Assessment of vitamin A status in chronic obstructive pulmonary disease patients and healthy smokers

Sergio AR Paiva, Irma Gody, Hélio Vannucchi, Rosa MD Fávaro, Rosana RC Geraldo, and Alvaro O Campana

ABSTRACT The relation between vitamin A status and the degree of lung airway obstruction was examined in a cross-sectional study of 36 male subjects aged 43–74 y who were assigned to five groups as follows: healthy nonsmokers (n = 7), healthy smokers (n = 7), mild chronic obstructive pulmonary disease (COPD-mild) patients (n = 9), COPD–moderate-severe patients (n = 7), and COPD–moderate-severe with exacerbation (+ex; n = 6). Smoking habits, pulmonary function tests, and energy-protein status were assessed; serum concentrations of retinyl esters, retinol, retinol binding protein, and transthyretin and relative dose responses were measured. In addition, 12 male smokers aged 45–61 y with mild COPD were randomly assigned to two groups for a longitudinal study: six subjects consumed vitamin A (1000 RE/d; COPD–vitamin A) and six subjects received placebo for 30 d. Lowered serum retinol concentrations were found in the COPD–moderate-severe and COPD–moderate-severe +ex groups. Measurements of vitamin A status in healthy smokers and in COPD–mild patients were not different from those in healthy nonsmokers. The improvement of pulmonary function test results after vitamin A supplementation [mean increase for 1-s forced expiratory volume (FEV₁) = 22.9% in the COPD–vitamin A group] may support the assumption of a local (respiratory) vitamin A deficiency in patients with this disease.


KEY WORDS Vitamin A status assessment, chronic obstructive pulmonary disease, smoking, pulmonary function tests, retinol, retinol circulating complex

INTRODUCTION

The relation between vitamin A intake and degree of pulmonary airway obstruction in chronic lung diseases has been examined epidemiologically. A strong inverse association between these two variables was found in a subsample of the first National Health and Nutrition Examination Survey (1). It was further reported that lower concentrations of vitamin A are associated with lower values for FEV₁/FVC (1-s forced expiratory volume/forced vital capacity), measured 5 y after serum vitamin A measurements (2). It was also shown that concentrations of retinol and carotenoids are inversely correlated with the number of cigarettes smoked in the previous 24 h (3). In addition, it has been found that serum concentrations of β-carotene are lower in smokers (4). Experimental work has shown that rats fed a diet low in vitamin A developed alterations of the airway epithelial cells similar to those induced by cigarette smoking in human lung (5).

These findings suggest a possible association of vitamin A nutritional status and obstructive lung disease and lifetime cigarette smoking. Lower concentrations of serum retinol have been found by Woo et al (6) and by Vannucchi et al (7) in hospitalized patients with chronic obstructive pulmonary disease (COPD). However, these works did not examine the retinol metabolic pathways and did not consider concurrent protein-energy malnutrition (8) or acute-phase responses (9) that may interfere with serum retinol concentrations.

To test the hypothesis that vitamin A deficiency is associated with COPD, we assessed the vitamin A nutritional status of COPD patients and healthy heavy smokers and nonsmokers. This permitted us to examine the relation between vitamin A nutriture and different degrees of airway obstruction and the effects of cigarette smoking on vitamin status. The nutritional status of vitamin A was assessed by evaluating its major pathways: dietary intake, intestinal absorption, hepatic uptake and storage, and serum transport. Additionally, we investigated the effects of vitamin A supplementation during a 30-d period on lung function tests (FEV₁/FVC) in patients with mild COPD.

SUBJECTS AND METHODS

The protocol for this study was approved by the ethics committee of Botucatu Medical School. All subjects gave their informed consent to participate. The procedures followed were in accordance with the Helsinki Declaration as revised in 1983.

Cross-sectional study

To investigate the nutritional status of vitamin A, we carried out a cross-sectional study of healthy nonsmokers and smokers and of patients with COPD. Sixty-five adult male subjects aged

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43–74 y were invited and agreed to participate in this study. The subjects were examined in the outpatient unit or during specialized consultations in the pulmonary unit of the Botucatu Medical School. Subjects entered the study over an 8-mo period from March to December 1993. The subjects were submitted to a medical examination and laboratory tests. Patients were excluded if their health was impaired primarily by some disease process other than COPD. The 36 participants remaining after screening were divided into five groups as follows: seven healthy nonsmokers (healthy nonsmoker group), seven healthy subjects who currently smoked (healthy smoker group), nine patients with mild COPD who were current smokers and had FEV1/FVC values between 61% and 74% (COPD-mild group), seven patients with moderate or severe COPD who were former smokers and had FEV1/FVC values between 30% and 55% (COPD–moderate-severe group), and six patients with moderate or severe COPD with exacerbation who also were former smokers and had FEV1/FVC values between 32% and 55% in previous evaluations (COPD–moderate-severe + ex group).

COPD was diagnosed by clinical history, physical examination, radiologic criteria, and lung function tests performed when the patients were in stable clinical condition. Eligible COPD patients showed postbronchodilator FEV1/FVC values < 75%; they did not have other medical problems that might interfere with nutritional status and pulmonary function (such as malignancies, systemic liver or renal disease, alcoholism, or diabetes mellitus). Patients in the COPD-mild and COPD–moderate-severe groups had been in stable clinical condition for 3 mo before the study.

Assessment of vitamin A nutritional status

An estimate of usual daily nutrient intake during the past 6 mo was obtained from a food-frequency questionnaire (10). This instrument listed 120 food and beverage items. Food records were coded, entered into the computer, and analyzed by a trained dietitian throughout the study to minimize variability. Dietary information was converted to energy, protein, fat, vitamin A, and vitamin E intakes with the computer software PROGRAMA DE APOIO À NUTRIÇÃO (Centro de Informática em Saúde da Escola Paulista de Medicina, São Paulo, Brazil). This program uses the tables of food composition of the US Department of Agriculture (11) and, for foods that were missing from the US Department of Agriculture tables, data from the Fundação Instituto Brasileiro de Geografia e Estatística (12).

Venous fasting blood samples were drawn for laboratory analyses. Serum samples were labeled, stored at −20°C, and analyzed within 6 mo of collection. Retinol, retinyl esters, α-carotene, and β-carotene were analyzed by HPLC (Shimadzu SPD-6AV, with controller system SCL 6B and an integrator chromatopac C-R6A; Shimadzu Corporation, Analytical Instruments Division, Kyoto, Japan); retinol, α-carotene, and β-carotene according to Arnaud et al (13) and retinyl esters according to Bankson et al (14). Retinol binding protein (RBP) and transthyretin were measured with commercial radial immunodiffusion plates (15) (Behringwerke AG, Marburg, Germany).

Immediately after the fasting blood sample was obtained, a standardized breakfast containing 13.4 REs was given to the participants in the investigation in addition to 1000 μg retinyl palmitate given orally. A second blood sample was obtained 5 h later for determination of retinol and retinyl ester. Measurement of fasting retinyl ester and retinyl ester after supplementation allowed us to assess intestinal absorption and hepatic uptake of the vitamin (16–18). In addition, values for the relative-dose-response (RDR) test were obtained from the estimation of fasting retinol and retinyl after vitamin A ingestion, according to Loerch et al (19). The test consists of the determination of retinol serum concentrations at baseline and 5 h after an oral dose of retinyl palmitate. The response depends on the release of apo-RBP as holo-RBP in the blood within 5 h of the dose. The RDR is expressed as a percentage and is defined as the magnitude of rise in the serum vitamin A concentration at 5 h compared with baseline, divided by the final serum concentration of vitamin A at 5 h. Any response that was ≥ 20% was considered to be abnormal (20).

Smoking habits and pulmonary function tests

Information was obtained with an adapted questionnaire from the American Thoracic Society, Division of Lung Disease (ATS-DLD 78) (21). Four indexes were selected to be presented in this paper: duration of smoking, number of cigarettes smoked per day, number of cigarettes smoked in the previous 24 h, and number of pack years (packs smoked daily times number of years smoked) (3).

Spirometry was performed with a spirometer (Med-Graph 200; Medical Graphics Corporation, St Paul) according to the criteria of the American Thoracic Society (22). FEV1 was expressed in mL, as a percentage of FVC, and as a percentage of the reference values (23). Arterial blood gases were measured with a 165/2 blood gas analyzer (Corning Medical, Corning Glass Works, Medfield, MA).

Assessment of energy-protein nutritional status and of acute-phase reactants

Nutritional status was assessed by use of anthropometric indexes and hematologic and biochemical data. Anthropometric indexes included body weight and height; triceps, bicipital, subscapular, and suprailiac skinfold thicknesses (TSF, BSF, SSF, and SIF, respectively); midarm circumference; and the following derived values: ideal body weight (IBW), body mass index (BMI), midarm muscle circumference, and the sum of four skinfold thicknesses (SSF). The procedures for measurement and calculations were those recommended by Durnin and Womersley (24), Frisancho (25), and Blackburn and Thornton (26). Percentage IBW was derived from the present weight divided by the midpoint of the weight range for sex, height, and medium frame in the Metropolitan Insurance Company weight standards (27).

For hematologic and biochemical studies venous blood samples were taken for estimation of hematocrit, hemoglobin, number of blood cells [through use of a Coulter counter (Coulter Corporation, Miami)], total serum proteins [through use of the biuret method, adapted to the automatic analyzer ABBA 100 (Abbott Technical, Diagnostics Division, South Pasadena, CA)], and albumin (through use of the brom cresol green reaction) (28). Serum concentrations of C-reactive protein (CRP) and ceruloplasmin were measured with commercial radial immunodiffusion plates (15) (Behringwerke AG).
Longitudinal study

A study of the effects of vitamin A supplementation on lung function tests was also undertaken in patients with mild COPD. A double-blind longitudinal study was designed in which 12 male current smokers (aged 45–61 y with FEV₁/FVC values between 63% and 75%) were randomly assigned to one of two groups: a group supplemented with 1000 RE retinyl palmitate+d for 30 d (COPD–vitamin A group, n = 6) or a group that received placebo (COPD-placebo group, n = 6). Lung function tests were carried out three times: at the beginning of the study, after 30 d of vitamin A supplementation or placebo, and again after a 30-d period of vitamin A withdrawal.

Statistical analyses

When there was a normal distribution, comparisons between two groups were made by Student’s t test; analysis of variance (ANOVA) was performed when comparisons included more than two groups. Repeated-measures ANOVA was used for the longitudinal study. Intergroup comparisons were made with the Student-Newman-Keuls test. When data showed a non-normal distribution, comparisons between two groups were made with the Mann-Whitney U test; the Kruskall-Wallis test was used when comparisons included more than two groups. Intergroup comparisons were made with Dunn’s test. To analyze interrelations between variables, Pearson’s or Spearman’s correlation coefficients were calculated. Statistical significance was set at the P < 0.05 level. Values are presented as means (±SD) or medians (including the lower quartile and upper quartile). Data analysis was carried out with SIGMASTAT for Windows (29).

RESULTS

Cross-sectional study

Characteristics of the subjects

Data related to smoking habits and values for age, pulmonary function tests, protein-energy status, and CRP are listed in Table 1. The average age of the five groups studied was > 50 y; COPD–mild severe and COPD–mild–severe+ex patients were significantly older than subjects in the other groups. Univariate correlations between age and variables related to the assessment of vitamin A were not significant. Duration of smoking, number of cigarettes smoked per day, and number of pack-years did not differ significantly between the healthy smoker, COPD–mild, COPD–moderate–severe, and COPD–mild–severe+ex groups. Values of variables related to the degree of bronchial obstruction (FEV₁, mL, FEV₁ %, and FEV₁/FVC%) were significantly different between the healthy nonsmoker and COPD–mild and COPD–mild–severe groups, and between the healthy smoker and COPD–mild and COPD–mild–severe groups. Recent loss of weight was more frequently reported by patients in the COPD–mild–severe and COPD–mild–severe+ex groups (healthy nonsmoker, 2/7; healthy smoker, 1/7; COPD–mild, 1/9; COPD–mild–severe, 4/7; and COPD–mild–severe+ex, 2/6).

Anthropometric indexes (body weight, IBW, BMI, TSF, SSF, SIF, ΣSF, and midarm muscle circumference) were significantly lower in the COPD–mild–severe+ex group than in the control subjects. In the COPD–mild–severe patients these indexes were also lower than in the control group but the

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Characteristics of subjects in the cross-sectional study</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Healthy nonsmoker (n = 7)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>52.4 ± 6.2^a</td>
</tr>
<tr>
<td>Pack-years</td>
<td>—</td>
</tr>
<tr>
<td>Cigarettes/d</td>
<td>—</td>
</tr>
<tr>
<td>FEV₁ (l/min)</td>
<td>104.4 ± 10.9^a</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>81.0 ± 4.6^a</td>
</tr>
<tr>
<td>IBW (%)</td>
<td>101 (98-122)^a</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9 (22.6-30.0)^a</td>
</tr>
<tr>
<td>TSF (mm)</td>
<td>10 (7.5-14)^b</td>
</tr>
<tr>
<td>SSF (mm)</td>
<td>17 (13-22)^a</td>
</tr>
<tr>
<td>SIF (mm)</td>
<td>13 (10-16)^b</td>
</tr>
<tr>
<td>BSF (mm)</td>
<td>4 (4-7)^ab</td>
</tr>
<tr>
<td>MAMC (mm)</td>
<td>272 (256-296)^a</td>
</tr>
<tr>
<td>ΣSF (mm)</td>
<td>45 (37.5-59)^a</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>46.6 ± 4.2^a</td>
</tr>
<tr>
<td>Number of lymphocytes (cells/mm³)</td>
<td>2643 (2380-2997)^ab</td>
</tr>
<tr>
<td>CRP (µg/L)</td>
<td>0 (0-185)^a</td>
</tr>
</tbody>
</table>

1 COPD, chronic obstructive pulmonary disease; ex, with exacerbation; KW, Kruskall-Wallis test; pack-years, number of packs smoked daily times number of years smoked; FEV₁, 1 s forced expiratory volume; FVC, forced vital capacity; IBW, ideal body weight; TSF, SSF, SIF, and BSF, triceps, subscapular, suprailiac, and bicipital skinfold thickness, respectively; MAMC, midarm muscle circumference; ΣSF, sum of four skinfold thicknesses; CRP, C-reactive protein. Means with different superscript letters are significantly different, P < 0.05.

2 ± SD.

3 Median (range from quartile 1 to quartile 3).
differences were not significant. Four patients had values lower than 90% of IBW: one in the COPD–moderate-severe group and three in the COPD–moderate-severe+ex group. Lower values were found for serum albumin, RBP, transthyretin, and lymphocyte number in the COPD–moderate-severe and COPD–moderate-severe+ex groups. However, differences were only significant in the comparison of the healthy nonsmoker group with the COPD–moderate-severe and COPD–moderate-severe+ex groups, respectively, for serum albumin and transthyretin. Serum CRP was significantly higher in COPD–moderate-severe+ex patients than in all other groups.

In addition, no group differences existed for ceruloplasmin, serum total proteins, hemoglobin, and number of blood cells. Hematocrit (mean values) was significantly higher in the healthy smoker group (47.7%) and in the COPD–moderate-severe group without (48.3%) and with exacerbation (49.2%) than in the healthy nonsmoker group (43.2%). The mean value for the COPD-mild group was 46.4%, which was not significantly different from the control group.

Assessment of vitamin A status

Estimates of vitamin A intake were not significantly different among healthy subjects, smokers, and COPD patients. In the groups investigated, 67.3–83% of the ingested vitamin came from vegetarian sources. Additionally, no differences were detected among groups in serum concentrations of α-carotene and β-carotene (Table 2).

No significant differences were detected among groups in serum retinyl ester concentrations after administration of retinyl palmitate. A significant correlation was found between serum concentrations of retinyl ester and FEV₁/FVC in the healthy smoker and COPD–moderate-severe groups (healthy smoker: $r = 0.721$, $P = 0.039$; COPD–moderate-severe: $r = 0.673$, $P = 0.049$) but not in the healthy nonsmoker or COPD-mild group. Additionally, none of the subjects presented a positive RDR test and no significant differences in the results of the RDR test were found among the groups studied (Table 2).

Also shown in Table 2 are the values of the components of the retinol circulating complex. No differences were observed in retinol, RBP, or transthyretin concentrations between healthy smokers and nonsmokers. The concentrations of the three components of the retinol circulating complex were lower in the COPD–moderate-severe group than in the healthy nonsmoker group (Table 2); however, only the difference in serum retinol was significant. These changes were not present in the COPD-mild group. On the other hand, the values of the components of the retinol circulating complex were significantly lower, with the exception of RBP, in the COPD–moderate-severe+ex group.

Longitudinal study

There were no significant differences between the COPD-vitamin A and COPD-placebo groups for the variables studied at the beginning of the experiment (Table 3). Mean values for FEV₁ (expressed in L and as % of reference values) and FVC were significantly higher in vitamin A–supplemented subjects after 30 d of supplementation than at the start of the study. In the placebo group, these differences were not significant (Table 3). In the COPD–vitamin A group, the mean increase in FEV₁ (% of reference values) was 22.9% and in FVC (L) was 24.5%. The withdrawal of the vitamin A supplement returned the FEV₁ and FVC values to baseline levels.

DISCUSSION

In COPD, the long evolution of the illness is frequently associated with acute exacerbations and with complications such as secondary infections or energy-protein malnutrition. These events may have some effects on the metabolic pathways of vitamin A. Therefore, the current study design included patients with mild COPD (COPD-mild, COPD–vitamin A, and

### TABLE 2

<table>
<thead>
<tr>
<th>Vitamin A intake (IU)</th>
<th>Healthy nonsmoker (n = 7)</th>
<th>Healthy smoker (n = 9)</th>
<th>COPD-mild (n = 7)</th>
<th>COPD-moderate-severe (n = 7)</th>
<th>COPD-moderate-severe+ex (n = 6)</th>
<th>P (test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum α-carotene (μmol/L)</td>
<td>0.10 (0.02-0.19)</td>
<td>0.10 (0.02-0.16)</td>
<td>0.09 (0.02-0.20)</td>
<td>0.07 (0.06-0.08)</td>
<td>0.07 (0.03-0.12)</td>
<td>0.984 (KW)</td>
</tr>
<tr>
<td>Serum β-carotene (μmol/L)</td>
<td>0.61 (0.13-0.95)</td>
<td>0.20 (0.13-0.33)</td>
<td>0.27 (0.15-0.29)</td>
<td>0.17 (0.04-0.33)</td>
<td>0.20 (0.11-0.42)</td>
<td>0.539 (KW)</td>
</tr>
<tr>
<td>Retinyl ester (nmol/L)</td>
<td>212 (140–338)</td>
<td>187 (162–398)</td>
<td>212 (149–529)</td>
<td>204 (164–230)</td>
<td>181 (117–308)</td>
<td>0.903 (KW)</td>
</tr>
<tr>
<td>RDR (%)</td>
<td>0.6 (0-5.9)</td>
<td>2.0 (0–7.0)</td>
<td>4.4 (0-6.4)</td>
<td>0 (0–3.9)</td>
<td>1.3 (0-8.7)</td>
<td>0.885 (KW)</td>
</tr>
<tr>
<td>Retinol (μmol/L)</td>
<td>2.43 ± 0.57ab</td>
<td>2.01 ± 0.40ab</td>
<td>2.38 ± 0.42a</td>
<td>1.72 ± 0.38a</td>
<td>1.62 ± 0.50a</td>
<td>0.004 (ANOVA)</td>
</tr>
<tr>
<td>RBP (μmol/L)</td>
<td>2.49 ± 0.44a</td>
<td>2.07 ± 0.38a</td>
<td>2.51 ± 0.41a</td>
<td>2.09 ± 0.40a</td>
<td>1.84 ± 0.64a</td>
<td>0.031 (ANOVA)</td>
</tr>
<tr>
<td>Transthyretin (μmol/L)</td>
<td>6.42 ± 1.37a</td>
<td>6.06 ± 0.99a</td>
<td>6.42 ± 1.21b</td>
<td>4.94 ± 1.46ab</td>
<td>4.04 ± 1.20a</td>
<td>0.004 (ANOVA)</td>
</tr>
</tbody>
</table>

1 COPD, chronic obstructive pulmonary disease; ex, with exacerbation; KW, Kruskall-Wallis test; RDR, relative dose response; RBP, retinol binding protein. Means with different superscript letters are significantly different, $P < 0.05$.
2 Median (range from quartile 1 to quartile 3).
3 5 h after supplementation.
TABLE 3
Variables related to the pulmonary function tests and measured during the longitudinal study

<table>
<thead>
<tr>
<th></th>
<th>t0 (n = 6)</th>
<th>t1 (n = 6)</th>
<th>t2 (n = 6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COPD–Vitamin A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.75 ± 0.39</td>
<td>4.67 ± 0.65b</td>
<td>3.81 ± 0.48a</td>
<td>0.003</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>2.72 ± 0.36a</td>
<td>3.32 ± 0.69a</td>
<td>2.75 ± 0.46a</td>
<td>0.004</td>
</tr>
<tr>
<td>FEV1 (% of reference)</td>
<td>83.0 ± 7.8a</td>
<td>102.0 ± 16.0a</td>
<td>85.3 ± 12.1a</td>
<td>0.004</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>71.7 ± 4.4</td>
<td>70.5 ± 4.7</td>
<td>72.0 ± 5.6</td>
<td>0.151</td>
</tr>
<tr>
<td>MMER25–75 (L/s)</td>
<td>1.94 ± 0.59</td>
<td>2.15 ± 0.73</td>
<td>1.91 ± 0.58</td>
<td>0.243</td>
</tr>
<tr>
<td><strong>COPD-placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (L)</td>
<td>4.52 ± 0.80</td>
<td>5.00 ± 1.28</td>
<td>4.90 ± 0.71</td>
<td>0.161</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>3.11 ± 0.51</td>
<td>3.55 ± 0.88</td>
<td>3.42 ± 0.51</td>
<td>0.086</td>
</tr>
<tr>
<td>FEV1 (% of reference)</td>
<td>89.3 ± 9.3</td>
<td>101.7 ± 16.6</td>
<td>98.3 ± 7.5</td>
<td>0.076</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>68.8 ± 3.2</td>
<td>71.0 ± 3.9</td>
<td>69.8 ± 2.3</td>
<td>0.087</td>
</tr>
<tr>
<td>MMER25–75 (L/s)</td>
<td>2.06 ± 0.52</td>
<td>2.42 ± 0.79</td>
<td>2.11 ± 0.57</td>
<td>0.070</td>
</tr>
</tbody>
</table>

1 ± SD. t0, beginning of the study; t1, after a period of 30 d of vitamin A supplementation or placebo; t2, after a period of 30 d of vitamin withdrawal; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; FEV1, 1-s forced expiratory volume; MMER25–75, maximal midexpiratory flow rate measured between 25% and 75% of the total FVC. Student’s t test was used to compare values found in the COPD–vitamin A and COPD-placebo groups at t0; no significant differences were observed. P values are by repeated-measures ANOVA. Means with different superscript letters are significantly different, P < 0.05.

COPD-placebo groups), patients with moderate or severe COPD (COPD–moderate-severe group), and patients with exacerbation of the respiratory condition in addition to moderate or severe COPD (COPD–moderate-sever+ex).

Patients in the COPD-mild group did not show any alterations regarding vitamin A intake, intestinal absorption, hepatic uptake, or hepatic reserve (Table 2). In addition, no differences were observed in serum retinol, RBP, and transthyretin concentrations when COPD-mild values were compared with those of the control group (healthy nonsmoker group) (Table 2). These findings indicate a maintained integrity of the investigated retinol metabolic pathways in mild COPD and do not appear to support the occurrence of vitamin A deficiency in these patients.

However, in the longitudinal study, patients in the COPD–vitamin A group showed significant improvement in airway obstruction after a 30-d period of supplementation with retinyl palmitate (Table 3). The percentage changes in FEV1 and in FVC in this group were 22.9% and 24.5%, respectively. These changes in spirometry values after vitamin A supplementation were greater than the variability due to the procedure of data acquisition and to the equipment performance. In fact, in patients with asthma, Pennock et al (30) found CVs for FEV1 and FVC to be 13% and 11%, respectively, from week to week. In addition, in patients with different clinical conditions, the CV for FEV1 was 12.3% after administration of placebo aerosol (31). In our study, the increase of the spirometry values in the placebo group after 30 d (13.9% for FEV1 and 10.6% for FVC) is similar to the results reported above. Therefore, we believe that the increase in spirometry values in our vitamin A–supplemented group is of biological relevance.

Biesalski and Stofft (32) also found significant increases in FEV1 and FVC after vitamin A supplementation (25 000 IU/d for 30 d) in chronic smokers with disturbances of pulmonary function. In this respect, it has been shown that respiratory cell damage, as provoked by benzo[a]pyrene, which is present in cigarette smoke (33), decreases the uptake of vitamin A into lung cells (34) and leads to a local vitamin A deficiency of the lung tissues (35). Other pathways for vitamin A transport might be operating in these conditions; for example, retinyl esters present in the chylomicron remnants might be taken up by the respiratory cells (36). This would explain the effectiveness of retinyl palmitate in Biesalski and Stofft’s work and in our study.

These data suggest that in patients with mild COPD, despite normal serum retinol transport, a local vitamin A deficiency can occur that induces pathophysiologic consequences such as loss of normal secretion of goblet cells and other secretory cells, narrowing of the lumina, and loss of distensibility of the Airways (37). Therefore, the improvement in pulmonary function tests after vitamin A supplementation might be due to a tissue repletion of vitamin A with reversal of histopathologic changes in the respiratory airways.

In the group of patients with moderate or severe COPD with exacerbation we found lowered serum retinol concentrations. Circulating concentrations of retinol can be modified by a variety of situations and clinical conditions (38). In fact, it has been considered that serum concentrations become predictive of vitamin A status only when body reserves have been critically depleted or overfilled (39). Liver concentrations of vitamin A reflect total body stores and are considered to be the best indicator of vitamin A status (20). Concentrations of vitamin A in the liver can be evaluated with the RDR test, developed in rats (19) and extensively used in human studies (17, 40, 41). In the COPD–moderate-severe+ex group of patients, none of the individuals tested had results higher than 20% (20). Therefore, our results indicate that these patients had adequate hepatic stores of vitamin A.

These patients also showed significantly lower values for all the anthropometric indexes estimated and for serum transthyretin and a tendency toward a decrease in serum RBP concentrations (Tables 1 and 2). These results appear to indicate a concurrent energy-protein malnutrition in this group. Because protein deficiency reduces the synthesis of RBPs by the liver, serum retinol concentrations are likely to be depressed (42, 43).

CRP was also found to be increased in the COPD–moderate-sever+ex group (Table 1). Elevated concentrations of CRP are an important indicator of an acute inflammatory state (9,
Therefore, other acute-phase responses were to be expected in these patients, such as decreased concentrations of serum transthyretin (43, 45) and also a decreased concentration of serum retinol (46–50).

Our data for this group showed adequate liver vitamin A stores and depressed serum retinol concentrations. Because it has been shown that serum concentrations of retinol and transthyretin can be modified by a variety of situations including energy-protein malnutrition and stressful conditions (43), we believe that these two last disturbances are factors to be considered for explaining the lowered serum retinol concentration in the COPD–moderate-severe+ex group.

A significant decrease in serum retinol concentrations was also observed in patients with stable, moderate, or severe COPD (COPD–moderate-severe group) (Table 2). These patients did not show any changes related to the intake, absorption, or liver uptake of vitamin A; in addition, their RDR tests were normal, indicating adequate vitamin A liver stores.

Although patients of both groups (COPD–moderate-severe and COPD–moderate-severe+ex) have significantly lower serum retinol concentrations, these concentrations are not indicative of vitamin deficiency status (51). However, it may be assumed that lesser amounts of vitamin A become available to target cells (including respiratory cells), with a consequent depletion of tissue vitamin A.

In the medical literature, concentrations of serum retinol in cigarette smokers compared with nonsmokers have been reported to be increased (52), decreased (3, 53), or unchanged (54, 55). In our work, serum retinol concentrations of the healthy smokers were not significantly different from those of healthy nonsmokers. In healthy smokers and in patients with moderate to severe COPD, we found a positive correlation between serum retinyl ester concentrations, measured after administration of retinyl palmitate, and values for FEV1/FVC. This finding may represent one possible link between vitamin A metabolic pathways and pulmonary function.

In summary, our data do not support the hypothesis that COPD patients have vitamin A deficiency, that is, diminished body vitamin A stores. However, our results do suggest an association between COPD and vitamin A status. Both the COPD–moderate-severe and COPD–moderate-severe+ex groups had depressed serum retinol concentrations. Because the serum retinol values were lower, it is likely that lesser amounts of vitamin might be available to target cells, leading to a depletion of tissue vitamin A stores.

In patients with mild COPD we did not find any alterations in the investigated vitamin A metabolic pathways. However, the improvement of airway obstruction after vitamin A supplementation suggests the existence of a local vitamin deficiency, which might be due to a blockade of the regular uptake of retinol from the plasma retinol circulating complex.

The above findings are limited to the subjects we studied and cannot be readily generalized to all patients with COPD. In addition, caution should be exercised in interpreting the results of our work, which involved a small number of participants in both cross-sectional and intervention trial studies. Long-term, controlled intervention trials that include more patients are needed to understand the effect of vitamin A supplementation on airway obstruction and the mechanisms behind it.

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