown to have an unexpected and crucial effect on the immune response. Vitamin A supplementation is known to decrease the risks of mortality and morbidity from some forms of diarrhea, measles, human immunodeficiency virus (HIV) infection and malaria. These effects are likely to be the result of the actions of vitamin A on immunity. The effects on morbidity from measles are related to enhanced antibody production and lymphocyte proliferation. Benefits for severe diarrhea could be attributable to the functions of vitamin A in sustaining the integrity of mucosal epithelia in the gut, whereas positive effects among HIV-infected could also be related to increase T-cell lymphopoiesis. There is no conclusive evidence for a direct effect of vitamin A supplementation on cytokine production or lymphocyte activation. Under certain circumstances, vitamin A supplementation to infants has the potential to improve the antibody response to some vaccines, including tetanus and diphtheria toxoids and measles. There is limited research on the effects of vitamin A supplementation to adults and the elderly on their immune function; currently available data provide no consistent evidence for beneficial effects.

Keywords Vitamin A,innate, adaptive, immunity, HIV, and breastfeeding.

Introduction

The term vitamin A (VA) designates a group of retinoid compounds with the biologic activity of all- trans- retinol. Retinoids usually consist of four isoprenoid units with five conjugated carbon- carbon double bonds [1]. Preformed vitamin A can be obtained mostly from dietary animal sources (liver, fish liver oils, eggs, and dairy products) as retinyl palmitate, whereas carotenoids that can be converted into retinol are obtained from vegetable foodstuffs (dark-green leafy vegetables and deep-orange fruits). Vitamin A plays an essential role in a large number of physiological functions that encompass vision, growth, reproduction, hematopoiesis, and immunity [2]. Despite major advances in the knowledge of vitamin A biology, its deficiency is still a serious public health problem that affects an estimated 127 million preschool children and 7.2 million pregnant women worldwide [3]. In children, vitamin A deficiency results in increased risks of mortality and morbidity from measles and diarrheal infections [4], blindness [5] and anemia [6]. Among women it is likely to be associated with high mortality related topregnancy [7]. Vitamin A is required for innate and adaptive immunity and is an immune enhancer that potentiates the antibody response, maintains and restores the integrity and function of all mucosal surfaces [8].

Vitamin A metabolism

VA is usually acquired from the diet either as all- trans retinol, retinyl esters, or β-carotene [9-10]. All- trans retinol is esterified to retinyl esters and stored in the liver or it can associate to retinol binding protein (RBP), which transports retinol to target tissues. All- trans retinol is then oxidized intracellularly to all - trans retinal by ubiquitously expressed retinol dehydrogenases (RDH), which belong to the short chain dehydrogenase reductase (SDR) gene family. At least three RDH seem to be physiologically involved in this rate-limiting step: RDH1, RDH10 and DHRS9 [9]. Then cytosolic retinal dehydrogenase enzymes (RALDH) catalyze the irreversible oxidation of all- trans retinal to RA [9-10].

Overview of the immune system

The immune system protects the body against infection and disease. It is a complex and integrated system of cells, tissues, and organs that have specialized roles in defending against foreign substances and pathogenic microorganisms, including bacteria, viruses, and fungi. The immune system also functions to guard against the development of cancer. For these actions, the immune system must recognize foreign invaders as well as abnormal cells and distinguish them from self [11]. However, the immune system is a double-edged sword, in that host tissues can be damaged in the process of combating and destroying invading pathogens. A key component of the immediate immune response is inflammation, which can cause damage to host tissues, although the damage is usually not significant [12].

Cells of the immune system originate in the bone marrow and circulate to peripheral tissues through the blood and lymph. Organs of the immune system include the thymus, spleen, and lymph nodes. T - lymphocytes develop in the thymus, which is located in the chest directly above the heart. The spleen, which is located in the upper abdomen, functions to coordinate secretion of antibodies into the blood and also removes old and damaged red blood cells from the circulation [13]. Lymph nodes serve as local sentinel stations in tissues throughout the body, trapping antigens and infectious agents and promoting organized immune cell activation.The immune system is broadly divided into two major components: innate immunity and adaptive immunity. Innate immunityinvolves immediate, nonspecific responses to foreign invaders, while adaptive immunityrequires more time to develop its complex, specific responses [11].

Vitamin A and innate immune responses

Vitamin A is fundamental in maintaining the integrity of epithelia and function as barrier and mucosal immunity [14]. When added to monocytic, myelomonocytic or dendriticcell line cultures, retinoic acid promotes cellular differentiation [15-16] and influences the secretion of key cytokines produced by macrophages, including tumor necrosis factor (TNF-α), IL-1β, IL-6, and IL-12. All- trans-retinoic acid was shown to decrease secretion of TNF-α in murine peripheral blood mononuclear cells, myelomonocytic [17] and macrophagecell lines [18-19]. NK cells are important in the first line of defense against tumors and viral infections. In humans, one cross-sectional study found that children with low serum retinol concentrations had a greater proportion of NK cells than those with higher retinol concentrations. The development of neutrophils in the bone marrow is controlled by retinoic acid receptor-modulated genes [20] and retinoic acid in cultures accelerates neutrophil maturation [21].

Vitamin A and adaptive immune responses

T-cell immune competence can be affected by vitamin A deficiency at various levels, including lymphopoiesis, distribution, expression of surface molecules, and cytokine production. The end points examined in human clinical trials could be grouped into T-lymphocyte counts and function. Daily supplementation with vitamin A during 6 weeks in Kenyan HIV-infected women resulted in a modest, marginally significant greater mean CD4 cell count [22]. One study among elderly men and women reported an apparent adverse effect of daily vitamin A supplementation on total lymphocyte counts at the expense of CD4 [23]. This effect seemed to be ameliorated by the concomitant administration of zinc. Studies indicate a role for vitamin A in the regulation of IL-10 secretion; IL-10 produced by Th2-helper T cells inhibits the synthesis of proinflammatory Th1-type cytokines, including IFN-γ and

IL-2, in both T and NK cells. This mechanism is important in limiting inflammatory responses to some pathogens [24].

Vitamin A and protective immunity

Vitamin A and Tuberculosis

The effect of vitamin A supplementation on tuberculosis outcomes was studied in a clinical trial among hospitalized children who received 200,000 IU vitamin A during two consecutive days or a placebo [25]. No effects were found on radiological or other outcomes after 3 months.

Vitamin A and HIV

Among HIV-infected children, vitamin A decreases mortality [26] and morbidity from diarrheal disease [27], improves growth [28] and reduces viral load [29]. When administered daily during pregnancy and lactation, combined vitamin A and β - carotene could increase the risk of mother-to-child transmission (MTCT) of HIV [30]. The suggestion that daily vitamin A supplementation to HIV-infected mothers increases MTCT and the recent finding that vitamin A reduces the benefits of multivitamins (B, C, and E) on HIV-related outcomes cast some doubts on the safety of providing vitamin A/β- carotene to HIV-infected adults [31].

Vitamin A in cell trafficking, cell differentiation, lymphoid organogenesis, and cytokine production

RA has diverse functions in the regulation of versatile immunological events including cell trafficking, differentiation, cytokine production, and lymphoid organogenesis. In addition to the effects of RA on DCs and B cells, RA affects T cell differentiation [32]. Indeed, preferential differentiation of T cells into T cells is mediated by CD103 DCs that are capable of producing RA and activating latent TGF-β [33-35]. Reciprocally, RA failed to enhance differentiation of naïve T cells into Th17 cells in the absence of DCs [36]. In this regard, DCs in the intestinal lamina of vitamin-A-deficient mice reportedly show impaired production of IL-6, a cytokine that is essential in the differentiation of Th17 cells [37].Although there are controversial reports on the production of IL-6 by MLN-DCs from vitamin-A-deficient mice [38]. In agreement with these functions of RA, vitamin-A- deficient mice have decreased numbers of both T and Th17 cells in the intestine mainly due to the defect of T cell trafficking into the small intestine [39].

The importance of vitamin A in the regulation of intestinal immunity has long been indicated. Epithelial cells and dendritic cells (DCs), especially CD103 DCs, in the intestine uniquely express RALDH and thus are capable of synthesizing RA; therefore the lymphocytes activated by intestinal DCs and epithelial cells express α4β7 integrin and CCR9, which allow them to return to the intestinal compartment [40]. In agreement with this understanding, vitamin-A-deficient mice lack T cells and IgA-PCs in the intestine [41].

Supplementation of vitamin A through breast feeding in relation to immunity

Vitamin A deficiency increases the risk of death from infections in children and is still a major public health problem in developing countries [42]. Up to age 6 months, breast milk is the only source of vitamin A for infants. However, there is ample evidence that, in addition to essential nutrients, breast milk contains numerous immune-protective components [43]. Proteomic analysis reveals 268 proteins in human milk, of which 44 are related to host defense, mostly involved in the immune system [44] and several of them are regulated by vitamin A [45-48].

Vitamin A supplementation and clinical outcomes

A major motivation to study the effects of vitamin A on the immune function is the search for mechanistic explanations of the impact of supplementation on mortality and morbidity among children and pregnant women that has been documented in clinical trials [7, 49]. Vitamin A supplementation after 6 months of age is associated with a reduction in all-cause child mortality of about 23 to 30% [50].Vitamin A also appears to decrease the severity of some diarrheal episodes in childhood and their incidence when administered in combination with zinc [51]. Vitamin A also decreased parasite density and spleen enlargement [28]. It has been proposed that the beneficial effects of vitamin A supplementation on malaria could be due to increased phagocytosis of nonopsonized erythrocytes

mediated through up regulation of CD36 cytoadherence receptors and decreased secretion of TNF-α through down-regulation of the peroxisome proliferator activated receptor γ - retinoic X receptor [52].

A number of community-based trials have also found an apparent increase in respiratory symptoms in relation to vitamin A supplementation [53].Vitamin A interventions, including 6-monthly, large-dose Vitamin A capsule (VAC) distribution, reduce early childhood mortality and blindness in undernourished populations [54]. Vitamin A supplementation to children ≥6 months is a useful public health strategy to improve child survival and to decrease the risk of nutritional blindness and of morbidity of infectious origin from measles, severe diarrhea, HIV, and possibly malaria and intestinal helminthiases [55]. Vitamin A deficiency has plagued human society throughout history. We must all strive to improve the diets of those who are now vulnerable. Until then, periodic large-dose vitamin A delivery has a vital public health role in protecting child health and survival [54].

Conclusion and Recommendations

Vitamin A may have the potential to increase the antibody response to tetanus toxoid when administered some time before immunization. A similar positive effect in response to the diphtheria toxoid might exist and needs to be confirmed. Effects on cytokine production have not been well documented in clinical trials. The beneficial effects of vitamin A supplementation among children with severe measles could be mediated by a short-term increase in antibody production, possibly as a result of increased lymphocyte proliferation. The effect on severe diarrhea is likely due to the role of vitamin A in restoring and maintaining gut mucosal integrity. There is limited research on the effects of vitamin A supplementation to adults and the elderly on their immune function; currently available data provide no consistent evidence for beneficial effects. Additional studies with these age groups are needed.

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