

Vitamin A status in children with asthma

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Low vitamin A levels have been found in a number of diseases in children. The aim of this study was to examine the vitamin A status in children with asthma and to correlate the changes with severity of disease. Serum levels of vitamin A, retinol-binding protein (RBP), and albumin were estimated in 35 asthmatic children (24 males) in the age group of 2–12 years (mean 5.89 years) and 29 controls (19 males). Both study and control groups were similar with respect to age, sex, and overall nutritional status. Twenty-four children in the study group (68.6%) had moderate to severe persistent asthma and eight children had mild persistent asthma. Only three patients suffered from mild intermittent asthma. Vitamin A levels in children with asthma (mean $\pm$ SD 22.14 ± 5.38 μ g/dl) were found to be significantly lower than their controls (mean $\pm$ SD 27.54 ± 4.83 μ g/dl) ($p = 0.0001$). Age, age of onset of asthma, and gender had no correlation with serum vitamin A levels. Low serum vitamin A levels (<20 μ g/dl) were observed four times more commonly in the study group (28.6%) than controls (6.9%). Severity of asthma had a negative correlation with serum vitamin A levels ($r = -0.61$, $p = 0.0001$). Children with severe persistent asthma had markedly low serum vitamin A levels (mean $\pm$ SD 13.42 ± 5.19 μ g/dl) as compared with mild intermittent asthma (mean $\pm$ SD 24.61 ± 2.32 μ g/dl). Therapeutic trials are needed to prove whether low vitamin A levels contribute to asthma severity and the clinical utility of vitamin A supplementation in asthmatic children.

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Asthma, a chronic respiratory disorder, is characterized by airway inflammation and bronchial hyperresponsiveness to various stimuli. Persistent inflammation and frequent exacerbation are known to produce severe epithelial changes such as denudation of airway epithelium, leaving only a layer of basal epithelial cells; thickening of the subbasement membrane; hyperplasia of goblet cells and mucus glands; and infiltration of eosinophils and mononuclear cells into the mucosa and submucosa of airways (1). Repair of epithelial and other structural changes is of utmost importance for the relief of symptoms and control of the disease.

Vitamin A is essential for cellular and sub-cellular membrane stability and influences the growth and repair of epithelial cells (2). At the airways level vitamin A deficiency has been shown to decrease proliferation of mucus and basal cells, resulting in squamous metaplasia (3). The epithelial change disrupts the normal barrier function, exposing the airways to viral or bacterial infec-

tions and obstruction (by increasing bronchial reactivity) in the susceptible host (4).

Because little information is available concerning vitamin A status and its influence on the disease, this preliminary study was designed to assay serum vitamin A in children with asthma and to correlate the changes with severity of asthma.

Material and methods

Study subjects were enrolled from the pediatric pulmonology clinic of Kalawati Saran Children's Hospital, New Delhi. Thirty-five children with asthma, aged 2–12 years, fulfilling the inclusion criteria, were randomly assigned to the study group. The diagnosis of asthma was established on a documented clinical history of recurrent cough and/or wheezing and previous demonstration of improvement of symptoms in response to asthma medication. Severity staging was carried

out as per the guidelines for the diagnosis and management of asthma (5).

An equal number of age- and sex-matched children with minor surgical problems but without atopy or allergy or systemic diseases were enrolled as controls. Six of them were excluded from the final analysis due to technical error in processing the samples.

Any children with a history of prolonged diarrhea (>7 days duration), exanthematous illness in the past 8 weeks, tuberculosis and severe malnutrition (weight for age <60% of expected) were excluded from the study. None of the patients received oral corticosteroids and multi-vitamin supplementation 4 weeks before enrollment. As per the protocol of the clinic, 28 children (80%) were receiving inhaled steroids and 20 (57.1%) of them were also taking low-dose sustained release oral theophylline. Seven children were taking inhaled sodium chromoglycate with intermittent short-acting beta stimulants.

After informed parental consent, 3 ml of venous blood was collected in a light-protected test tube from each patient and serum was separated by centrifugation within 30 min of collection and stored at -10°C . All blood samples were processed and analyzed in a dark room. Vitamin A levels were assessed using high-performance liquid chromatography (HPLC; Shimadzu, Kyoto, Japan). As per World Health Organization guidelines, serum vitamin A levels of more than 20 $\mu\text{g/dl}$ were taken as normal (6). Levels of retinol-binding protein (RBP) were measured with the help of an ELISA reader using a Randox kit (Randox Laboratories, Antrim, UK), and albumin levels were assessed using a Sigma kit on an Olympus (Repl) autoanalyzer (Olympus Repl, Tokyo, Japan).

The data were processed and analyzed on a computer using Epi Info 5 statistical package (AG Dean, EPO, MSG34, Centers for Diseases Control, Atlanta, GA, USA). For the purpose of analysis the severity of asthma were classified as mild intermittent, mild persistent, moderate persistent and severe persistent and labeled as

grade one to four, respectively. Levene's test for equality of variances was performed to find out the distribution of data. Comparison between controls and subjects were analyzed using unpaired Student's *t*-test and *z*-test. Linear regression analysis was used to determine the relationship of different variants with serum vitamin A levels. A *p*-value of <0.05 was taken as significant.

Results

Of the 35 children enrolled in the study group 24 were boys and 11 girls. Their age ranged from 2 to 12 years with median age of 6 years. Seventeen (48.6%) children were under 6 years of age. Children in the control group were similar with respect to their age, sex, and overall nutritional status to the study group (Table 1).

Thirty-three (94.3%) children with asthma had an onset of their disease before 5 years of age (mean $\pm$ SD 2.66 ± 1.9 years). Among the study group, three children had mild intermittent, eight had mild persistent, 19 cases had moderate persistent, and five patients had severe persistent asthma. The overall nutritional status of children with asthma (weight and height for age 82.1% and 94.5%, respectively) was similar to controls (weight and height for age 85.3% and 95.1%, respectively). On further analysis, it was found that the nutritional status of the children with severe disease was low compared with those with mild disease (weight for age $71.8 \pm 7.9\%$ vs. $85.1 \pm 9.3\%$, $p=0.035$ and height for age $91.9 \pm 3.24\%$ vs. $95.2 \pm 0.52\%$, $p=0.17$). Only two children with asthma had clinical signs of vitamin A deficiency (X1A, X1B) and both of them had severe persistent disease.

Table 2 shows the serum levels of vitamin A, RBP, and albumin in children with asthma and controls. The mean serum vitamin A levels of children with asthma were significantly lower than controls (Fig. 1). There was no significant difference for the levels of RBP and serum albumin in the two groups. Age, gender, and

Table 1. Clinical characteristics of children in the study and control groups

Variables	Study group (n=35)	Controls (n=29)
Age (years)	5.89 (2.3)	5.50 (1.9)
Male:female	2.2:1	1.9:1
Age at onset (years)	2.66 (1.9)	—
Nutritional status		
Weight for age* (%)	82.1 (8.10)	85.2 (1.11)
Height for age* (%)	94.5 (2.3)	95.1 (2.9)

*As per NCHS standards.
Values in parentheses, SD.

Table 2. Comparative values of vitamin A, RBP and albumin in the study and control groups.

Variables	Study group (n=35)	Controls (n=29)	p-value
Vitamin A (µg/dl)	22.14 (20.29–23.99)	27.54 (25.7–29.38)	0.0001
RBP (mg/dl)	27.13 (24.14–30.12)	26.86 (24.79–28.93)	0.47
Albumin (gm/dl)	4.14 (3.95–4.33)	4.22 (4.04–4.4)	0.21

Values in parentheses, 95% confidence interval.

nutritional status did not show any significant correlation with vitamin A, RBP or serum albumin levels. On multivariate analysis, severity of disease was the only determinant of the serum vitamin A levels. Serum vitamin A levels in controls and different severities of asthma are shown in Fig. 1. Biochemically, vitamin A deficiency was observed more frequently in children with asthma than controls (28.6% vs. 6.9%; $z=2.21$, $p=0.013$).

As illustrated in Fig. 2 there was a significant negative correlation between serum vitamin A and severity of asthma ($r=-0.61$, $p=0.0001$). Serum vitamin A levels were significantly lower in grade four asthma (mean $\pm$ SD 13.2 ± 5.19 µg/dl) compared with grade one to three asthma (mean $\pm$ SD 26.87 ± 2.32 , 24.61 ± 3.41 , and 22.64 ± 3.98 µg/dl, respectively). Two children, who had eye signs of vitamin A deficiency, had severe persistent asthma and their serum vitamin A levels were 13.8 and 4.7 µg/dl, respectively. The severity, however, did not show a significant correlation with RBP or serum albumin.

Discussion

Although several studies have shown effects of vitamin A and carotenoids in various diseases in humans such as diarrhea, acute respiratory infections, cancers, ischemic heart disease, and immunological disorders (7–9), no useful information is available on vitamin A status in children with asthma. Some authors have observed an association between low levels of serum vitamin A and chronic airway obstruction in adults, but patients with asthma were not included in these studies (3,10). In children, Powell et al. studied the status of antioxidant in asthma. The plasma retinol levels were found to be above the deficiency thresholds. However, no attempt was made to analyze the data with respect to their nutritional status and severity of asthma. Moreover, the children who were enrolled had controlled asthma and 35% of them were either on prophylactic or intermittent therapy (11).

In our study, we observed that the vitamin A deficiency was four times more common in

children with asthma, the levels being lowest in severe disease. As observed in earlier studies there was no influence of age and gender on vitamin A status (7). Though primary nutritional deficiency may have contributed to the low serum retinol levels, on multivariate analysis, among age, sex, weight, height, and severity of disease, only severity was a determinant of serum retinol levels.

There have been a number of hypotheses to explain the altered state of vitamin A status in asthma. Children with asthma are known to have frequent exacerbation because of airway inflammation, infection, exertion or stress. All these factors have been shown to decrease the serum retinol levels by increasing cellular demand for retinol and increasing the urinary loss (12,13).

The airway inflammation in asthmatic patients is associated with increased production of reactive oxygen metabolites (superoxide anion, hydrogen peroxide, and hydroxyl radicals) by peripheral blood eosinophils, neutrophils and alveolar macrophages (14). Beta-carotene by quenching the singlet oxygen (antioxidant effect) may reduce the airway inflammation in asthma (15). This utilization of vitamin A as an antioxidant may be a factor for reduced serum vitamin A levels.

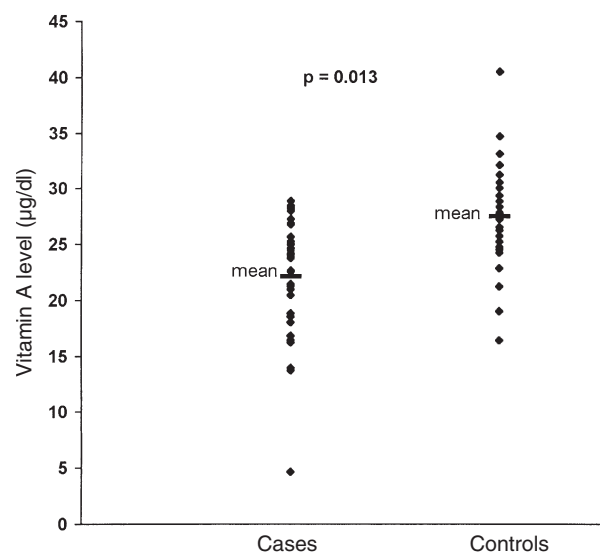


Fig. 1. Distribution of serum vitamin A levels in children with asthma and controls.

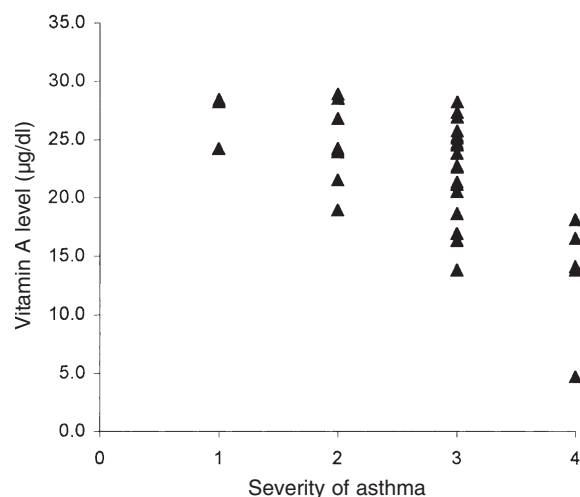


Fig. 2. Serum vitamin A levels with respect to the severity of asthma (1, mild intermittent; 2, mild persistent; 3, moderate persistent; 4, severe persistent).

The hypovitaminosis A may induce respiratory epithelial changes such as metaplasia (16) and may predispose to respiratory infections (17,18), which may further exacerbate acute asthmatic attack in these children and a vicious cycle of severe asthma and vitamin A deficiency may evolve.

World-wide, of an estimated 125 million pre-school children with vitamin A deficiency only 5–10 million children show clinical evidence of severe vitamin A deficiency (19). In our population, only two children (5.7%) had clinical vitamin A deficiency, whereas on biochemical analysis 40% had low serum retinol levels. Under such circumstance, whatever the relationship to etiology, the difference reported here may have therapeutic implications especially in developing countries. Supplementation of vitamin A may help in achieving a better control of the disease. To document this further, however, therapeutic trials are needed to prove the concept and the clinical utility of vitamin A supplementation in asthmatic children.

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