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Original article

Individualized vitamin A supplementation for patients with cystic fibrosis

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SUMMARY

Background & aims: To determine the vitamin A status and appropriate supplementation dosage of cystic fibrosis (CF) patients who received vitamin A supplementation based on annual serum retinol measurements.

Methods: Vitamin A food intake, supplementation dosage, and serum retinol levels were obtained for 32 CF patients >4 years of age (4.3–27.3 years old) who had pancreatic insufficiency and mild-to-moderate lung disease (percent predicted of forced expiratory volume in 1 s > 40%). These measurements were compared with the dietary reference intake for healthy children and adults (D–A–CH dietary recommendations), US and German CF recommendations, and serum retinol concentrations from National Health and Nutrition Examination Survey (NHANES) data.

Results: Total vitamin A intake from food and supplementation was 315% ± 182% of D–A–CH recommendations, with 65% from supplements. The range of the prescribed vitamin A supplementation dosage was 0–20,000 IU/day (median 5500 IU), and it was consistent with CF recommendations in 28% of participants. A quarter of all patients did not need any vitamin A supplementation. The total vitamin A intake exceeded the recommended upper limit of intake in 69% of subjects. The mean (range) serum retinol was 38.6 μg/dl (22.1–59.1 μg/dl). All subjects had serum retinol levels above 20 μg/dl and below 72 μg/dl (95th percentile of NHANES reference range).

Conclusion: Individualized vitamin A supplementation of 0–20,000 IU/day based on annual serum retinol measurements may prevent deficiency and high serum retinol levels, but it may lead to vitamin A intake above the tolerable upper intake level.

1. Introduction

Approximately 85–90% of patients with cystic fibrosis (CF) suffer from pancreatic insufficiency, which predisposes them to malabsorption of fat and fat-soluble vitamins. Vitamin A deficiency has been described in 10–40% of CF patients independent of vitamin A supplementation.[1–3] Symptoms include abnormal dark adaptation (night blindness), conjunctival and corneal xerosis leading to blindness, phrynoderma (follicular hyperkeratosis), impaired host resistance, and poor growth.[4] In addition to pancreatic enzyme replacement therapy, supplementation of fat-soluble vitamins like vitamin A has become the standard of care.[5–9] However, the dosage of vitamin A supplementation in patients with CF is not based on clinical studies.[10] Different guidelines recommend different age-based dosages in combination with annual serum retinol measurements and individual dosage adjustment. In the last decade, vitamin A deficiency has become a very rare event in CF patients, one that is documented by case reports.[11] On the other hand, a high vitamin A intake has been associated with hepatotoxicity and lower bone mineral density.[12] The upper limits (UL) for vitamin A intake have been established for healthy subjects.[13,14] A retrospective study from the United States described vitamin A intake above the recommended UL in 86% of CF patients and elevated serum retinol levels (>95th percentile of US National Health and Nutrition Examination Survey [NHANES] for the general population) in 58% of CF patients.[15] To our knowledge, no studies have been conducted to investigate whether individual adjustments to the level of vitamin A supplementation in response to serum retinol measurements can prevent overdosage of vitamin A.

Abbreviations: D–A–CH recommendations, dietary recommendations from the D–A–CH countries (Germany (D), Austria (A), and Switzerland (CH)); FEV1%pred, percent predicted of forced expiratory volume in 1 s; NHANES, National Health and Nutrition Examination Survey; UL, upper limit of intake.

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To determine the vitamin A status and supplementation dosage of CF patients who were receiving vitamin A supplementation based on annual serum retinol measurements, we analyzed vitamin A food and supplement intake and serum retinol levels in CF patients >4 years of age who had exocrine pancreatic insufficiency. We compared our findings to D–A–CH intake recommendations (dietary recommendations from the D–A–CH countries [Germany, Austria, and Switzerland]),[16] UL of intake,[13] supplementation recommendations,[5–9] and age- and sex-matched serum retinol reference data from NHANES.[15]

2. Materials and methods

Between 01 December 2011 and 30 April 2012, CF patients from the CF center in Giessen, Germany were recruited. Subjects were included if they fulfilled the established diagnostic criteria for CF, were 4 years of age or older, suffered from pancreatic insufficiency (fecal elastase < 200 μg/g stool), and were able to provide a 4-day written food record. Exclusion criteria were poor lung function (percent predicted of forced expiratory volume in 1 s [FEV1% pred] < 40%), diabetes mellitus and acute exacerbations. The institutional review board of the University of Giessen approved the protocol. Informed written consent was obtained from each subject 18 years and older. For subjects between 4 and 18 years of age, written consent was obtained from each subject's parents or legal guardian, and age-appropriate consent was obtained from each subject.

Height and weight were measured by standard techniques. Overall age group Z-scores for BMI by age were calculated based on reference values for children[17] and adults.[18] Lung function analysis was performed in all of the participating patients, according to the criteria of the American Thoracic Society and the European Respiratory Society.[19] FEV1%pred was calculated in accordance with Knudson et al. for adults[20] and Zapletal et al. for children and adolescents.[21]

Serum retinol was measured once a year in each CF patient while they were clinically stable. In the years prior to the commencement of our study, the dosage of vitamin A supplementation had been adapted in order to reach vitamin A serum levels in the normal range (>20 μg/dl[4] and <72 μg/dl[15]), without determining or analyzing vitamin A intake from food. Instead of multivitamin preparations or water-soluble vitamin A preparations, only oil-based vitamin A preparations were prescribed (Vitadral™ Tropfen [Steiner&Co, Deutsche Arzneimittel Gesellschaft, Berlin, Germany]: 1 drop contains 2033 IU of vitamin A; Vitamin A-saar™ [MIP Pharma GmbH, Blieskastel, Germany]: 1 tablet contains 10,000 IU of vitamin A; Vitamin A 30000 IE JENAPHARM™ [mibe GmbH Arzneimittel, Brehna, Germany]: 1 tablet contains 30,000 IU of vitamin A). Drugs were prescribed so that they would be administered from once weekly to as frequently as once daily. The weekly dosage was reported as the average daily dosage of vitamin A.

A research dietician determined the dietary intake from 4-day food records. The analysis was performed with DGE-PC Professional software (release 5.1.0.013; Gesellschaft für optimierte Ernährung mbH, Linden, Germany). Vitamin A intake, food and supplement based, was reported in retinol equivalents per day (1 μg of retinol-equivalent = 1 μg of all-trans-retinol = 2 μg of β-carotene in oil = 12 μg of β-carotene in food = 24 μg of other provitamin A carotenoids).[14] The vitamin A intake was compared with age- and gender-based D–A–CH recommendations,[16] age-based UL of intake,[13] and age-based supplementation recommendations for CF patients from the United States,[5] Europe,[6] United Kingdom,[7] Australia,[8] and Germany.[9]

Serum retinol (μg/dl) was analyzed by high-performance liquid chromatography (HPLC) (Labor Limbach, Heidelberg, Germany) under clinical protocols with quality assurance measures while the participants were clinically stable. Serum retinol levels were compared with NHANES 1999–2002 serum reference ranges (5th–95th percentiles) from age-equivalent white subjects, obtained with HPLC similar protocols and quality assurance measurements.[15] Vitamin A deficiency was defined as serum retinol concentration <20 μg/dl.[4] In addition serum C-reactive protein (CRP), immunoglobulin G (IgG), alanine transaminase (ALT), aspartate transaminase (AST), zinc and retinol-binding protein (RBP) were measured and the ratio of serum retinol:RBP calculated. RBP <15 mg/l[22] and a retinol:RBP ratio <0.8[2] were considered abnormal.

Data are presented as mean ± standard deviation (SD) (normally distributed variables), respective median values, and 25th and 75th percentile (non-normally distributed variables). Group comparisons were performed with Student's *t*-test or Mann–Whitney *U*-Test for normally or non-normally distributed variables, respectively. Pearson correlation coefficients, Spearman rank correlations, or Kendall tau-b correlations were performed to test for significant associations between variables, as appropriate. Statistical significance was defined as $p < 0.05$. All analyses were performed with IBM SPSS Statistics 20 (release 20; IBM, Armonk, USA).

3. Results

Our study comprised 32 CF patients with a mean age of 14.6 ± 6.0 years (Table 1). Total vitamin A intake (mean ± SD) from food and supplementation was 315 ± 182% of D–A–CH recommendations, with 65% from supplements (Table 2). The total vitamin A intake exceeded the UL in 69% of subjects (Table 2). The prescribed vitamin A supplementation dosage was 0–20,000 IU/day (median 5500 IU) (Fig. 1). The supplementation dosage fulfilled US[5] and German[9] CF recommendations, respectively, in 50% (age 4–8 years, recommended dosage 4000–10,000 IU/day) and 25% (age >8 years, recommended dosage 10,000 IU/day) of patients (Table 3). All subjects had serum retinol levels >20 μg/dl and <72 μg/dl (95th percentile of NHANES reference range) (Fig. 2) in spite of a highly variable total intake (Fig. 3). Differences in serum retinol levels were found between children and adolescents (<11 years of age: 33.6 ± 6.6 μg/dl (A); 11–18 years of age 41.2 ± 7.9 μg/dl (B); >18 years of age 40.2 ± 12.2 μg/dl (C); A versus B: $p = 0.019$, A versus C ns, B versus C ns), but not between genders. There was no correlation between FEV1%pred and serum retinol concentrations ($r = 0.27$, $p = 0.14$) (Fig. 4). Elevated CRP respectively IgG as marker of a acute respectively chronic inflammation were detected in 19% of clinical stable patients. Serum retinol levels were significant lower in patients with elevated compared to normal IgG serum levels (29.6 ± 3.9 μg/dl versus 40.0 ± 9.0 μg/dl; $p = 0.017$), but not different between patients with CRP serum levels < 0.5 versus ≥ 0.5 mg/l (38.5 ± 8.1 μg/dl versus 38.2 ± 10.9 μg/dl; ns). Two patients suffered from liver cirrhosis and 19% had atleast an elevation of AST or ALT. Zinc-deficiency was detected in one patient. The serum level of retinol-binding protein (RBP) was 29.9 ± 8.1 mg/l and >15 mg/l in all patients. The correlation between serum

Table 1
Patient characteristics ($n = 32$).

Characteristics	Mean ± SD (range)
Age, years	14.6 ± 6.0 (4.3–27.3)
Gender, % male	47%
BMI for age Z-score	−0.71 ± 1.04 (−2.6–2.1)
FEV1%pred	88 ± 24 (42–138)
Serum retinol, μg/dl	38.6 ± 9.2 (22.1–59.1)