Vitamin D, hydroxyapatite, and calcium gluconate in treatment of cortical bone thinning in postmenopausal women with primary biliary cirrhosis[1, 2]

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ABSTRACT Women with primary biliary cirrhosis malabsorb calcium, phosphate and vitamin D, and develop accelerated cortical bone thinning. We have assessed the value of parenteral vitamin D, oral hydroxyapatite (HA), and calcium gluconate (CG) in the treatment of cortical bone thinning in primary biliary cirrhosis. Sixty-four postmenopausal women with primary biliary cirrhosis were assigned randomly into three groups: one group receiving no mineral supplements (control), one group receiving HA, and one group receiving CG. All patients received parenteral vitamin D_2 (100,000 IU monthly). Eleven patients withdrew from the study and 10 withdrew due to poor compliance (six HA, four CG). Over a 14-month follow-up period, none of the groups showed a significant change in serum calcium or inorganic phosphate levels. Pre- and posttreatment hand radiographs were used to assess changes in metacarpal cortical thickness using the technique of caliper radiogrammetry. Cortical bone loss occurred in the control group ($p < 0.01$). The HA group showed a significant gain in cortical bone thickness ($p < 0.01$), while no significant change occurred in the CG group. This study indicates that vitamin D_2 does not halt metacarpal cortical bone thinning in primary biliary cirrhosis. The addition of CG prevents bone thinning, and HA promotes positive cortical bone balance. *Am J Clin Nutr* 1982;36:426–430.

KEY WORDS Postmenopausal women, primary biliary cirrhosis, vitamin D, calcium, phosphate, hydroxyapatite, cortical bone thickness, metacarpal bone

Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease occurring predominantly in women. These patients are predisposed to developing metabolic bone disease (1, 2) and premature cortical bone thinning can be demonstrated radiologically (3) (**Fig 1**). The marked tendency to develop bone demineralization precludes the use of corticosteroids in the treatment of this disease (4). A combination of factors predispose these patients to the development of bone disease. The majority of patients is menopausal or postmenopausal and the chronic cholestasis causes steatorrhea with malabsorption of calcium (5), phosphate (6), and vitamin D. Inactivity and renal tabular acidosis which also occurs in this disease, may further contribute to the development of bone disease. Osteomalacia occurring in PBC responds to treatment with vitamin D or its synthetic metabolites (2, 7), but osteopenia may progress despite vitamin D supplementation (2, 5). In PBC, the effect of calcium and phosphate supplementation on osteopenia has not been assessed in controlled trials. We have used caliper radiogrammetry (8) to study the effect of vitamin D_2, calcium, and phosphate supplementation on the abnormal pattern of cortical bone thinning occurring in PBC.

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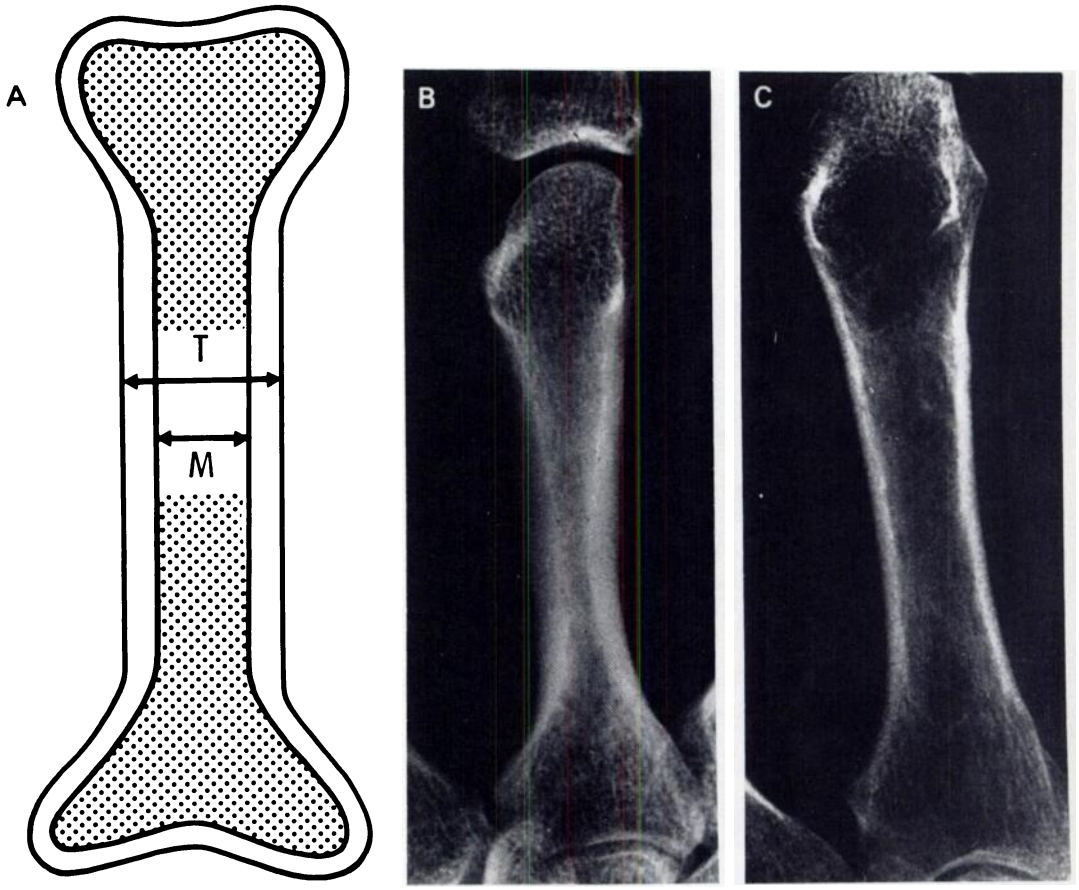

FIG. 1. *A*, measurements of metacarpal bone. Total shift width = T, medullary cavity width = M, cortical thickness = T-M (T and M both measured at metacarpal mid point). *B*, 2nd right metacarpal bone showing cortical thickness in a healthy 53-yr-old woman. *C*, 2nd right metacarpal bone showing marked cortical bone thinning in a 53-yr-old woman with PBC.

Methods

We randomly allocated 64 postmenopausal women with PBC into three groups; one group receiving no mineral supplements (controls), one group receiving a refined bone powder extract of hydroxyapatite (HA) (Ossopan powder, Welbeck Medical Distributors Limited, England), and one group receiving an effervescent preparation of calcium gluconate (CG) (Sandocal tablets, Sandoz Products Limited, England). The HA powder was given as a daily dose of 8 g, providing 35 mmol of calcium, 22 mmol of phosphate, and 2 mmol of sodium. The CG was prescribed at a dose of 2 tablets taken twice daily, the 4 tablets providing 40 mmol of calcium and 24 mmol of sodium. All patients received monthly injections of vitamin D_2 (100,000 IU). Base-line biochemical investigations included liver tests, blood urea and creatinine levels, and fasting serum levels of calcium and phosphate. Each patient had a standardised posteroanterior radiograph of the right hand, with a tube-to-film distance of 36 inches (9). At 3 monthly intervals, side effects were recorded and biochemical tests repeated. Drug compliance was assessed by careful questioning at each visit, and monitoring repeat prescription requirements. After 12 to 18 month follow-up, the hand radiograph was repeated, and the metacarpal bones of the right hand were used to evaluate changes in cortical bone modelling. At the end of the treatment period, pre- and posttreatment hand radiographs were coded and randomized, and metacarpal bone measurements were performed by a single investigator (YK) who was unaware of the treatment regimens. The total metacarpal shaft width (T) and medullary cavity width (M) of the 2nd, 3rd, 4th, and 5th metacarpal bones were measured at the metacarpal midpoint using a fine-reading caliper with a 0.01 mm visual readout (Fig 1) (8, 9). Mean values derived from the four bones were used to calculate the cortical bone thickness (CT = T-M), cortical area (CA = 0.785 (T^2-M^2), and percentage cortical area (PCA = $100\,\frac{T^2-M^2}{T^2}$) which is directly related to bone density (8). Patients withdrawing from the study within 12 wk were excluded from the analysis. The paired *t* test was used to evaluate changes occurring over the follow-up period within

groups, and the unpaired *t* test was used to compare changes occurring between groups.

Results

The control group consisted of 22 patients, 21 patients received HA, and 22 patients received CG. Eleven patients withdrew from the study due to poor compliance (six on HA, four on CG) and death (one control). The effect of treatment on cortical bone modeling was assessed over a mean period of 14 months in 21 controls, 15 patients received HA, and 17 patients received CG. On entry to the study, the clinical, biochemical, and radiological features of the three groups were similar (**Table 1**). Over the course of the study, none of the groups showed a significant change in serum calcium or phosphate levels (**Table 2**), and no patient developed hypercalcemia, hyperphosphatemia, or elevation of serum creatinine levels.

Over the 14-month follow-up, there was a significant loss of cortical bone in controls ($p < 0.01$, **Fig 2**, Table 2), a significant increase in cortical bone thickness in the HA group ($p < 0.01$, Fig 2, Table 2), and no change in the CG group (Fig 2, Table 2). The cortical bone loss in the control group and cortical bone gain in the HA was reflected by parallel changes in cortical bone area and percentage cortical bone area (Table 2). When compared to the control group, patients receiving HA had a net cortical bone gain of 11.6% (Table 2, unpaired *t* test $p < 0.01$), and the CG group showed a net gain of 7% (Table 2, unpaired *t* test $p < 0.01$). In controls, an increase in medullary cavity width accounted for the cortical bone thinning (Table 2) whereas in

TABLE 1
Pretreatment clinical, biochemical, and radiological features of patients treated with vitamin D (controls), HA, and CG*

	Controls	HA	CG
n	21	15	17
Age (yr)	55	55	56
Follow-up (mo)	14.3	14.5	14.6
Low fat diet	4	3	4
Bilirubin (mg/100 ml)	2.8 ± 2.1	3.5 ± 2.7	3.7 ± 3.4
Serum calcium (mmol/l)	2.36 ± 0.15	2.37 ± 0.09	2.38 ± 0.25
Serum phosphate (mmol/l)	1.14 ± 0.11	1.03 ± 0.27	1.04 ± 0.18
Total metacarpal width (mm)	7.53 ± 0.63	7.6 ± 0.56	7.52 ± 0.79
Medullary cavity width (mm)	3.72 ± 0.92	4.11 ± 0.52	3.71 ± 1.02
Cortical thickness (mm)	3.85 ± 0.42	3.48 ± 0.57	3.85 ± 0.64
Cortical area (mm^2)	33.67 ± 4.25	32.61 ± 6.16	33.2 ± 6.08
% Cortical area	75.3 ± 7.2	70.0 ± 7.10	76.6 ± 10.35

* Results expressed as mean ± SD. Normal serum bilirubin 0.3 to 1 mg/100 ml, serum calcium 2.1 to 2.6 mmol/l (8.4 to 10.4 mg/100 ml), serum inorganic phosphate 0.7 to 1.25 mmol/l (2.5 to 4.5 mg/100 ml).

TABLE 2
Change in serum calcium and phosphate, and absolute and percentage change in metacarpal bone indices in controls, patients treated with HA and CG*

Biochemical/radiological measurement (mean change)	Controls	HA	CG
$\bar{\Delta}$ serum calcium (mmol/l)	+0.09 ± 0.06	−0.04 ± 0.02	+0.01 ± 0.02
$\bar{\Delta}$ serum phosphate (mmol/l)	−0.01 ± 0.03	+0.05 ± 0.04	+0.02 ± 0.03
$\bar{\Delta}$ T (mm)	−0.08 + 0.03	+0.08 ± 0.07	−0.02 ± 0.05
%$\bar{\Delta}$ T	−0.8	+1.3	−0.2
$\bar{\Delta}$ M (mm)	+0.13 ± 0.05	−0.11 ± 0.05	−0.03 ± 0.21
%$\bar{\Delta}$ M	+4.2	−2.9	−0.5
$\bar{\Delta}$ CT (mm)	−0.21 ± 0.05	+0.2 ± 0.06	+0.05 ± 0.09
%$\bar{\Delta}$ CT	−5.5	+6.1	+1.5
$\bar{\Delta}$ CA (mm^2)	−1.62 ± 0.43	+1.6 ± 0.67	−0.14 + 0.47
%$\bar{\Delta}$ CA	−4.9	+5.6	0
$\bar{\Delta}$ PCA (%)	−2.05 ± 0.62	+2.19 ± 0.64	+0.37 ± 0.47

* Results expressed as mean change (± SEM). T, total metacarpal width; M, medullary cavity width; CT, cortical thickness; CA, cortical area; PCA, % cortical area.

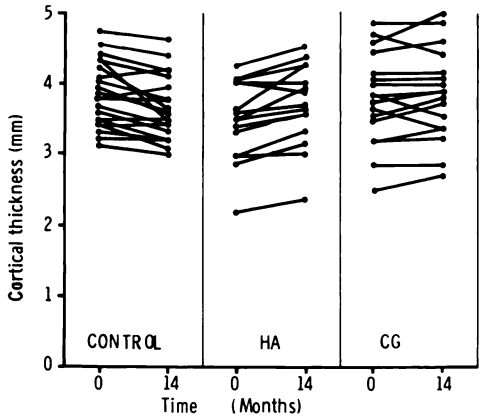

FIG. 2. Directional changes in cortical bone thickness in PBC controls, and patients receiving HA or CG. Each *point* represents mean cortical thickness derived from cortical thickness measurement of 2nd, 3rd, 4th, and 5th metacarpal bone of right hand.

the HA group a reduction in medullary cavity width occurred (Fig 2).

Discussion

The accelerated cortical bone thinning occurring in PBC is due to widening of the medullary cavity rather than thinning of the bone shaft width (3).

Change in medullary cavity width reflects endosteal bone resorption, whereas change in the total shaft width reflects subperiosteal accretion of bone (8, 10). The patern of cortical bone thinning in PBC indicates excessive endosteal resorption of bony cortex rather than failure of subperiosteal bone accretion (3). This pattern of cortical bone thinning resembles the normal pattern occurring after menopauses (8, 10), but in PBC, the changes are more profound and occur prematurely. Excessive cortical bone resorption is characteristic of malabsorption syndromes, chronic renal tubular acidosis, and physical inactivity (8) all of which are complications of PBC. The pathological cortical bone thinning in PBC is, therefore, multifactorial. This study indicates that parenteral vitamin D_2 supplementation alone does not prevent cortical bone cortical bone loss. Because both calcium and phosphate are malabsorbed in PBC, HA is a highly suitable mineral supplement.

HA powder is prepared from bovine bone and provides both the organic and inorganic constituents occurring in normal bone. The powder contains hydroxyapatite microcrystals [$3Ca_3(PO_4)_2 \cdot Ca(OH)_2$], trace metals (including zinc, strontium, silicon, and iron), protein, amino acids, and aminoglycans. There has been speculation as to why an essential insoluble calcium preparation should be more readily absorbed than soluble alternatives. This apparent paradox is probably the result of a number of factors. Calcium absorption is enhanced in the presence of protein (11) or an organic matrix (12), and the microcrystalline structure gives a large surface area from which the minerals may be released from the organic matrix in the intestine. Calcium balance studies in patients with osteogenesis imperfecta indicate that HA produces more prolonged positive calcium balance than soluble calcium salts (13). The induction of positive calcium balance with HA contraindicates its use in patients with hypercalcemia or nephrolithiasis. The effectiveness of HA treatment on cortical bone balance in PBC is not related to stimulation of cortical bone accretion, but rather to reduction in endosteal cortical bone resorption. The mechanism of this action is unknown. CG treatment was effective in preventing cortical bone thinning and its effect was immediate between controls receiving vitamin D alone, and the HA group.

Patients taking both HA and CG withdrew from the study because of poor compliance. HA has a pasty texture and sweet taste when mixed with water, and six patients found the preparation unpalatable. Most patients found the taste and texture could be disguised by adding the powder to porridge or mixing it with carbonated soft drinks. The formulation of HA in powder form offers a more flexible preparation than effervescent CG tablets. The low sodium content of HA (2.0 mmol per 8 g of powder) compared to CG (24 mmol in 4 calcium gluconate tablets), confers an additidonal advantage to HA in the long-term treatment of patients with cirrhosis or other diseases complicated by salt retention.

From the results of this study, we conclude that in postmenopausal patients with PBC, calcium supplements given in addition to parenteral vitamin D prevents or retards pathological cortical bone thinning. The provision of calcium and phosphate in the form of HA powder offers additional benefit as both min-

erals are malabsorbed in PBC. Although calcium and phosphate supplementation favorably alters the abnormal pattern of cortical bone modeling in PBC, long-term prospective studies are required to determine whether mineral supplements reduce the morbidity associated with osteopenia.

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