Vitamin A intake and elevated serum retinol levels in children and young adults with cystic fibrosis

Asim Maqbool a,⁎, Rose C. Graham-Maar b, Joan I. Schall a, Babette S. Zemel a, Virginia A. Stallings a

a Division of Gastroenterology, Hepatology, and Nutrition, The Children's Hospital of Philadelphia, Department of Pediatrics, University of Pennsylvania School of Medicine, 34th Street and Civic Center Boulevard Philadelphia PA 19104, USA
b Division of Gastroenterology, Hepatology, and Nutrition, St. Christopher's Hospital for Children, Drexel University College of Medicine, E Erie Avenue & North Front Street Philadelphia PA 19134, USA

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Abstract

Background: Individuals with cystic fibrosis (CF) and pancreatic insufficiency (PI) are at risk for fat-soluble vitamin deficiency, including vitamin A. Recent evidence suggests current practices of vitamin A intake results in elevated serum retinol.

Methods: Serum retinol was assessed in 78 subjects (8 to 25 years old) with CF and PI by high performance liquid chromatography, and compared to the U.S. National Health and Nutrition Examination Survey (NHANES) data of subjects of similar age and gender. Vitamin A intake, anthropometry and FEV1 were measured, and their relationship to serum retinol status was assessed.

Results: Median (range) serum retinol was 80 μg/dL (33 to 208) in subjects with CF; 58% were above the NHANES reference range (30 to 72 μg/dL). Total vitamin A intake from diet and supplements was high (608 ±431% Recommended Dietary Allowance). Serum retinol was not correlated with vitamin A intake, age or gender, and was inversely correlated with weight and height z scores (r=−0.28, p<0.05) in the subjects with CF.

Conclusions: Both vitamin A intake and serum retinol were elevated in subjects with CF and PI, corroborating recent evidence of elevated serum retinol in preadolescent children with CF. These findings indicate the need for further study of dosing and monitoring care practices of vitamin A, to ensure adequacy and to avoid toxicity.

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Keywords: Cystic fibrosis; Children; Vitamin A; Toxicity; Serum retinol

1. Introduction

Cystic Fibrosis (CF) and pancreatic insufficiency (PI) predisposes patients to fat and fat-soluble vitamin malabsorption, despite pancreatic enzyme replacement. Historically, individuals with CF have been prone to vitamin A deficiency [1]. A recent study reported unexpectedly high serum retinol concentrations and raised the question of excessive supplementation. Current patterns of vitamin A intake and supplementation may increase the risk for vitamin A toxicity [2]. The goal of this study was to document the vitamin A status and to verify or refute these unexpected findings with a broader age range cohort of children and...
young adults with CF and PI, and to compare the findings to age- and sex-matched reference data from the U.S. National Health and Nutrition Examination Survey (NHANES) [3].

2. Materials and methods

Children and young adults (8 to 25 years old) with CF and PI were recruited from a pediatric and adult CF Center. Inclusion criteria included diagnosis of CF and PI by standard methods [2]. Subjects with FEV1 <40% predicted and those with other major medical illnesses that affect growth were excluded.

Serum retinol (µg/dL) was collected by research personnel at The Children’s Hospital of Philadelphia Clinical Translational Research Center and analyzed by high performance liquid chromatography (HPLC) (Clinical Nutrition Research Unit Nutrition Assessment Laboratory, University of California, Davis) under research protocols with quality assurance measures. Serum retinol levels of subjects with CF were compared with NHANES 1999–2002 [3] serum reference ranges (5th to 95th percentiles) from age-equivalent white subjects (88% of which were non-hispanic whites), using HPLC (Division of Environmental Health Services, Centers for Disease Control and Prevention, Atlanta, GA) and with similar research protocol and quality assurance measures.

Height and weight were measured using standard techniques [4], with a stadiometer accurate to 0.1 cm (Holtain, Crymych, UK) and a digital scale accurate to 0.1 kg (Scaletronic, White Plains, NY). All measurements were obtained in triplicate and the mean used in the analyses. Z scores for height (HAZ), weight (WAZ), and body mass index (BMI; kg/m², BMIZ) were computed [5]. Pulmonary function was evaluated by standard methods for spirometry [6,7]. FEV1 percent predicted was calculated using the Wang et al [8] and Hankinson et al [9] equations.

Research dieticians determined dietary intake from 3-day weighted food records. Vitamin A intake, as food- and supplement-based, pre-formed and total retinol, were reported weighed food records. Vitamin A intake, as food- and supplement (Table 2) was 608±431% RDA, with 67% from supplements. Total preformed retinol intake was 564±409% RDA, with 86% of subjects exceeding the UL [10].

All variables were tested for normality and skewness. Group comparisons were tested using Student’s t-test or Wilcoxon rank sum test for normally or non-normally distributed variables, respectively. Data were presented as mean±standard deviation; median values and range were used for the serum retinol due to non-normality. Pearson correlation coefficients or Spearman rank correlations were performed to test for significant associations between variables as appropriate. Statistical significance was defined as a P-value < 0.05. All analyses were performed with STATA release 8.2 (STATA Corporation, College Station, TX).

The protocol was approved by the Committee for the Protection of Human Subjects of the Institutional Review Board at the Children’s Hospital of Philadelphia and the Hospital of the University of Pennsylvania. Informed written consent was obtained from each subject 18 years and older. For subjects between 8 and 18 years of age, written consent was obtained from each subject’s parent or legal guardian, and written assent was obtained from every study subject under 18 years of age.

3. Results

Serum retinol, anthropometry and FEV1 were available for 78 subjects (Table 1). Seven subjects (9%) participated in both the previously cited pre-adolescent study [2] and the current study. Dietary intake data were available for 53 subjects. In comparison to subjects with complete dietary data, the subjects without dietary data had lower %FEV1 (81±13 versus 89±16; p = 0.04). Forty-two percent of subjects had serum retinol within and 58% had concentrations above the NHANES reference range of 30 to 72 µg/dL (Fig. 1); none of the subjects with CF and PI had a serum retinol below the lower reference range value of 30 µg/dL.

Total vitamin A intake (mean±sd) from food and supplement (Table 2) was 608±431% RDA, with 67% from supplements. Total preformed retinol intake was 564±409% RDA, with 86% of subjects exceeding the UL [10].
Table 2
Energy and Vitamin A intake for the subjects with cystic fibrosis and pancreatic insufficiency (n=53)

<table>
<thead>
<tr>
<th>Dietary intake</th>
<th>Mean±SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake, kcal/d</td>
<td>2786±827</td>
<td>2616</td>
<td>1617 to 5293</td>
</tr>
<tr>
<td>Vitamin A intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preformed retinol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>µg RAE/d</td>
<td>1107±1410</td>
<td>852</td>
<td>120 to 10,499</td>
</tr>
<tr>
<td>µg RAE/kg/d</td>
<td>26±25</td>
<td>21</td>
<td>3 to 172</td>
</tr>
<tr>
<td>%RDA</td>
<td>167±204</td>
<td>132</td>
<td>17 to 1500</td>
</tr>
<tr>
<td>Total Vitamin A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>µg RAE/d</td>
<td>1279±1510</td>
<td>1012</td>
<td>150 to 11,330</td>
</tr>
<tr>
<td>µg RAE/kg/d</td>
<td>216±252</td>
<td>169</td>
<td>25 to 1888</td>
</tr>
<tr>
<td>Supplemental</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preformed retinol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>µg RAE/d</td>
<td>2580±1905</td>
<td>2700</td>
<td>0 to 9188</td>
</tr>
<tr>
<td>µg RAE/kg/d</td>
<td>61±56</td>
<td>54</td>
<td>0 to 350</td>
</tr>
<tr>
<td>%RDA</td>
<td>397±362</td>
<td>333</td>
<td>0 to 2297</td>
</tr>
<tr>
<td>Total Vitamin A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>µg RAE/d</td>
<td>2692±1908</td>
<td>2700</td>
<td>0 to 9188</td>
</tr>
<tr>
<td>µg RAE/kg/d</td>
<td>415±364</td>
<td>375</td>
<td>0 to 2297</td>
</tr>
<tr>
<td>Combined food and supplement</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Preformed retinol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>µg RAE/day</td>
<td>3687±2223</td>
<td>3332</td>
<td>437 to 12,479</td>
</tr>
<tr>
<td>µg RAE/kg/d</td>
<td>87±61</td>
<td>78</td>
<td>9 to 386</td>
</tr>
<tr>
<td>%RDA</td>
<td>564±409</td>
<td>485</td>
<td>73 to 2538</td>
</tr>
<tr>
<td>% CF Recommendations</td>
<td>123±74</td>
<td>111</td>
<td>15 to 416</td>
</tr>
<tr>
<td>Total Vitamin A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>µg RAE/day</td>
<td>3972±2359</td>
<td>3614</td>
<td>503 to 13,850</td>
</tr>
<tr>
<td>µg RAE/kg/d</td>
<td>608±431</td>
<td>521</td>
<td>84 to 2631</td>
</tr>
<tr>
<td>%RDA</td>
<td>132±79</td>
<td>120</td>
<td>17 to 462</td>
</tr>
</tbody>
</table>

1 Recommended dietary intake is age and gender based, and ranges from 400 to 900 µg RAE/day (10). CF recommendations are age-based, and for children 4 to 8 years of age are from 5000 to 10,000 IU/day, and for children and adults greater than 8 years of age are 10,000 IU day±1500 to 3000 RAE/day (11,12). The conversion of IU to RAE is: 1 IU retinol=0.3 µg RAE. 1 µg RAE=1 µg retinol.

and 73% of subjects exceeding the CF Foundation Recommendations [11].

For the subject sample with dietary data, serum retinol was inversely correlated with HAZ and WAZ (−0.28, P<0.04; −0.28, P<0.05), and not associated with FEV1, age, gender, or vitamin A intake (food, supplement-based, and/or total). When the study subjects were divided into groups as within or above the NHANES serum retinol reference ranges, there were no group differences in anthropometry, %FEV1, and food and supplement-based (pre-formed or total) vitamin A intake.

4. Discussion

These results showed that under current patterns of care, 58% of subjects with CF and PI had elevated serum retinol concentrations using NHANES reference data for comparison. None of these subjects were vitamin A deficient based on serum retinol status.

Elevated serum retinol was previously documented in a study involving 13 US CF Centers. Mean serum retinol was 52±13 µg/dL (range: 26 to 98), significantly higher than the age-similar NHANES reference group mean of 37±10 µg/dL. In the pre-adolescent group, 47% of subjects had serum retinol concentrations >95th percentile, compared with 58% in the current study. Our present study corroborates these findings in a broader age range, raising further concerns about elevated serum retinol concentrations, high vitamin A intake, and the risk for vitamin A toxicity in the CF population.

The term “vitamin A” refers to a family of compounds important for cellular integrity, growth, and immune function, that is comprised of preformed retinoids and provitamin A carotenoids. Retinoids are fat-soluble, animal-derived compounds that include retinol, retinal, and retinoic acids. Ingested retinoids are solubilized and esterified into retinyl esters (RE) in the intestine, circulated as both bound RE and unbound retinol, and stored in the liver as retinol. While the serum retinol concentration is homeostatically maintained, hepatic stores accumulate indefinitely with increased ingestion. Conversely, provitamin A carotenoids are water-soluble, plant-derived compounds that include carotene, lutein, and xanthophylls. They are less bioavailable than retinoids and amounts ingested in excess of needs are not stored but are excreted.

The amount of vitamin A contained in a given food or supplement is described using either international units (IU) or microgram retinol activity equivalents (µg RAE). The former is an outdated unit that does not account for discrepant bioavailability and bioactivity of the different forms of vitamin A. The RAE is the current standard unit which incorporates these differences and allows direct comparison among all different forms of vitamin A. Conversion equations: one µg RAE=1 µg retinol=12 µg β-carotene from food=24 µg other provitamin A carotenoids. One IU retinol=0.3 µg RAE=3.6 µg β-carotene from fruits and vegetables=7.2 µg other pro-vitamin A carotenoids [13].

In addition to the form of vitamin A, the specific preparation of vitamin A supplement is relevant when considering the potential for toxicity [10]. Some vitamin A formulas used in the CF population are now biochemically engineered to increase the water-solubility of retinoids, to allow for easier absorption in the setting of pancreatic insufficiency. These preparations are helpful when there is ongoing malabsorption, but may also confer more risk for the development of elevated serum retinol and potential vitamin A toxicity in this population. A meta-analysis of 259 case reports of chronic hypervitaminosis A in children and adults without CF suggested relatively smaller doses (200 µg RAE/kg/day) of water-miscible, emulsified, and solid forms of retinol supplements ingested over shorter time intervals (weeks to months) induced similar toxicity as oil-based preparations given in larger doses (2,000 µg RAE/kg/day) over months to years [14]. Water-miscible preformed vitamin A supplements were used by 58% of our subjects.
The 2002 CF Nutrition Consensus Report [11] made age-specific vitamin A supplement-based intake recommendations; children between four and eight years of age were recommended to take between 5000 and 10,000 IU/day, and children greater than eight years of age and adults were to take 10,000 IU/day. Further, both the pediatric and adult consensus reports [11,12] recommend monitoring of vitamin A status by serum retinol concentration determination at the time of diagnosis, and annually afterwards.

The commonly used CF-specific vitamin products contain water-miscible vitamin A, between 897 to 2520 μg RAE per dosage unit, with 40 to 100% as preformed retinol [2]. Preformed vitamin A is more bioavailable, more readily stored, and not subject to the same feedback control as provitamin A carotenoids. Therefore, knowledge of each specific vitamin A formulation is important to the proper evaluation and monitoring of vitamin A supplementation. In the current study, many individuals with CF took many different vitamin supplement products, and some used more than one type of vitamin A supplement per day. In the current study, 27 different vitamin A supplement products were used, and 11% of subjects used more than one type of vitamin A supplement per day; one subject used three different vitamin A-containing supplements per day.

Vitamin A toxicity primarily affects the bone and liver. The bone fracture rate was increased by 64% among non-CF Swedish men with serum retinol above 76 μg/dL compared to those with concentrations between 62 and 67 μg/dL [15]. Mean serum retinol in the current study was similar to this higher fracture risk group. Vitamin A intake and bone toxicity has been reported with preformed vitamin A intakes as low as 1500 μg RAE/day in non-CF subjects [16]. Preformed retinol intake between 1500 to >14,000 μg RAE/day over one to 30 years was associated with a spectrum of liver abnormalities [10,17]. Pre-existing/coincident liver disease may alter the threshold for vitamin A associated toxicity [10,18]. This is an important clinical concern for patients with CF, since CF associated liver disease is usually diagnosed in children and adolescents [19].

Hepatic vitamin A status of subjects with CF has been investigated in a limited number of studies in the past. The liver is the main storage site for vitamin A, and vitamin A status has previously been described in subjects with CF, examining both serum and hepatic vitamin A status. A 1972 study [20] reported significantly higher hepatic and lower serum retinol concentrations in 12 vitamin A supplemented subjects with CF (8 to 23 years old) compared to healthy controls. Another study found normal hepatic retinol concentrations in 15 vitamin A supplemented Swedish subjects with CF (8 to 34 years old) compared to healthy controls [19]; hepatic retinyl palmitate decreased with age, serum retinol was 36±17 μg/dL (range 2 to 57 μg/dL), and 33% of subjects had values less than 30 μg/dL. In contrast to this study, we found normal and high serum retinol levels in subjects of comparable age range, and no subjects with low levels. Similar to the Swedish study [19] however, we did not find an association between serum retinol and age.

The limitations of this study included its cross-sectional design, and the fact that the vitamin A analysis was secondary within the bone health in people with cystic fibrosis study. Currently there is no well-accepted, non-invasive marker for the assessment of vitamin A excess. Serum retinol is tightly regulated, decreases with depleted hepatic stores [21], and is likely a better bio-marker of vitamin A deficiency rather than excess. Serum retinol increases with long-term supplement use, and intake of foods high in preformed vitamin A. Serum retinol elevations may reflect increased hepatic stores; however, the threshold value to indicate elevated hepatic stores is not known. Retinyl esters have been noted to be elevated with excess vitamin A intake or increased liver stores [22]; these were not available in the current study. Retinol binding protein usually parallels the serum retinol level; both these biomarkers of vitamin A status can be depressed in the setting of inflammation, and thus is not an optimal indicator of vitamin A status in diseases such as CF, with a chronic inflammation component. This is particularly concerning when serum retinol is elevated in these subjects with CF, as it may underestimate degree of vitamin A excess.

In summary, these findings raise concern about current vitamin A supplementation practices and products. Children and young adults had similar findings of high vitamin A intake and elevated serum retinol concentrations as compared to pre-adolescent children with CF and PI. Routine use of preformed, water-miscible vitamin A supplements may result in elevated serum retinol concentrations and may increase the risk for hypervitaminosis A in this population. It is unknown if CF-related liver or bone disease alters the risk for hypervitaminosis A. Serum retinol should be routinely monitored at least on an annual basis, as recommended by the 2002 and 2004 Pediatric and Adult Consensus Reports on Nutrition for Patients with CF [11,12]. We suggest adjusting the dose accordingly to the results in order to maintain normal serum retinol. Further studies of vitamin A status are warranted, including determination of serum retinyl esters, and possibly even liver biopsy to determine hepatic vitamin A stores. Furthermore, the development of non-invasive methods to measure hepatic and total body stores of vitamin A would enhance the ability to monitor vitamin A supplementation. A better understanding of the relationship between serum and tissue vitamin A is needed for patients with CF. In the meanwhile clinicians should be aware of the composition of different vitamin A supplement preparations and dosing equivalents taken by their patients.

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