RESEARCH ARTICLE

Altered Bone Metabolism and Bone Density in Patients with Chronic Pancreatitis and Pancreatic Exocrine Insufficiency

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ABSTRACT

Context Due to maldigestion, pancreatic exocrine insufficiency (PEI) in chronic pancreatitis may lead to deficiencies in fat-soluble vitamins, including vitamin D. This may, in turn, can cause disturbances in bone metabolism and reduce bone mineral density. **Objective** To conduct a prospective study of maldigestion, bone metabolism, and bone mineral density in a group of patients with chronic pancreatitis. **Methods** A total of 50 male patients with proven chronic pancreatitis (36/50 alcohol; 42/50 smokers) were studied. Pancreatic exocrine function was assessed using the fecal elastase-1 test. Blood and urine samples were analyzed for parameters related to pancreatitis, nutrition, endocrine status, and bone metabolism. Bone mineral density was measured with dual-energy X-ray absorption (DXA) and conventional vertebral X-rays. A standardized questionnaire for osteoporosis was given. **Results** Twenty-eight of the patients had PEI (fecal elastase-1 < 200 μg/g), 25 had bone pain, and 21 had a history of bone fractures. Serum 25-OH-cholecalciferol and urine calcium were decreased and deoxypyridinoline concentrations were increased in urine. Serum calcium, bone-specific alkaline phosphatase, and parathyroid hormone were within normal limits. There was no statistical correlation between three classes of fecal elastase-1 (< 100μg/g; 100-200 μg/g > 200 μg/g) and calcium, 25-OH-cholecalciferol, or deoxypyridinoline. Of the 15 patients who underwent DXA, 5 had normal bone mineral density (T score > -1), 9 had osteopenia (T score -1 to – 2.5), and 1 had osteoporosis (T score < -2.5). There was a trend toward a correlation between low fecal elastase-1 and low T scores (p=0.065). Low fecal elastase-1 correlated with low bone mineral density in conventional X-rays (p<0.05). Patients receiving pancreatic enzyme replacement therapy (PERT) had significantly higher DXA values (p<0.05). **Conclusions** Patients with chronic pancreatitis have osteoporosis, along with abnormal bone metabolism and reduced bone mineral density as measured by DXA and X-ray. PERT is associated with less osteopathy.

INTRODUCTION

In chronic pancreatitis, progressive ongoing inflammation destroys the exocrine pancreatic tissue and produces pancreatic exocrine insufficiency. Because the pancreas has a large functional reserve capacity, the effects of this destruction of exocrine pancreatic tissue becomes clinically apparent only after about 90% of the acinar parenchyma has been lost [1]. The severe decrease in secretion of digestive enzymes means that patients lose the ability to absorb macronutrients adequately. This has a negative impact on the absorption of trace elements and vitamins as well, especially the fat-soluble vitamins (A, D, E,

K). Deficiencies of essential nutrients increase health risks and produce serious symptoms. Vitamin D (cholecalciferol) deficiency has attracted attention because it increases the risk of impaired bone metabolism that can lead to decreased bone mineral density and subsequent bone disorders, such as osteopenia and osteoporosis. Guideline recommendations have been published for managing the decrease in vitamin D absorption seen in other gastrointestinal diseases associated with malabsorption, such as Crohn's disease, celiac disease, and cystic fibrosis [2]. While there are recommendations related to vitamin D in the current guidelines for management of chronic pancreatitis [3-6], prospective studies are need to evaluate the extent of the problem and determine the effectiveness of different treatment strategies.

The current prospective study investigated bone mass and bone metabolism in a well-defined group of patients with chronic pancreatitis who had varying degrees of pancreatic exocrine insufficiency.

PATIENTS AND METHODS

In this prospective cohort study, a total of 50 male patients with confirmed chronic pancreatitis were recruited from the pancreas outpatient clinic. The diagnosis of chronic pancreatitis was based on clinical symptoms and morphology (imaging). Pancreatic function was evaluated using the fecal elastase-1 test as described previously

[7]. Only male patients were recruited in order to avoid the hormonal variations found in women and the effects these variations could have on bone metabolism. Patients with other malabsorption conditions (*e.g.* celiac disease, Crohn's disease) or other diseases known to affect bone metabolism (*e.g.* kidney disease, hyperparathyroidism, rheumatoid arthritis) were excluded from the study. Patients taking drugs known to influence bone metabolism (*e.g.* steroids or hormone therapy for prostate cancer) were also excluded. The study was approved by the local ethics committee. All patients gave informed consent prior to inclusion in the study.

Clinical Data

Were collected concerning alcohol intake, smoking, and other life style factors. Alcohol intake was assessed with the self-reported alcohol intake questionnaire (SRAI) [8]. Patient history of previous injuries, particularly broken bones, was recorded. Current and previous medications were recorded, especially pancreatic enzymes. A standardized questionnaire for osteoporosis was given [9].

Laboratory Parameters

Laboratory parameters were measured in samples obtained during routine blood draws. Pancreatitis was assessed through measurement of white blood cell counts, C-reactive protein, amylase, and lipase. Total protein, albumin, and vitamin K were measured to assess nutritional status. Endocrine status was evaluated by measuring parathyroid hormone, thyroid-stimulating hormone (TSH), and testosterone. Bone metabolism was assessed through measurement of serum calcium, phosphate, bone-specific alkaline phosphatase, and 25-OH-cholecalciferol. Calcium and deoxypyridinoline were determined in 24h urine samples.

Bone Density

It was determined using dual-energy X-ray absorption (DXA; QDR-1000, Hologic Instruments) at the standard measurement sites in the lumbar spine and the femur. Results are presented as T scores and Z scores as previously described [10]. Classification of bone density was done according to the WHO standard [11]. Patients were advised about the added radiation risk when asked to volunteer to undergo conventional vertebral X-rays. All of the patients who were asked agreed to the X-rays. The BMD on the conventional X-ray was graded semi-quantitatively, as described: normal = 0, mild = 1, moderate = 2, and

severe = 3. Once a reduction is clearly seen, this can be considered already substantial (scored 2) [12]. Complete demineralisation, i.e. osteoporosis was scored 3.

Statistical Analysis

It was done using SPSS software (version 10.0). U tests were used for two independent analytes. The Kruskal-Wallis test was used for more than two independent analytes. Values are reported as medians ± standard deviation. $P<0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Alcohol abuse (SRAI 25 – 900 g/day) was identified in 36 of the 50 patients. Forty-two patients were smokers (5-70 pack years) (Table 1). Twenty-eight patients met the criterion for pancreatic exocrine insufficiency (fecal elastase < 200 µg/g) and were receiving pancreatic enzyme replacement therapy (PERT) (Tables 1 and 2). Patient BMI values were between 15-35 kg/m2 (<20: n=10; 20-25: n=32; >25: n=8). The duration of chronic pancreatitis was 1-23 years (median: 12).

Half of the patients reported regular pain in the bones. Twenty patients reported fractures in response to low trauma [13]. One patient also reported a fracture without trauma.

Bone Metabolism

Urine calcium, deoxypyridinoline, and vitamin D (25-OH cholecalciferol) were significantly decreased whereas serum calcium, phosphate, bone-specific alkaline phosphatase, and parathyroid hormone were normal (Table 2). Nutritional parameters were also normal for the entire group.

Pancreatic Function

In relation to bone metabolism. There was no correlation between three classes of fecal elastase-1 (< 100 µg/g: n = 22; 100-200 µg/g: n = 8; > 200 µg/g: n = 17) and serum calcium, 25-OH-cholecalciferol, or deoxypyridinoline (Figure 1).

Bone Density

Fifteen patients underwent DXA. The median T score was -1.1. Five patients had normal bone density (T score > -1), nine had osteopenia (T score -1 to – 2.5), and one patient had osteoporosis (T score < -2.5) (Table 3). There

Table 1. Patient characteristics (total group n = 50)

	Value	unit	No. of cases
Age (median±SD)	45.2 ± 8.38	years	50
Body weight (median±SD)	69.7 ± 12.7	kg	50
BMI (median±SD)	22.5 ± 3.6	kg/m^2	50
Smoking (median±SD)	23.6 ± 12.5	packs x year	42
Alcohol (median±SD)	210 ± 193	g/day	34
Duration of CP (range)	1-23	years	50
PERT	-	-	28
Bone pain	-	-	25
Fractures	-	-	20

Table 2. Serum parameters of bone metabolism and nutrition

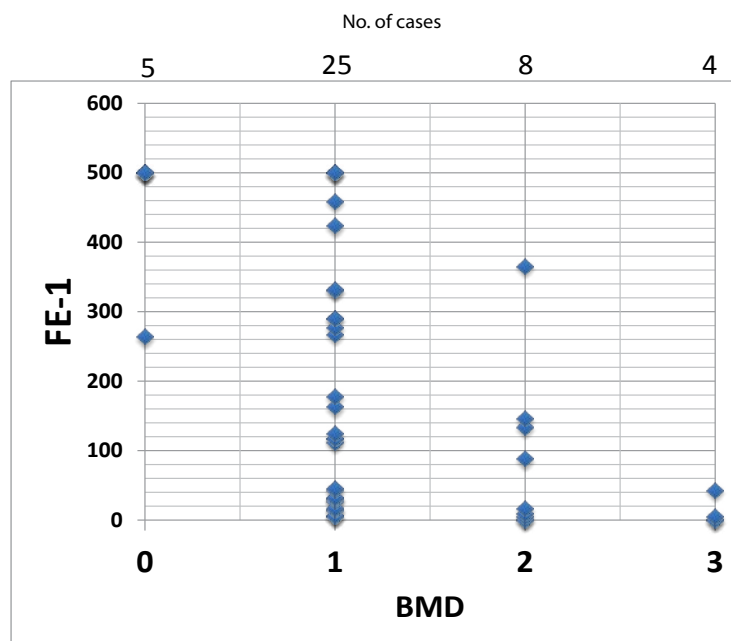|	Reference range	Median ± SD	Range	Units
- **Bone metabolism**				
- Calcium (serum)	2.20–2.55	2.35 ± 0.13	2.02 – 2.6	mmol/l
- Calcium (urine)	2.5–8.0	2.70 ± 2.56	0.04 – 10.93	mmol/l
- Phosphate	0.81–1.45	1.19 ± 0.25	0.68 – 1.93	mmol/l
- Alkaline phosphatase (bone-specific)	<69	28.71 ± 23.40	6.0 – 109.0	U/l
- 25-OH-cholecalciferol	40–185	39.06 ± 20.65	7.5 – 77.5	nmol/l
- Parathormone	12–72	37.98 ±28.74	2.0 – 141.0	pg/ml
- Deoxypyridinoline (urine)	2.3–5.4	6.94 ± 4.11	1.82 – 27.5	μmol/mol creatinine
- **Pancreatic function**				
- Fecal elastase-1[1]	>200	182 ± 193	0.1 – 500	μg /g feces
- **Serum parameters**				
- Total protein	63-82	71.10 ± 9.01	41.4 – 87.6	g/l
- Albumin	35-50	35.87 ±6.48	17.8 – 46.3	g/l
- Alkaline phosphatase	38-126	104.80 ± 35.77	49.0 – 350.0	U/l
- ASAT	17-59	35.09 ± 32.35	12.0 – 171.3	U/l
- ALAT	21-56	41.75 ± 43.0	11.0 – 279.0	U/l
- γ-GT	15-73	142.39 ± 184.65	13.0 – 759.6	U/l
- Cholesterol	3.6-6.2	4.78 ± 1.18	2.21 – 8.17	mmol/l
- Testosterone	2.8-8.0	5,30 ± 2.86	0.46 – 11.14	ng/ml
- TSH	0.27-4.2	1.37 ±0.82	0.11 – 3.83	μU/ml
- Vitamin K	0.09-2.12	1.05 ± .77	0.04 – 3.09	ng/ml
- Zinc	9.18–18.3	14.03 ± 3.54	7.0 – 25.5	μmol/l

[1]: n = 48 for fecal elastase-1

Figure 1. Bone mineral density (BMD), as measured by conventional X-ray, in correlation with fecal elastase-1 (FE-1). BMD 0 = normal, 1 = mild, 2 = moderate, 3 = severe (complete demineralization)[11, 12]. Note that datapoints can be superimposed.

was a trend toward a correlation between patients with low fecal elastase-1 and low T scores (p = 0.065). When patients receiving PERT (n = 9) were compared to those not receiving enzymes (n = 5), the patients receiving PERT had significantly higher DXA scores (-0.80 ± 0.6 vs. -1.51 ± 0.55; p < 0.05).

Conventional vertebral X-rays showed normal bone mineral density (BMD) in 3 of the 42 patients tested, mildly-reduced density in 32, moderately-reduced density in 6, and severely-reduced density with a fracture in one patient. All ten patients whose bone density was assessed as reduced by DXA also had assessments of reduced BMD by conventional X-ray. Reduced BMD measurement by conventional X-ray correlated with low fecal elastase-1 (p < 0.05; Figure 1). Patients who had fecal elastase-1 concentrations greater than 200 μg/g FE-1 (394 ± 99) had DXA scores of -0.44 ± 0.2 and X-ray BMD scores of 0.93 ± 0.23 in contrast to patients with pancreatic exocrine insufficiency (FE-1 < 200 μg/g; 38 ± 48), who had DXA scores of -1.76 ± 0.5 and X-ray BMD scores of 1.2 ± 0.31 (p = 0.04 for FE-1 and BMD scores).

DISCUSSION

Normal bone mineral density and bone metabolism require adequate concentrations of vitamin D. The absorption of vitamin D in turn depends on the uptake of lipids,

something that can only occur if sufficient pancreatic enzymes are available at the right time and place in the intestine [14]. In the current study, a significant decrease was seen in serum vitamin D (25-OH cholecalciferol), along with a significant increase in deoxypyridinoline in urine. Bone mineral density was reduced in the majority of patients with chronic pancreatitis. There was a correlation between pancreatic exocrine function and bone mineral density (Figure 1).

The current study differs from previous studies in that it is the only prospective study in males. Only male patients were recruited in order to avoid the hormonal variations found in women. Concern about hormonal variations and associated effects on bone metabolism was raised in a study that included both women and men with PEI due to cystic fibrosis [15]. However, in a more recent study no differences were found between male and female patients [16]. The results of the current prospective study are consistent with the significant decrease in bone mineral density seen in other European and non-European cohorts using DXA [10, 17] and conventional X-ray [17]. Vitamin D deficiency has been found in a number of studies of patients with chronic pancreatitis [10, 15, 17]. Some studies found a correlation between PEI and decreased BMD [18] but did not find a correlation between vitamin D levels or supplementation and decreased BMD [16, 17-19]. Haaber *and colleagues* did not find significant differences in BMD between pancreatitis patients with and without PEI [10], however, BMD as measured with DXA was significantly lower in the PEI group, as in our study. The percentage of patients with decreased bone mineral density (osteopathy) ranged from 34% to 100% in previous studies (Table 4) and did correlate with the severity of chronic pancreatitis in at least one study [18]. Although DXA is routinely used in endocrinology and is considered the gold standard for assessing reduction of bone mineral density, the current study showed that conventional X-ray, which is more accessible, may be sufficient. The fact that osteopathy is common in older cystic fibrosis patients has been firmly established [2], but osteopathy in chronic pancreatitis has only recently begun to receive attention.

The way clinicians and investigators view pancreatic exocrine insufficiency has been changing. Elegant studies using the C^{13} mixed-triglyceride breath test have made it clear that malnutrition persists even after the symptoms of *chronic pancreatitis-induced pancreatic exocrine insufficiency* have been treated [20]. (Persistent) nutritional deficiency can be measured easily by using serum parameters such as prealbumin, vitamin D, retinol binding protein, zinc and magnesium [21]. Although we could correlate low fecal elastase-1 to low bone mineral density, in our patients, in our study, nutritional parameters were remarkably normal. However, we did not measure all of the recommended parameters and the majority of our patients was on pancreatic enzyme replacement therapy.

Fecal elastase-1 is not helpful in detecting mild to moderate pancreatic exocrine insufficiency [7]. However, according to published guidelines, a fecal elastase-1 value below 200 µg/g is considered reliable in establishing the diagnosis of PEI [3-6]. A very low level of fecal elastase-1 can, therefore, be considered to be a valid indication of pancreatic exocrine insufficiency [22, 23]. In agreement with the current study, several previous investigations have shown a link between significant secondary disease, osteoporosis (decreased bone mineral density), nutritional deficiency (low vitamin D), and pancreatic exocrine insufficiency (low fecal elastase-1). A recent systematic review showed that one out of four patients with chronic pancreatitis had osteoporosis and two-thirds had either osteoporosis or osteopenia [24] (Table 4). As a result, these patients had a high prevalence of low-trauma fractures, and their risk of fracture was greater than that seen in patients with Crohn's disease [13].

Table 3. Parameters of bone metabolism and bone mineral density

	DXA					BMD		
Reference	osteopenia	osteoporosis	all path	normal	mild	moderate	severe	all path
> -1	-1 - -2.5	< -2.5	-	n = 3	n = 32	n = 6	n = 1	n = 7
n=5 (33%)	n=9 (60%)	n=1 (7%)	n=10 (66%)	(7%)	(76%)	(14%)	(2%)	(93%)

DXA = dual energy X-ray absorption; BMD = bone mineral density according to WHO criteria [11].

Table 4. Rates of osteopathy (osteoporosis, osteopenia, fractures) in patients with chronic pancreatitis

year	# of pt	method	Osteopathy total (%)	osteoporosis %	Osteopenia %	Osteomalacia %	unspecified %	comments		ref.
1997	14	DXA	71	21	50	-	-	men only	Moran et al.	15
2000	58	DXA	85	64	22	-	-	-	Haaber et al.	10
2003	42	DXA	100	-	-	-	100	men only	Mann et al.	18
2008	73	DXA	39	5	26	8	-	-	Djusikova et al.	25
2011	31	DXA	100	-	-	-	-	-	Sudeep et al.	17
2012	62	DXA	34	-	-	-	-	-	Duggan et al.	16
2013	N/a	DXA	-	-	-	-	-	-	Sikkens et al.	19
2014	42	DXA, XR	-	16	76	-	-	men only	Haas et al.	current
-	322	-	-	64	-	-	-	-	-	-
2014	513	DXA, XR	65	23	40	-	-	Systematic review	Duggan et al.	24

N/a: not available

The treatment of pancreatic exocrine insufficiency should aim to correct malnutrition and prevent secondary damage outside the pancreas. Rather than simply relieve symptoms. A prospective cohort study is needed to determine whether intervention that corrects pancreatic exocrine insufficiency results in an improvement of osteopathy in patients with chronic pancreatitis.

Acknowledgement

Conflict of Interest

There are no conflicts of interest to declare.

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