Original Article

PREDICTORS OF OSTEODYSTROPHY IN PATIENTS WITH CHRONIC NONALCOHOLIC PANCREATITIS WITH OR WITHOUT DIABETES

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ABSTRACT

Objective: To study bone mineral content (BMC), bone mineral density (BMD), vitamin D status, and bone mineral variables in patients with chronic nonalcoholic pancreatitis and to determine the relationship between pancreatic dysfunction and these variables.

Methods: Thirty-one eligible nonalcoholic men with proven chronic pancreatitis and 35 male control subjects were studied. Biochemical data, variables of malabsorption, and BMD of the lumbar spine were evaluated.

Results: In patients with chronic pancreatitis, the mean body mass index (BMI) was 18.46 kg/m^2 and the median 25-hydroxyvitamin D value was 15.5 (range, 5.0 to 52.0) ng/mL. A T-score of less than −2.5 was found in a higher proportion of study patients (9 of 31, 29%) than of control subjects (3 of 35, 9%). BMI correlated significantly with BMC (r = 0.426; P = .017). There was an inverse correlation between stool fat and BMC (r = −0.47; P = .03) in patients with chronic pancreatitis and steatorrhea. There was no significant correlation between serum 25-hydroxyvitamin D or biochemical variables and BMD. Patients with steatorrhea had a significantly lower BMC than did those without steatorrhea, and this difference could not be accounted for by differences in BMI, presence of diabetes, or hypovitaminosis D.

Conclusion: Pancreatic osteodystrophy is a novel entity consisting of osteopenia, osteoporosis, and osteomalacia in patients with chronic pancreatitis. The inverse correlation between stool fat and BMC in patients with chronic pancreatitis, the strong positive correlation between BMI and BMC, and the lack of difference in BMC between subjects with vitamin D sufficiency and those with vitamin D deficiency suggest that long-standing malabsorption with attendant chronic undernutrition is the major factor contributing to the changes in BMC. **(Endocr Pract. 2011;17:897-905)**

Abbreviations:
BMC = bone mineral content; **BMD** = bone mineral density; **BMI** = body mass index; **25(OH)D** = 25-hydroxyvitamin D

INTRODUCTION

Chronic pancreatitis is a progressive condition in which permanent changes occur in the pancreas attributable to inflammation, leading to deficiency of pancreatic exocrine and endocrine functions (1). Tropical pancreatitis, prevalent in developing countries, is a form of chronic calcific nonalcoholic pancreatitis in younger patients who present with steatorrhea or diabetes mellitus (or both) (2,3). Many patients have abdominal pain, weight loss, symptoms of maldigestion, and diabetes; in contrast, some patients have a paucity of symptoms. Functional tests for pancreatic insufficiency (4) during the early stages of pancreatitis are of limited utility, and biopsy of the pancreas for the diagnosis of pancreatitis is impractical. Calcifications within the pancreatic ducts or parenchyma, dilated pancreatic ducts, or both, in combination with pancreatic atrophy,

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are virtually pathognomonic of chronic pancreatitis and occur in 90% of those patients with late-stage disease (5,6).

In chronic pancreatitis, the chronic inflammation, low body mass index (BMI), undernutrition, coexisting diabetes, poor exposure to sunlight, and decreased physical activity because of chronic illness are factors that may increase the risk of bone loss. Deficiency of fat-soluble vitamins is to be expected in patients with pancreatic insufficiency and steatorrhea (1). Vitamin D enhances calcium absorption, mineralization of osteoid, and osteoblastic activity, and vitamin D deficiency leads to reduced bone mineral density (BMD) to an extent seen in osteopenia and osteoporosis before overt osteomalacia ensues. Osteoporosis leads to increased bone fragility and increased frequency of fractures (7,8). There is limited knowledge about the bone mineral status in patients with chronic pancreatitis. In recent years, a few groups have studied BMD in chronic pancreatitis (9-11). These studies with small numbers of patients have shown variable prevalence of metabolic bone disease and vitamin D deficiency. One of these studies (9) reported a significant positive correlation between 25-hydroxyvitamin D [25(OH)D] levels and BMD at the lumbar spine and worsening BMD with increasing severity of chronic pancreatitis. No prospective study thus far has addressed the relative contributions of overall undernutrition, vitamin D deficiency, associated diabetes mellitus, and effect of chronic illness per se on the pathogenesis of pancreatic osteodystrophy. Long-term studies on the prevalence of fractures in these patients have not been conducted, and the potential effects of interventions to improve bone health are unknown. With current treatment modalities, patients with chronic pancreatitis with or without diabetes survive longer, and awareness and early recognition of these skeletal problems may pave the way for interventional studies to improve bone health. Therefore, the current study was undertaken to assess the prevalence of osteoporosis in male patients with chronic nonalcoholic pancreatitis and to evaluate potential contributing factors.

RESEARCH DESIGN AND METHODS

We recruited consecutive male patients between 20 and 60 years of age with proven chronic nonalcoholic pancreatitis seen as outpatients in the Department of Endocrinology or the Department of Gastroenterology (Fig. 1). Women, men with a history of alcohol dependence (12), immobilized persons, those with lower limb amputation, cardiovascular disease, liver disease, renal disease, or hypogonadism, and patients taking drugs that could affect bone metabolism (hormones, antiepileptic agents, antituberculosis drugs, diuretics, glucocorticoids, and antiresorptive drugs) were excluded from the study.

Clinical assessment included the following: (*1*) a detailed history of abdominal pain, steatorrhea, weight loss, bone pain, fractures, complications of diabetes, drugs taken, and concomitant illnesses; (*2*) an assessment of dietary calcium intake by using an oral semiquantitative food frequency questionnaire (13,14); and (*3*) an examination to search for complications of diabetes, proximal myopathy, signs of malnutrition, hypocalcemia, and skeletal deformities.

Fasting serum calcium, phosphorus, alkaline phosphatase, albumin, and creatinine, plasma glucose, and 24-hour urine calcium, phosphorus, and creatinine were measured by a fully automated microanalyzer (Hitachi 912). Serum 25(OH)D was measured by radioimmunoassay (DiaSorin, Stillwater, Minnesota). Patients were maintained on a high-fat diet (50 g daily) for 5 days (starting 2 days before stool collection), and 72-hour stool fat was estimated. Stool fat excretion of ≥18 g in 72 hours was considered abnormal (15).

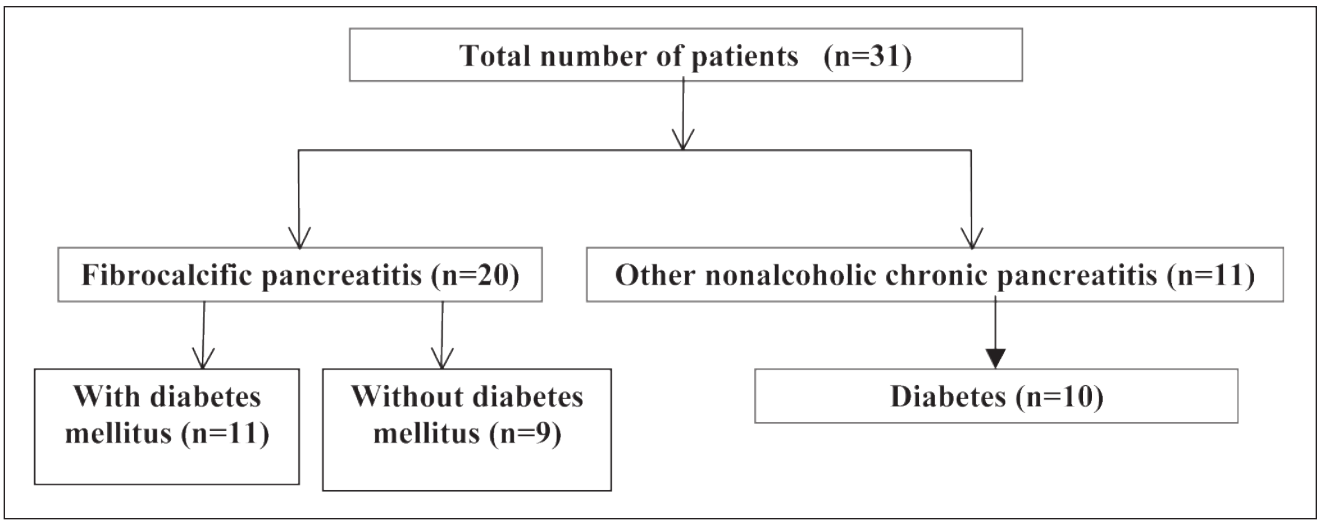

Fig. 1. Flow chart, showing study patient characteristics.

BMD was assessed by a dual-energy x-ray absorptiometry scanner (QDR 4500; Hologic, Inc, Waltham, Massachusetts) at the lumbar spine. We did not measure BMD at the hip or forearm because of resource constraints. Daily calibration graphs were maintained with use of phantoms, and the precision of measurement was 2%. The reference population consisted of normal white subjects (manufacturer's database). The results obtained in the study patients were compared with those in 35 control subjects who were age- and socioeconomic status-matched normal lean men without chronic pancreatitis or diabetes mellitus.

STATISTICAL ANALYSIS

The SPSS version 11 software package was used (SPSS Inc., Chicago, Illinois). Pearson correlation was used to study the relationship between normally distributed continuous variables. An independent Student 2-tailed *t* test was used to compare the means of 2 continuous variables if they were normally distributed, and nonparametric tests were used if their distribution was not normal. *P* values ≤.05 were considered statistically significant. Linear regression was used to analyze the relationship between a dependent variable and one or more independent variables.

ETHICS

The study protocol was approved by the Christian Medical College Institutional Review Board. It conforms to the ethical guidelines of the "World Medical Association Declaration of Helsinki—ethical principles for medical research involving human subjects," adopted by the 18th World Medical Association general assembly, Helsinki, Finland, June 1964 and revised in Tokyo, Japan, in 2004, as reflected in a priori approval by the Institutional Review Board. The study was also approved by the Institutional Research Committee (RC minute no. 5693).

RESULTS

A total of 31 male patients were studied (Fig. 1). The majority (91%) were from a middle-class background, were gainfully employed, and had unrestricted outdoor physical activity, but exposure to sunlight was not quantified in these patients. All the patients had features of chronic pancreatitis substantiated by ultrasonography, computed tomography, or endoscopic retrograde cholangiopancreatography. Eleven patients (35%) had chronic pancreatitis of unknown cause. Twenty patients (65%) had pancreatic duct dilatation with ductal calculi and parenchymal atrophy, suggesting tropical fibrocalculous pancreatitis. Of these 20 patients, 11 had diabetes (fibrocalculous pancreatic diabetes). Some patients had received irregular treatment with pancreatic enzymes in the past from other hospitals, but none of them had taken calcium or vitamin D supplements. The study patients had not taken pancreatic enzymes for at least 3 months before presentation at our center.

Abdominal pain and weight loss (50% of patients) were the most common symptoms. The median duration of symptoms of abdominal pain, steatorrhea, or both was 72 months (range, 3 to 300). BMD was found to have a significant correlation with the duration of symptoms (r = 0.431; P = .016). A typical clinical history of steatorrhea was elicited in only 31% of the patients, but 69% had steatorrhea (stool fat ≥18 g in 72 hours). The mean BMI was 18.46 kg/m^2 (Table 1), and 45% of patients had a BMI <18 kg/m^2. All patients had normal corrected serum calcium and phosphorus values (Table 1). The mean renal threshold for maximal tubular reabsorption of phosphate corrected for glomerular filtration rate was 3.73 mg/dL. The mean dietary calcium intake (and standard deviation) was lower—749 (170.15) mg daily—than that recommended for normal healthy adults, and 6.4% of patients had a dietary calcium intake <500 mg. None of the patients had clinical features of overt osteomalacia, such as bone pain or skeletal deformities. Furthermore, none of the patients had clinical features of vitamin A deficiency. The total 24-hour urine calcium value in most of our patients was either normal or low (Table 1).

In comparison with normal healthy age- and socioeconomic status-matched adult male subjects, our study patients had significantly lower BMI (P = .001) and lower 25(OH)D levels (P = .020), and 24% of them had vitamin D deficiency (P = .04). On the basis of current criteria (16), 16 (52%) of our patients had 25(OH)D insufficiency or deficiency (<20 ng/mL), and 6 (19%) had vitamin D levels <10 ng/mL. Neither BMD (r = 0.3; P = .093) nor bone mineral content (BMC) (r = 0.298; P = .147) was found to correlate significantly with 25(OH)D levels in the study patients.

Nine of our patients with chronic pancreatitis (29%) had a T-score of less than −2.5 in comparison with 3 age-matched normal subjects (9%) (P<.02). The mean BMD (and standard deviation) was 0.891 (0.135) g/cm^2 and the mean BMC was 51.9 (10.3) g/cm in patients with chronic pancreatitis in comparison with the corresponding values in healthy control subjects—BMD = 0.946 (0.098) g/cm^2 (P = .052); BMC = 50.51 (7.62) g/cm (P = .540). BMI correlated significantly (Fig. 2) with both BMD (r = 0.523; P = .003) and BMC (r = 0.426; P = .017), as has been described for normal subjects (17).

When compared with the subjects having a normal T-score (Table 2), patients with a T-score of less than −2.5 were found to have a significantly lower BMI (P = .029) and a nonsignificant trend toward higher stool fat excretion, but the 25(OH)D levels were similar in the 2 groups.

Twenty-one patients (68%) had diabetes mellitus; of these, 4 were consuming a diabetic diet, 4 were taking orally administered diabetic agents, and 13 were

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Table 1
Demographic Characteristics and Biochemical Variables, Stratified by Cases Versus Control Subjects

Characteristic	Reference range	Cases Mean (SD) (n = 31)	Control subjects Mean (SD) (n = 35)	*P* value
Age (y)	…	35.8 (9.0)	38.6 (5.2)	.128
Weight (kg)	…	51.2 (9.3)	64.3 (9.3)	.001
Body mass index (kg/m^2)	…	18.46 (2.86)	22.6 (3.1)	.001
Serum calcium (corrected) (mg/dL)[a]	8.3-10.5	9.02 (0.37)	8.61 (0.29)	.001
Serum phosphorus (mg/dL)[a]	2.5-4.6	3.93 (0.58)	3.64 (0.54)	.001
Creatinine (mg/dL)	0.5-1.4	0.94 (0.15)	0.99 (0.11)	NS
Alkaline phosphatase (U/L)	40-125	114.4 (52.7)	77.3 (17.8)	.001
Urine calcium (mg/24 h)[b]	50-300	157 (15-492)[c]	67 (4-235)[c]	.001
Maximal tubular reabsorption of phosphate corrected for GFR (mg/dL)	2.5-5.0	3.73 (0.68)	3.4 (0.85)	NS
72-Hour stool fat (g)	<18	22.8 (9.70-93.70)[c]	Not done	…
72-Hour stool volume (g)	<600	1,320.9 (598.52)	Not done	…
25-Hydroxyvitamin D (ng/mL)	>20	15.5 (5.0-52.0)[c]	22.2 (5.6)	.020
Bone mineral density (g/cm^2)	…	0.891 (0.135)	0.946 (0.098)	.052
Bone mineral content (g/cm)	…	51.9 (10.3)	50.51 (7.62)	.540

Abbreviations: GFR = glomerular filtration rate; NS = no significant difference; SD = standard deviation.
[a] Even though the cases had higher serum corrected calcium and phosphorus levels, the values were within the normal range, and none had hypercalcemia. The reason for these differences in the urine calcium and serum calcium and phosphorus values between the cases and control subjects is unclear.
[b] Three cases had urine calcium values of 375, 397, and 492 mg/24 h urine specimen, respectively, resulting in a median of 157 mg/24 h. If these values are excluded, the median value is 134 mg, which is still significantly higher than that for the control subjects (P = .003). These 3 patients did not have severe bone disease or renal calculi.
[c] Median and range.

receiving insulin therapy. Four patients had a family history of diabetes. The median duration of diabetes was 36 months (range, 3 to 204). Patients with diabetes had a lower mean BMI than those without diabetes (17.7 versus 20.0 kg/m^2, respectively; P = .087) (Table 3). In comparison with patients without diabetes, significant positive linear correlations were found between BMI and BMD (r = 0.578; P = .006; Fig. 3) and BMI and BMC (r = 0.448; P = .041) only in the patients with diabetes mellitus. In patients with diabetes, the median 25(OH)D value of 12.6 ng/mL (range, 5.0 to 35.8) showed a nonsignificant trend to be lower than in those without diabetes (20.15 ng/mL; range, 15.5 to 52.1) (P = .056). The median 72-hour stool fat value of 25.2 g (range, 9.7 to 93.7) among patients with pancreatic diabetes was higher than the median value of 12.55 g (range, 12.3 to 28.6) among those without diabetes, but this difference was not statistically significant (P = .417).

In patients with steatorrhea, the 25(OH)D levels, BMI, and BMD had a nonsignificant trend to be lower and BMC was significantly lower (P = .010) than in those without steatorrhea (Table 4). There was a significant negative correlation (r = –0.468; P = .028; Fig. 4) between stool fat and BMC, but the correlation between stool fat and BMD did not achieve statistical significance (r = −0.386; P = .076). Patients with steatorrhea had a significantly lower mean BMC (45.6 g/cm) than did age-matched control subjects (56.3 g/cm) (P = .010) (Table 4).

When a linear regression analysis pooling both the cases and control subjects was performed to determine whether other factors contributed to the low BMD, BMI alone was found to have a significant correlation

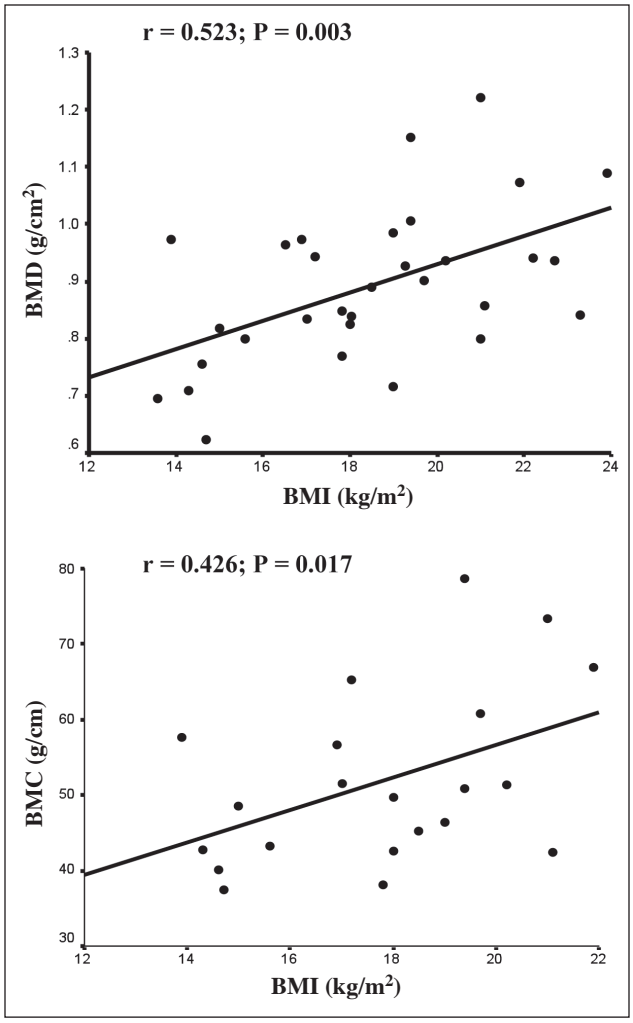

Fig. 2. Results of linear regression analysis, showing correlations of body mass index (*BMI*) with bone mineral density (*BMD*) and bone mineral content (*BMC*) in patients with chronic nonalcoholic pancreatitis.

(r = 0.361; P = .003). Levels of 25(OH)D (r = 0.220; P = .092), dietary calcium (r = 0.233; P = .06), and urine calcium (r = −0.029; P = .819) did not show any correlation.

DISCUSSION

Chronic pancreatitis with or without diabetes is a relatively common problem in India and other tropical countries (18,19). Although it is well known that patients with type 1 diabetes have a low BMD (20), BMD has not been extensively studied in patients with chronic pancreatitis and associated diabetes mellitus. A few published reports, however, have indicated that skeletal problems do occur in these patients.

The reported prevalence of low BMD (29%) in our patients with chronic pancreatitis is nearly 1.5 to 2 times the prevalence of osteoporosis (14% to 19%) reported in patients with type 1 diabetes mellitus (21,22). Unlike the situation in patients with type 1 diabetes, in whom BMD has been shown to correlate with the duration and the severity of the diabetes mellitus (21), we did not find such a correlation in our patients with chronic pancreatitis and secondary diabetes mellitus. Patients with fibrocalculous pancreatic diabetes are not entirely insulin deficient, and this factor may be one reason why they differ from patients with type 1 diabetes relative to their skeletal problem. The combination of steatorrhea, associated weight loss, and related vitamin D deficiency may predispose these patients to an even greater skeletal problem than just type 1 diabetes mellitus.

In the current prospective study, we found that patients with chronic pancreatitis with or without associated diabetes mellitus have a state of chronic undernutrition with very low BMI in comparison with age- and socioeconomic status-matched control subjects (18.46 kg/m^2 versus 22.6

Table 2
Comparison of Patients With and Without Abnormal Bone Mineral Density

	T-score				
	Between –1 and –2.5		Less than –2.5		*P*
Factor	Mean	SD	Mean	SD	value
Body mass index (kg/m^2)	19.40	2.48	16.17	2.51	.029
Bone mineral content (g/cm)	56.04	9.07	41.77	4.46	.001
Bone mineral density (g/cm^2)	0.952	0.103	0.742	0.06	.001
25-Hydroxyvitamin D (ng/mL)[a]	21.5	5-52	16.97	8.80-29.1	.77
72-Hour stool fat (g)[a]	19.15	10.50-29.20	36.06	9.70-93.66	.059

Abbreviation: SD = standard deviation.
[a] Median and range.

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Table 3
Comparison of Patients With and Without Diabetes Mellitus

Factor	With diabetes		Without diabetes		*P* value
	Mean	SD	Mean	SD	
Age (y)	37.3	9.4	32.6	7.7	.228
Weight (kg)	48.7	7.9	56.5	10.3	.036
Body mass index (kg/m^2)	17.7	2.4	20.0	3.31	.087
Corrected calcium (mg/dL)	8.98	0.36	9.1	0.41	.230
25-Hydroxyvitamin D (ng/mL)[a]	12.60	5.0-35.8	20.15	15.5-52.1	.056
72-Hour stool volume (g)	1,360	686.5	1,216.6	269.6	.941
72-Hour stool fat (g)[a]	25.2	9.7-93.7	12.55	12.3-28.6	.417
Alkaline phosphatase (U/L)	121	60.1	99.5	30.9	.235
Bone mineral density (g/cm^2)	0.873	0.147	0.902	0.110	.597
Bone mineral content (g/cm)	51.88	11.56	51.9	7.52	.526

Abbreviation: SD = standard deviation.
[a] Median and range.

kg/m^2), and nearly half of our study patients (14 of 31 [45%]) had a BMI <18 kg/m^2. Our patients with chronic pancreatitis and a T-score of less than −2.5 had a significantly lower BMI (P = .029) than those with a T-score between −1 and −2.5. This observation along with the strong positive correlation seen between BMI and BMD (P = .003) implies that the chronic undernutrition in these patients is an important contributor to the skeletal problem. The mean BMD and mean BMC of patients with chronic pancreatitis and diabetes were not significantly lower than in their counterparts without diabetes (P = .597 and P = .526, respectively); these findings suggest that the presence or absence of diabetes mellitus may not be an important determinant of BMD in this disorder. Even

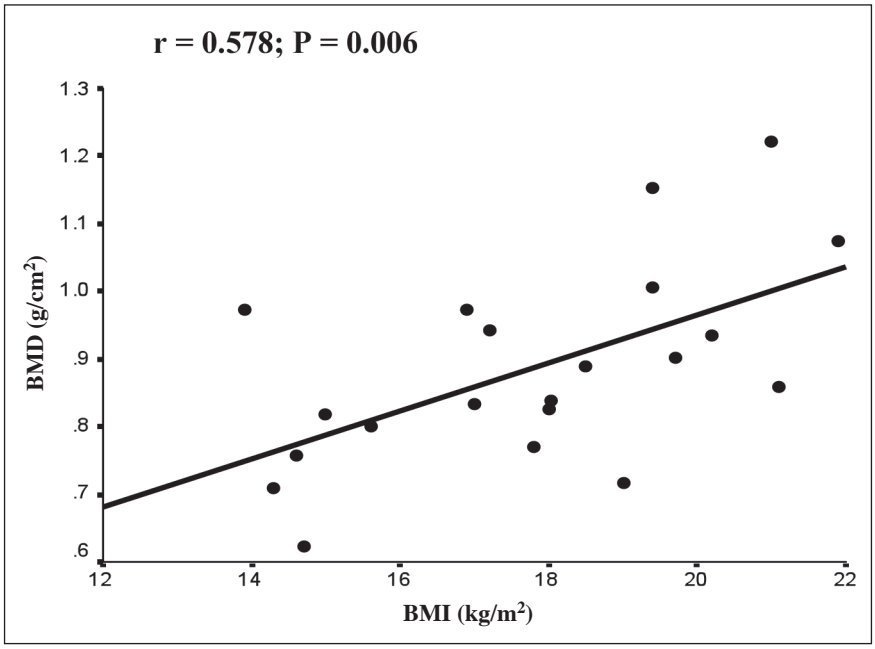

Fig. 3. Results of linear regression analysis, demonstrating correlations between bone mineral density (*BMD*) and body mass index (*BMI*) in patients with chronic nonalcoholic pancreatitis who had diabetes.

Table 4
Comparison of Patients With and Without Steatorrhea

Factor	With steatorrhea		Without steatorrhea		*P* value
	Mean	SD	Mean	SD	
Body mass index (kg/m^2)	17.7	2.24	19.34	3.22	.230
25-Hydroxyvitamin D (ng/mL)[a]	13.35	6.9-31.0	17.85	7.5-52.1	.487
Bone mineral density (g/cm^2)	0.822	0.09	0.93	0.16	.095
Bone mineral content (g/cm)	45.6	5.47	56.3	12.5	.010
72-Hour stool fat (g)[a]	28.4	21.4-93.7	12.4	9.7-17.4	.004

[a] Median and range.

among patients with chronic pancreatitis and diabetes mellitus, however, we found significant positive linear correlations between BMI and BMD ($r = 0.578$; $P = .006$) and BMI and BMC ($r = 0.448$; $P = .041$), an indication of the importance of overall undernutrition as reflected by low BMI as a determinant of BMD.

In our patients, both BMD and BMC correlated significantly with BMI. Only BMC correlated negatively with the 72-hour stool fat in our study patients ($r = -0.468$; $P = .028$). BMD did not show such a correlation ($r = -0.386$; $P = .076$). This lack of correlation between BMD and 72-hour stool fat could be attributable to the inherent differences between these 2 variables representing bone strength.

Even though most published studies have used BMD for defining osteoporosis, areal BMD does not take the volume of bone into consideration when the bone strength is assessed. This would be a paradox because bone strength is related to bone volume also. Therefore, Heaney (23) argues that studies assessing bone strength should measure and report BMC.

Our study confirms that, among patients with chronic pancreatitis, those with exocrine pancreatic deficiency and steatorrhea are a subgroup with the most severe reduction

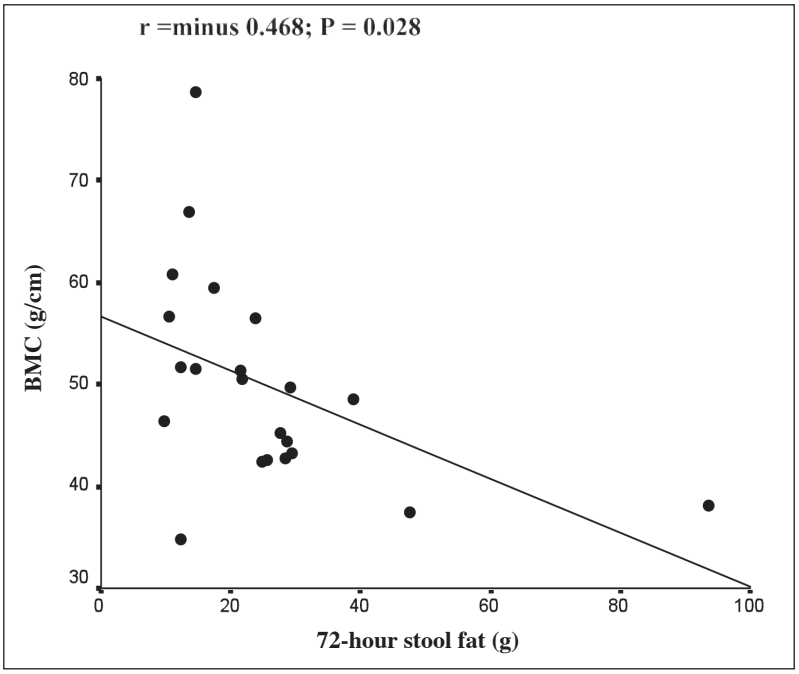

Fig. 4. Results of linear regression analysis, showing correlation between stool fat and bone mineral content (*BMC*) in patients with chronic nonalcoholic pancreatitis who had steatorrhea.

in BMC, whereas those without steatorrhea seem to be relatively protected. The significant inverse correlation between stool fat content and lumbar spine BMC in the entire group further strengthens our argument that long-term undernutrition is a major determinant of BMD and BMC in patients with chronic pancreatitis. Adipose tissue is known to be an important source of estrogen in both sexes, and it is possible that the lack of adipose tissue is partly responsible for the skeletal problem. These undernourished persons have poor muscle mass as well, and this could be an additional important contributing factor (24,25).

Depending on the criteria used to define vitamin D deficiency, 52% of our patients with chronic pancreatitis had biochemical evidence of vitamin D insufficiency or deficiency. Our observation that patients with chronic pancreatitis and steatorrhea have a lower mean 25(OH)D level than those without steatorrhea is in agreement with the observations of Mann et al (9). In our study, 19% of the patients with chronic pancreatitis had severe vitamin D deficiency, and overall the mean 25(OH)D level was significantly lower in the patients than in the control subjects. Nevertheless, we were unable to find a significant correlation between 25(OH)D levels and BMD or BMC at the lumbar spine. We did not measure BMD at the femoral neck or distal radius. It is possible that low 25(OH)D levels may be selectively related to BMD at these sites. Overall, our findings imply that chronic general malnutrition rather than selective vitamin D deficiency may be more important in the pathogenesis of pancreatic osteodystrophy.

Metabolic bone diseases are potentially treatable comorbidities in patients with chronic pancreatitis. With appropriate treatment of their diabetes and pancreatic malabsorption, these patients live longer and are at risk for skeletal problems during their extended life span. Paying scrupulous attention to their nutrition and restoration of ideal body weight while maintaining optimal glycemic control may be of crucial importance in optimizing bone health in these patients. Awareness of the magnitude of the skeletal problem associated with chronic pancreatitis and appropriate evaluation are important steps in the identification and management of patients at risk for pathologic fractures.

We have studied only a small number of these patients. Prospective long-term studies in larger numbers of these patients with use of preestablished interventional strategies are warranted.

CONCLUSION

Among 31 male patients with chronic nonalcoholic pancreatitis, at a mean age of 36 years, 29% had a T-score of less than –2.5. In comparison with control subjects, our patients had a significantly lower BMI and 25(OH)D level. Patients with chronic pancreatitis and steatorrhea had a significantly reduced BMC in comparison with similar patients without steatorrhea. This difference could not be accounted for by the presence or absence of either diabetes mellitus or vitamin D deficiency. Patients with chronic pancreatitis and a T-score of less than –2.5 had a significantly lower BMI, showed a trend toward higher stool fat excretion, but did not have significantly lower mean 25(OH)D levels. In patients with chronic pancreatitis who had diabetes, there was a significant positive linear correlation between BMI and BMD. No correlation was found between 25(OH)D levels and BMD or BMC in our study patients. Overall undernutrition in chronic pancreatitis rather than vitamin D deficiency may be an important determinant of BMD and BMC in these patients. Pancreatic osteodystrophy in chronic pancreatitis is an underrecognized comorbidity necessitating further study.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

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