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The effect of medium-chain triglyceride on ^{47}calcium absorption in patients with primary biliary cirrhosis

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SUMMARY Calcium absorption, as measured by whole-body retention of isotopic ^{47}calcium, was investigated in 10 controls and 10 patients with primary biliary cirrhosis before and after medium-chain triglyceride therapy. Absorption of calcium was impaired in eight patients with primary biliary cirrhosis, three of whom had normal serum bilirubin. Mean absorption was significantly less in patients with primary biliary cirrhosis than in controls. Impaired calcium absorption correlated well with increased faecal fat excretion and less well with the intensity of jaundice. Osteoporosis was diagnosed radiologically in seven patients with primary biliary cirrhosis, and calcium absorption was restored to normal in seven out of eight patients after medium-chain triglyceride therapy. Decrease of steatorrhoea, weight gain, and relief of bone pain have been noted in most patients with primary biliary cirrhosis after therapy. It is concluded that bone disease occurs early in primary biliary cirrhosis, and early medium-chain triglyceride therapy in these patients is suggested.

Osteoporosis is common but osteomalacia also occurs, and both have been noted in patients with prolonged cholestatic jaundice (Atkinson, Nordin, and Sherlock, 1956; Deller, Edwards, and Addison, 1963). These conditions may also be found with any form of chronic liver disease (Summerskill and Kelly, 1963; Paterson and Losowsky, 1967).

In primary biliary cirrhosis and in extrahepatic biliary obstruction, impaired ^{47}calcium absorption has been demonstrated (Kehayoglou, Holdsworth, Agnew, Whelton, and Sherlock, 1968a; Whelton, Kehayolgou, Agnew, Turnberg, and Sherlock, 1971). In rats with biliary obstruction, medium-chain triglyceride stimulates significantly the impaired ^{47}calcium absorption (Kehayoglou, Williams, Whimster, and Holdsworth, 1968b; Kostamis, Kehayoglou, Constantinides, Binopoulos, and Malamos, 1970). In normal subjects, in patients after partial gastrectomy, and in malabsorptive disease medium-chain triglyceride treatment had no effect on ^{47}calcium absorption (Agnew and Holdsworth, 1971), though its value in decreasing the steatorrhoea associated with various malabsorptive disorders has been demonstrated (Kuo and Huang, 1965; Law, 1966).

In the present study the effect of medium-chain triglyceride therapy on calcium absorption and its effect on various clinical and biochemical measurements in patients with primary biliary cirrhosis has been investigated.

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Patients and Methods

The 10 patients with primary biliary cirrhosis were all female (table). Their ages ranged from 43 to 62 years, and the duration of illness was from one to five years. The diagnosis was made on the basis of clinical and biochemical criteria, liver histology, and serological tests (Sherlock, 1968). Pruritus was present in nine patients. Two had xanthelasma (cases 1 and 6) and none had xanthomas. All had hepatomegaly and eight had splenomegaly. All but one (case 4) had frequency of defaecation with two or more bowel motions daily and nine had lost weight. Nine patients complained of bone pains and tenderness. No patient was in hepatic coma or pre-coma or had ascites. Values for serum bilirubin, calcium, phosphate, CaXP product, alkaline phosphatase, and faecal fat are given in the table. Control studies were carried out in 10 subjects with various conditions, none of which would be likely to affect calcium absorption (table).

The absorption of ^{47}calcium was measured by the method of Agnew, Kehayoglou, and Holdsworth (1969) before and after the oral administration of medium-chain triglyceride. After an overnight fast,

10 μc of $^{47}CaCl_2$ in a carrier dose containing 10 mg calcium as calcium chloride was taken in water. Using a whole-body counter, retention of ^{47}Ca was calculated as whole-body count per minute after seven days, expressed as a percentage of the counts per minute three hours after the dose.

$$\text{Retention} = \frac{\text{Whole-body count rate at seven days}}{\text{Whole-body count rate at three hours}} \times 100.$$

Medium-chain triglyceride was obtained from commercial sources and it was given as an oily preparation in small amounts, in a total daily dose of 60 ml for four weeks, while the patient was on a low-fat diet. Gas liquid chromatography of the oil showed the constituent fatty acid to be C_8:0(octanoic) 23·2%, C_{10}:0 (decanoic) 59·4%, and lauric acid (C_{12}:0) 17·4%. Faecal fat was estimated in three-day specimens by the method of van de Kamer, ten Bokkel Huinink, and Weyers (1949) on those patients who were studied. Standard radiographs of the hands, femora, and lumbar spine were taken on all patients. Seven patients had osteoporosis, but none had radiological signs of osteomalacia.

Results

The results of the whole-body ^{47}Ca retention measurements are shown in figures 1 and 2. The mean seven-day retention in the controls was 55·6% ± 11·16 (1SD) and after medium-chain triglyceride therapy the mean retention remained unaltered (55·9% ± 12·04), the difference of retention after therapy not being statistically significant (fig 1, $P \simeq 0.95$). The mean retention in patients with primary biliary cirrhosis was 34·2% ± 8·46 and before therapy eight patients had a subnormal retention (fig 2). After therapy the mean retention increased and in seven of the eight patients with a previously subnormal retention the values were in the normal range. The mean increase in retention (15%) after therapy was statistically significant (fig 2,

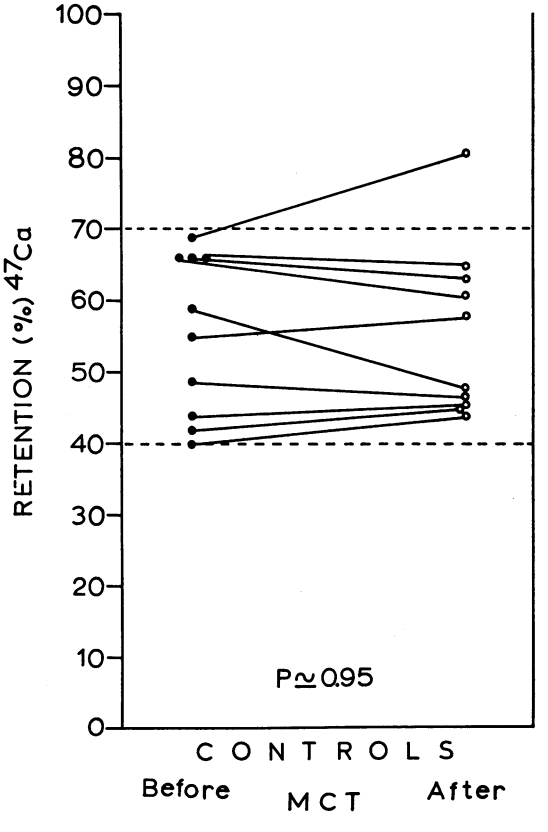

Fig 1 *Whole-body retention of ^{47}calcium in controls before and after four weeks of medium-chain triglyceride therapy* ($P \simeq 0.95$).

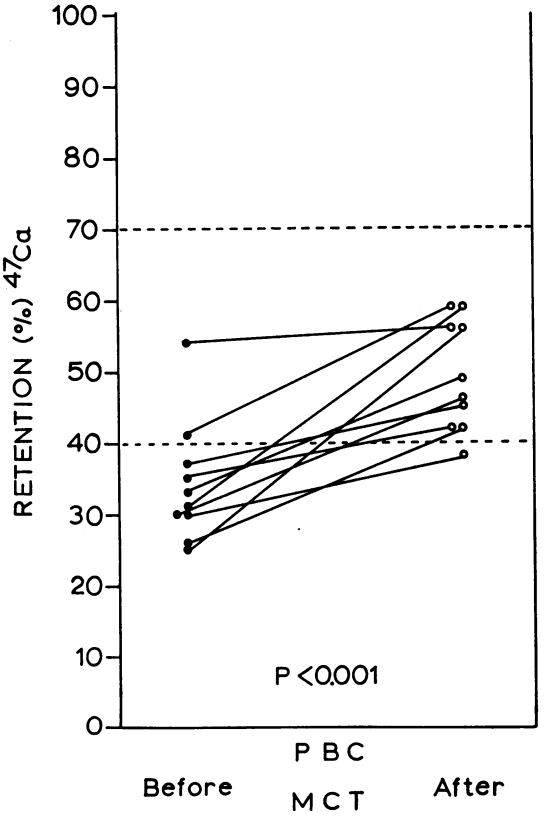

Fig 2 *Whole-body retention of ^{47}calcium in 10 patients with primary biliary cirrhosis before and after four weeks of medium-chain triglyceride treatment* ($P < 0.001$).

Case	*Sex*	*Age*	*Serum Levels*												*Before Faecal Fat (g/day)*
			Bilirubin (mg/100 ml)		*Calcium (mg/100 ml)*		*Phosphate (mg/100 ml)*		*CaXP Product*		*Alkaline Phosphatase (K-A units)*		*Albumin (g/100 ml)*		
			Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	
1	F	48	6·25	1·8	10·0	10·0	3·6	3·5	36·0	35·0	35·0	28·0	3·5	3·4	19·0
2	F	59	1·75	1·20	9·0	10·0	3·9	3·7	35·1	37·0	67·0	56·0	3·3	3·2	33·0
3	F	43	2·55	3·50	9·8	9·8	3·0	3·1	29·4	30·3	80·0	67·0	3·1	3·1	17·0
4	F	62	3·00	2·00	9·6	9·8	3·2	3·2	30·7	31·3	50·0	52·0	3·0	3·2	—
5	F	48	3·60	2·80	8·8	9·0	3·0	3·1	26·4	27·9	45·0	40·0	3·2	3·3	9·0
6	F	61	0·50	0·80	9·6	9·6	3·2	3·3	30·7	31·6	19·0	24·5	4·0	3·8	14·5
7	F	60	1·00	1·00	9·6	9·8	3·4	3·4	32·6	33·4	19·0	20·0	3·8	3·9	20·0
8	F	55	0·8	0·8	8·8	9·0	3·1	3·2	27·2	28·8	23·0	25·0	3·7	3·6	17·0
9	F	45	1·70	1·50	9·1	9·0	4·1	4·1	37·3	36·9	50·0	40·0	3·1	3·3	31·5
10	F	53	1·80	0·90	9·2	9·3	3·0	3·1	27·6	28·8	47·0	46·5	3·6	3·3	13·0
Control group	7:F 3:M	Mean 53 (27-71)[1]	Mean < 1·0 (0·5-0·9)	Mean < 1·0 (0·5-0·9)	Mean 9·6 (9-10)	Mean 9·7 (9·3-10)	Mean 3·5 (3·0-4·2)	Mean 3·5 (3·2-4)	Mean 33·3 (30-37·3)	Mean 33·4 (30·6-38·4)	Mean 7·5 (4·2-12)	Mean 7·2 (4-10·2)	Mean 4·8 (4·5-5·1)	Mean 4·7 (4·2-5)	

Table *Clinical and biochemical data of patients with primary biliary cirrhosis and control subjects.*

[1]The values within brackets denote the range of the corresponding values.

P < 0·001). The difference in calcium retention between controls and patients with primary biliary cirrhosis was statistically significant before therapy only (P < 0·001) but after therapy it was not (P < 0·20).

In patients with primary biliary cirrhosis calcium retention correlated poorly with serum bilirubin levels before as well as after therapy (r = 0·137 and r = 0·194, respectively). Three patients with primary biliary cirrhosis with normal serum bilirubin levels had impaired calcium absorption and all three restored absorption to normal after therapy (table). In nine patients with primary biliary cirrhosis there was a significant inverse correlation between faecal fat and calcium retention before therapy (r = 0·923, P < 0·001). After therapy eight of these nine patients with primary biliary cirrhosis showed a decrease in steatorrhoea and six of them gained weight. Eight patients with primary biliary cirrhosis reported relief from bone pain during therapy. One patient with primary biliary cirrhosis developed diarrhoea while receiving the oil but the problem was overcome by giving the oil in frequent small doses. All the other patients with primary biliary cirrhosis and controls tolerated the oil well.

Discussion

The impaired calcium absorption in anicteric patients with primary biliary cirrhosis, as observed in three patients in the present study, could be due to a relative deficiency of intraluminal bile salts (Badley, Murphy, and Bouchier, 1969), which interferes indirectly with calcium absorption. This finding shows that malabsorption of calcium and bone disease may occur early in the course of primary biliary cirrhosis. The defective ^{47}calcium absorption demonstrated in eight of 10 patients with primary biliary cirrhosis here could be due to a mucosal defect in calcium absorption secondary to vitamin D deficiency or to a defect of the intraluminal phase of calcium absorption. This may also be due to the formation of insoluble calcium soaps in the presence of excess of fat in the lumen, and there is enough evidence to suggest that the excess fat in the lumen directly affects the absorption of calcium (Southgate, Widdowson, Smits, Cooke, Walker, and Mathers, 1969; Agnew and Holdsworth, 1971). Finally, the low calcium absorption may also be due to reduced intraluminal bile salt secretion, which impairs the absorption of fat and vitamin D and indirectly the absorption of calcium (Schachter, Finkelstein, and Kowarski, 1964). In the present study, treatment with medium-chain triglyceride restored to normal the impaired calcium absorption in patients with primary biliary cirrhosis. The marked increase in calcium absorption after therapy could be due to increased intraluminal solubilization of calcium by medium-chain triglyceride and also to a decrease in the intraluminal excess of fat, as may be inferred by the clinical improvement in the steatorrhoea. Although in primary biliary cirrhosis an inverse correlation between calcium retention and serum bilirubin should be expected, in this study there was a poor correlation between the two parameters, before and after therapy. No significant difference was found between the mean calcium absorption in controls and patients with primary biliary cirrhosis after therapy. In six of our patients with primary biliary cirrhosis and malabsorption after therapy there was a

decrease in steatorrhoea accompanied by a gain in weight. This is in agreement with the data of others, who have reported after therapy with oil a significant weight gain in malabsorption states (Kuo and Huang, 1965; Law, 1966) and improved growth and well-being in children with liver disease (Burke and Danks, 1966).

The low levels of calcium and phosphate in the serum in three patients with primary biliary cirrhosis, two of whom had impaired ^{47}calcium absorption, may indicate gross osteomalacia, though in neither was bone biopsy performed or measurements of the urinary output of calcium made. Medium-chain triglyceride therapy has relieved the bone pain in most patients with primary biliary cirrhosis.

Although parenteral vitamin D therapy restores calcium absorption to normal, it does not halt the progression of bone thinning (Atkinson *et al*, 1956; Kehayoglou *et al*, 1968a). The early administration of medium-chain triglyceride with a low-fat diet in patients with primary biliary cirrhosis restores the defective calcium absorption to normal, improves patients' well-being, decreases steatorrhoea, and it could in part inhibit the progression of bone disease. This treatment could also be given to patients with extrahepatic biliary obstruction and patients with parenchymatous liver disease, in which there is steatorrhoea and malabsorption of calcium.

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