Effects of β-carotene supplementation for six months on clinical and laboratory parameters in patients with cystic fibrosis

S Renner, R Rath, P Rust, S Lehr, Th Frischer, I Elmadfa, I Eichler

Abstract

Background—Patients with cystic fibrosis (CF) have significantly decreased plasma concentrations of nutrient antioxidant vitamins, especially of β-carotene, which is thought to result from fat malabsorption and chronic pulmonary inflammation. The aim of this double blind, placebo controlled study was to investigate the effect of oral β-carotene supplementation for six months on clinical parameters.

Methods—Twenty four patients with CF were randomised to receive β-carotene 1 mg/kg/day (maximum 50 mg/day) for three months (high dose supplementation) and 10 mg/day for a further three months (low dose supplementation) or placebo. At monthly follow up visits the plasma β-carotene concentration, total antioxidant capacity, malondialdehyde (MDA) as a marker of lipid peroxidation, and clinical parameters (Shwachmann-Kulczycki score, body mass index (BMI), height, and lung function (FEV₁)) were assessed. The number of pulmonary exacerbations requiring antibiotic treatment (in days) three months before and during the study were evaluated.

Results—The plasma concentration of β-carotene increased significantly to the normal range during the three months of high dose supplementation (baseline 0.08 (0.04) μmol/l to 0.56 (0.38) μmol/l; p<0.001) but decreased to 0.32 (0.19) μmol/l in the period of low dose supplementation. Initially raised plasma levels of MDA fell to normal levels and the total antioxidant capacity showed a non-significant trend towards improvement during high dose supplementation. Antibioc treatment decreased significantly in the supplementation group from 14.5 (14.9) days/patient during the three months before the study to 9.8 (10.3) days/patient during low dose supplementation, but increased in the placebo group. The Shwachmann-Kulczycki score, lung function, and BMI did not show any changes in either of the treatment groups. No adverse events were observed during the study period.

Conclusion—Oral β-carotene supplementation in a dose of 1 mg/kg/day only was effective in normalising the plasma concentration of β-carotene and resulted in a decrease in pulmonary exacerbations. These data suggest that patients with CF may benefit clinically from supplementation with β-carotene and further studies are warranted.

Keywords: cystic fibrosis; β-carotene supplementation; pulmonary exacerbations; clinical parameters; lung function
Effects of $\beta$-carotene supplementation in patients with cystic fibrosis

The primary aim of our study was to assess whether oral supplementation with $\beta$-carotene normalises the plasma concentration of $\beta$-carotene in addition to reducing the number of pulmonary exacerbations in patients with CF. Since long term studies of $\beta$-carotene supplementation in patients with CF are limited, the dosage needed to achieve a $\beta$-carotene level comparable to that in healthy control subjects is not well defined. The second aim of the study was therefore to assess whether, after normalisation of the serum $\beta$-carotene concentration has been achieved, high dose supplementation can be reduced to low dose supplementation to maintain the $\beta$-carotene levels within the normal range.

Methods

Between July 1995 and October 1996 24 patients with CF (18 female) of mean age 11.7 years (range 6.7–27.7) were enrolled for six months in a randomised, double blind, placebo controlled study.

To conceal treatment allocation all patients received capsules of identical appearance. Thirteen patients (nine female) of mean age 12.8 years (range 6.8–27.7) were randomised to receive $\beta$-carotene supplementation in a dose of 1 mg/kg/day (maximum 50 mg/day) for three months (high dose supplementation) followed by a period of a further three months with a weight independent low dose regime of 10 mg/day $\beta$-carotene in a single dose (all-trans $\beta$-carotene was used and mixed with starch 1:1). The prepared capsules had to be taken in the morning with a fat containing meal after the patients had taken their pancreatic enzymes. Eleven patients with CF (nine female) of mean age 10.5 years (range 6.7–17.3) received placebo for six months. The placebo capsules were prepared with starch.

To assess compliance a bottle containing the number of capsules handed over to the patients or their parents at each visit including an explanation from the investigator was used for calculations. The results are expressed as percentage predicted normal values based on accepted reference standards.

At each clinical visit height and weight were recorded for each patient and blood samples were taken for measurement of $\beta$-carotene, retinol, MDA, total antioxidative capacity, red and white blood count, and serum chemistry. Height was measured using a Harpenden stadiometer, recording the mean of three consecutive measurements, and was expressed as age independent z score (delta height standard deviation score) with reference to the population specific reference data of Prader et al. Weight was expressed as body mass index (BMI, weight (kg)/height (m$^2$)).

Plasma concentrations of $\beta$-carotene, retinol, and $\alpha$-tocopherol were determined by HPLC according to the method of Jakob and Elmadfa. The interassay coefficient of variation was <9%. The total antioxidative capacity was measured by a modification of the photometric method according to Rice-Evans and Miller with an interassay coefficient of variation of <5%. MDA was determined by HPLC using the method of Wong et al. The interassay coefficient of variation was <8%.

To examine the potential beneficial effect of $\beta$-carotene supplementation on the frequency of pulmonary exacerbations, the numbers of days on which systemic (oral or intravenous) antibiotics were used for the treatment of an acute pulmonary exacerbation were evaluated three months before and during the six months of the study. In this study population antibiotics were prescribed solely by the doctors at the Vienna CF centre (SR, IE). Pulmonary exacerbations were defined by weight loss, anorexia, increased cough, increased respiratory rate, increased sputum production, fever with or without evidence of new pulmonary infiltrates, deterioration of oxygen saturation and of lung function. Carotenodermia was assessed by examining the palms and soles of the patients and by questioning parents and/or patients about any changes in skin colour.

Approval of the institutional review boards was granted for the study and informed consent was obtained from each patient and/or their parents.

Statistical Methods

To examine the influence of treatment on FEV$_1$, total antioxidative capacity, antibiotic days, z score of height, BMI, Shwachmann score, and $\beta$-carotene concentration, baseline values and mean values over the following two periods of three months each were analysed. The differences between baseline values and those following treatment (12 weeks average minus baseline value and 24 weeks average minus baseline) were calculated. Analysis of variance (ANOVA) with the grouping factor treatment (two levels: placebo/supplementation) and the repeated factor time (two levels) was performed for the maximum expiratory flow volume curve (Masterlab; E Jäger, Wuerzburg, Germany) according to the American Thoracic Society (ATS) standards. The best of the three efforts was used for calculations. The results are expressed as percentage predicted normal values based on accepted reference standards.

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FEV1 = forced expiratory volume in one second; BMI = body mass index.

**p value of the group factor from the repeated ANOVA model**

### Table 1 Mean (SD) baseline data

<table>
<thead>
<tr>
<th></th>
<th>Supplementation group (n=13)</th>
<th>Placebo group (n=11)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>14.6 (7.7)</td>
<td>10.5 (4.0)</td>
<td>0.115</td>
</tr>
<tr>
<td>FEV1, (% predicted)</td>
<td>72.2 (32.2)</td>
<td>83.7 (21.1)</td>
<td>0.324</td>
</tr>
<tr>
<td>z score of height</td>
<td>−1.13 (1.08)</td>
<td>−1.12 (0.75)</td>
<td>0.977</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>16.8 (3.5)</td>
<td>16.8 (3.1)</td>
<td>0.979</td>
</tr>
<tr>
<td>Shwachmann-Kulczycki score</td>
<td>53.7 (13.0)</td>
<td>61.6 (6.2)</td>
<td>0.067</td>
</tr>
<tr>
<td>Total antioxidative capacity (nmol)</td>
<td>0.85 (0.34)</td>
<td>0.86 (0.26)</td>
<td>0.844</td>
</tr>
</tbody>
</table>

### Table 2 Main outcome variables before and after β-carotene supplementation

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 weeks supplementation</th>
<th>24 weeks supplementation</th>
<th>p value of the group factor**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supplementation group</td>
<td>Placebo group</td>
<td>Supplementation group</td>
<td>Placebo group</td>
</tr>
<tr>
<td>FEV1, (% pred)</td>
<td>72.2 (32.2)</td>
<td>83.7</td>
<td>71.6 (34.0)</td>
<td>82.2 (15.1)</td>
</tr>
<tr>
<td>Antibiotic days/patient</td>
<td>14.5 (14.9)</td>
<td>10.5 (11.2)</td>
<td>9.8 (10.3)</td>
<td>24.8 (19.1)</td>
</tr>
<tr>
<td>Total antioxidative capacity (nmol)</td>
<td>0.85 (0.34)</td>
<td>0.86 (0.26)</td>
<td>0.96 (0.19)</td>
<td>0.87 (0.21)</td>
</tr>
</tbody>
</table>

*95% confidence interval for the group difference of the post/pre differences.
**p value of the group factor from the repeated ANOVA model.

Figure 1 Mean (SD) plasma concentrations of β-carotene in patients with CF supplemented with β-carotene (○) and those given placebo (□) during 12 weeks of high dose treatment and 12 weeks of low dose treatment; p<0.001.
Effects of β-carotene supplementation in patients with cystic fibrosis

At the beginning of the study MDA concentrations were significantly higher in the patients than in the control subjects (1.6 (0.6) versus 1.1 (0.4) µmol/l, p<0.05). After three months of high dose supplementation the MDA values of the supplementation group decreased to normal concentrations of 1.1 (0.4) µmol/l. However, this positive effect was not sustained during low dose supplementation and MDA concentrations increased to 1.3 (0.6) µmol/l. No comparison between the groups was done because of missing values.

A significant increase in height was observed in both groups over the six month period (time trend of the height z score: p = 0.045). The height z score in the supplementation group decreased to –1.04 (1.00) and in the placebo group from –1.12 (0.75) to –0.81 (0.63) after 24 weeks.

FEV₁ did not change significantly in either group during the 24 weeks (table 2), nor did the other secondary variables (BMI and Shwachman-Kulczycki score) show any significant group difference or time trend.

Beta-carotene supplementation was well tolerated in all patients. None developed signs of carotenodermia, although some patients reported a better tanning after exposure to sunlight. The plasma retinol concentration of the CF patients was in the lower normal range (0.8 (0.3) µmol/l) at the beginning of the study and did not rise during supplementation (0.9 (0.2) µmol/l). Thus, no risk of retinol toxicity even during high dose supplementation could be detected.

Discussion

There are two major findings in this study. Firstly, β-carotene supplementation appears to be associated with a clinical benefit for patients with CF and, secondly, normalisation of the plasma concentration of β-carotene can only be achieved and maintained with a high dose of 1 mg/kg/day. To our knowledge this is the first double blind, placebo controlled study to demonstrate a beneficial clinical effect of β-carotene supplementation in patients with CF.

In CF progressive lung disease is characterised by chronic endobronchial infection and a chronic, predominantly neutrophilic inflammatory response. Neutrophils—which are maximally stimulated as a result of ineffective phagocyte with persistence of endobronchial bacteria, mostly Pseudomonas aeruginosa or Staphylococcus aureus—release large amounts of both reactive oxygen species and proteolytic enzymes, overwhelming the existing protective systems of both antioxidants and antiproteases. However, neutrophil inflammation was also seen in patients with CF even in the absence of any endobronchial infection. Patients with CF therefore usually receive additional supplementation with the nutrient antioxidants α-tocopherol and ascorbate. However, compared with the levels of a healthy population, they also frequently have a decreased plasma concentration of β-carotene, another nutrient antioxidant. The possible factors which may explain this finding are malabsorption and thus decreased fat soluble vitamin and provitamin intake on the one hand, and chronic pulmonary inflammation causing severe oxidative stress which may increase the turnover of nutrient antioxidants, possibly due to their reaction with reactive oxygen derived species, on the other, resulting in an oxidant-antioxidant imbalance in favour of the former.

Our data show that only during the three months of supplementation with 1 mg/kg/day β-carotene could plasma concentrations be maintained in a range that was associated with a decrease in the initially raised levels of MDA—a marker of lipid peroxidation—to values equal to those of healthy individuals. This positive influence of β-carotene supplementation on parameters of lipid peroxidation has already been reported in earlier studies. The main purpose of the present study, however, was to assess whether normalisation of the plasma concentration of β-carotene might also be associated with a clinical benefit. We therefore evaluated the number of antibiotic treatment days necessitated by an acute pulmonary exacerbation.

The need for systemic antibiotics for treatment of an acute exacerbation in the β-carotene group was significantly lower than in the placebo group and, indeed, the placebo group showed an
increase in the number of antibiotic treatment days. This increase was not entirely unexpected since the study period coincided with the cold season and most of the patients were included during autumn and winter months. We hypothesise that, by normalising plasma concentrations of vitamin C, together with improved lipid peroxidation, the antioxidative-oxidative imbalance might be corrected, providing better protection and thus reducing the susceptibility to pulmonary exacerbations. There were no changes in FEV₁ during the study period in either group and no changes in the Shwachman-Kulczycki score, with no significant differences between the supplemented and placebo groups. These findings must be interpreted with caution because of the small number of patients. The frequent follow up visits on a monthly basis and our strict regime of treating pulmonary exacerbations immediately with antibiotics according to the results of microbiology tests may be another explanation why no changes in lung function or Shwachman-Kulczycki score were detected during the six months of the study.

No adverse events were observed during the study and beta-carotene was well tolerated. This is in agreement with Winkelloe-Roob et al who also found no serious adverse effects in their beta-carotene supplementation study over 16 months.¹⁵ Because of the small number of patients and the high variability in clinical presentation, a characteristic phenomenon in patients with CF, our data must be treated with caution. Yet, our first data from this pilot study appear to be encouraging enough to justify further studies to assess the clinical effects of beta-carotene supplementation in a larger cohort of patients. However, in the light of previous studies¹⁶‑¹⁸ indicating an increased risk of lung cancer in smokers after 5‑8 years of dietary beta-carotene supplementation, any long term supplementation with beta-carotene must be followed closely and cautiously.

In conclusion, our data demonstrate that oral beta-carotene supplementation in a dose of 1 mg/kg/day is effective in normalising beta-carotene plasma concentrations and the parameters of lipid peroxidation. This normalisation is associated with a clinical benefit by significantly decreasing the number of days of antibiotic treatment necessitated by acute pulmonary exacerbations. Our data suggest that patients with CF may benefit from oral beta-carotene supplementation.


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