Vitamin A status in acute exacerbations of cystic fibrosis¹–⁴

Christopher Duggan, Andrew A Colin, Ahmad Agil, Laurie Higgins, and Nader Rifai

ABSTRACT Vitamin A is an essential nutrient for epithelial cell maintenance and repair, and it is known that infectious stresses may depress plasma vitamin A concentrations. Patients with cystic fibrosis are at risk for vitamin A deficiency because of fat malabsorption as well as for the inflammatory stresses of pulmonary exacerbations of their underlying disease. We therefore hypothesized that acute pulmonary exacerbations of CF would depress plasma retinol concentrations, and that these concentrations would return to baseline values when clinical symptoms improved. We prospectively studied 35 CF patients (mean age: 24.2 y) consecutively admitted with pulmonary exacerbations. Plasma retinol, vitamin E, retinol binding protein (RBP), and C-reactive protein (CRP) concentrations were measured on hospital admission and discharge. Dietary intake was measured by using a semiquantitative food-frequency questionnaire. Regression analysis was used to identify significant clinical and laboratory correlates of retinol concentrations. On admission, mean (± SD) concentrations of plasma retinol were 1.14 ± 0.5 μmol/L compared with 1.70 ± 0.6 μmol/L on discharge (P = 0.0001). Of 35 subjects, 8 (22.9%) had plasma retinol concentrations considered to be in the deficient range (< 0.70 μmol/L). Concurrently, mean concentrations of plasma RBP increased during hospital admission (from 1.46 to 2.24 μmol/L, P = 0.003), and the mean CRP concentration declined (from 25.7 to 9.8 mg/L, P = 0.002). Significant positive correlations were found between plasma retinol concentrations at admission and age, weight, body mass index, triceps-skinfold-thickness percentile, midupper arm circumference percentile, plasma vitamin E, and RBP concentration, thus suggesting that better-nourished patients had more optimal vitamin A status. At admission, plasma retinol concentrations were negatively correlated with maximum body temperature and CRP concentrations, which indicated that the body’s acute-phase response was associated with the depression in retinol concentrations. We conclude that plasma retinol concentrations are depressed in acute pulmonary exacerbations of cystic fibrosis, and that concentrations considered to be in the deficient range are common. Vitamin A metabolism during acute inflammatory stress deserves further study. Am J Clin Nutr 1996;64:635–9.

KEY WORDS Cystic fibrosis, vitamin A, retinol binding protein, C-reactive protein, pulmonary disease, micronutrient status in infections

INTRODUCTION Vitamin A is a fat-soluble micronutrient that has come under increased study because of data linking poor vitamin A nutritional status with excessive childhood morbidity and mortality in developing countries. Children with mild vitamin A deficiency are at higher risk of death than their nondeficient peers, largely as a result of respiratory and diarrheal diseases (1, 2). Community-wide vitamin A supplementation can reduce mortality rates in select populations (3, 4). These data emphasize the physiologic role of vitamin A as an important nutrient for the maintenance of respiratory and gastrointestinal epithelial cell integrity (5). In addition, recent studies suggest that vitamin A deficiency may adversely affect immunocompetence because deficient children have a reversed ratio of CD4 to CD8 T cells (6) and exhibit a poorer response to immunizations (7).

A relevant aspect of vitamin A nutrition is its metabolism during infectious illnesses. An important example is measles, which has long been known to precipitate a blinding episode of xerophthalmia. Two important observations have been made in patients with measles: 1) plasma vitamin A concentrations decrease during the acute phase of illness (8), probably in parallel with lower concentrations of retinol binding protein (RBP), a known negative acute-phase reactant, and 2) vitamin A supplementation of children hospitalized with measles results in reduced mortality, both all-cause and that due to pneumonia (9, 10). The latter phenomenon suggests that a conditional deficiency of vitamin A exists in measles, presumably because other tissues (eg, the lung and eye) have increased needs for mucosal barrier repair. Indeed, the American Academy of Pediatrics now recommends that US children hospitalized for measles be given vitamin A supplements (11), despite the fact that vitamin A deficiency is not a public health problem in the United States. A similar situation may exist with respiratory syncytial virus infections (12), wherein low serum vitamin A and RBP concentrations have been associated with more severe respiratory disease.

Lung disease in CF patients is marked by recurrent exacerbations of pulmonary disease treated with antibiotics, chest

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physical therapy, and mucolytic agents. Previous studies of patients with CF have not addressed the possibility that the infectious and/or inflammatory stress of acute pulmonary exacerbations could further compromise a patient’s vitamin A status. We therefore hypothesized that acute pulmonary exacerbations of CF would depress plasma retinol concentrations, and that these would return to baseline values when clinical symptoms improved. Whether this response represented an acute-phase shift in protein synthesis was addressed by concomitant measures of RBP and C-reactive protein (CRP).

SUBJECTS AND METHODS

We performed a prospective cohort study among patients followed at Children’s Hospital, Boston, who met the following inclusion criteria: 1) diagnosis of CF confirmed by standard analysis of sweat chloride concentrations, 2) pancreatic insufficiency (as defined by the clinical requirement of supplemental pancreatic enzymes), 3) age ≥ 6 y, and 4) symptoms of pulmonary exacerbation of their disease requiring inpatient treatment. A pulmonary exacerbation was defined as clinical worsening of a patient’s lung disease, resulting in increasing shortness of breath, decreasing exercise tolerance, and/or a forced expiratory volume in one second (FEV1) > 10% lower than baseline. Patients with known, chronic intestinal diseases that would affect the absorption of retinol were excluded. The study protocol was approved by the Children’s Hospital Committee on Clinical Investigation.

Patients were clinically assessed by their pulmonary physicians to determine the need for hospitalization, and then were asked for written informed consent to participate in the study. Pulmonary functions tests, including forced vital capacity (FVC) and FEV1, were obtained at admission. Disease severity was assessed by the National Institutes of Health (Tausig) scores for all participants (13). Anthropometric measurements on all subjects were also made at admission by one study dietitian, and included weight, height, triceps skinfold thickness, and midarm circumference (14). Clinical data, including respiratory rate, maximum body temperature, pulse oximetry readings on room air, need for supplemental oxygen, and use of vitamin supplements during hospitalization were obtained by reviewing nursing flow sheets. Genotype data were kindly supplied by Richard Parad, Children’s Hospital, Boston.

Use of pancreatic enzyme supplements and multivitamin preparations were assessed by face-to-face interview with a physician who was not part of the patient’s medical team (CD). Subjects were asked first whether pancreatic enzymes and vitamins had been prescribed in the past, and then whether they were taking them currently. Subjects were then asked to state the number of days in the week before admission on which they had taken these medications. Dietary intake data were collected from subjects aged ≥ 12 y by using a semiquantitative food-frequency questionnaire that asked about customary food intake over the past year (15). This questionnaire was filled out either shortly after discharge or during hospitalization.

Laboratory assessment of vitamin A status included plasma retinol (retinol) and RBP measurements. Blood was drawn on admission and at the end of hospitalization. The results of only the admission samples were known to the medical team, whereas subsequent samples were batched and run after discharge. Blood samples were protected from light and stored at −70 °C until analyzed. Plasma vitamins A and E were measured by HPLC. Plasma RBP and CRP were measured by the Behring Nephelometer System (Behring Diagnostics Inc, Westwood, MA). Standard biochemical analyses were used to measure plasma albumin, alkaline phosphatase, and γ-glutamyltranspeptidase (GGTP).

Data were entered via Epi-Info (version 6) and analyzed with SAS. Paired t tests were used for normally distributed continuous variables, and nonparametric tests were used for skewed continuous variables. Pearson correlation and multivariate linear-regression analyses were performed to relate vitamin A status with select clinical variables.

RESULTS

During the study period (January 10, 1995, through March 3, 1995), 40 patients with CF were admitted for pulmonary exacerbations. Of these, three declined to participate and two had celiac disease and were therefore ineligible. The clinical characteristics of the remaining 35 patients are listed in Table 1. The mean age was 24.2 y and the mean body mass index (BMI; in kg/m2) was 19.5. Anthropometric measures of triceps skinfold thickness, midarm circumference, and midarm muscle area were all below the mean for age and sex (range: 18th-29th percentile). Pulmonary disease was also moderately advanced, with a mean Tausig score of 67.9, a mean predicted FEV1 of 49.5%, and a mean predicted FVC of 65.3%. Thirty-four of 35 subjects reported having had pancreatic enzyme therapy, with the mean daily dose of lipase reported as 6664 U/kg. Thirty-one of 35 patients reported having taken some form of a

<p>| TABLE 1 |</p>
<table>
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<th>Clinical characteristics on admission</th>
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<tr>
<td><strong>Demographics</strong></td>
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<td>Age (y)</td>
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<tr>
<td>Sex (%)</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td><strong>Nutritional status</strong></td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>Body mass index (kg/m2)</td>
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<tr>
<td>Triceps skinfold (percentile)</td>
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<tr>
<td>Midarm circumference (percentile)</td>
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<tr>
<td>Midarm muscle area (percentile)</td>
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<tr>
<td>Dose of supplemental retinol (IU/d)</td>
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<tr>
<td><strong>Pulmonary status on admission</strong></td>
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<tr>
<td>Tausig score</td>
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<td>FEV1 (percentile)</td>
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<td>FVC (percentile)</td>
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<tr>
<td>Maximum body temperature (°C)</td>
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<tr>
<td>Oxygen saturation (%)</td>
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<td>Laboratory data (%)</td>
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<tr>
<td>Albumin &lt; 30 g/L</td>
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<tr>
<td>Elevated alkaline phosphatase</td>
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<tr>
<td>Alanine aminotransferase &gt; 30 U/L</td>
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<tr>
<td>GGTP &gt; 32 U/L</td>
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<td>ΔF508 homozygotes</td>
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1 ± SD; n in brackets. FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GGTP, γ-glutamyltranspeptidase.  
2 Compared with age- and sex-matched control values (16).  
3 31 of 35 subjects were taking retinol supplements before admission.
multivitamin supplement in the past, with 23 of 31 stating that they had taken at least one such tablet daily for all 7 d preceding admission. The mean dosage of retinol taken by these 31 subjects was 9371 IU/d. The correlation between the dose of retinol supplementation reported during the face-to-face interview and reported via food-frequency questionnaire was excellent ($r = 0.77, P < 0.001$). The mean total intake of vitamin E was 225 mg/d, including a mean of 8.1 mg from the diet and 216.9 mg from vitamin supplements.

Laboratory analysis showed that 1 of 32 subjects (3.1%) had depressed plasma albumin concentrations (< 30 g/L), 5 of 34 (14.7%) had elevated alanine aminotransferase concentrations (> 30 U/L), 7 of 32 (21.9%) had elevated alkaline phosphatase concentrations (compared with age- and sex-matched control values), and 5 of 16 (31.2%) had elevated GGTP concentrations (> 32 U/L). Six of 24 patients (25%) for whom genotype was available were homozygous for the ΔF508 mutation.

During hospitalization, 31 of 35 patients were given a multivitamin supplement that contained retinol. The mean dose of supplemental retinol during hospitalization was 8774 IU/d. Plasma retinol, vitamin E, RBP, and CRP values at hospital admission and discharge are shown in Table 2. Follow-up plasma concentrations were available for 31 of 35 subjects; 27 of these samples were obtained during the hospital admission whereas 4 were obtained at the next outpatient visit. The mean elapsed time between blood draws was 16.2 d, with a range of 3–54 d. The mean length of stay for the cohort was 15.4 d (range: 8–27 d).

Significant increases in plasma concentrations of retinol were seen during inpatient treatment for CF. The mean (± SD) concentration of plasma retinol at admission was 1.14 ± 0.5 μmol/L, whereas on discharge it had risen to 1.70 ± 0.6 μmol/L (paired t test: $P = 0.0001$). Of note, 8 of 35 subjects (22.9%) had plasma concentrations that were below the lower limit of normal for retinol (0.70 μmol/L), a concentration below which some clinical signs of deficiency may be seen. Retinol concentrations on discharge were < 0.70 μmol/L in 2 of 31 (6.5%) subjects (Fisher’s exact test: $P = 0.09$ compared with concentrations on admission). Vitamin E values also increased significantly between admission and discharge, rising from a mean of 18.3 to 23.0 μmol/L ($P = 0.017$). Vitamin E concentrations were not corrected for plasma lipid concentrations.

Concurrent with these changes in plasma vitamin concentrations were changes in the circulating proteins RBP and CRP.

The mean value for RBP rose significantly during treatment for the acute CF exacerbation, from 1.46 to 2.24 μmol/L ($P = 0.0003$), and CRP concentrations fell from 25.7 to 9.8 mg/L ($P = 0.002$). On admission, 4 of 16 (20%) males and 4 of 19 (21%) females had low plasma retinol concentrations (< 0.70 μmol/L); 2 of 6 (33%) in ΔF508 homozygotes compared with 5 of 18 (27.7%) in nonhomozygotes, and 4 of 23 (17.4%) in those reporting use of supplemental retinol for all 7 d before admission compared with 3 of 10 (30%) in those reporting use for < 7 d (Fisher’s two-tailed $P$ value: NS for all of these comparisons).

Univariate-regression analysis was performed to identify relations among continuous variables and retinol concentrations (Table 3). Retinol concentrations on admission correlated best with RBP concentrations on admission ($r = 0.87$), which was not unexpected given the ratio (1:1) with which RBP and retinol circulate in the plasma. The retinol concentration on admission also correlated moderately though significantly with age, weight, BMI, triceps-skinfold-thickness percentile, midupper arm circumference percentile, and the vitamin E concentration on admission. Of note, there was a negative correlation between plasma retinol concentration and both peak body temperature on admission and CRP concentration. The plasma retinol concentration on admission did not correlate with dietary intakes of energy, protein, β-carotene, or retinol in food or vitamin supplements.

We then examined the relations between length of stay and changes in pulmonary function testing with measures of vitamin A status (admission plasma concentration and the increment in plasma concentration between admission and discharge). Although the retinol concentration on admission did not correlate with length of stay, there was a moderate negative correlation ($r = −0.27, P = 0.14$) between increment in retinol concentration and length of stay. No significant correlation was found between plasma retinol concentration and Taussig score, pulmonary function tests, or their changes over the course of hospitalization.

Finally, stepwise-multivariate linear regression was performed by using the plasma retinol concentration on admission as the dependent variable, and select clinical indexes as the independent variables. Clinical variables placed in the model

**TABLE 2**

<table>
<thead>
<tr>
<th>Vitamin and plasma protein concentrations at admission and discharge</th>
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<tr>
<td>Normal range (30)</td>
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<tr>
<td>Vitamin A (μmol/L)</td>
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<tr>
<td>Vitamin E (μmol/L)</td>
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<tr>
<td>RBP (μmol/L)</td>
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<td>CRP (mg/L)</td>
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$^1$ x ± SD; n in brackets. RBP, retinol binding protein; CRP, C-reactive protein.

$^2$ Significantly different from admission (paired t test): $^2 P < 0.0001$.

$^3$ Significantly different from admission (Mann-Whitney nonparametric test): $^3 P = 0.017$.

$^4$ Significantly different from admission (Fisher’s exact test): $^4 P = 0.0003$.

$^5$ Spearman correlation coefficient used because of nonnormal variable.

$^6$ Pearson correlation coefficient (r) between select clinical and laboratory variables at admission.

<table>
<thead>
<tr>
<th>Vitamin A concentration (μmol/L)</th>
<th>Age (y)</th>
<th>Weight (kg)</th>
<th>Body mass index (kg/m$^2$)</th>
<th>Triceps skinfold thickness (%)</th>
<th>Midupper arm circumference (%)</th>
<th>Maximum body temperature (°C)</th>
<th>Admission CRP (mg/L)</th>
<th>Admission vitamin E (μmol/L)</th>
<th>Admission RBP (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.34$^2$</td>
<td></td>
<td>0.45$^4$</td>
<td>0.40$^2$</td>
<td>0.39$^2$</td>
<td>0.35$^4$</td>
<td>−0.41$^2$</td>
<td>−0.44$^2$</td>
<td>0.37$^2$</td>
<td>0.87$^4$</td>
</tr>
</tbody>
</table>

$^1$ CRP, C-reactive protein; RBP, retinol binding protein.

$^2$ $P < 0.05$.

$^3$ Spearman correlation coefficient used because of nonnormal variable.

$^4$ Pearson correlation coefficient (r) between select clinical and laboratory variables at admission.

$^5$ Spearman correlation coefficient used because of nonnormal variable.
included age, weight, BMI, maximum temperature, and percentile values for midupper arm circumference and triceps skinfold thickness. Plasma RBP was not chosen as one of the independent variables because of its collinear relation with vitamin A. The only variables selected for the model were maximum temperature \((P = 0.01)\) and triceps-skinfold-thickness percentile \((P = 0.04)\). The overall model had a significant though low explanatory value \((R^2 = 0.27, P = 0.007)\).

**DISCUSSION**

The interrelation between vitamin A deficiency and CF has been noted for > 60 y. In 1933, Blackfan and Wolbach (5) presented a case series of 13 infants with vitamin A deficiency. The earliest appearance of the characteristic histologic finding of keratinizing metaplasia was noted to be in the trachea and bronchi, and 6 of 11 cases had “dilatation of the acini and ducts, . . . inspissated secretion, . . . and fibrosis” of the pancreas. Soon thereafter, Anderson (17) was credited with the first description of CF; clinical signs of vitamin A deficiency were found in 20% of this cohort. The characteristic bronchiectasis was even ascribed to vitamin A deficiency because the changes in the bronchial epithelium resembled those of prior histologic studies in both animals and humans who were vitamin A deficient.

Patients with CF and pancreatic insufficiency are at risk for fat-soluble vitamin deficiencies because of fat malabsorption and resultant steatorrhea. Previous surveys of CF patients have shown a prevalence of vitamin A deficiency of 20–40% (18–20), although some of these studies were performed in the years before the introduction of microsphere pancreatic enzyme replacement therapy. Such treatment improves the absorption of macro- and micronutrients from the diet (21). Moreover, it is generally recommended to supplement CF patients with a multivitamin preparation to help ensure adequate micronutrient status (22). For example, Sokol et al (23) showed that among patients whose CF is diagnosed at birth, correction of deficiencies of vitamins A and D, plus normalization of serum albumin, may be obtained by using standard pancreatic enzyme replacement therapy, 1 mL multivitamins, plus added vitamin E.

Nonetheless, case reports of vitamin A deficiency in CF patients continue to be published (24–26). Because the early data from Underwood et al (18) documented adequate hepatic stores of vitamin A concurrent with low blood concentrations, one recurring hypothesis has been that the mechanism of depressed plasma concentrations of vitamin A is impaired release of vitamin A due to reduced synthesis of its transport protein, RBP (27). In knockout mice incapable of synthesizing prealbumin, plasma concentrations of retinol and RBP are extremely low but liver stores of RBP are high, also suggesting a block in hepatic release of retinol-RBP complex (28). Our data, which show reduced concentrations of RBP early in the course of an acute exacerbation with subsequent recovery, are consistent with this hypothesis but do not distinguish between decreased protein synthesis or decreased hepatic release of the nutrient-carrier complex.

Alternatively, more recent data have suggested that urinary loss of circulating retinol may be a factor in depressed blood concentrations (29, 30). The presence of prealbumin as the third component in the circulating form of the vitamin A-RBP-prealbumin complex makes the complex unable to be filtered by the kidney. Because hepatic synthesis of prealbumin is also depressed in the acute-phase response, more retinol-RBP unbound to prealbumin is available and this smaller complex is more liable to escape into the urine. Stephensen et al (29) found that patients with pneumonia and sepsis had rates of urinary retinol excretion significantly greater than those of healthy control subjects, and that the presence of fever and the use of aminoglycoside antibiotics increased the urinary loss of vitamin A. Because patients with CF are often treated with aminoglycosides, the possibility exists that low plasma concentrations are due in part to this mechanism.

In summary, our data show that plasma retinol concentrations are depressed during acute pulmonary exacerbations of CF, and that plasma concentrations in the deficient range are common. Moreover, it appears that the depression of plasma retinol concentrations is associated with an acute-phase shift in hepatic protein synthesis because parallel increases in plasma RBP and retinol occurred during hospitalization in concert with decreasing CRP concentrations. Moreover, initial plasma retinol concentrations were significantly and inversely related to peak body temperature and CRP on admission. No correlation was found between retinol concentrations and measures of disease severity (ie, Taussig scores, tests of pulmonary function).

Nonetheless, excess urinary losses and/or increased metabolic demands for the nutrient in peripheral tissues are also possible mechanisms for the depression of plasma retinol, and it is conceivable that multiple factors are at work. The significant correlation between plasma retinol concentration and the many anthropometric measurements noted above all point to an important relation between general nutritional status and micronutrient status. Moreover, because 8 of 35 subjects (22.9%) had plasma concentrations below the range normally considered deficient, important physiologic consequences may occur regardless of the route of nutrient loss or redistribution in the body. Further studies could examine the physiologic implications of vitamin A nutrition during acute inflammatory stress before more aggressive supplementation is recommended.

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