ORIGINAL ARTICLES

The clinical impact of metabolic bone disease in coeliac disease

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Abstract

Bone mineral density was measured by dual energy *x* ray absorptiometry (DEXA) at the lumbar spine and femoral neck in 15 adults who had metabolic bone disease in association with coeliac disease (mean age at diagnosis 53.5 years, range 37 to 66). Results were expressed as a T score (the number of standard deviations by which patient's bone density differed from the sex matched young adult mean). Three patients had no skeletal symptoms and normal routine calcium biochemistry but severely reduced axial bone mineral density on DEXA. Eleven patients had symptomatic skeletal fractures, including fractures of proximal femur (3), vertebrae (4), and radius (6). Three patients had osteomalacia confirmed on bone biopsy, two of whom had characteristic biochemistry. Secondary and tertiary hyperparathyroidism were seen. Seventy five further patients (60 female) with coeliac disease (mean age 52.0 years, median duration of gluten-free diet 3.4 years) and 75 paired healthy age and sex matched controls were questioned on past fracture history. Patients with coeliac disease underwent detailed studies of calcium biochemistry, dietary intake, and bone mineral density. Sixteen had a past history of fractures ($\chi^2 = 10.7$, $p = 0.0004$, *v* controls), which were of typical osteoporotic type. Ten patients had fracture before diagnosis of coeliac disease and six after diagnosis. Patients who had a fracture were older (56.3 *v* 50.3 years, $p < 0.02$, Wilcoxon rank sum test) than those with no fracture. There was no significant difference in bone mineral density (z score −0.31 *v* −0.77), serum calcium (2.30 *v* 2.26 mmol/l), 25-hydroxyvitamin D (19.7 *v* 23.7 nmol/l), parathyroid hormone (2.6 *v* 3.1 pmol/l), or dietary calcium intake (1021.0 *v* 1033.0 mg/day) in patients with fracture compared with those without fracture. Metabolic bone disease is common in coeliac disease and is associated with premature osteoporotic fractures.

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Early studies of metabolic bone disease in coeliac disease showed that osteomalacia, tetany, and bone fracture can be the presenting symptoms of coeliac disease, especially when the malabsorption is florid.[1 2] Such severe malabsorption is rarely seen in modern clinical practice, and coeliac disease usually presents with mild nutritional deficiency, for example iron deficiency.[3]

There have now been several reports of reduced bone mineral density in adult coeliac disease.[4–12] These studies indicate that osteopenia is common in such patients, and the magnitude of the reduction in bone mineral density suggests that bone fractures are likely,[13] despite adequate treatment with a gluten-free diet. Although low bone mineral density is the major risk factor for fracture, there are no studies of fracture prevalence in coeliac disease. The value of bone mineral density measurements as a tool to predict fracture risk has been demonstrated in idiopathic or primary osteoporosis, with a twofold increase in risk for each standard deviation reduction in bone mineral density below the age and sex matched mean.[13] We report our clinical experience of both symptomatic and occult bone disease in patients with adult coeliac disease over a two year period in a district general hospital, and the results of a retrospective study of fracture occurrence in patients compared with age and sex matched controls.

Methods

Bone mineral density was measured by dual energy *x* ray absorptiometry (DEXA) at the lumbar spine and femoral neck using a Hologic QDR 1000 absorptiometer. The result for each patient at each site is expressed as the absolute bone mineral density (in g/cm^2 calcium hydroxyapatite) and as a T score (number of standard deviations by which patient's bone mineral density differs from the mean of a sex matched reference young adult population); 2.5 SD below that mean defines osteoporosis (T score < 2.5).[14] Bone biopsy was performed at the iliac crest, in two cases after tetracycline double labelling.[15]

PATIENTS

There were 15 index patients with coeliac disease complicated by significant metabolic bone disease (mean age at diagnosis 53.5 years, range 37 to 66). Eight had symptomatic metabolic bone disease at the time of presentation with coeliac disease, and in seven a reduction in bone mineral density was identified after the diagnosis of coeliac disease. Six patients had an iliac crest bone biopsy (including two who had

a tetracycline double labelled bone biopsy). Patients were observed in the context of a two year study of bone density in coeliac disease. All were currently attending our outpatient department for follow up of their coeliac disease, or were newly diagnosed during the study period.

An additional 75 patients (60 female) with coeliac disease (mean age 52.0 years, median duration of gluten-free diet 3.4 years) and 75 paired healthy age and sex matched controls (mean age 52.1 years) completed a questionnaire on past fracture history. The 75 index cases comprised patients with coeliac disease attending our gastroenterology outpatients department and also people with coeliac disease who were members of the local coeliac society and were invited to participate in the study (at the time of the study, 423 people with coeliac disease were registered with the local coeliac society). Patients with coeliac disease underwent detailed studies of calcium biochemistry, dietary intake, and bone mineral density, measured at the lumbar spine and expressed as a T score. The 75 controls were selected from a database of 137 normal adults (83 female), age range 21.6 to 79.1 years, who had had bone densitometry performed with the same scanner and had also completed a questionnaire on past fracture history. One unique control was selected for each patient, matched for sex and as closely as possible for age. We attempted to verify a reported history of fracture by reviewing previous case notes, but we could not obtain records dating back to the time of fracture in all cases.

Results

Clinical details of the 15 patients are shown in tables 1 and 2. In cases 1–8 bone disease was part of the presenting syndrome of coeliac disease.

FRACTURE HISTORY IN TREATED COELIAC DISEASE

Of the 75 patients studied, 16 (21%) had a past history of fracture. This was a significantly higher proportion ($\chi^2 = 10.7$, $p = 0.0004$) than the two controls (3%). The relative risk for history of fracture in patients with coeliac disease compared with the paired controls was 7.0. Patients had sustained Colle's, pelvic, tibial, and clavicular fractures. Ten patients had fracture before the diagnosis of coeliac disease and six after diagnosis. Fractures sustained before the diagnosis of coeliac disease occurred between 42 years and 1.6 years (median 18.2 years) before diagnosis. Fractures sustained after the diagnosis of coeliac disease occurred

Table 1 Clinical and laboratory features in 15 patients with bone disease in association with coeliac disease

Patient	*Sex*	*Age (years)*	*Skeletal abnormality*	*Phosphate (mmol/l)*	*Calcium (mmol/l)*	*Alkaline phosphatase (IU/l)*	*iPTH (IU/l)*	*25-OH vit D (IU/l)*	*Lumbar spine T score*
1	F	66	Bone pain; myopathy	1.06	2.25	289	143.0	2.8	−4.44
2	M	43	Fracture T 7	1.25	2.31	85	2.9	12	−2.6
3	F	57	Multiple vertebral fractures	0.97	2.18	126			−4.0
4	F	63	Colle's fracture; back pain; myopathy	0.58	2.65	1602	>1000		−0.7
5	F	61	Fractured neck of femur	0.85	2.26	82			−1.5
6	F	44	Fractured shaft of femur; Colle's fracture	1.22	2.17	99	17.5	6.9	−2.6
7	F	77	Fractured neck of femur	1.49	2.12	113			−2.8
8	F	35	Multiple spine fractures	1.4	2.02	114	5.3		−3.67
9	F	59	T 10 fracture	0.9	2.24	224			−4.7
10	F	42	Multiple fractures in childhood	1.05	2.45	87		13.3	−1.4
11	F	37	Asymptomatic, but severe osteoporosis	1.17	2.14	74	3	33	−3.2
12	F	38	Asymptomatic, but severe osteoporosis	0.96	2.59	42	1	35	−3.11
13	M	64	Colle's fracture	1.28	2.1	75	8.2	7.7	−3.43
14	F	54	Pathological fracture of radius	1.0	2.3	94		17	−3.17
15	F	55	Colle's fracture	1.3	2.16	78			−2.9

In patients 1–8, bone disease was part of the presenting syndrome of coeliac disease.
Normal ranges for laboratory values: phosphate, 0.8–1.5 mmol/l; calcium, 2.2–2.7 mmol/l; alkaline phosphatase, 21–92 IU/l; immunoreactive parathyroid hormone (iPTH), < 4.3 IU/l; 25-hydroxy vitamin D (25-OH vit D), 4–40 IU/l; T score, lumbar spine and femur, > –2.5.

Table 2 Additional clinical features in 15 patients with coeliac disease and metabolic bone disease

Patient	*Femur T score*	*% change spine/year*	*% change femur/year*	*Bone biopsy*	*Comments*	*Other abnormalities*
1	−3.1	21.3	15.7	Osteomalacia	Initially diagnosed as Paget's disease	MCV 114
2	−2.4	18.4	10.3	Osteomalacia		Iron deficiency
3	−4.6	11.9	6.1	Osteomalacia		Rheumatoid disease
4	1.8				Tertiary hyperparathyroidism	Parathyroid adenoma
5	−2.9					B-12 and folate deficiency
6	−3.2	−2	12.6	Normal		Iron deficiency
7	−3.2				Previous Colle's fracture	B-12 and folate deficiency
8	−4.15				Steroid and diet resistant coeliac disease	Iron, B-12, and folate deficiency
9	−2.08					B-12 and folate deficiency; diabetes
10	−0.2					Iron and folate deficiency
11	−3.6	0.9	4.9	Osteoporosis	Late menarche; early menopause	Macrocytosis
12	−3.48	1.1	4.2	Osteoporosis		Unresponsive iron deficiency
13	−2.2	7.7	8.0			Iron deficiency
14	−3.1	−0.9	−0.3		Failure to comply with gluten-free diet	Iron deficiency
15	−3.2	4.1	−5.4		BMD improved on cyclical etidronate	

BMD, bone mineral density; MCV, mean corpuscular volume.

between 0.8 and 6.5 years (median 4.6 years) after diagnosis. Patients who had a fracture were older (56.3 *v* 50.3 years, $p < 0.02$, Wilcoxon rank sum test) than those with no fracture. There was no significant difference ($p > 0.10$) in bone mineral density (T score −0.31 *v* −0.77), serum calcium (2.30 *v* 2.26 mmol/l), 25-hydroxyvitamin D (19.7 *v* 23.7 nmol/l), parathyroid hormone (2.6 *v* 3.1 pmol/l), or dietary calcium intake (1021.0 *v* 1033.0 mg/day) in patients with fracture compared with those without fracture.

Discussion

The mechanism of development of bone pathology in patients with untreated coeliac disease is not fully defined, but chronic negative calcium balance[16] caused by loss of villous surface area,[17] binding of calcium to fatty acids in the intestinal lumen,[18] and impairment of active intestinal calcium transport mechanisms because of depletion of calbindin from the enterocyte[19] are all potential factors. Secondary hyperparathyroidism may develop as a compensatory response to hypocalcaemia, and this will tend to cause increased bone resorption. Furthermore, the tendency of parathyroid hormone to reduce serum phosphate will decrease the calcium:phosphate product,[20] further diminishing one of the important driving forces for mineralisation of bone osteoid. The role of vitamin D deficiency in the metabolic bone disease of coeliac disease is also debated; it is not certain whether hypovitaminosis D contributes to the intestinal calcium malabsorption. It appears that mild deficiency can lead to so called pre-osteomalacia,[20] in which increased bone turnover caused by secondary hyperparathyroidism is associated with accelerated bone loss. More marked hypovitaminosis D leads to the accumulation of osteoid and the mineralisation defect characteristic of osteomalacia.

Case 1 presented with classical symptoms and signs of osteomalacia, complicated by secondary hyperparathyroidism, and showed an excellent response to gluten-free diet and oral calcitriol treatment. Osteomalacia, but without the additional factor of secondary hyperparathyroidism, was also present in cases 2 and 3. Again, serial bone density measurements showed major improvements in bone mineral density after treatment. Case 4 demonstrates the potency of a chronic negative calcium balance in stimulating the parathyroid glands, with the apparent development of an autonomous parathyroid adenoma in this patient.

Ten of the 15 patients had either forearm, vertebral, or proximal femoral fractures, the classic osteoporotic fractures. In four patients fractures occurred after they had started on a gluten-free diet. One of the principal risk factors for fracture at any given skeletal site is the bone mineral density at that site,[13] and it is the occurrence of potentially debilitating fractures resulting from minor injury in patients with coeliac disease that has led to concern over the effect of coeliac disease on bone density at sites of fracture risk. Screening with bone densitometry is helpful in detecting patients at risk of fracture,[21] and as shown in cases 6, 9, 14, and 15 the presence of severely reduced bone mineral density is associated with fracture at these sites. These patients are probably at the upper end of the coeliac disease fracture risk spectrum, but bone mineral density studies in coeliac disease suggest that as many as 40% of patients may have osteoporosis, with associated increased lifetime fracture risk.

Cases 11, 12, and 13 had no current symptoms of bone disease but there was severe reduction in bone mineral density and a potential increase in these individuals' lifetime risk of fracture. Bone density increased on treatment with gluten-free diet in all three of these cases. However, even after these increases, the density was still low compared with normal age and sex matched adult controls. In case 14, low bone mineral density was observed but it did not improve with treatment because of poor compliance with a gluten-free diet, and the patient went on to develop a pathological fracture.

In the case–control study we have shown for the first time that patients with coeliac disease are at increased risk of fracture. We did not find a strong correlation between the occurrence of fracture and low bone mineral density in this survey, and this suggests that—as in the general population—other determinants of fracture risk such as the incidence of trauma and bone quality may be additional predisposing factors in coeliac disease. Bone fracture was seven times as common in coeliac disease patients as in controls. We were surprised at the magnitude of the difference.

CONCLUSIONS

Metabolic bone disease remains a significant and common complication of coeliac disease. Osteomalacia may occur without clinical or biochemical abnormalities and in the absence of steatorrhoea. Bone densitometry is a sensitive test for reduced bone mass but will not determine the underlying bone pathology. However, significant osteomalacia can be present even with normal bone mineral density, serum calcium phosphate, and parathyroid hormone, and bone biopsy may be appropriate in some patients. Osteoporosis may be severe and yet remain occult until symptomatic fracture occurs. Treatment with a gluten-free diet can dramatically improve bone density, especially where there is osteomalacia, but it can also lead to improvement when osteoporosis is the underlying lesion.[22]

Maintenance of bone density may be one of the most compelling reasons for remaining on a gluten-free diet, especially in patients who have few symptoms on normal diet.

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