Vitamin D and parathyroid hormone and bone mineralisation in adults with cystic fibrosis

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ABSTRACT Vitamin D and parathyroid hormone concentrations were assessed in 31 adults with cystic fibrosis (mean age 24, range 17–52 years), in 28 of whom the bone mineral index in the forearm was also determined. Serum 25-hydroxyvitamin D was subnormal in eight patients, of whom five were receiving vitamin D supplements in standard doses. 1,25-dihydroxyvitamin D and parathyroid hormone concentrations showed no consistent abnormalities. The bone mineral index was lower in patients with cystic fibrosis (p < 0.02) than in controls. Five patients with unequivocally reduced bone mineral index had a subnormal mean serum 25-hydroxyvitamin D and significantly worse lung function than the other patients. There was a positive correlation between age and bone mineral index (r = 0.68, p < 0.001). Thus a significant proportion of patients with cystic fibrosis living in a temperate climate are at risk of vitamin D deficiency. Osteopenia is common and is probably related to a combination of hypovitaminosis D, delay in puberty, hypo-oestrogenism in women, and reduced physical activity, rather than to secondary hyperparathyroidism. Since most patients with deficiency of 25-hydroxyvitamin D were receiving oral supplements, parenteral vitamin D supplementation may be appropriate for selected patients who are unable to maintain adequate 25-hydroxyvitamin D concentrations despite oral vitamin D supplements.

Cystic fibrosis is a disorder associated with pancreatic insufficiency and abnormalities of bile salt metabolism that lead to steatorrhoea and malabsorption of fat soluble vitamins. Despite these features, there are very few reports of patients with cystic fibrosis presenting with rickets.1,2 Reductions in circulating 25-hydroxyvitamin D (25(OH)D) concentrations have been reported in patients with cystic fibrosis who were receiving oral vitamin D supplements in the United States,3,4 the United Kingdom,4 and Ireland,5 although no differences between patients and controls have been reported.6 These differences may be partly related to varying degrees of sunlight exposure as reported from the United States.9 Increased parathyroid hormone concentration has also been found in patients with cystic fibrosis,3,10 as might be expected in response to vitamin D deficiency.

In addition to these biochemical abnormalities, substantial demineralisation of bone has been found in adolescents and young adults with this disease3,11 and it has been suggested that the degree of demineralisation may increase with age.11

There is therefore considerable evidence for abnormalities of vitamin D metabolism in patients with cystic fibrosis. Much of the previous work was performed in the United States, where exposure to sunlight would be expected to be greater than in regions with a cooler climate, such as Britain. As any abnormality might increase with age, the present study aimed to assess vitamin D concentrations and bone mineral metabolism in adults with cystic fibrosis.

Methods

We studied 31 patients with cystic fibrosis attending the Brompton Hospital cystic fibrosis clinic. Their mean age was 24.5 (range 17–52) years. All had typical clinical features of cystic fibrosis with pulmonary disease and a sweat sodium concentration of over 70
mmol/l. All except two patients were taking pancreatic enzyme supplements. The faecal fat excretion of one of these two had been measured and was within the normal range. None of the patients had biochemical evidence of liver disease and they were clinically stable. Informed consent was obtained from the patients, who were all studied in the autumn and early winter. The study was approved by the Brompton Hospital ethics committee.

A detailed drug and dietary history, including intake of vitamin supplements, was obtained by questionnaire. Dietary intake of vitamin D was assessed by a dietician. Sunlight exposure was assessed in terms of hours a week spent out of doors during the previous summer. Height and weight were measured, and weight was expressed as a percentage of the predicted value for sex and height.\(^\text{12}\) Forced expiratory volume in one second (FEV\(_1\)) and forced vital capacity (FVC) were measured by dry spirometer and expressed as a percentage of predicted values for sex, age, and height.\(^\text{13}\) The values for FEV\(_1\) and FVC used in the analysis were the means of the highest and lowest values recorded within three months of the study.

**BLOOD SAMPLES**

Blood samples were obtained from September to November. After an overnight fast venepuncture was performed without a tourniquet and blood was collected into lithium heparin and plain tubes. Serum was separated by centrifugation at 4°C immediately after clotting had occurred. All samples were stored at −20°C until analysis.

**BIOCHEMICAL METHODS**

Plasma calcium and albumin concentrations were estimated in a SMAC Autoanalyzer (Technicon) and the calcium concentrations corrected by +0.02 mmol/l for each g/l of albumin concentration below 40 g/l.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical and biochemical data (means with standard deviations in parentheses)</th>
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<tbody>
<tr>
<td></td>
<td>Patients</td>
</tr>
<tr>
<td>Weight (% predicted)</td>
<td>97±1 (11-4)</td>
</tr>
<tr>
<td>FEV(_1), (% predicted)</td>
<td>41±5 (19-7)</td>
</tr>
<tr>
<td>Forced vital capacity (% predicted)</td>
<td>57±1 (20-4)</td>
</tr>
<tr>
<td>25-hydroxyvitamin D (mmol/l)</td>
<td>26** (16) 35 (10)</td>
</tr>
<tr>
<td>1,25-dihydroxycholecalciferol (pmol/l)</td>
<td>75 (35) 79 (21)</td>
</tr>
<tr>
<td>Parathyroid hormone (pmol/l)</td>
<td>43 (13) 55 (14)</td>
</tr>
<tr>
<td>Calcium (nmol/l)</td>
<td>2.26* (0.11) 2.40 (0.10) 2.3-2.6</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>38.4 (3.5) 39 (4)</td>
</tr>
<tr>
<td>Calcium (corrected for albumin) (nmol/l)</td>
<td>2.30* (0.11) 2.40 (0.1) 2.2-2.6</td>
</tr>
<tr>
<td>Magnesium (mmol/l)</td>
<td>0.78 (0.05) 0.80 (0.12)</td>
</tr>
</tbody>
</table>

\(*)^p < 0.05; **^p < 0.02, in the comparison with controls.

Plasma magnesium concentration was measured by atomic absorption. Serum 25(OH)D concentration was measured by the method of Preece et al.,\(^\text{14}\) and serum 1,25-dihydroxycholecalciferol (1,25(OH)\(_2\)D) concentration by a radioreceptor assay.\(^\text{15}\) Serum parathyroid hormone concentration was estimated by a radioimmunoassay by using an antibody to the mid-region of the molecule.\(^\text{16}\) Normal ranges in our laboratory for 25(OH)D, 1,25(OH)\(_2\)D, and parathyroid hormone are derived from at least 50 normal subjects in each case (table 1). The reagents for the 1,25(OH)\(_2\)D and parathyroid hormone assays were obtained from Immunonuclear Corporation, Stillwater, Minnesota, USA.

**BONE DENSITOMETRY**

In 28 of the patients single photon beam densitometry\(^\text{17,18}\) was performed on the right radius with an americium-241 source. Duplicate scans were performed at a site about one third of the distance from the ulnar styloid process to the olecranon, the arm being immersed in water. A bone mineral index (proportional to bone mass per unit length at the measurement site) was calculated as a function of the radiation transmitted through the bone. Bone density data were compared with results from 28 healthy control subjects matched for age and sex. Because bone mineral readings are age and sex dependent, bone mineral data for patients and controls were expressed as percentages of mean normal values established in the department for men or women aged 18–39 or 40–59.

**STATISTICAL METHODS**

Results were compared by means of Student’s (two tailed) t test and linear regression analysis.

**Results**

Patients had a mean daily intake of 1500 mg calcium, the recommended daily allowance (RDA) being 500 mg.\(^\text{19}\) In only one patient was intake less than the recommended allowance. The mean daily intake of vitamin D was 19.1 µg (764 IU), range 0.6–54.3 µg (24–2172 IU). Only seven of the 31 patients were not taking supplements of vitamin D.

The mean total plasma calcium concentration, even when corrected for serum albumin concentration, was lower in patients (2.30 mmol/l) than in controls (2.40 mmol/l). The plasma magnesium concentration was normal in all patients. The mean 25(OH)D concentration (26 (SD 16) mmol/l) in patients was significantly less than that in controls (35 (10) mmol/l). In eight patients, five of whom were receiving vitamin D supplements, serum 25(OH)D concentrations were less than the lower limit of the normal range (15 mmol/
I. The remaining four patients not taking additional vitamin D had normal 25(OH)D serum concentrations. There was no relationship between serum 25(OH)D concentration and vitamin D intake. In the patient without steatorrhoea the serum 25(OH)D concentration was reduced at 6 nmol/l. Eighteen patients reported spending at least four hours a day outside during the previous summer, but this was also unrelated to serum 25(OH)D concentration, though there was a weak correlation with percentage predicted body weight (r = 0.35, p < 0.05). Serum 1,25(OH)2D concentration was normal in all patients. There was no relationship between serum 25(OH)D and 1,25(OH)2D concentrations. Serum parathyroid hormone concentrations were normal except in three patients (<25 pmol/l).

The bone mineral index in the patients with cystic fibrosis was significantly lower than that in control subjects (table 2). The diminution in bone mineral index was more marked and was significant in women. The bone mineral index was much lower in patients aged under 25 years than in control subjects of similar age. Within this age group, significant differences occurred between patients with cystic fibrosis and controls in both men and women. For all the patients the bone mineral index showed a positive correlation with age (r = 0.68, p < 0.001); significant correlations between bone mineral index and age were also found for female (r = 0.76, p < 0.01) and male (r = 0.67, p < 0.01) patients. There was no correlation between bone mineral index and 25(OH)D or parathyroid hormone concentrations. Bone mineral index values in five patients (four of them female) lay below the normal range; all were under 21 years and were among the youngest patients studied. The man had delayed puberty, as did two of the women, who also had prolonged secondary amenorrhoea. These five patients also showed poorer lung function, with FVC 39.4% (SD 7.4%) predicted, compared with 62.9% (20.3%) in the remainder (p < 0.02), and their mean 25(OH)D concentration (13.6 nmol/l) was below the lower limit of normal.

Discussion

These data show that a significant proportion (8/31) of adults with cystic fibrosis in our series, mostly from the South of England, have subnormal 25(OH)D serum concentrations. Five of eight patients with subnormal 25(OH)D concentrations were receiving vitamin D supplements (around 800 IU daily); thus regular oral vitamin D supplementation did not prevent subnormal 25(OH)D concentrations. The bone mineral index was lower in these patients than in age matched controls.

None of the patients studied had a raised parathyroid hormone concentration indicative of secondary hyperparathyroidism. This contrasts with the findings of previous studies in cystic fibrosis and nutritional hypovitaminosis D, which indicated frequent secondary hyperparathyroidism. The absence of secondary hyperparathyroidism in the presence of subnormal 25(OH)D concentrations is probably explained by the normal serum concentrations of 1,25(OH)2D. The presence of normal 1,25(OH)2D concentrations may also ensure that the occurrence of rickets or osteomalacia in these patients is relatively rare, despite the frequency of subnormal 25(OH)D concentrations. We have previously reported the absence of secondary hyperparathyroidism despite low 25(OH)D concentrations in anorexia nervosa and β thalassaemia major with iron overload, but 1,25(OH)2D concentrations were normal. There is no definite evidence that hypovitaminosis D causes demineralisation in the absence of secondary hyperparathyroidism. Preliminary evidence from our laboratory, however, shows that some patients with vitamin D deficiency due to malnutrition may have osteopenia in the absence of raised concentrations of parathyroid hormone. The lack of parathyroid hypersecretion might have been due to a deficiency of magnesium, since magnesium is known to modulate parathyroid hormone secretion; but there was no evidence of magnesium deficiency in our patients.

The weak correlation between lung function and bone mineral index and the finding of a lower FVC in patients with a reduced bone mineral index suggests that severe lung disease may contribute to osteopenia. As four of the five patients with a reduced bone mineral index were female, we considered the possibility that hypo-oestrogenism might also have contributed to their osteopenia; two of the four had prolonged secondary amenorrhoea. Duration of amenorrhoea has been related to the degree of

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Bone mineral index</th>
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<tbody>
<tr>
<td>All subjects:</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis (n = 28)</td>
<td>25.5</td>
</tr>
<tr>
<td>Control (n = 28)</td>
<td>24.5</td>
</tr>
<tr>
<td>Subjects &lt;25 years:</td>
<td></td>
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<tr>
<td>Cystic fibrosis (n = 18)</td>
<td>21.3</td>
</tr>
<tr>
<td>Control (n = 19)</td>
<td>22.5</td>
</tr>
<tr>
<td>Men:</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis (n = 14)</td>
<td>25.3 (8.9)</td>
</tr>
<tr>
<td>Control (n = 14)</td>
<td>25.4 (8.9)</td>
</tr>
<tr>
<td>Women:</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis (n = 14)</td>
<td>23.6 (5.6)</td>
</tr>
<tr>
<td>Control (n = 14)</td>
<td>23.6 (5.4)</td>
</tr>
</tbody>
</table>

*p < 0.02 in comparison with controls.
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osteopenia in patients with anorexia nervosa and women athletes.

The mechanism underlying osteopenia in our patients is therefore complex. The probable contributory factors are, firstly, hypovitaminosis D (but not through secondary hyperparathyroidism); secondly, delay in puberty and hence bone maturation and, in female patients, hypo-oestrogenism resulting from delayed puberty or prolonged secondary amenorrhoea; and, thirdly, lack of physical activity due to severe lung disease and repeated admission to hospital. A correlation of bone mineral index with age in cystic fibrosis has also been noted in an American study, and may reflect the fact that patients with reduced bone mineral indices also had poorer lung function and thus a worse prognosis. Thus the longest surviving patients would have more normal bone mineral indexes.

Sunlight is the major source of vitamin D in healthy people, and evidence for an effect of sunlight exposure on serum 25(OH)D concentrations in cystic fibrosis has been reported. It is not surprising that a large proportion of our patients living in a temperate climate with limited sunshine should be deficient in 25(OH)D, and our assessment of sunlight exposure is likely to have been too crude to expose a relationship with circulating vitamin D concentrations. A recent study from Ireland found three quarters of adult patients with cystic fibrosis had subnormal 25(OH)D concentrations, although oral vitamin D intake was lower than in our group. They also showed a relatively poor response to 800 IU of supplemental vitamin D daily. Forty per cent failed to achieve normal circulating concentrations of 25(OH)D after 4–10 weeks' supplementation, and none of these had a normal concentration after one year. The lack of response to oral vitamin D supplements may be due to poor compliance, malabsorption, or interruption of the enterohepatic circulation. Whatever the cause, it would seem reasonable to continue to supplement patients with cystic fibrosis with more than 800 IU vitamin D daily. In those patients whose serum concentrations remain low on this regimen the dose should be increased and in some unresponsive cases parenteral treatment may be a logical approach.

RJS was supported by the Frances and Augustus Newman Foundation. We thank Pam Middleton for help with the bone mineral determinations. We thank Miss S Hockley and Mrs P Dale for preparing the manuscript.

References


18 Karjalainen P, Alhava EM. Bone mineral content of the


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**Book notices**


This book is intended for everyone who uses oxygen therapy, from ambulance men and first aid workers to nursing and medical staff. It describes the physiological basis of hypoxia and the principles of oxygen therapy, with particular emphasis on delivery systems and masks. The section intended specifically for the medically qualified is extremely brief, dealing with the interaction of drugs with oxygen, pulmonary hypertension, mechanisms of oedema, bronchodilator drugs, and ventilatory failure in less than three pages. Of course, it is a short book that is not intended to be comprehensive and therefore provides the lay reader with a list of references of review articles and original papers, together with a glossary of terms and symbols. The important sections that discuss controlled and long term oxygen therapy are clear and concise and there are useful sections describing the techniques available for measuring the response to oxygen therapy and the use of oxygen in special circumstances, such as in special care baby units, ambulances, and aircraft. This is a helpful book that is easy to read and brings together all the information that prescribers of oxygen would require. It will find a niche in many intensive care units, anaesthetic departments, chest wards, and ambulance stations.—JEH


This book covers the full range of occupational diseases, but is weighted towards respiratory disease. It is aimed at health professionals to help them in the early detection of occupational diseases and then lists the major diseases, with sections on the occurrence, occupations at risk, mechanisms of action, assessment of exposure, clinical effects, exposure-effect relationships, and details of suitable pre-employment screen tests and periodic examinations. The next section deals with clinical laboratory tests for the early detection of occupational diseases with a section on the respiratory system, and finally there are chapters on biological monitoring and assessment of environmental exposure. Despite the original aims, it is unclear who would benefit from reading this book. It is written in medical language and so is less suitable for an occupational administrative audience, for which the level of information ought to be most suitable. The medical content has a strong epidemiological bias and lacks the detail necessary for a clinician dealing with a patient exposed to any occupational risks. Although the aim of the book is to teach how to detect preclinical disease, in the respiratory section at least this has not been achieved. The section on immunological occupational respiratory disease is poor; this is an area where sensitisation may be detected before disease, but there is no discussion at all of this topic. There are some extremely surprising statements, such as “There is no relationship between the concentration of a sensitising agent and adverse effects.” This statement is hardly likely to encourage a reduction of exposure to occupational sensitising agents. I fear that this book has tried to tackle too big a subject too superficially and has tried to satisfy the WHO’s directive about detecting preclinical disease in many situations where the relationship between early changes—for instance, in lung function or immunology—and subsequent disease has not been established.—PSB
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R J Stead, S Houlder, J Agnew, M Thomas, M E Hodson, J C Batten and P Dandona

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Correspondence

Use of nebulised saline and nebulised terbutaline as an adjunct to chest physiotherapy

Sir,—We were interested to read the article by Dr PP Sutton and others (January 1988;43:57–60). The magnitude of the increase in sputum weight after saline or terbutaline, compared with that after chest physiotherapy alone, is small (estimated from figure 1 as being 5 g after saline and 6 g after terbutaline with saline) and is similar to the weight of inhaled saline (4 g). We would be interested to know the character of the sputum collected after the chest physiotherapy with and without nebuliser treatment. In particular, did the proportion of liquid increase or the viscosity decrease after nebuliser treatment? We contend that the increase in sputum weight after 4 ml nebulised saline may simply be due to clearance of nebulised saline. Home nebuliser treatment is expensive and it is important to know the answer to this question before it is advised as an adjunct to home physiotherapy.

NEIL C MUNRO
DAVID C CURRIE
PETER J COLE
Host Defence Unit
Cardiothoracic Institute
Brompton Hospital
London SW3 6HP

* * *This letter was sent to the authors, and Dr Sutton replies below.

Sir,—Lewis and Fleming1 have shown that only about one tenth of a nebulised aerosol is retained in the lung, so the equivalent amount (considerably less than 1 g in our study) is unlikely to contribute directly to the increased sputum yield found after saline or terbutaline. We could not comment on the physical characteristics of each sputum sample as objective measurements of viscoelasticity are notoriously difficult to make and interpret.

Although we did not advocate home nebuliser treatment as an adjunct to physiotherapy this would seem logical in certain patients such as those with cystic fibrosis.

PHILIP P SUTTON
General Hospital
Hartlepool TS24 9AH


Notices

Activity holidays for asthmatic children

The Asthma Society is arranging activity holiday courses, under medical supervision, for young people with asthma (aged 8–16) in Cumbria, Northumberland, and Hampshire at the end of July and in August 1988. Each course is of a week’s duration. Physicians are asked to consider encouraging parents of their asthmatic patients to apply for a place at one of these centres. Parents are invited to pay for the cost of the accommodation, though the Asthma Society is willing to provide grants when necessary. Details and application forms from H Faulkner, Asthma Society, 300 Upper Street, London N1 2XX.

The Dr HM (Bill) Foreman Memorial Fund

The trustees of the Dr HM (Bill) Foreman Memorial Fund invite applications for grants relating to study in respiratory disease. Limited funds are available for registered medical practitioners, for helping them to travel to countries other than their own to study respiratory disease, and also for support of clinical research abroad. Intending applicants should write for further details to Dr B H Davies, Sully Hospital, Sully, S Glamorgan, CF6 2YA.

Conference on health related effects of phyllosilicates

The first International Conference on Health Related Effects of Phyllosilicates will be held in Paris on 16 and 17 March 1989 and will include sessions on clinical and epidemiological evidence of health effects, biological responses, and industrial aspects. Details from Professor J Bignon, INSERM U 139, Chu H Mondor, 94010 Creteil cedex, France.

Correction

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Two errors occur in the paper by Dr RJ Stead and others (March 1988;43:190–4): in table 1 the first value under Patients should be 97.1, and in table 2 the p value for the third line under Bone mineral index should be < 0.001.