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Original Article

Serum retinol levels and pulmonary function in children and adolescents with cystic fibrosis

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Abstract

Background: It has been suggested that higher serum retinol levels could have protective effects on pulmonary function (PF) in patients with cystic fibrosis (CF). However, serum retinol levels will be transiently decreased during pulmonary exacerbation. Therefore, the extent of chronic pulmonary inflammation should be included when describing the association between PF and serum retinol. We assessed the longitudinal relation between serum retinol, immunoglobulin G (IgG) and PF in paediatric CF patients.
Methods: We studied the serum retinol, IgG and forced expiratory volumes in one second (FEV_1% pred.) of 228 CF patients during a seven-year follow up period. The cross-sectional and longitudinal relations between these variables were assessed.
Results: Serum retinol, with medians levels between 1.2 and 1.4 μmol/l, were relatively stable, while median serum IgG gradually increased during the age years. The FEV_1% pred. was longitudinally inversely associated with serum IgG and age, but not with serum retinol. Each g/l increase in serum IgG level was associated with an accelerated yearly decline in FEV_1% pred. of 0.5% (95% CI −0.8 to −0.1, $p = 0.008$), and each year increase in age was associated with a 1.7% (95% CI −2.1 to −1.3, $p = 0.000$) decline in FEV_1% pred. This effect was not observed with respect to serum retinol levels (95% CI −1.9 to 2.2, $p = 0.570$).
Conclusions: In this large sample of children and adolescents with CF, we found no evidence that higher serum retinol levels had protective effects on PF.

Keywords: Retinol; Respiratory function; Immunoglobulin G; Cystic fibrosis

1. Introduction

Cystic fibrosis (CF) is a lethal genetic disorder, characterized by pulmonary inflammation that causes a gradual, progressive decline in pulmonary function (PF). Most CF patients also have pancreatic insufficiency [1], leading to intestinal malabsorption of fat and fat soluble vitamins.

Abbreviations: PF, pulmonary function; IgG, immunoglobulin G; FEV1%, forced expiratory volumes in one second; NHANES, National Health and Nutrition Examination Survey.

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Therefore, lifelong treatment with both pancreatic enzymes and fat-soluble vitamins has become standard care [2,3]. Vitamin A is routinely administered to all pancreatic insufficient patients, with a recommended daily dosage varying between 1500 and 10,000 international units [2,3]. This vitamin, measured as serum retinol, is an antioxidant and essential for epithelial cell integrity in the respiratory tract. It has therefore been suggested that higher serum retinol levels have a protective effect on pulmonary condition in CF [4–7]. However, serum retinol levels are compromised during a pulmonary exacerbation and recover with resolution of the inflammation [5,6,8–10]. Likewise, chronic pulmonary inflammation may reduce serum retinol levels, and the reported association between serum retinol and PF may be secondary. Consequently, the extent of chronic pulmonary inflammation should be included when investigating the association between PF and serum retinol. In this respect, immunoglobulin G (IgG), the level of which increases once a chronic infection has set in [11,12], might be a good marker. At present, the long-term relationship between serum retinol and PF is poorly understood as most studies have follow-up periods of less than three years only and/or lack data on inflammation [4–7]. We therefore described the long-term effect of serum retinol and serum IgG on PF in paediatric CF patients during a seven-year follow up period.

2. Materials and methods

2.1. Study population

This retrospective study included Dutch children (born between 1988 and 2012) with proven CF and who received medical care in the CF Centre of the University Medical Centre Utrecht. Each child was confirmed as having CF by a positive sweat test and/or the presence of two CF mutations, as well as clinical signs of CF. PF was measured during routine clinical care; serum retinol level and serum IgG level were measured during the annual review. This study included data of children and adolescents obtained between January 2007 and December 2013, whose serum retinol level was measured at least once and whose PF was measured at the age of 6 years and older and who were receiving pancreatic enzyme replacement therapy. All patients or the parents or guardians of young patients provided written informed consent for the storage and analysis of their data. The study was performed in accordance with the guidelines of the medical ethics board of the University Medical Centre Utrecht.

2.2. Clinical measurements

Pulmonary function, assessed as forced expiratory volume in one second (FEV_1), was obtained from maximal expiratory flow-volume curves (Masterscreen; Viasys Healthcare, Hochberg, Germany) and was expressed as the percentage of the predicted value for a given height, age and gender (FEV_1% pred.) [13]. For each child, the highest FEV_1% pred. measured in the preceding calendar year (beginning at 6 years of age) was used in the analysis. Serum retinol levels, expressed as micromole/litre (μmol/l), were measured once a year and analysed by high-performance liquid chromatography. Outcomes were compared with reference values for age-equivalent white healthy controls (US National Health and Nutrition Examination Survey (NHANES) 2005–2006) [14]. Serum IgG levels were also measured once a year and expressed as gramme/litre (g/l). Outcomes were compared with reference values for Caucasian children [15].

2.3. Statistics

Descriptive statistics of categorical variables were examined. All continuous variables were examined for normality and skewness. Due to repeated measures on individual patients in different years of age, children were stratified according age year (year 0 = birth to <1 year, year 1 = 1 year to <2 year etc.). Serum retinol levels, serum IgG levels and FEV_1% pred. for each group of age were described. The cross-sectional relationships between serum retinol levels, serum IgG levels and FEV_1% pred. were determined for each age group.

We then assessed if higher serum retinol levels were associated with a better PF. For this purpose, the children were categorized, based on their serum retinol levels as having a level $<50^{th}$ or $>50^{th}$ percentile, or as having a level $<2.5^{th}$, between 2.5^{th} and 50^{th}, between 50^{th} and 97.5^{th}, or $>97.5^{th}$ percentile of the NHANES. The mean FEV_1% pred. outcomes among the categories of serum retinol levels were compared, using Mann–Whitney test and Kruskal–Wallis test respectively.

Subsequently, we examined if higher serum IgG levels were associated with lower PF. Based on their IgG level, the children were categorized into those having a serum IgG level $<50^{th}$ or $>50^{th}$ percentile, or as having a level $<2.5^{th}$, between 2.5^{th} and 50^{th}, between 50^{th} and 97.5^{th}, or $>97.5^{th}$ percentile of the paediatric reference intervals for Caucasian children. We compared the mean FEV_1% pred. outcomes among the categories of serum IgG levels, also by using Mann–Whitney test and Kruskal–Wallis test, respectively.

For longitudinal analyses, the linear mixed effect regression was performed to evaluate the effect of serum retinol and serum IgG on FEV_1% pred.. This model allows inclusion of variable numbers of measurements per child and irregularly times and missing observations. Included were fixed effects for serum retinol, serum IgG and age of child and a random intercept and random slope for age of child to account for correlations between measurements within children. Values were considered significant at $\alpha < 0.05$. Statistical analyses were performed by using the Statistical Package for the Social Sciences Computer Software (SPSS Inc. version 20, IBM, Chicago, IL).

3. Results

A total of 228 patients with proven CF (98% Caucasian) were eligible for inclusion. In these patients, we obtained a total of 1033 measurements of serum retinol and 669 and 846 measurements respectively of serum IgG and FEV_1% pred.