Archives of Disease in Childhood 1996; **74**: 314–318

Bone mineral content in cystic fibrosis patients: correlation with fat-free mass

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Abstract

***Objective*—To assess the bone mineral content in well nourished patients with cystic fibrosis and to seek a correlation with fat-free mass.**

***Methods*—Fourteen cystic fibrosis patients aged 6 to 20 years were studied and compared to 14 healthy controls matched for gender, age, and nutritional status. Bone mineral content was determined by dual energy *x* ray absorptiometry (DEXA).**

***Results*—Nutritional inquiry showed higher ingestion of macronutrients and micronutrients by cystic fibrosis patients than by controls. Mean whole skeleton bone mineral content was 1·184 (SD 0·536) kg in cystic fibrosis patients and 1·229 (0·576) kg in controls (p=0·84). Mean lumbar spine bone mineral content was 0·031 (0·013) kg and 0·031 (0·016) kg, respectively (p=0·99). Anthropometry, bioelectrical impedance analysis, and DEXA showed that fat-free mass was similar in the two groups. Bone mineral content was strongly correlated to fat-free mass. Mean blood calcium, phosphorus, serum 25-hydroxyvitamin D (25-OHD), parathyroid hormone (PTH), and osteocalcin were similar in both groups.**

***Conclusions*—Bone mineral content and body composition are normal in a well nourished young cystic fibrosis population. Osteopenia previously reported in cystic fibrosis patients probably has nutritional origins and is therefore not related to a primary defect in bone mineral metabolism.**

(*Arch Dis Child* 1996; **74**: 314–318)

Keywords: cystic fibrosis, bone, nutrition.

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Accepted 16 January 1996

The prognosis of cystic fibrosis patients has improved greatly in recent decades. As the mean survival time is now 30 years,[1] the incidence of new medical problems has been increasing. Those related to protein-energy malnutrition are particularly compelling because they have an impact on the long term prognosis. Body composition in cystic fibrosis patients differs from that in healthy controls[2 3] and both demineralisation and osteoporosis have been reported in cystic fibrosis patients.[4–6] Whether this is a result of protein-energy malnutrition or is due to an isolated calcium-vitamin D metabolic disorder remains unclear. It might also be due to lack of weight bearing physical activity brought on by general deterioration in health in cystic fibrosis patients, especially in adults. In healthy subjects, peak bone mass is reached at the end of the growth spurt[7 8] and bone mineral content in adulthood depends more on peak bone mass than on subsequent mineral loss.[9] As cystic fibrosis patients enjoy longer lives, assessment of their bone mineralisation during childhood and adolescence is important for the eventual prevention of osteopenia.

In this study we investigated whether cystic fibrosis patients have a primary defect in bone mineral and vitamin D metabolism independent of protein-energy malnutrition. We also examined the relations between the bone mineral content, fat-free mass, and indices of bone mineralisation in well nourished patients with cystic fibrosis.

Methods

SUBJECTS

Fourteen well nourished (weight for height ratio 0·85 or above) cystic fibrosis patients (four females, 10 males), 6·6 to 19·9 years old, were recruited from our cystic fibrosis outpatient clinic. All but two received enteric coated microspheres of pancreatic enzymes and multivitamin supplements providing at least 500 IU of vitamin D daily. Seven were on a polymeric liquid formula as a dietary supplement. The most common cystic fibrosis mutations (DF508, 3905insT, G542X, R553X, G551D, 1717-1G-A) were looked for. The severity of cystic fibrosis disease was evaluated by the Shwachman-Kulczycki score (possible scores range from 0 to 100, the lowest being the worst),[10] and pulmonary *x* ray lesions by the Chrispin-Norman score (possible scores range from 0 to 38, the highest being the worst).[11] Pubertal stage was determined using the Tanner score.[12] Patients with clinical heart failure or oedema, and those receiving insulin, corticosteroids, thiazides, anticonvulsants, and other drugs affecting bone were excluded.

Fourteen healthy subjects were recruited as controls by cystic fibrosis patients among their schoolmates or friends. They were matched one to one for gender, age, and height. They underwent exactly the same procedure as cystic fibrosis patients except that no chest radiography was done.

Energy, protein, calcium, phosphorus, and vitamin D intakes were estimated by a 72 hour recall.[13–15]

All cystic fibrosis patients and controls lived in Switzerland (latitude of 46° north), a country with a mean of 1800 hours of sunlight per year.

Informed consent was obtained from each subject and from parents when the subject was a minor. The study was approved by the ethics committee of the Faculty of Medicine of Lausanne. The procedures followed were in accordance with the Helsinski Declaration of 1975, as revised in 1983.

BODY COMPOSITION AND BONE MINERAL CONTENT

Weight and height were measured using standard techniques. Weight for height ratio, which is the ratio between the actual weight of the studied subject and the theoretical weight of an 'ideal' person of the same height, was calculated.[16] Fat-free mass was assessed by anthropometry,[16 17] bioelectrical impedance analysis,[18–20] and dual energy *x* ray absorptiometry (Hologic QDR 2000).[21] Bone age was determined according to Greulich and Pyle.[22] Bone mineral content of the whole skeleton and of the lumbar spine (L1-L4) were evaluated by DEXA.

LABORATORY DETERMINATIONS

Plasma calcium and phosphorus, and urinary calcium, creatinine, and hydroxyproline were measured by standard methods. Serum 25-OHD was determined by a protein binding assay (25-hydroxyvitamin D [^{3}H] assay system, code TRK 860, Amersham International), serum PTH by a radioisotopic assay (INTACT PTH parathyroid hormone 100T-kit; catalogue No 40-2170, Nichols Institute), and serum osteocalcin by immunoradiometric assay (ELSA-OSTEO, CIS Bio International). Molar calcium/creatinine and hydroxyproline/creatinine ratios were calculated in the morning urine.

STATISTICAL ANALYSIS

After a test for normality of distribution, unpaired *t* tests and Mann-Whitney U tests were used to compare the two groups of subjects. Standard linear regression analysis was used to relate bone mineral content to age and fat-free mass. An analysis of variance was used to compare the slopes of the regression lines obtained from the two groups. Results are given as mean (SD) and 95% confidence intervals. A probability value of less than 0.05 was considered significant.

Results

Cystic fibrosis patients and controls were similar for age, bone age, pubertal stage, weight, height, and weight for height ratio (table 1).

Six cystic fibrosis patients were homozygotes and five were heterozygotes for the mutation F508. One patient had none of the mutations tested for. Controls were not carriers for these mutations. Mean Shwachman-Kulczycki and Crispin-Norman scores of 76 (range 55 to 90) and 9 (range 4 to 24), respectively, suggested that the patients were not severely affected (table 2).

The 72 hour dietary recalls showed that cystic fibrosis patients ingested significantly more energy, protein, calcium, phosphorus, and vitamin D than controls (table 3).

Mean fat-free mass did not differ between cystic fibrosis patients and controls, whether assessed by skinfold thickness [30·9 (SD 10·6) kg and 31·4 (10·8) kg, respectively], bioelectrical impedance analysis [28·2 (9·4) kg and 28·4 (9·9) kg, respectively], or DEXA [30·2 (10·7) kg and 29·7 (10·8) kg, respectively]. Fat-free mass measured by skinfold thickness and DEXA were highly correlated for both cystic fibrosis patients [FFM_{DEXA} (kg) = 1·01*$FFM_{skinfold}$ (kg) − 0.96, r^2 = 0.99, $p < 0.001$] and controls [FFM_{DEXA} (kg) = 0·95*$FFM_{skinfold}$ (kg) − 0·10, r^2 = 0·91, $p < 0.001$]. Fat-free mass measured by bioelectrical impedance analysis gave lower results in both groups by comparison with the two other methods ($p < 0.05$). Fat-free mass values measured by bioelectrical impedance (BIA) and DEXA were also highly correlated in cystic fibrosis patients [FFM_{DEXA}

Table 1 Gender, age, bone age, pubertal stage, and anthropometric characteristics of subjects (cystic fibrosis/control)

Pair	Gender	Age (years)	Bone age (years)	Pubertal stage*	Weight (kg)	Height (m)	Weight for height ratio†
1	M/M	9·1/9·8	12·5/10·0	P3/P1	30·4/26·4	1·40/1·31	0·96/0·97
2	M/M	11·1/10·2	9·0/8·5	P1/P1	29·0/28·9	1·39/1·35	0·92/0·99
3	M/M	6·6/7·4	5·0/4·5	P1/P1	21·8/19·0	1·20/1·13	0·97/0·96
4	M/M	19·9/20·5	18·0/20·5	P5/P5	60·8/56·9	1·76/1·71	0·85/0·86
5	F/F	17·3/17·0	17·0/17·0	P5/P5	56·2/56·6	1·67/1·69	0·99/0·97
6	M/M	16·5/16·8	16·0/17·0	P4/P4	55·4/58·8	1·75/1·72	0·90/0·97
7	M/M	11·6/11·3	11·0/11·0	P1/P1	32·3/38·8	1·40/1·42	1·00/1·16
8	F/F	11·9/11·6	10·0/ND	P2/P2	37·3/31·2	1·50/1·43	0·93/0·85
9	F/F	11·8/11·9	12·0/11·0	P3/P2	35·2/35·0	1·47/1·47	0·93/0·92
10	F/F	12·8/12·5	11·0/12·0	P3/P3	34·7/42·4	1·46/1·46	0·91/1·12
11	M/M	10·6/10·5	9·0/10·0	P1/P1	30·9/31·7	1·39/1·44	0·98/0·91
12	F/F	9·4/10·6	9·0/10·0	P1/P2	26·4/28·1	1·36/1·39	0·87/0·86
13	M/M	11·5/11·3	12·5/11·0	P1/P1	37·4/34·1	1·47/1·44	1·02/0·97
14	M/M	10·2/10·3	9·0/9·0	P1/P1	25·6/27·3	1·31/1·35	0·94/0·93
Mean		12·2/12·3	11·5/11·7		36·7/36·8	1·47/1·45	0·94/0·96
SD		3.5/3·5	3·6/4·2		12·1/12·5	0·16/0·16	0·05/0·09
CI		10·2–14·2/ 10·0–14·0	9·4–13·6/ 9·2–14·2		29·7–43·7/ 29·6–44·0	1·38–1·56/ 1·36–1·54	0·91–0·97/ 0·91–1·01
p‡		0·94	0·92		1·00	0·80	0·60

ND=not done; CI=95% confidence interval.
*Pubertal stage according to Tanner (reference 12).
†Weight for height ratio according to Jelliffe (reference 16).
‡Cystic fibrosis group *v* control group.

Table 2 Mutations and disease status in cystic fibrosis (CF) patients

CF patients	Mutations		Shwachman-Kulczycki score*	Crispin-Norman score†
1	ΔF 508	ΔF 508	80	19
2	G 542 X	–‡	75	12
3	ΔF 508	–	70	11
4	ΔF 508	G 542 X	65	11
5	–	–	90	5
6	ΔF 508	ΔF 508	80	4
7	ΔF 508	ΔF 508	80	5
8	ΔF 508	ΔF 508	85	6
9	ΔF 508	ΔF 508	80	9
10	ΔF 508	ΔF 508	75	4
11	R 553 X	3905insT	75	9
12	ΔF 508	3905insT	55	24
13	ΔF 508	3905insT	80	4
14	ΔF 508	3905insT	75	4
Mean			76	9
SD			9	6

*Severity of CF disease according to Shwachman and Kulczycki (reference 9).
†Severity of *x* ray pulmonary lesions according to Crispin and Norman (reference 10).
‡No usual mutation found.

Table 3 72 Hour nutrient intake investigation (cystic fibrosis/control)

Pair	Energy (kcal)	Protein (g)	Calcium (mg)	Phosphorus (mg)	Vitamin D* (IU)
1	3339/2147	132/67	1844/974	1888/1160	1332/82
2	2700/2220	126/60	1668/323	1703/805	658/33
3	2438/2593	85/81	1695/1167	1782/1395	982/61
4	ND/ND	ND/ND	ND/ND	ND/ND	ND/ND
5	2441/1918	84/60	887/392	1549/888	44/66
6	3000/2883	95/80	1469/1194	1773/1451	1072/64
7	2475/1446	114/54	1244/542	1744/1055	572/35
8	2424/1888	95/50	1432/1063	1580/1061	1061/77
9	2522/2223	89/72	1420/979	1372/1231	1017/52
10	2051/1991	82/69	554/390	1538/1226	942/146
11	ND/ND	ND/ND	ND/ND	ND/ND	ND/ND
12	2120/2028	94/56	1157/754	1317/1091	1117/50
13	3086/1795	116/49	2325/698	2342/765	1007/41
14	2566/2108	97/58	2167/813	2235/1134	994/54
Mean	2596/2103	101/63	1489/773	1735/1105	900/63
SD	380/370	17/11	502/310	309/212	334/30
CI	2355–2837/ 1868–2338	90–112/ 56–70	1170–1808/ 576–970	1539–1931/ 870–1340	688–1102/ 44–82
p†	<0·01	<0·0001	<0·0005	<0·0001	<0·0001

ND=not done; CI=95% confidence interval.
*For cystic fibrosis patients, from nutritional source and medication.
†Cystic fibrosis group *v* control group.

Table 4 Bone mineral content (BMC) of subjects (cystic fibrosis/control)

Pair	Whole skeleton BMC (kg)	Lumbar spine BMC (kg)
1	0·774/0·810	0·019/0·019
2	0·715/0·864	0·020/0·018
3	0·568/0·435	0·018/0·013
4	2·268/2·199	0·061/0·059
5	2·042/2·192	0·053/0·054
6	1·954/2·258	0·045/0·066
7	1·089/1·237	0·025/0·022
8	1·141/0·894	0·035/0·025
9	1·123/1·221	0·029/0·027
10	1·235/1·477	0·029/0·030
11	0·908/0·972	0·023/0·025
12	0·692/0·892	0·019/0·021
13	1·245/1·066	0·030/0·029
14	0·828/0·764	0·025/0·022
Mean	1·184/1·229	0·031/0·031
SD	0·536/0·576	0·013/0·016
CI	0·875–1·493/0·896–1·562	0·024–0·038/0·022–0·040
p*	0·84	0·99

CI=95% confidence interval.
*Cystic fibrosis group *v* control group.

(kg)=1·13*FFM_{BIA} (kg) −1·59, r^2=0·99, p<0.001] and in controls [FFM_{DEXA} (kg)= 1·08*fat-free $mass_{BIA}$ (kg) −1·02, r^2=0·99, p<0·001]. Whole skeleton and lumbar spine bone mineral content were not different from controls in cystic fibrosis patients (table 4). Bone mineral content was highly correlated with fat-free mass (fig 1, data shown only for whole skeleton bone mineral content) and the regression equations were not different among the two groups. Bone mineral content increased during growth spurt between pubertal stages P1-3 and P4-5 in both groups (fig 2).

Plasma concentrations of calcium, phosphorus, 25-OHD, PTH, and osteocalcin were similar in cystic fibrosis patients and in controls (table 5). Urinary calcium, hydroxyproline, calcium/creatinine ratio, and hydroxyproline/creatinine ratio were also similar (data not shown). Stratification according to gender did not provide more information.

Discussion

This study shows that bone mineral content of well nourished young cystic fibrosis patients is similar to healthy subjects matched for gender, age, and nutritional status. Our data do not support the suggestion that cystic fibrosis patients may have a primary defect in bone mineral and vitamin D metabolism.

We follow 21 cystic fibrosis children aged 6 to 20 years old in our outpatient clinic. To avoid a bias of selection, all but one (parental refusal) well nourished patients with a weight to height ratio of 85% or above were included in the present study. Three patients with protein-energy malnutrition, two with insulin dependent diabetes, and one receiving corticosteroids were not recruited.

Our results have not shown evidence of demineralisation and osteoporosis which has been reported in cystic fibrosis patients.[4–6] Unfortunately the nutritional status is not well described in these studies. As a whole, our cystic fibrosis patients were not undernourished and had a normal body composition.

Protein-energy malnutrition and growth delay are common features of cystic fibrosis.[23 24] The major cause is an energy intake which corresponds to 80% of the US recommended dietary allowance.[25] The good nutritional status of our cystic fibrosis patients was undoubtedly related to their high protein-energy intake. They ingested about 25% more energy and about 30% more protein than controls. Their calcium, phosphorus, and total vitamin D intake was also much higher, though their dietary vitamin D intake was very low as there is no vitamin D fortification of milk in Switzerland. A single 72 hour dietary recall does not reflect nutritional intake over a period of many years. However, our cystic fibrosis patients are seen regularly by dieticians and are encouraged at each visit to

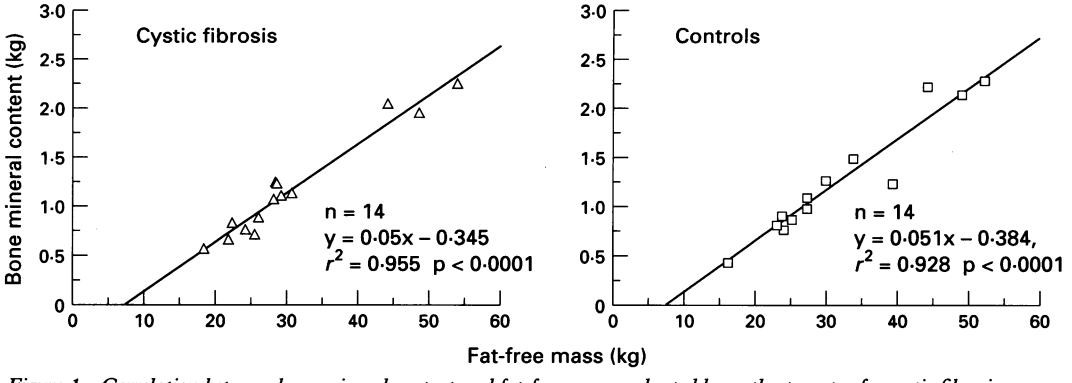

Figure 1 Correlation between bone mineral content and fat-free mass evaluated by anthropometry for cystic fibrosis patients and controls.

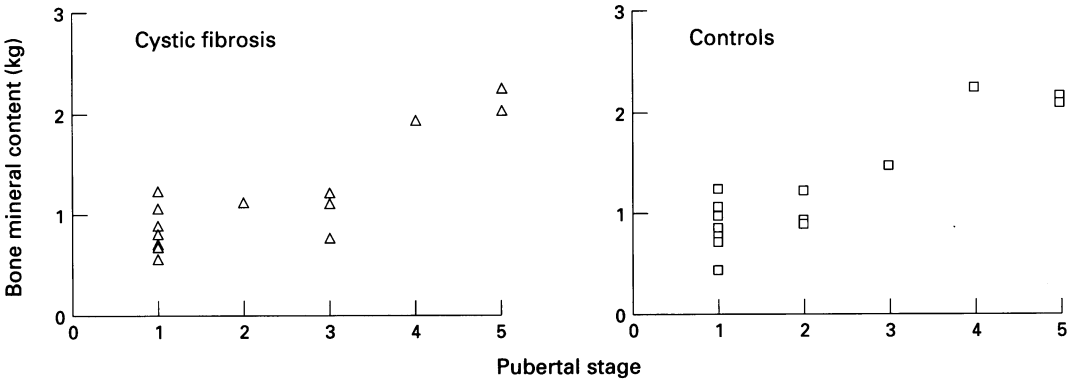

Figure 2 Bone mineral content related to pubertal stages for cystic fibrosis patients and controls.

increase their food intakes. None of our cystic fibrosis patients had manifest clinical malabsorption and all were highly compliant with pancreatic enzyme replacement therapy.

Dual energy *x* ray absorptiometry is now the gold standard reference method of measuring bone mineral content. Its major advantage is high precision by comparison with carcass analysis (<1%), good reproducibility (1%), and low irradiation (5 mrem).[26] DEXA also allows precise measurement of body composition.[21] However, in order to correlate bone mineral content with body composition, it is mandatory to use independent methods such as anthropometry and bioelectrical impedance analysis. For an unknown reason, fat-free mass measured by bioelectrical impedance is less than by anthropometry and DEXA. Consequently, we used fat-free mass measured by anthropometry to correlate bone mineral content with body composition. In our study whole skeleton and lumbar bone mineral content of cystic fibrosis patients were not different from those of healthy subjects according to age and pubertal stage. Strong and similar correlations were found between bone mineral content and fat-free mass in both groups.

Bone mineral content increases mainly in the late phases of puberty.[27 28] Our well nourished cystic fibrosis patients undergo a normal puberty, which in turn results in normal bone mineralisation. Physical activity is known to have a positive influence on lumbar mineralisation.[29] In a recent study, we have shown that our cystic fibrosis population has only slightly reduced spontaneous physical activity.[30] Serum 25-OHD depends on sunlight exposure and for this reason we measured the patients and their controls at the same time. The lowest value of serum 25-OHD was measured in cystic fibrosis patient number 7 in December. This may have been the result of faster depletion of reserves stocked in summer in cystic fibrosis patients than in controls.[31 32] No secondary hyperparathyroidism was observed, except perhaps in patient number 7. The protein turnover of bone seems to be similar in cystic fibrosis patients and controls, as suggested by identical levels of osteocalcin.

From our data we conclude that cystic fibrosis patients probably have no primary defect in bone mineral and vitamin D metabolism, and consequently a normal bone mineral content when they are not malnourished. A bone mass deficit in a particular cystic fibrosis patient reflects general malnutrition, as reported recently in adults.[33] A larger population has to be studied for a definitive answer.

Table 5 Laboratory indices of bone mineralisation (cystic fibrosis/control)

Pair	Calcium (mmol/l)	Phosphorus (mmol/l)	25 OH-vitamin D (nmol/l)	PTH (pg/ml)	Osteocalcin (ng/ml)
1	2·30/2·39	1·2/1·5	73·9/93·6	18/29	49·8/82·3
2	2·60/2·37	1·6/1·4	78·1/71·9	7/20	53·5/91·6
3	2·36/2·43	1·7/1·4	196·2/153·0	16/8	47·8/58·8
4	2·46/2·23	1·3/1·1	70·4/86·4	19/28	35·2/23·5
5	2·23/2·21	1·1/1·4	82·4/70·4	21/23	44·4/33·8
6	2·40/2·43	1·4/1·3	51·9/107·8	28/12	82·1/102·5
7	2·39/2·37	1·5/1·5	18·2/67·9	62/30	69·0/82·6
8	2·48/2·36	1·5/1·4	64·4/118·3	25/7	94·1/74·9
9	2·40/2·39	1·5/1·5	72·9/116·8	31/27	80·1/76·3
10	2·33/2·34	1·2/1·7	92·4/101·3	12/39	92·9/142·5
11	2·56/ND	1·6/ND	52·4/ND	23/ND	64·1/ND
12	2·34/2·43	1·8/1·4	41·4/82·9	20/24	81·9/108
13	2·49/2·44	1·6/1·6	80·9/133·3	20/15	92·6/106·2
14	2·47/2·46	1·5/1·3	103·8/130·3	25/31	84·0/90·3
Mean	2·42/2·37	1·5/1·4	77·1/102·6	23/22	69·4/82·6
SD	0·10/0·08	0·2/0·1	40·6/26·8	13/10	20·1/31·4
CI	2·36–2·48/ 2·32–2·42	1·3–1·6/ 1·3–1·5	53·7–100·5/ 86·4–118·8	15–31/ 16–28	57·8–81·0/ 63·6–101·6
p*	0·24	0·55	0·67	0·85	0·20

PTH=parathyroid hormone; ND=not done; CI=95% confidence interval.
*Cystic fibrosis group *v* control group.

We thank Dr Francine Thonney for genetic screening; Dr Claude Roy for advices and manuscript corrections; Nicoletta Bianchi, dietetician, for nutritional inquiry; Anne-Françoise Jacquet for special laboratory analysis; Françoise Dubied for technical assistance; Philippe Frascarolo for statistical advice; and radiologic technologists for DEXA examination. This work was supported by the Swiss Society for Cystic Fibrosis.

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