A prospective study of change in bone mineral density over one year in adults with cystic fibrosis

C S Haworth, P L Selby, A W Horrocks, E B Mawer, J E Adams, A K Webb

Background: Low bone mineral density (BMD) is prevalent in adults with cystic fibrosis. To identify appropriate therapeutic strategies and the optimal time for intervention, it is necessary to document the natural history of cystic fibrosis related low BMD.

Methods: 114 adults with cystic fibrosis underwent bone densitometry a median (25–75% interquartile range) of 12 (12–13) months after initial assessment of bone density. BMD was measured in the lumbar spine, femoral neck, total hip, and distal forearm on recruitment to the trial and at follow up.

Results: In patients ≤24 years of age (n=55, mean (SD) age 19.5 (2.6) years) in whom an annual increase in BMD would normally be expected, BMD increased by a mean (95% CI) 2.9% (1.6 to 4.2) per year in the distal forearm (p<0.001), but decreased by 2.5% (95% CI –3.8 to –1.2) per year in the femoral neck (p<0.001) and by 2.2% (95% CI –3.3 to –1.0) per year in the total hip (p<0.001). In patients ≥25 years of age (n=59, mean (SD) age 30.3 (5.4) years) in whom no annual change in BMD would normally be expected, BMD decreased by 1.9% (95% CI –2.9 to –0.8) per year in the femoral neck (p<0.001), by 1.5% (95% CI –2.4 to –0.6) per year in the total hip (p=0.001), and by 0.8% (95% CI –1.5 to –0.1) per year in the distal forearm (p=0.026). There was no significant annual change in lumbar spine BMD in either patient cohort.

Conclusions: Reduced rates of bone accretion and accelerated rates of bone loss explain the high prevalence of low BMD in adults with cystic fibrosis.
coefficient of variation (CV) = 0.63% for the Osteometer DTX-100 SXA forearm scanner and 0.22% for the Hologic QDR 4500 DXA scanner.

The BMD results were expressed as absolute values (DXA and SXA measure areal BMD in g/cm² and QCT measures volumetric bone density in mg/ml). The annual change and the annual percentage change in BMD were then calculated from these absolute values. The baseline BMD results were also expressed as Z scores (SDs above or below the mean BMD of an age and sex matched control population). The reference data used to calculate the BMD Z scores were provided by the DXA and SXA densitometer manufacturers and by the manufacturers of the QCT lumbar reference simulator. Reference data were available for patients ≥16 years of age for the DXA measurements in the lumbar spine, and for patients ≥18 years of age for the other BMD measurements.

Biochemical measurements

Morning non-fasting blood and urine samples were taken from patients on recruitment to the study and on follow up, at a time when their lung disease was stable. Serum samples were separated within 30 minutes of sampling and frozen at −20°C. Serum corrected concentrations of calcium, phosphate, total alkaline phosphatase, C reactive protein (CRP), HbA1c, 25-hydroxyvitamin D, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, parathyroid hormone (PTH), bone specific alkaline phosphatase (BSAP), and urinary deoxypyridinoline crosslinks were analysed as described previously. The inter-assay and intra-assay coefficients of variation were 8.8% and 7.8%, respectively, for the 25-hydroxyvitamin D measurements and 10.7% and 7.8%, respectively, for the 1,25-dihydroxyvitamin D measurements.

Clinical assessment

The best recorded, forced expiratory volume in one second (FEV₁), weight, and height in the 4 months before the recruitment and follow up visits were used to calculate the percentage predicted FEV₁, and body mass index (BMI). Daily calcium intake was assessed from a validated questionnaire. In female patients the age at menarche, menstrual history, and use of hormonal contraception were recorded. Patients were asked whether they had sustained a radiographically confirmed fracture since starting the study. Levels of physical activity performed over the previous year were assessed using the Baecke physical activity questionnaire, which has been validated in young adults. The questionnaire documents the amount of physical activity performed during work, sport and leisure times, and each section is scored between 1 and 5, the total score ranging from a minimum of 3 to a maximum of 15. The total oral corticosteroid usage between recruitment and follow up was recorded prospectively for each patient.

Table 1 Bone biochemistry in 96 adults with cystic fibrosis

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Difference between baseline and follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected calcium (mmol/l)</td>
<td>2.36 (95% CI 2.34 to 2.38)</td>
<td>−0.06 (95% CI −0.09 to −0.04)†</td>
</tr>
<tr>
<td>Phosphate (mmol/l)</td>
<td>1.10 (95% CI 1.05 to 1.14)</td>
<td>0.03 (95% CI −0.02 to 0.08)</td>
</tr>
<tr>
<td>Total alkaline phosphatase (IU/l)</td>
<td>93.0 (25–75% IQR 67.0–125.0)</td>
<td>7.0 (25–75% IQR −3.0–19.0)‡</td>
</tr>
<tr>
<td>25-hydroxyvitamin D (ng/ml)</td>
<td>18.9 (95% CI 16.5 to 21.2)</td>
<td>2.40 (95% CI 0.04 to 4.78)*</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/ml)</td>
<td>31.4 (95% CI 28.9 to 33.9)</td>
<td>4.62 (95% CI 1.54 to 7.71)†</td>
</tr>
<tr>
<td>Bone specific alkaline phosphatase (U/l)</td>
<td>23.0 (25–75% IQR 16.0–31.0)</td>
<td>2.7 (25–75% IQR −6.4–10.1)</td>
</tr>
<tr>
<td>Deoxypyridinoline crosslinks (nM/Mm)</td>
<td>18.5 (25–75% IQR 14.3–24.3)</td>
<td>1.1 (25–75% IQR −1.4–4.2)†</td>
</tr>
<tr>
<td>(normal range 2.3–7.4)</td>
<td>5.8 (25–75% IQR 4.7–9.3)</td>
<td>0.0 (25–75% IQR −2.1–1.8)</td>
</tr>
</tbody>
</table>

Values are mean (95% CI) or median (25–75% IQR). *p<0.05; †p<0.01; ‡p<0.001.

Statistical analysis

Data were analysed using SPSS version 7.0 (SPSS Inc. Chicago, Illinois) and variables were summarised using the mean (SD), mean (95% confidence intervals (CI)), or median (25–75% interquartile range (IQR)). Annual change (change corrected for the varying time between recruitment and follow up) was calculated for each variable. A one sample t test or the Wilcoxon signed rank test were used to determine whether these changes were significantly different from zero. Independent sample t tests were used to identify whether there were differences in the annual change in BMD between specific patient groups. Spearman’s rank correlations were used to identify the clinical and biochemical correlates of the annual change in BMD at each skeletal site.

RESULTS

Patient characteristics

Seventy one patients were homzygous and 35 were heterozygous for the delta F508 cystic fibrosis mutation. Seven patients had other mutations and the complete genotype in one patient has not been identified. None of the patients included in this analysis were taking any specific bone sparing agents (except standard oral vitamin D supplements) and none had received a transplant.

On recruitment the mean (SD) age, BMI, percentage predicted FEV₁, and physical activity score of the whole group were 25.1 (6.9) years (range 15–49), 21.3 (2.4) kg/m², 61.7 (23.4)%, and 7.8 (1.3), respectively. The mean (SD) annual change in BMI was 0.2 (1.2) kg/m² (p=0.033) and in FEV₁ was −2.2 (8.8)% predicted (p=0.010). There was no significant annual change in physical activity.

Nine patients had been taking continuous oral corticosteroid therapy (prednisolone 5–15 mg/day) throughout the follow up period; three patients for allergic bronchopulmonary aspergillosis and six for unstable lung disease. Seventy nine patients had been taking inhaled corticosteroid therapy (budesonide 200–400 µg twice daily or fluticasone propionate 250–500 µg twice daily). The median (25–75% IQR) oral corticosteroid usage during the follow up period was 0.6 (0.0–2.5) mg prednisolone per day. Forty of the 114 patients (35%) received no oral corticosteroid therapy and, in the remaining 74 patients (65%), the median (25–75% IQR) oral corticosteroid usage was 1.7 (0.7–4.4) mg prednisolone per day. One patient was taking azathioprine for coexisting inflammatory bowel disease.

All pancreatic insufficient patients were prescribed 22.5 µg (900 IU) oral vitamin D (calciferol) daily, but seven patients admitted to not taking their vitamin supplements on a regular basis. Four patients were pancreatic sufficient. At the time of
recruitment the median (25–75% IQR) daily calcium intake was 1321 (926–1729) mg. There was no significant change in calcium intake during the follow up period.

The mean (SD) age at menarche was 13.6 (1.7) years. One patient aged 17 had primary amenorrhoea and four patients reported menstrual irregularity (having less than nine periods in the last year), one of whom was peri-menopausal. Sixteen patients reported taking the combined oral contraceptive pill or depot medroxyprogesterone acetate at the time of follow up.

Nineteen patients had cystic fibrosis related diabetes, of which 15 required insulin and four were taking oral hypoglycaemic agents. Seven patients admitted to smoking regularly and 19 patients admitted to consuming 20 or more units of alcohol per week.

Three patients, all male, sustained symptomatic fractures over the follow up period. One fractured a rib after falling when skiing, another fractured his wrist following blunt trauma to his fist, and the third sustained cough induced rib fractures on two separate occasions.

Biochemical measurements
Serum and urine samples were collected on recruitment and at follow up from 96 of the 114 patients (84%). The bone biochemistry results are shown in table 1. The median (25–75% IQR) concentrations of CRP and HbA1C on recruitment to the study were 5.5 (5.0–23.5) mg/l and 4.7 (4.3–5.0)%, respectively. There was no significant change in these variables during the follow up period.

Bone mineral density measurements
114 of the initial 151 patients recruited to the study had one or more BMD measurements repeated. However, not all patients attended for all types of densitometry.

For the whole group, the mean (95% CI) BMD Z scores on recruitment to the study were in the lumbar spine (measured by QCT, n=74) –0.48 (–0.76 to –0.20), in the femoral neck (n=84) –1.13 (–1.39 to –0.87), in the total hip (n=83) –0.93 (–1.16 to –0.70), and in the distal forearm (n=82) –0.81 (–1.01 to –0.61). Thirty seven of the 114 patients (32%) had a baseline BMD Z score ≦–2 at one or more skeletal sites. Reference data and therefore Z scores were not available for all patients. However, the annual change in absolute BMD could still be calculated for these individuals. The annual percentage change in BMD at each skeletal site for each patient is shown in fig 1.

In normal subjects BMD increases during childhood/adolescence until peak bone mass is achieved in early adulthood, and then between the ages of 25 years BMD remains almost stable. In order to interpret the longitudinal BMD data in a meaningful fashion, it was therefore necessary to divide the cohort by age into those above and below the age of 25 years at the time of recruitment to the study. The mean (SD) age, BMI, and percentage predicted FEV1 were 19.5 (2.6) years, 21.0 (2.5) kg/m2, and 69.3 (23.1)%, respectively, in the 55 patients aged ≦24 years, and 30.3 (5.4) years, 21.5 (2.2) kg/m2, and 54.6 (21.5)%, respectively, in the 59 patients aged >25 years. BMD in the younger cohort would normally be expected to increase annually before reaching peak bone mass, whereas BMD in the older cohort would normally be expected to remain stable, having achieved peak bone mass. The baseline, annual change, and annual percentage change in BMD in these two patient cohorts are shown in tables 2 and 3.

Within the whole cohort (n=114), femoral neck BMD reduced more in men than in women (p=0.050), total hip BMD reduced more in those patients who received oral corticosteroids than in those who did not (p=0.022), and lumbar spine BMD (measured by DXA) reduced more in patients colonised with Burkholderia cepacia (n=25) than in patients colonised with other organisms (n=89; p=0.046). However, these differences were not apparent at other skeletal sites. There was also no significant difference in the annual change in BMD at each skeletal site between delta F508 homozygotes and non-homozygotes, those taking inhaled corticosteroids and those not, those with a previous history of fracture and those not, and women taking hormonal contraception and those not. Finally, there was no significant difference in the annual change in biochemical markers of bone turnover between those patients taking inhaled glucocorticoid therapy and those not.

When the clinical and biochemical variables measured on recruitment to the study and at follow up were correlated with the annual change in BMD at each skeletal site for the whole cohort, few consistent relationships were apparent. However, when the annual change in these variables was correlated with the annual change in BMD, more consistent and biologically meaningful relationships emerged (table 4). The change in age, oral calcium intake, phosphate, total alkaline phosphatase, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, CRe and HbA1C, did not correlate significantly with change in BMD at any skeletal site.

**DISCUSSION**

This is the largest and most comprehensive study to date documenting the natural history of cystic fibrosis related low

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**Table 2** Annual change in bone mineral density in 55 patients with cystic fibrosis aged ≦24 years

<table>
<thead>
<tr>
<th>Skeletal site</th>
<th>Baseline BMD*</th>
<th>Difference between baseline and follow up BMD*</th>
<th>Annual % change in BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine (QCT) (n=40)</td>
<td>176.1 (166.9 to 185.2)</td>
<td>−2.0 (−6.0 to 1.9)</td>
<td>−1.7 (−4.4 to 1.1)</td>
</tr>
<tr>
<td>Lumbar spine (DXA) (n=43)</td>
<td>0.918 (0.882 to 0.953)</td>
<td>−0.007 (−0.016 to 0.002)</td>
<td>−0.9 (−2.0 to 0.2)</td>
</tr>
<tr>
<td>Femoral neck (DXA) (n=43)</td>
<td>0.839 (0.801 to 0.877)</td>
<td>−0.022 (−0.032 to −0.011)</td>
<td>−2.5 (−3.8 to −1.2)</td>
</tr>
<tr>
<td>Total hip (DXA) (n=43)</td>
<td>0.917 (0.880 to 0.953)</td>
<td>−0.019 (−0.029 to −0.009)</td>
<td>−2.2 (−3.3 to −1.0)</td>
</tr>
<tr>
<td>Distal forearm (DXA) (n=42)</td>
<td>0.462 (0.446 to 0.479)</td>
<td>0.013 (0.007 to 0.018)</td>
<td>2.9 (1.6 to 4.2)</td>
</tr>
</tbody>
</table>

Values are shown as mean (95% CI). *BMD is measured in g/cm2 by DXA and SXA and in mg/ml by QCT. †p<0.001.
bone density. It is now clear that reduced bone accretion and accelerated rates of bone loss explain the high prevalence of low BMD in this population.

Bone accretion was reduced in the younger cohort, in whom a significant annual increase in BMD would normally be expected. Although distal forearm BMD increased by almost 3% per year, BMD in the lumbar spine remained static and actually reduced by over 2% in the proximal femur. This failure to accrete sufficient axial bone mass in early adult life is likely to compromise peak bone mass. In addition, the site-dependent pattern of bone accretion explains why we observed that forearm BMD was relatively well preserved compared with the axial skeleton.

An accelerated rate of bone loss was the predominant feature in patients ≥25 years of age. The mean annual decline in BMD in the femoral neck, total hip, and distal forearm was 1.9%, 1.5%, and 0.8%, respectively. As DXA and SXA are areal (g/cm²) measures of BMD, these techniques could exaggerate the deficit in BMD in patients with small bones. The fact that the mean percentage change in BMD in the lumbar spine measured by both DXA and QCT (which is a true volumetric measure of BMD) were similar suggests that these reductions were valid and not significantly influenced by body size.

The only other longitudinal study documenting change in BMD in a cystic fibrosis population involved 41 patients aged 9–50 years. BMD increased by 1–2% per year in the axial skeleton, except in adult men (n=6) who experienced a 1.2% reduction in the femoral neck. The BMD Z scores of the younger patients reduced as they aged, suggesting that the increases in BMD were less substantial than those expected in normal age matched controls. Our findings confirm that bone accretion is reduced in patients before reaching peak bone mass and demonstrate an accelerated rate of bone loss thereafter.

Change in bone turnover correlated with change in BMD across several skeletal sites, increased turnover being associated with increased bone loss. Delta F508 homozygotes had a higher rate of bone turnover than non-homozygotes in the cross sectional analysis of this cohort, but in the present study there was no difference in the annual change in BMD between these two groups. Change in FEV1, BMI, and physical activity correlated with change in BMD at one or more skeletal sites. Although these variables are likely to have an individual impact on BMD, taken together they also reflect an overall change in cystic fibrosis disease severity. The relationship between disease severity and BMD may be mediated by proinflammatory cytokines, which are increased in cystic fibrosis as a consequence of chronic pulmonary infection. Proinflammatory cytokines influence osteoclast recruitment and differentiation, and a recent study by Ionescu and colleagues in 22 patients with cystic fibrosis showed that BMD was related to levels of tumour necrosis factor alpha soluble receptors and interleukin 6. These findings were supported by Aris and colleagues who found a temporal relationship between changes in inflammatory markers and bone metabolic markers. Chronic antibiotic treatment during a pulmonary exacerbation in 17 adults with cystic fibrosis. Thus, chronic pulmonary infection might explain the high bone turnover and the low BMD characteristic of cystic fibrosis patients with advanced lung disease.

Vitamin D insufficiency, a condition also associated with high bone turnover, is an additional risk factor for the development of low BMD in patients with cystic fibrosis; 38% of the original cohort had 25-hydroxyvitamin D levels below 15 ng/ml, a level suggested as indicating vitamin D insufficiency. The high prevalence of vitamin D insufficiency may reflect the UK climate, although similar levels of vitamin D insufficiency were recorded in patients with cystic fibrosis from Seattle. Changes in PTH levels in our patients were significantly related to changes in BMD in the femoral neck and lumbar spine (measured by QCT), and these data further support a link between vitamin D insufficiency and low BMD in patients with cystic fibrosis. The increase in serum vitamin D levels over the study period might reflect greater patient awareness of the potential benefits of adhering to their multivitamin supplements. The reduction in serum calcium over the study period and its inverse relationship with distal forearm BMD is more difficult to interpret, but might indicate reduced body stores of calcium.

As in other conditions, oral corticosteroid treatment was strongly associated with a decline in BMD, particularly in the axial skeleton. Patients who received oral corticosteroids sustained a greater reduction in total hip BMD than those who did not. The use of oral corticosteroids should therefore be

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**Table 3** Annual change in bone mineral density in 59 patients with cystic fibrosis aged ≥25 years.

<table>
<thead>
<tr>
<th>Skeletal site</th>
<th>Baseline BMD*</th>
<th>Difference between baseline and follow up BMD*</th>
<th>Annual % change in BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine (QCT) (n=44)</td>
<td>170.8 (161.3 to 180.3)</td>
<td>0.6 (-3.4 to 4.5)</td>
<td>0.7 (-1.5 to 2.8)</td>
</tr>
<tr>
<td>Lumbar spine (DXA) (n=57)</td>
<td>0.942 (0.909 to 0.975)</td>
<td>-0.001 (-0.011 to 0.010)</td>
<td>-0.0 (-1.3 to 1.2)</td>
</tr>
<tr>
<td>Femoral neck (DXA) (n=57)</td>
<td>0.781 (0.746 to 0.816)</td>
<td>-0.015 (-0.022 to -0.007)</td>
<td>-1.9 (-2.9 to -0.8)</td>
</tr>
<tr>
<td>Total hip (DXA) (n=57)</td>
<td>0.881 (0.844 to 0.918)</td>
<td>-0.013 (-0.020 to -0.006)</td>
<td>-1.5 (-2.4 to -0.6)</td>
</tr>
<tr>
<td>Distal forearm (SXA) (n=56)</td>
<td>0.513 (0.497 to 0.532)</td>
<td>-0.004 (-0.008 to -0.001)</td>
<td>-0.8 (-1.5 to -0.1)</td>
</tr>
</tbody>
</table>

Values are mean (95% CI). *BMD is measured in g/cm² by DXA and SXA and in mg/ml by QCT. †p<0.05; ‡p<0.01.

**Table 4** Correlates of annual change in bone mineral density in 114 adults with cystic fibrosis (whole group).

| Annual change in: | Annual change in BMD in: | | |
|------------------|-------------------------| | |
| | Lumbar spine (QCT) | Lumbar spine (DXA) | Femoral neck | Total hip | Distal forearm |
| Body mass index | 0.16 | 0.25* | 0.21* | 0.28† | 0.09 |
| FEV1, % predicted | 0.22* | 0.07 | 0.04 | 0.14 | -0.07 |
| Prednisolone use | -0.24* | -0.27* | -0.12 | -0.30† | -0.02 |
| Physical activity | 0.13 | 0.11 | 0.22* | 0.27* | 0.03 |
| Serum corrected calcium | -0.16 | -0.07 | -0.06 | -0.08 | -0.22* |
| Parathyroid hormone | -0.32† | 0.02 | -0.23* | -0.09 | 0.09 |
| Bone specific alkaline phosphatase | -0.27* | -0.30† | -0.20 | -0.21* | -0.29† |
| Deoxypyridinoline crosslinks | 0.07 | -0.26* | -0.25* | -0.33† | -0.29† |

*p<0.05; †p<0.01.
minimised to preserve BMD. There was no evidence to suggest that inhaled glucocorticoids influenced BMD or levels of bone turnover in this patient population, but a longer term study is required to confirm this observation.

This study has a number of limitations. Firstly, the duration of the study was limited to 1 year, but we do not believe that this reduces the validity of our observations. The large number of subjects makes the precision of the estimate of rate of change adequate to draw meaningful conclusions. Furthermore, these observations were made in individuals who had not undergone any specific therapeutic intervention for their bones. Thus, transient changes in BMD due to alterations in bone turnover, which can give false impressions of bone mass changes in therapeutic studies, were not present. Secondly, the 37 patients who were not followed up might have influenced the natural history data. As cystic fibrosis is a lethal disease it is sadly inevitable that some patients will not be followed up. However, as the baseline BMD Z scores were lower in the patients not followed up than in those who continued in the study, we believe that the annual reductions in BMD might have been greater. Thirdly, the study uses multiple correlations to identify potential aetiological factors involved in the development of cystic fibrosis related low BMD. To compensate for this a p value of <0.01 rather than <0.05 might have been more appropriate. Furthermore, some of the correlations are relatively weak. However, the aetiology of cystic fibrosis related low BMD is multifactorial and we have attempted to demonstrate very subtle changes in BMD and bone biochemistry within a short period of time. Had the follow up period been longer, the drop out rate would inevitably have been greater. For these reasons a p value of <0.05 was considered acceptable. Finally, the relationships between the aetiological variables could not be further explored by multiple linear regression analysis as many of the data were non-normally distributed and could not be adequately corrected by transformation. Despite these limitations, this study contributes significantly to our knowledge of the natural history of cystic fibrosis related low BMD and furthers our understanding of its aetiology.

The results of this study suggest several possible therapeutic approaches to the management of low BMD in patients with cystic fibrosis. General measures to improve the situation include weight gain, participation in regular weight bearing exercise, limiting oral corticosteroid use, and the aggressive control of pulmonary infection. Hormone replacement therapy should be offered to patients with delayed puberty or hypogonadism. In patients with suboptimal 25-hydroxyvitamin D levels (in whom adherence with vitamin D supplements is considered maximal), greater solar exposure and increased levels of vitamin D supplementation are advisable. Dietary calcium intake should also be assessed, taking into account that calcium is malabsorbed from the gastrointestinal tract. Finally, bisphosphonate therapy may be indicated in patients who lose bone despite implementation of these measures.7–20,35 Future research should evaluate interventions aimed at increasing peak bone mass in adolescents and young adults with cystic fibrosis and preventing bone loss thereafter.

In conclusion, reduced rates of bone accretion and accelerated rates of bone loss explain the high prevalence of low BMD in adult patients with cystic fibrosis. Reductions in BMD were primarily associated with high levels of bone turnover, advanced cystic fibrosis disease, oral corticosteroid therapy, and vitamin D insufficiency.

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References


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