Bone disease after jejuno-ileal bypass for morbid obesity

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Summary

Fifteen patients who had undergone a 14 inches $\times$ 4 inches jejuno-ileal bypass operation for obesity, 3 to 4 years earlier, were investigated by iliac bone biopsy, radiology and routine biochemistry, including 25-hydroxy-vitamin D and parathyroid hormone estimations. Two patients had histological osteomalacia which was mild in one. A further 9 patients had abnormal bone biopsies, there being an excess of trabecular bone surface covered by osteoid with a normal or reduced amount of calcification front. Six of these 9 showed an increase in trabecular resorption, although in none were there excessive numbers of osteoclasts. The likely explanation for these findings is that these 9 patients had early osteomalacia with mild hyperparathyroidism, making a total of 11 patients out of 15 with osteomalacia. Radiology and blood chemistry were poor predictors of histological bone disease.

KEY WORDS: obesity, jejuno-ileal bypass, osteomalacia, hyperparathyroidism.

Introduction

Bypass of the small intestine is an established treatment for morbid obesity, more than 6000 operations having been reported by 1976 (Phillips, 1978). Although osteomalacia is a possible complication of this procedure, it was not systematically studied until 1978 when Compston *et al.* (1978) reported histological osteomalacia in 10 of 21 unselected patients who had undergone surgery at least 3 years earlier. This

unexpectedly high prevalence requires confirmation, for it implies that thousands of patients are at risk from metabolic bone disease.

Patients and methods

Patients

A standard end-to-side jejunal bypass operation, leaving 14 inches of jejunum and 4 inches of ileum in continuity (Payne and DeWind, 1969), had been performed on 20 patients between April 1974 and September 1975 (Mr B.P. Bliss) (Table 1). Fifteen agreed to be investigated. There were 11 women and 4 men, aged 31 to 64 years (mean 48 years). Pre-operative body weights ranged from 105 kg to 153 kg (mean 133 kg). Weight loss following the operation was 18 to 71 kg (mean 47 kg), and none had significant symptoms of bone pain or tenderness. Although all but one had diarrhoea, with a daily stool frequency of 3 to 20, 14 were delighted with the results of the operation. One patient (patient 11) was receiving oral treatment with 62 μ g of cholecalciferol and 64 mg of calcium daily; the remaining patients were on no therapy apart from anti-diarrhoeal agents.

Methods

Blood samples were taken for serum calcium, phosphorus and alkaline phosphatase. Plasma 25-OH-vitamin D was measured by a competitive protein-binding assay (Haddad and Chyu, 1971) and plasma parathyroid hormone by two methods, a sensitive bioassay (Chambers *et al.*, 1978; Fenton,

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TABLE 1. Details of the 15 patients. Plasma values given are those taken at the time the bone biopsy was done, with the exception of the plasma parathyroid hormone samples which were taken as a group 9 months later.

Patient	Age (years)	Sex	Initial weight (kg)	Weight loss (kg)	Stools (number per day)	Plasma						
						Calcium (mmol/l)	Phosphorus (mmol/l)	Alkaline phosphatase (KA units/100ml)	Albumin (g/l)	25-OH-vitamin D (nmol/l)	Parathyroid hormone (cytochemical) (pg/ml)	Parathyroid hormone (C-terminal) (µg Eq/ml)*
1	49	M	132	58	10	2.20	0.8	20	38	13	—	—
2	53	F	145	60	6	1.95	1.1	9	32	14	—	—
3	31	F	153	71	6-8	2.04	0.8	14	37	7	2.6	12.0
4	51	M	142	64	10	2.28	0.9	8	38	47	13.2	8.9
5	47	M	144	60	3	—	—	—	—	21	—	—
6	55	M	126	39	6-12	2.38	0.9	10	48	4	1.3	—
7	46	F	136	46	12	2.40	1.5	9	40	53	2.1	8.5
8	52	F	118	46	5	2.24	0.8	9	38	23	22.8	14.5
9	50	F	140	35	1	2.29	1.3	8	41	25	1.8	14.0
10	45	F	114	34	3	2.42	1.0	10	43	17	2.1	5.7
11	45	F	148	18	12	2.12	1.0	11	40	16	10.8	14.0
12	59	F	125	42	10	2.38	1.0	7	30	21	1.3	9.7
13	46	F	131	46	7-10	2.30	1.0	7	41	6	1.9	6.7
14	64	F	105	38	3	2.26	1.1	16	37	8	3.3	6.8
15	33	F	143	55	3-8	2.34	1.1	5	39	111	3.7	6.2
Normal values						2.20-2.60	0.8-1.4	3-13	35-45	15-100	1-12	2.0-8.0

*Using pooled serum from patients with chronic renal failure as the standard. Conversion factors: Calcium, 1.0 mmol/l = 4.0 mg/100 ml; Phosphorus, 1.0 mmol/l = 3.1 mg/100 ml; 25-OH-vitamin D, 100 nmol/l = 40 ng/ml.

Somers and Heath, 1978) and a double antibody technique (Conaway and Anast, 1974) using a C-terminal-specific antibody (E. Slatopolsky, Washington University School of Medicine, St. Louis, Missouri). All patients were submitted to a radiographic survey of the skeleton including films of hands, feet, pelvis and thoraco-lumbar spine.

The iliac bone biopsies were taken between April and September, 1978. The procedure (Bordier *et al.*, 1964) was done under local anaesthetic, the patient having received 1800 mg oral dimethylchlortetracycline over 2 days, 1 week earlier. The biopsy was of the through-and-through type and was taken from an area about 5 cm below the right iliac crest, a cylinder of bone 5 mm in diameter and consisting of the 2 cortices with intervening cancellous bone being obtained. Undecalcified sections, 6 μ m thick, were prepared and stained with toluidine blue (Eastwood *et al.*, 1974), and measurements made in the area between the cortices, i.e. in the cancellous region (Bordier and Tun Chot, 1972; Bordier *et al.*, 1973; Merz and Schenk, 1970). Using a point sampling graticule (Zeiss I), values were obtained for total bone tissue as a percentage of total cancellous volume and for the area occupied by osteoid as a proportion of total bone tissue. Using a graticule consisting of parallel lines (Zeiss II), the proportion of trabecular surface covered by osteoid and that showing resorption were measured. When graticule lines intersected osteoid, it was further noted whether there was evidence of calcification front, expressed as a percentage of osteoid surface. The numbers of osteoclasts were counted and expressed per unit area of section. Unstained sections were examined under ultraviolet light for tetracycline fluorescence.

Results

Histology

Bone histology was abnormal in 11 of the 15 patients (Table 2). In 2 patients (patients 1 and 2), there was an increase in volume of osteoid together with a diminution in calcification front, i.e. classical osteomalacia, mild in one. In the remaining 9 patients (patients 3–11) with abnormal histology, there was an increase in trabecular surface covered by osteoid, but a normal volume of osteoid. The extent of calcification front quantitated on toluidine blue stained slides was normal or reduced, an observation that was confirmed on tetracycline fluorescence. One of these 9 patients was exceptional in that he had an increase in volume of osteoid, but because there was a normal amount of calcification front he has not been considered as having osteomalacia. In 6 of the 9 patients, there was an increase in trabecular resorption (expressed as percentage of 'available' surface), but the number of osteoclasts was

normal. In the remaining 4 patients (patients 12–15), there was no histological abnormality apart from osteopenia in two.

Plasma biochemical values and X-rays

Plasma values were largely unhelpful in detecting histological bone disease. Nevertheless, one of the 2 patients with a particularly low plasma calcium had histological osteomalacia. Plasma ionised calcium (range 1.09–1.21 mmol/litre, 4.36–4.84 mg/100 ml) was normal in all 11 patients in whom it was measured (patients 3, 4, 7–15). Three patients had a raised serum concentration of alkaline phosphatase; two (patients 1 and 14) of these had cirrhosis of the liver with raised plasma γ -glutamyl-transpeptidase concentrations. Plasma 25-OH-vitamin D was low in 6 of the 15 patients, but no lower in those with bone disease than in those without; nevertheless the two with osteomalacia were among the 6 low values. Plasma levels of parathyroid hormone were raised in 3 patients by cytochemical assay and in 7 patients by C-terminal assay. The blood urea (range 2.0–5.3 mmol/litre, 12.0–31.8 mg/100 ml) and plasma creatinine (range 44–105 μ mol/litre, 0.5–1.2 mg/100 ml) were normal in all 15 patients.

Skeletal radiographs revealed no evidence of metabolic bone disease in any patient.

Clinical features

Stool frequency was unrelated to histological bone disease, but the 2 patients with osteomalacia were among 5 who had lost more than 55 kg since the operation.

Discussion

This study of 15 patients 3 to 4 years after jejunio-ileal bypass, shows that the majority (11 patients) had histological abnormalities in the bone. In 2 patients, there was clear evidence of osteomalacia, in that there was an excessive volume of osteoid tissue as well as a diminution in calcification front. In a further 9 patients, although the volume of osteoid was normal, there was an increase in trabecular surface covered by osteoid and the amount of calcification front was normal or reduced. Six of these 9 patients showed an increase in the amount of trabecular surface showing resorption. These findings are similar to those reported by Parfitt *et al.* (1978) who performed bone biopsies in 10 patients who had been selected because of suspicion of metabolic bone disease from a group of 52 patients with a jejunio-ileal bypass. They found an increase in the amount of trabecular surface showing resorption in 5 patients, and their measurements of osteoid showed that the rate of osteoid formation and mineralisation was reduced in all 10 patients. In other words, the

TABLE 2. Quantitative bone histology data in the 15 patients. (In patients 4 and 9, the very high value for total bone tissue is accounted for by biopsy being mainly of iliac crest).

Patient	Volumes		Surfaces			
	Total bone tissue (% of total cancellous volume)	Osteoid (% of total bone tissue)	Trabecular surface covered by osteoid (%)	Calcification front* (%)	Resorption (% of available surface)†	Osteoclasts (number per sq. mm of bone section)
1	12.6	17.3	68.9	31.1	73.3	0.19
2	15.0	9.8	75.4	37.8	76.7	0.13
3	21.5	7.1	62.1	43.9	59.7	0.14
4	52.1	2.5	56.9	43.1	39.5	0.05
5	12.0	7.0	64.5	63.1	33.9	0.12
6	12.9	10.6	70.6	73.2	62.9	0.09
7	16.4	1.9	31.3	56.7	41.3	0.27
8	11.5	7.1	47.2	72.9	26.3	0
9	51.9	4.0	54.5	51.2	29.2	0.10
10	20.4	3.0	34.5	48.7	10.6	0.11
11	14.5	4.6	48.5	48.0	17.4	0.01
12	7.7	1.2	23.5	58.0	11.0	0
13	19.1	1.2	21.9	53.4	23.2	0
14	8.6	1.8	16.5	53.3	22.1	0
15	16.0	1.5	9.4	65.9	9.3	0
Normal subjects ± s.d.‡	§	5.7 ± 2.0	14.6 ± 6.0	78.0 ± 7.0	17.8 ± 4.4	< 0.30

*Extent of osteoid showing calcification front expressed as % of total extent of osteoid.

†'available' surface is trabecular surface not covered by osteoid i.e. available for resorption.

‡Bordier and Tun Chot (1972); Bordier *et al.* (1973).

§Age 30–39, 21.1 ± 4.05; 40–49, 21.0 ± 4.01; 50–59, 19.6 ± 4.15; 60–69, 19.1 ± 4.90 (Merz and Schenk, 1970).

increase in trabecular resorption was probably due not only to increased resorption, but also to diminished repair. It is quite probable, therefore, that our 9 patients and those of Parfitt *et al.* (1978) were manifesting early osteomalacia; indeed Parfitt *et al.* (1978) considered 3 of their patients to have unequivocal osteomalacia. Mosekilde *et al.* (1980) have reached similar conclusions.

Definite histological evidence of hyperparathyroidism in our patients was lacking. Nevertheless, as mentioned above, 6 of the 9 patients showed an increase in trabecular surface showing resorption, although the number of osteoclasts was normal. Circulating levels of parathyroid hormone were raised in 6 out of 7 patients using the C-terminal immunoassay, but in only 3 of these 6 patients by

cytochemical assay. A possible explanation for this discrepancy is that the C-terminal assay is known to recognise at least one fragment as well as whole hormone (Arnaud *et al.*, 1974), whereas the cytochemical assay, which measures biological activity, recognises whole hormone but not C-terminal fragments. Our findings are similar to those of Parfitt *et al.* (1978) who, in addition to finding increased resorption in 5 patients, found raised levels of parathyroid hormone by C-terminal assay in 3 out of 10 patients. As in our patients, osteoclast numbers were normal. It is probable that in both series, the patients had mild hyperparathyroidism, as has been suggested by others (Compston *et al.*, 1978; Thode, Madsen and Hey, 1978), in addition to the defect in osteoid formation and mineralisation mentioned earlier.

In other words, our 15 patients show a spectrum of histological appearances from normality to classical osteomalacia. In this study and the study from Mosekilde *et al.* (1980), there is no evidence to support the suggestion of a bone disease characterised by bone loss and possibly due to absorption from the bowel of 'resorptive factors' such as endotoxin (Simmonds *et al.*, 1975; Fumarola, 1978). The incidence of osteomalacia varies in different reports. Compston *et al.* (1978) found histological evidence of osteomalacia in 10 out of 21 patients studied up to 7 years after bypass. It is possible that the higher incidence in their series as compared with those of Parfitt *et al.* (1978), Baddeley (1979) and ourselves is related to the type of operation performed. In the series of Compston *et al.* (1978), the majority of patients had had almost complete bypass of the jejunum, only 4 inches remaining compared with 14 inches in the present series, so it is possible that there was greater interference with vitamin D absorption in the jejunum in their patients than in ours. Another factor to be considered is the interval between operation and the assessment of bone histology.

To our knowledge there are no quantitative histological studies of bone in untreated grossly obese patients. Therefore, before concluding that the abnormalities seen in the bone biopsies in the present and other studies are related to the bypass procedure, it is important to know that the bones are normal at the time of operation. Until detailed studies of bone histology are carried out, both before and at intervals after the operation, with particular attention being paid to the type of operation performed, the relationship between obesity, bypass procedures and bone disease will remain uncertain. Nevertheless, doctors involved in the care of these patients should be aware of the high risk of bone disease which may not be detected by conventional radiology and biochemistry.

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