

## Original articles

## Bone mineral density and body composition in adult patients with cystic fibrosis

A B Grey, R W Ames, R D Matthews, I R Reid

**Abstract**

**Background**—Cystic fibrosis is a multi-system disease characterised by chronic pulmonary sepsis and malnutrition. To ascertain whether osteoporosis is a feature of cystic fibrosis in adult patients, total body and regional bone mineral density (BMD) was measured in a group of eight men and eight women aged 17–42 years.

**Methods**—Total body and regional BMD (lumbar spine L2–L4, femoral neck, trochanteric, and Ward's triangle), as well as total body fat and lean mass, were measured by dual energy x ray absorptiometry. A range of biochemical, lifestyle, and anthropometric variables was also assessed.

**Results**—Patients with cystic fibrosis had significantly reduced bone density at all sites compared with normal young adults. The mean reductions ranged from 7% at Ward's triangle to 13% at the trochanter. Body mass index (BMI) was positively correlated with BMD at four sites and disease severity negatively correlated with BMD at two sites. Other biochemical and anthropometric variables were not predictive of bone density. Total body fat mass was reduced by 30% compared with normal young adults.

**Conclusions**—Bone density is decreased in adult patients with cystic fibrosis and BMI and disease severity are independent predictors of bone density.

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There is potential for decreased bone mineral density (BMD) in patients with cystic fibrosis as a result of the vitamin and mineral malabsorption, hypogonadism, malnutrition, and relative inactivity which characterise the disease. Previous studies to assess bone mass in patients with cystic fibrosis have produced conflicting results. Three studies have been undertaken using single photon absorptiometry. Normal metacarpal bone mineral content was found in a group of 18 patients aged 6–18 years.<sup>1</sup> Distal forearm bone mineral content was normal in six patients under the age of 10 years but the same authors found that 60% of subjects over the age of 15 years exhibited reduced bone mineral content at

the same site.<sup>2</sup> In this group of adolescents the reduction in bone mass correlated with the degree of observed weight reduction. The only published study on bone mass in adult patients with cystic fibrosis reported a 14% reduction in distal forearm bone mineral content in 21 subjects of average age 21 years.<sup>3</sup>

More recently Gibbens *et al* used quantitative computed tomography to compare the lumbar spinal BMD of a predominantly paediatric population of patients with cystic fibrosis (average age 12 years) with that of age matched, normal controls.<sup>4</sup> In addition to a 10% reduction in spinal BMD, they found that disease severity as measured by the Schwachman scoring system and poor nutritional state as assessed by anthropometric measurements (skin thickness, forearm circumference) correlated with BMD.

Improvements in the standard of care of patients with cystic fibrosis have resulted in a progressively increasing life expectancy and median survival is now well into the third decade.<sup>5</sup> It is likely that this trend will continue. If the osteopenia found in children with cystic fibrosis is confirmed in the adult population, morbidity from osteoporotic fractures is a potential consequence. The present study was therefore carried out to determine whether osteopenia occurs in adults with cystic fibrosis, and to delineate clinical and biochemical predictors of BMD.

**Methods****PATIENTS**

Of the 22 patients attending the adult cystic fibrosis clinic at Auckland Hospital, 16 (eight men, eight women) agreed to participate in the study. All were white and were aged 17–42 years. Cystic fibrosis had been diagnosed in each subject by the presence of abnormally increased electrolyte levels in sweat by pilocarpine iontophoresis. Pulmonary colonisation by *Pseudomonas aeruginosa* was present in 15 subjects. Mean forced expiratory volume in one second was 65% of predicted (range 35–100%). None of the subjects had a major systemic disease other than cystic fibrosis. None was taking corticosteroids, thiazide diuretics, anticonvulsants, or calcium preparations at the time of entry into the study. None of the men was taking sex hormones but two of the women were taking oestrogen containing contracep-

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tive pills. Two men and two women were taking calciferol in doses ranging from 1 to 40 µg per day. One man was taking 1 µg 1α-hydroxyvitamin D (α-hydroxycalciferol) daily.

#### CONTROLS

Body composition and BMD data in the patients were compared with those of 65 normal young adults (42 men, 23 women) of similar age and height. It has recently been shown that the BMD of postpubertal adolescents is within the normal young adult range.<sup>6</sup>

#### BONE DENSITY MEASUREMENTS

Total body BMD and BMD at the lumbar spine (L2–L4), femoral neck, Ward's triangle, and trochanter, as well as total body fat and lean mass, were measured by dual energy x ray absorptiometry with a Lunar DPX scanner (Lunar, Madison, Wisconsin). This technique has previously been described<sup>7</sup> and measures BMD, fat mass, and lean mass from the relative attenuation of two energies of x rays which are absorbed differently by the various tissues. The precision (coefficient of variances) of these measurements in our laboratory is 0.4% for total body BMD, 1.0% for lumbar spinal BMD, 1.4% for femoral neck BMD, 2.7% for fat mass, and 0.8% for lean mass. All scans were performed and analysed by one operator (RA).

#### CLINICAL ASSESSMENT

##### *Disease severity*

The NIH prognostic scoring system,<sup>8</sup> based on respiratory, nutritional, activity, and attitudinal aspects of the disease, was applied by the same investigator (AG) to each subject. Compared with earlier assessment procedures, this system places increased emphasis on the pulmonary aspects of the disease. The score has a maximum of 100 (75 for pulmonary factors and 25 for nutritional and general factors) with a higher score indicating more severe disease. All the radiological scoring was carried out by one radiologist (RM).

##### *Physical activity*

A validated seven day physical activity recall questionnaire was administered to each subject.<sup>9</sup> This provided an assessment of the amount of time spent in all physical activities.

The energy expenditure used in each type of activity had previously been determined,<sup>9</sup> and total energy expenditure could thus be calculated from the sum of the products of the time spent in each activity and its metabolic cost.

##### *Calcium intake*

Calcium intake was assessed by a previously described dietary recall questionnaire, modified for local requirements.<sup>10</sup>

##### *Physical examination*

Tanner pubertal staging was performed.<sup>11</sup> Clinical evidence of osteomalacia and chronic liver disease was sought and a respiratory examination performed. Body mass index (BMI = weight/height<sup>2</sup>) was calculated.

##### *Radiology*

Anteroposterior and lateral chest radiographs were taken for each subject at the same time as the densitometry was performed. The lateral films were examined for evidence of thoracic vertebral wedging. Anterior and posterior vertebral heights were measured and the difference expressed as a percentage of the latter.

#### BIOCHEMICAL DATA

All specimens were collected after an overnight fast.

##### *Serum*

The levels of calcium, phosphate, alkaline phosphatase, albumin, and liver enzymes in the serum were measured by an Hitachi 737 autoanalyser. Intact parathyroid hormone levels were measured by two site immunoradiometric assay (Nichols Institute, San Juan Capistrano, California); 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D by competitive protein binding assay (Nichols Institute, San Juan Capistrano, California); insulin-like growth factor 1 (IGF-1) by an acid ethanol cryoprecipitate method; vitamins A and E by hexane extraction high pressure liquid chromatography; oestradiol by radioimmunoassay; and testosterone by a commercially supplied direct radioimmunoassay (Coat-A-Count, Diagnostic Products, Los Angeles, California). The coefficients of variation for the hormone assays were 8% for parathyroid hormone, 11% for 25-hydroxyvitamin D and

Table 1 Mean (SD) population characteristics of study groups

	Patients			Controls		
	Men (n = 8)	Women (n = 8)	Total (n = 16)	Men (n = 42)	Women (n = 23)	Total (n = 65)
Age (years)	26 (8)	21 (7)	23 (8)	27 (7)	24 (4)	26 (6)
Weight (kg)	60 (9)**	56 (8)*	58 (8)**	78 (9)	62 (7)	72 (12)
Height (m)	1.75 (0.06)	1.64 (0.08)	1.69 (0.09)	1.76 (0.07)	1.66 (0.06)	1.72 (0.07)
BMI (kg/m <sup>2</sup> )	20 (2)**	21 (1)*	20 (2)**	25 (3)	24 (4)	25 (4)
Disease severity (max 100)	43 (17)	25 (11)	34 (17)			
Calcium intake (mg/day)	650 (305)	600 (373)	625 (330)			
Energy expenditure (kcal/kg/day)	38 (7)	39 (4)	39 (6)			

\*p < 0.05 v controls; \*\*p < 0.001 v controls.  
BMI—body mass index.

1,25-dihydroxyvitamin D, 9% for IGF-1, 10% for vitamins A and E, 10% for testosterone, and 15% for oestradiol.

#### Urine

Hydroxyproline levels were measured in two hour second-voided samples of urine in 10 subjects and expressed as a ratio to creatinine. Twenty four hour urinary calcium excretion was measured in 12 subjects on an unrestricted diet.

#### STATISTICAL ANALYSIS

Total body BMD and BMD values at each individual site were expressed as a percentage of the mean normal value and the difference of the patients' values from 100 assessed by the Student's *t* test. This process was repeated after adjustment for body weight. Relationships between variables were assessed with Pearson correlation coefficients. Multiple regression analysis was performed, with BMD as the dependent variable, when significant correlations were found between more than one variable and BMD at any site.

The study was approved by the Auckland Area Health Board Ethics Committee. Written informed consent was obtained from each subject.

#### Results

Table 1 records the population characteristics of the subjects with cystic fibrosis and controls. The men with cystic fibrosis were, on average, 5 years older than the women, which may explain the greater disease severity in this group ( $p = 0.02$  men *v* women). The patients with cystic fibrosis were relatively lean, as evidenced by a mean BMI of 20 kg/m<sup>2</sup>, and significantly lighter than the controls. Mean dietary calcium intake was modest at 625

mg/day.

All subjects were Tanner pubertal stage 5. One man and four women had sex hormone levels below the lower limit of the normal range. Two women were oligomenorrhoeic, one of whom had a subnormal oestradiol level. One man and one woman had clinical evidence of hepatic cirrhosis and portal hypertension. Both had longstanding abnormalities of liver function tests and ultrasonographic evidence of hepatic fibrosis, splenomegaly, and oesophageal varices. None of the subjects had suffered fractures, either spontaneously or as a result of minor trauma. None had symptoms or clinical evidence of osteomalacia.

Figure 1 illustrates total body BMD and BMD values at each site expressed as a percentage of mean normal young adult values. At each site the mean BMD of the subjects with cystic fibrosis was significantly lower than the corresponding mean of young normals. Mean reduction in total body BMD of the patients with cystic fibrosis was 10.5% ( $p < 0.001$ ). At the individual sites assessed, BMD in the study group was reduced by 12.5% at the lumbar spine ( $p < 0.001$ ), by 11.1% at the femoral neck ( $p < 0.001$ ), by 13% at the trochanter ( $p < 0.001$ ), and by 7% at Ward's triangle ( $p = 0.02$ ). The reductions in femoral neck and trochanteric BMD values were significantly greater in male than female subjects with cystic fibrosis ( $p < 0.01$  for both sites).

Figure 2 shows total body fat and lean mass expressed as a percentage of normal young adult values. Fat mass was reduced by 30% in the group as a whole ( $p < 0.001$ ), with the difference being greater in the men (mean reduction 41%) than in the women (mean reduction 19%). Lean mass was also

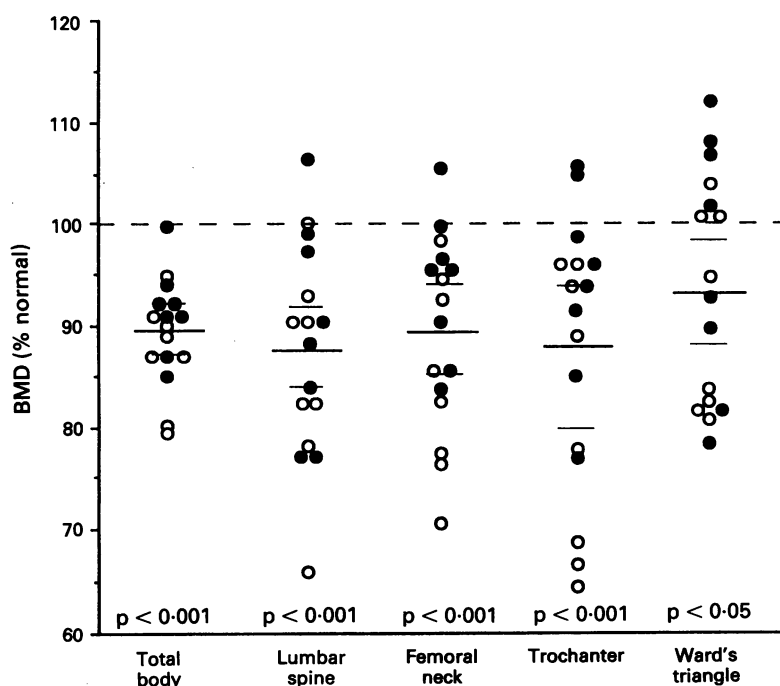


Figure 1 Plot of total body BMD and BMD values at individual sites expressed as a percentage of the normal young adult mean values for male (○) and female (●) patients with cystic fibrosis. Mean (SD) values are shown by the solid horizontal lines.

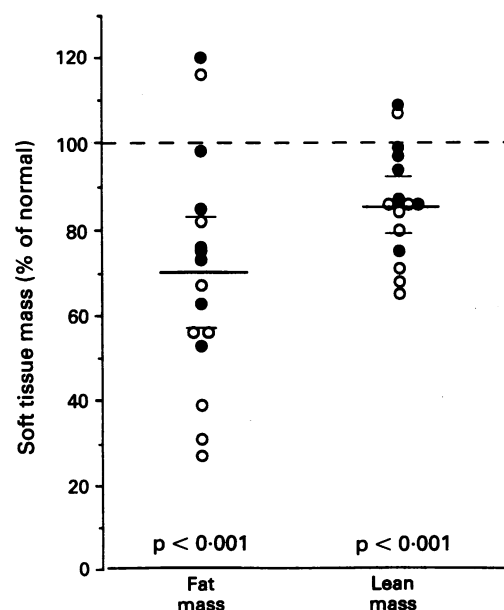


Figure 2 Fat and lean body mass of male (○) and female (●) patients with cystic fibrosis expressed as a percentage of normal young adult mean values. Mean (SD) values are indicated by the solid horizontal lines.

**Table 2** Mean (SD) calcium and calcium related biochemical results in patients with cystic fibrosis

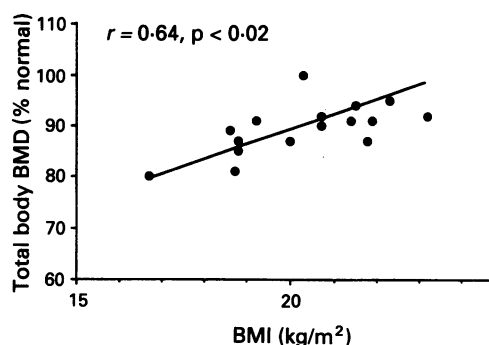
	Patients with cystic fibrosis	Normal range
<b>Serum</b>		
Total calcium (mmol/l)	2.33 (0.07)	2.10–2.55
Ionised calcium (mmol/l)	1.24 (0.03)	1.17–1.28
Parathyroid hormone (pmol/l)	2.5 (1.1)	1–5
25-hydroxyvitamin D ( $\mu$ g/l)	18.0 (7.4)	14–76
1,25-dihydroxyvitamin D (ng/l)	43.3 (12)	18–62
<b>Urine</b>		
24 hour calcium (mmol/day)	3.66 (2.2)	2.5–7.5
Hydroxyproline/creatinine ( $\mu$ mol/mmol)	36 (19)	< 30

lower in the patients with cystic fibrosis than in normal subjects (mean reduction 14%,  $p < 0.001$ ).

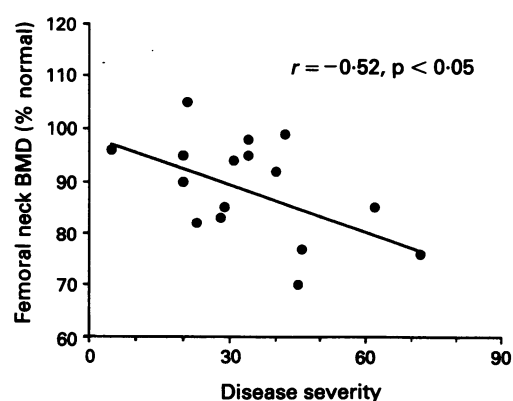
Table 2 details results of calcium and calcitropic hormone measurements performed in the patients with cystic fibrosis. Five had levels of 25-hydroxyvitamin D below the normal adult range; none had serum calcium or parathyroid hormone levels outside the normal range. Urinary hydroxyproline excretion (range 36–60  $\mu$ mol/mmol creatinine) was raised in 50% of the patients. Vitamin A and E levels were normal in 15 of the 16 subjects with cystic fibrosis.

Correlation coefficients were calculated between percentage normal BMD at each site and a number of lifestyle, anthropometric, and biochemical variables. BMI correlated positively with total body BMD ( $r = 0.64$ ,  $p < 0.02$ ; fig 3) and with BMD at the three femoral sites (femoral neck  $r = 0.56$ ,  $p < 0.05$ ; trochanter  $r = 0.64$ ,  $p < 0.02$ ; and Ward's triangle  $r = 0.51$ ,  $p < 0.05$ ). Disease

**Figure 3** Total body BMD of patients with cystic fibrosis expressed as a percentage of the normal young adult mean value plotted against body mass index (BMI).



**Figure 4** Femoral neck BMD of patients with cystic fibrosis expressed as a percentage of the normal young adult mean value plotted against disease severity.



severity correlated inversely with BMD at the femoral neck ( $r = -0.52$ ,  $p < 0.05$ ; fig 4) and trochanter ( $r = -0.57$ ,  $p < 0.05$ ). Multiple regression analyses were performed with BMI and disease severity as the independent variables, and either trochanteric or femoral neck BMD as the dependent variable. At each site the regression was significant ( $p < 0.01$  and  $p < 0.05$  for trochanter and femoral neck, respectively) and the two independent variables had a similar influence on BMD.

Other postulated influences on BMD such as dietary calcium intake and physical activity were not correlated with BMD. Adjustment of BMD for body weight resulted in serum albumin being significantly correlated with BMD at the lumbar spine ( $r = 0.54$ ,  $p < 0.05$ ) and Ward's triangle ( $r = 0.52$ ,  $p < 0.05$ ), but did not reveal any other significant associations.

Review of lateral chest radiographs of the subjects with cystic fibrosis revealed that 31% (five of 16) exhibited greater than 20% wedging of at least one thoracic vertebra. Four of these five subjects had a spinal BMD value more than one standard deviation below the mean for normal young adults.

## Discussion

This study has shown that adult patients with cystic fibrosis have reduced bone density at all the sites assessed, 69% and 44% of the subjects having reductions of greater than one standard deviation in spinal and femoral neck BMD, respectively. Individual site reduction of BMD of one standard deviation confers a relative risk of fracture of 2.2 at the lumbar spine,<sup>12</sup> and an estimated 30% lifetime risk of femoral neck fracture.<sup>13</sup> Reduction of spinal and femoral neck BMD of greater than two standard deviations was seen in 38% and 19% of the patients respectively, placing these individuals at substantially greater risk of fracture.

BMI correlated positively, and disease severity correlated negatively, with BMD. The positive relationship with BMI is consistent with the findings of Gibbens *et al* who reported that skinfold thickness and forearm circumference were predictive of spinal BMD in children with cystic fibrosis.<sup>4</sup> Body weight has previously been shown to be closely related to BMD in normal men<sup>14</sup> and women.<sup>15</sup> The negative effect of disease severity may in part be mediated by its effects on body weight, as chronic severe pulmonary and pancreatic disease leads to greater degrees of malnutrition. Multiple regression analysis, however, suggested that disease severity and BMI had independent influences on BMD. It is possible that cytokines produced in response to persisting sepsis may account for the influence of disease severity. Levels of tumour necrosis factor  $\alpha$ , which increases bone resorption,<sup>16</sup> are persistently raised in patients with cystic fibrosis, perhaps generated in response to pulmonary colonisation by *Pseudomonas aeruginosa*.<sup>17</sup>

Several other potential mechanisms for the

osteopenia in these patients were not supported by the correlation analyses reported herein. Delayed attainment of adult levels of sex hormones has been reported in cystic fibrosis,<sup>18</sup> and sex hormone deficiency is known to be associated with reduced trabecular and cortical bone mass in both young women<sup>19</sup> and young men.<sup>20</sup> We found no relationship between sex hormone levels and BMD in the patients with cystic fibrosis. The reduction in spinal BMD in children with cystic fibrosis also suggests that factors other than sex hormones are important.<sup>4</sup> We found lowered 25-hydroxyvitamin D levels in these patients, as have others,<sup>13</sup> but there was no correlation between levels of this vitamin D metabolite and BMD. Serum calcium levels have been noted to be lower, and immunoreactive parathyroid hormone levels higher, in patients with cystic fibrosis than in normal subjects,<sup>3</sup> leading to speculation that such abnormalities may contribute to the reduced bone mass of patients with cystic fibrosis. These indices were, however, normal in our subjects.

The clinical significance of these findings remains to be determined. Osteopenia and the resulting vertebral deformities are likely to contribute to the back pain which has been reported in 94% of patients with cystic fibrosis and which interferes with their work, exercise, coughing, and chest physiotherapy.<sup>21</sup> Limitations of physiotherapy techniques are known potentially to compromise respiratory function.<sup>22</sup> Osteoporosis is also a common complication of organ transplantation<sup>23-26</sup> and pre-existing bone disease may render patients with cystic fibrosis undergoing lung transplantation at a significantly higher risk of fractures.

At present therapeutic modalities for young adults with osteoporosis are limited, but new agents, particularly the expanding bisphosphonate class of drugs, show promise in its treatment.<sup>27</sup> As more patients with cystic fibrosis live into the third decade and beyond, with or without organ transplantation, the assessment and treatment of osteoporosis may need to become an integral part of the management of this multisystem disease.

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