Vitamin A absorption in cystic fibrosis: risk of hypervitaminosis A

D R James, G Owen, I A Campbell, M C Goodchild

Abstract
Vitamin A status was examined in nine adult cystic fibrosis patients and six control subjects, together with an assessment of their ability to absorb 10 000 IU of retinyl palmitate from a test meal, taken with appropriate pancreatic enzyme supplements. Median baseline values for plasma retinol and carotene, as well as median serum retinol binding protein concentrations, were significantly lower in cystic fibrosis patients than in control subjects. One cystic fibrosis patient had a raised fasting plasma retinyl ester concentration suggestive of chronic hypervitaminosis A, but no symptoms of toxicity. Measures of vitamin A absorption were also significantly lower in cystic fibrosis patients, although there was considerable overlap with control values. No correlation was observed between measures of baseline status and vitamin A absorption. Measurement of plasma retinyl esters may be an appropriate investigation in those patients considered to be at risk of chronic hypervitaminosis A.

Pancreatic exocrine insufficiency is usual in cystic fibrosis and it is not surprising that low serum concentrations of fat soluble vitamins, particularly A and E, have been observed. Low serum vitamin A concentrations may not be the result of malabsorption alone, as increased liver concentrations of vitamin A with low serum concentrations were reported by Underwood and Denning in 1972. Even with oral vitamin supplements, however, serum concentrations in cystic fibrosis patients remain below those of control populations.

Chronic hypervitaminosis A may exist for many years among members of the general public without recognition, resulting eventually in hepatocellular damage and hepatic fibrosis. Pre-existing liver disease may also affect the capacity of the organ to transport the vitamin into the circulation, thus potentiating its hepatotoxicity. As cystic fibrosis is a condition predisposing to liver pathology, it is not certain that supplementation of all patients with vitamin A is advisable. Doses of vitamin A need not be large to cause toxicity, as this has occurred with oral intakes of 20–45 000 IU/day. Raised plasma retinyl ester concentrations and biochemical evidence of liver damage have been reported in normal control subjects taking moderate doses only (10 000 IU or less daily) of the vitamin. It has been recommended that cystic fibrosis patients be supplemented with 10–25 000 IU/day, but little is known of how well these supplements are absorbed. Previous studies have examined the absorption of vitamin A in a fasting state, using a high dose (approximately 7000 IU/kg body weight) vitamin A absorption test without pancreatic enzyme supplements.

In this study the absorption of 10 000 IU vitamin A was examined in a group of adult cystic fibrosis patients who took a test meal, and pancreatic enzyme supplements as they judged appropriate.

Methods

SUBJECTS AND SAMPLES
Nine adult cystic fibrosis patients (seven men; median age 22 years (range 16–29)) and six control subjects (three men; median age 27 years (range 19–30)) took part in the study. All cystic fibrosis patients had been taking regular vitamin A supplements and all but one used pancreatic enzyme supplements regularly.

After an overnight fast (cystic fibrosis patients had been asked to omit vitamin supplements from mid-day on the day before the test) samples were taken for the assessment of vitamin A status, plasma retinol and retinyl esters, retinol binding protein, and prealbumin. Samples were also obtained for total plasma carotenes, reactive protein, and their biochemical profile (albumin, aspartate transaminase, y glutamyl transferase, alkaline phosphatase, and bilirubin).

A test meal consisting of 30 g cornflakes, 200 ml whole cow's milk, 120 g white bread, 20 g strawberry jam, 5 g sugar, and 10 000 IU vitamin A (as retinyl palmitate, supplied by Hoffman La-Roche, UK) in 1 ml arachis oil was eaten with pancreatic enzyme supplementation where appropriate. Hourly samples for plasma retinyl ester estimation were taken over the following six hours. All subjects were fasted during the study, but allowed free access to water. Cystic fibrosis patients also completed a questionnaire detailing regular medication, bowel function, and symptoms of hypo/hypervitaminosis A, as described elsewhere. They were also asked to undertake a Pancreolauryl test, again using whatever pancreatic supplements they considered necessary.

MATERIALS
Retinol, retinyl acetate, and retinyl palmitate were obtained from Sigma Chemical Company, Poole, UK, and purified as necessary by alumina column chromatography. All other chemicals and solvents were obtained from BDH Chemicals Ltd, Poole, UK, and were Analal or high performance liquid chromatography (HPLC) grade as appropriate. Plasma retinol was analysed by an isocratic reverse phase HPLC method, based on those previously described by
TABLE Biochemical data in control subjects and cystic fibrosis patients taking part in vitamin A absorption study

<table>
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<tr>
<th>Control subjects</th>
<th>Cystic fibrosis patients</th>
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<td>Age (yrs)</td>
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<td>Serum albumin (g/l)</td>
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<td>Plasma retinol (umol/l)</td>
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<td>Plasma retinol esters (nmol/l)</td>
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<td>Serum PA (mg/l)</td>
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<td>Plasma carotene (umol/l)</td>
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<td>Daily vitamin A supplements (IU/day×103)</td>
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<td>A Retinol esters (nmol/l)</td>
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<td>Area under curve (nmol.l-1 h)</td>
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<td>Lipase with test meal (IU/103)</td>
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<tr>
<td>Pancreolauryl test result (%)</td>
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*P<0.01 compared with controls; †P<0.05 compared with controls: Mann-Whitney U test.

McClean et al.11 and Bieri et al.12 Plasma retinyl esters were determined by a modification of the method of Bankson et al.13 Serum retinol binding protein was determined by Mancini radial immunodiffusion using commercially available plates and standards (Behring Diagnostics, Hounslow, UK), and prealbumin by rate nephelometry (Beckman Auto-ICS) with Beckman reagents and standards. Plasma carotenes were measured spectrophotometrically.14 Samples for the Pancreolauryl test were analysed in accordance with the manufacturer’s instructions.

STATISTICS

Results were analysed by Spearman’s rank order correlation test or Mann-Whitney U test with correction for ties, as appropriate.

Results

There was no significant difference in the age distribution of the patients and control subjects (Table). Serum C reactive protein concentrations were normal (<6 mg/l) in six of nine cystic fibrosis patients and not significantly raised (≤10-9 mg/l) in the remaining three.

None of the patients reported symptoms consistent with hypo- or hypervitaminosis A. The median daily quantity of vitamin A supplements taken regularly was 8000 IU (range 2500-41 000 IU); all but one patient (patient 9, who took 41 000 IU/day) took 16 000 IU/day or less (Table). The median lipase dose (in the form of Creon, Pancrease, Nutrizyme, or Cotarzime) taken with the test meal was 20 000 IU (range 0-112 000 IU). Some abnormalities of liver function were seen among the cystic fibrosis patients, who also showed lower concentrations of plasma retinol, carotenes, and serum retinol binding protein (Table). No significant difference was observed between the two groups for fasting plasma retinyl ester concentrations (Table).

Measurement of plasma retinyl ester concentrations after the test meal showed that absorption profiles were very variable in both control subjects (Fig 1) and cystic fibrosis patients (Fig 2). The results of the absorption test are also presented as the maximum rise in plasma retinyl esters (Δ RE) and the area under the curve (AUC), the baseline being taken as the fasting value (Fig 3A and B). The median values in

Figure 1: Vitamin A absorption profiles in control subjects.

Figure 2: Vitamin A absorption profiles in cystic fibrosis patients.
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cystic fibrosis patients were significantly lower than in control subjects, (p=0.05 for Δ RE and
p=0.01 for AUC), although there was considerable overlap. No correlations were found
between measures of vitamin A absorption and fasting plasma retinol or retinyl esters.

One patient (patient 9), who had been taking 41 000 IU vitamin A/day for at least one year and
used large quantities of pancreatic enzyme supplements with meals (112 000 IU lipase with the
test meal), had a fasting plasma retinyl ester concentration of 303 nmol/l, almost four times
greater than that seen in any of the controls (Table). Measures of his vitamin A absorption
(Δ RE and AUC) were the highest in the cystic fibrosis group. However, circulating retinol and
retinol binding protein concentrations were in keeping with those of the other cystic fibrosis
patients. He was a very fit patient who showed no clinical symptoms of hypervitaminosis A, and no
evidence clinically or biochemically of liver dys-
function.

Seven patients (including patient 9) undertook the Pancreolauryl test, and all had abnormal
results (<20%, Table). These results, in conjunction with low plasma carotenoid values
obtained in eight of nine patients (Table), indicate that it is very likely that all patients had
significant malabsorption. All patients had a clinical requirement for pancreatic enzyme
supplements, although these were not well tolerated (and not taken) by one patient
(patient 7).

Discussion
Retinol is absorbed by a carrier mediated passive absorption process under physiological condi-
tions, and by simple passive absorption at pharmacological concentrations. Absorption is
dependent on a number of factors, including the presence of pancreatic enzymes and bile salts.
Esterification of the newly absorbed retinol by acyl-Co A: retinyl acyl transferase within the
enterocyte is reported to be normal in cystic fibrosis.20 The newly esterified vitamin A is then
transported to the liver in association with chylolemic remnants.21

Observations on baseline vitamin A status of
cystic fibrosis patients in this study are similar to
those reported in other studies.42 Few data are
available on vitamin A absorption in cystic
fibrosis, but in our study of nine patients, all
of whom had pancreatic insufficiency, some
absorbed significant quantities of the preformed
vitamin while others did not. It seems that in
some patients, mechanisms for vitamin A
absorption are not compromised. This wide
variation in absorption of vitamin A is in keeping
with observations reported recently on faecal
losses of the vitamin in cystic fibrosis.21

Acute toxicity results from the ingestion of
large quantities of the vitamin over a short period
of time, leading to the appearance of free retinol
(that is, not bound to retinol binding protein) in
the circulation. Persistent consumption of
smaller quantities of vitamin A over a prolonged
period may result in chronic hypervitaminosis A,
with an increase in circulating vitamin A and in
the ratio of ester to alcohol forms.23 The con-
siderably raised fasting plasma retinyl ester con-
centration of 303 nmol/l seen in patient 9 (who
was taking 41 000 IU/day) suggests chronic
hypervitaminosis A, although the patient was
entirely asymptomatic. Traditionally, chronic
hypervitaminosis A has been associated with
an intake of larger quantities of the vitamin
(>100 000 IU/day) over a prolonged period.
However, the daily intake required to produce
toxicity is very variable, ranging from 5000 IU

Figure 3: Measures of vitamin A absorption in cystic fibrosis
cystic fibrosis patients and control subjects. (A) Maximum rise in plasma
patients and control subjects. (A) Maximum rise in plasma
retinol esters: p<0.05. (B) The area under the curve: p<0.01.
retinol esters: p<0.05. (B) The area under the curve: p<0.01.
normal plasma retinol concentration. This may be analogous to a report of a non-cystic fibrosis patient who had liver damage from massive vitamin A deposition, together with a depressed serum vitamin A concentration. He had consumed up to 25 000 IU/day of the vitamin for seven years and had a degree of protein-energy malnutrition as a result of a poor diet.16

Despite having the highest vitamin A absorption parameters, patient 9 ranked only 4th, 3rd, and 2nd for plasma retinol, carotenes, and serum retinol binding proteins concentrations respectively. Animal studies suggest that over supplementation may also suppress retinol binding proteins synthesis,16 thus further complicating the situation.

Our results suggest that care should be taken with preformed vitamin A supplementation as some cystic fibrosis patients may be at risk of developing hypervitaminosis A if oversupplemented.

The lower plasma carotene concentrations seen in the cystic fibrosis patients suggest that preformed vitamin A supplementation is necessary, as these patients may not be able to meet their daily requirements for this vitamin from dietary carotene alone.

The susceptibility of the liver to injury by increased stores of vitamin A in cystic fibrosis patients, especially those with liver dysfunction, is not known. It seems prudent therefore to assess in some way the extent of a patient's vitamin A stores, but unfortunately no simple non-invasive technique is available yet. Periodic estimation of fasting plasma retinyl ester seems to be the only option available at present; however, the plasma retinyl ester concentration may be raised only when liver stores of vitamin A are saturated. Further difficulties in interpretation may occur as plasma ester concentrations may be raised as a consequence of liver pathology.16 We are currently investigating the possible use of other vitamin A metabolites as markers of hepatic vitamin A stores.

We are grateful to Dr T J Morris for allowing us to include one of his patients in our study.

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