Vitamin A and lung function in CF

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Abstract

Laboratory evidence suggests that vitamin A could have a protective effect on respiratory status in patients with cystic fibrosis (CF). This study shows a significant correlation between serum vitamin A concentrations and every aspect of lung function tested in 38 patients with stable CF. Serum vitamin D and vitamin E concentrations were also measured but did not show any significant correlations with lung function.

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1. Introduction

Recent laboratory evidence suggests that vitamin A could have protective effects on the respiratory status of patients with cystic fibrosis (CF). Thus, while elastinolytic proteinases (elastases) constitute a likely cause of tissue injury in the lung in CF [1], vitamin A (retinoic acid, 100 nM), has been shown to protect against elastase-induced lung damage in bronchial epithelial cell lines in culture [2]. In addition, retinoic acid (1 μM) has an anti-oxidant effect in the lung, protecting against hyperoxia-mediated cell-cycle arrest of lung alveolar epithelial cells by preserving late G1 cyclin activities [3]. Inflammation has been shown to depress serum vitamin A levels in CF [4], with recovery in serum levels associated with the resolution of pulmonary exacerbations [4,5]. Serum vitamin A concentrations vary widely in stable CF and are generally lower than the concentrations observed in the general population [5]. The relationships between serum vitamin A concentrations and respiratory function in CF have not been studied.

For comparison, vitamin D and vitamin E concentrations were also measured and their relationships with lung function were studied. Vitamin D is not known to have any role on pulmonary inflammation, oxidative damage or growth and development. Vitamin E is an anti-oxidant and may have a role in the protection of lung tissue against oxidative damage [6].

2. Participants, methods and results

We studied 38 patients (mean age 15.3 years (range 6.1–25.2 years), 20 males, mean FEV1 77% predicted (range 30–119% predicted)) with CF attending the Tayside clinic for routine visits or annual reviews in the year 2002. Inclusion criteria were age 6 years and older, performance of reproducible spirometry and stable CF-related clinical status at the time of the review. The mean height centile was −0.59 (range −4.53 to +1.71, standard deviation (SD) 1.18) and the mean weight centile was −0.68 (range −5.33 to +1.98, SD 1.39). The patients were on a mean dose of 6000 (range 0–17000) lipase units/kg/day. 3 patients were pancreatic-sufficient. 5 had CF-related diabetes. 32 (82%)
were on long-term nebulised antibiotics and 8 (21%) on nebulised DNase. All patients were prescribed regular vitamin A, D and E supplementation as per the consensus document for the UK (Nutritional management of Cystic Fibrosis UK Cystic Fibrosis Trust Nutrition Working Group (April 2002) on www.cftrust.org.uk). The study protocol was approved by the Tayside Ethics Committee and informed consent was obtained from subjects and/or their parent(s).

History-taking and clinical examination was performed to confirm the absence of clinical exacerbation in order to minimise the effect of acute inflammation on vitamin A status. Although published evidence and consensus are lacking on the criteria used to define an exacerbation, we use criteria similar to those defined recently for a large, prospective, multicentric study: relative decrease in percent predicted forced expiratory volume in 1 second (FEV₁), increased cough frequency, new crackles and haemoptysis [7]. Spirometry was performed in the clinic according to the guidelines of the American Thoracic Society [8]. FEV₁, forced vital capacity (FVC) and peak expiratory flow (PEF) were expressed as a percentage of predicted normal. Serum vitamin A and E concentrations were measured by high precision liquid chromatography [9] and serum vitamin D concentrations as 25-hydroxy-vitamin D using the Nicholls Institute automated chemiluminescence immunoassay [10]. The data were non-normally distributed. The Spearman rank correlation coefficient was used to study the associations between serum concentrations of vitamins A, D and E and measures of lung function. Statistical significance was assumed for \( P < 0.05 \) (2-tailed).

Serum vitamin A concentrations were variable and significantly correlated with FEV₁ (\( r = 0.37, P = 0.02 \)), FVC (\( r = 0.39, P = 0.02 \)) and PEF (\( r = 0.41, P = 0.01 \)) (Fig. 1). There were no significant correlations between serum vitamin D concentrations and FEV₁ (\( r = 0.20, P = 0.21 \)), FVC (\( r = 0.20, P = 0.22 \)) and PEF (\( r = 0.27, P = 0.09 \)) (Fig. 1). In addition, no significant correlations between vitamin E concentrations and pulmonary function (FEV₁ (\( r = 0.08, P = 0.62 \)), FVC (\( r = 0.10, P = 0.44 \)) and PEF (\( r = 0.10, P = 0.43 \)) were observed.

3. Discussion

This is the first report of a consistent and specific relationship between serum vitamin A concentrations and all

![Fig. 1. Significant (\( p < 0.05 \)) correlations (Spearman’s) between (a) FEV₁ and (b) FVC versus serum vitamin A concentrations compared to the absence of correlation between (c) FEV₁ and (d) FVC versus serum vitamin D concentrations in patients with CF. A similar contrast in relationships with serum vitamin A compared to serum vitamin D concentrations is observed for PEF.](image)
aspects of pulmonary function measured in the clinic setting (FEV₁, FVC, PEF) in children and young adults with clinically stable CF. The observation was not replicated for serum vitamin D and E concentrations. As observed by others for CF, 40% of the serum vitamin A concentrations were placed outside the reference range for the general population (1.1–3.2 μmol/l).

A link between low dietary vitamin A intake and low forced expiratory flow at 25–75% vital capacity has been suggested in the general population of children, with the authors proposing an anti-oxidant role for vitamin A in the preservation of airway function [11]. Free neutrophil elastase activity in induced sputum was also inversely associated with FEV₁ in 20 clinically stable children with CF [12]. A potential mechanism is that relatively high vitamin A concentrations in the airway fluid, resulting from higher serum concentrations of vitamin A, inhibit elastase and oxidant-induced damage to the pulmonary epithelium, thus preserving pulmonary function in patients with CF. Further studies are required to define this possible protective pathway. The coefficient of determination ($r^2$) values calculated from the correlation coefficients suggest that serum levels of vitamin A ‘explain’ 14–17% of the observed variation in lung function, thus reflecting the biological complexity underlying our observations.

In view of our findings, and other work relating vitamin A status to respiratory health, it is important to study the relationships between body vitamin A status, serum vitamin A concentrations and airway surface fluid vitamin A concentrations, in patients with CF and normal controls. Other work has shown that a variable deficiency of acyl-CoA:retinol acyltransferase, an enzyme facilitating vitamin A absorption, occurs in CF and could be associated with excessive faecal loss of vitamin A [13]. We speculate that intrinsic differences in intestinal enzyme status could act as determinants for the large differences in vitamin A status in patients with CF.

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References