Alterations of Bone Mineral Density and Bone Metabolism in Patients With Various Grades of Chronic Pancreatitis

S.T.W. Mann, H. Stracke, U. Lange, H.U. Klör, and J. Teichmann

The aim of this study was to examine bone mineral density (BMD) and bone metabolism in patients with chronic pancreatitis to determine if increased severity of the disease would correlate with increased bone loss. Between October 1999 and September 2000, we investigated 42 patients with an average age of approximately 53 years suffering from chronic pancreatitis, as well as 20 healthy male controls with an average age of 49 years. Dual energy x-ray absorptiometry (DEXA) was performed on patients and controls, and serum levels of parathyroid hormone (PTH), osteocalcin (OC), carboxy-terminal propeptide of type I procollagen (CICP), bone-specific alkaline phosphatase (BAP), 1,25$(OH)_2$ vitamin D_3 and 25(OH) vitamin D_3, as well as fecal elastase 1 were also determined. The severity of chronic pancreatitis in patients was determined via endoscopic retrograde cholangiopancreatography (ERCP) and assigned to 1 of 3 grades based on the Cambridge classification. BMD of patients with chronic pancreatitis was markedly decreased compared to controls (means in patients: DEXA lumbar vertebra anterior/posterior (LV ap) 96.8% ± 4.2%, DEXA Ward's triangle (WARD) 92.2% ± 5.2%; controls: DEXA LV ap 98.7% ± 3.7%, DEXA WARD 97.1% ± 3.1%; $P < .05$ and $P < .0001$) and correlated with the various Cambridge-grades (DEXA LV ap and DEXA WARD, $P < .01$). Fecal elastase 1 showed sensitivities of 14%, 87%, and 95% for the Cambridge-grades I, II, and III, respectively, and correlated with this classification of severity of chronic pancreatitis ($P < .01$). Furthermore, fecal elastase 1 of patients correlated the same way with both D_3-vitamins ($P < .01$), as well as with parameters of BMD ($P < .01$). If fecal elastase 1 in patients was below 200 μg/g, then the BMD and vitamin D_3 values were also significantly decreased compared to those with fecal elastase 1 above 200 μg/g. In patients with Cambridge grades II and III 1,25$(OH)_2D_3$ was markedly decreased (26.7 ± 7.7 pg/mL and 27.6 ± 9.0 pg/mL) compared to those with Cambridge grade I (38.0 ± 10.5 pg/mL; between I and II, $P = .027$; between I and III, $P = .033$). 25$(OH)D_3$ was not significantly different within the various Cambridge groups ($P = .07$). Compared to controls, both D_3 vitamins, as well as fecal elastase 1, were extremely low (means in patients: fecal elastase 1, 140.7 ± 75.7 μg/g; 1,25$(OH)_2D_3$, 29.9 ± 9.5 pg/mL; 25$(OH)D_3$, 26.7 ± 9.7 nmol/L; controls: fecal elastase 1, 694.9 ± 138.6 μg/g; 1,25$(OH)_2D_3$, 67.5 ± 4.3 pg/mL; 25$(OH)D_3$, 69.5 ± 13.5 nmol/L). A significant correlation was observed between increased severity of chronic pancreatitis based on both endoscopic retrograde cholangiopancreatography and levels of fecal elastase 1, with decreased circulating levels of vitmain D_3 and decreased BMD. This supports a connection between the inflammatory destruction of the pancreas (Cambridge classification), exocrine pancreatic insufficiency (fecal elastase 1), altered levels of vitamin D metabolites, and loss of skeletal mass.

CHRONIC PANCREATITIS is a progressive inflammatory condition that results in permanent morphologic changes in the pancreas, which leads to impairment of endocrine and exocrine functions.[1] Endoscopic retrograde cholangiopancreatography (ERCP) is the most sensitive imaging procedure of diagnosing chronic pancreatitis.[2] The Cambridge classification[3] permits stratification of morphologic abnormalities. Compared with the "gold standard," the secretin caerulein test, fecal elastase 1 is a highly sensitive and specific noninvasive pancreatic function test.[4] A parallel between exocrine function and ERCP results is found in chronic pancreatitis,[5] even when using fecal elastase 1 to determine exocrine pancreatic insufficiency.[6,7] Methods for measuring bone mineral density (BMD) have improved in recent years.[8,9] Quantitative evaluation of the BMD in the skeleton performed mainly by dual energy x-ray absorptiometry (DEXA) is considered to be an appropriate method for clinical use with excellent precision and accuracy.[8] One field, which has until now received little attention, is the magnitude of changes in BMD and bone metabolism with respect to the different severity grades of chronic pancreatitis. The consequences of chronic pancreatitis may be relevant to serum levels of lipid soluble vitamin D_3 because of its dependence on photosynthesis in the skin, as well as on direct intestinal resorption. It should be investigated whether this creates a relevant link between chronic pancreatitis and bone metabolism or if there are any other connections. Until now, however, only very few investigators have described any conspicuous vitamin D deficiency in patients with chronic pancreatitis.[10-14] Also, there were no connections found between the severity grade of chronic pancreatitis, the decreased vitamin D serum levels, and the determined loss of BMD.[10,13,14] These connections should be further investigated.

MATERIAL AND METHODS

Patients and Controls

Between October 1999 and September 2000, 42 male patients were included in our studies. They were admitted to hospital for workup of chronic pancreatitis. All patients had a typical disease history, as well as a diagnosis based on abdominal sonography, computer tomography (criteria: structure inhomogeniety of the parenchyma, organ atrophy, expansion in the pancreatic duct, facultative existence of pseudo cysts or calcification), and laboratory routine parameters. Exclusion criteria were: female sex; ages under 17 or over 86 years; steatorrhea; pancreatic-biliary obstructions; actual and relevant alcohol consumption; medication with influence on osteologic and/or endocrine parameters (heparin, ketoconazol, glucocorticoids, thiacide-diuretics, psychopharmacologic agents, carbamazepin); chronic or severe concommitant

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Table 1. Age, PTH, OC, CICP, BAP, BMD, fecal elastase 1, 1,25(OH)$_2$D$_3$, and 25(OH)D$_3$ in Patients With Chronic Pancreatitis and Controls

Parameters	Controls (n = 20)	Patients				
		Cambridge Grade				
		I (n = 7)	II (n = 15)	III (n = 20)	*P*	Total (N = 42)
Age (yr)	48.9 ± 6.4	44.9 ± 21.2	55.1 ± 14.3	53.4 ± 8.6	.24	52.6 ± 13.5
PTH (pg/mL)	37.8 ± 4.8	28.7 ± 25.5	28.7 ± 13.7	35.4 ± 25.2	.61	31.9 ± 21.6
OC (ng/mL)	19.8 ± 3.9	24.1 ± 17.0	23.0 ± 13.5	22.2 ± 14.2	.95	22.8 ± 14.1
CICP (ng/mL)	121.0 ± 41.6	96.4 ± 44.3	95.8 ± 49.8	116.6 ± 119.2	.76	105.8 ± 88.5
BAP (U/L)	23.7 ± 11.2	26.8 ± 7.4	27.5 ± 12.3	30.8 ± 17.7	.73	29.0 ± 14.4
DEXA LV ap (% of normal)	98.7 ± 3.0	100.9 ± 2.7	97.8 ± 3.5	94.7 ± 3.8	<.01	96.8 ± 4.2
DEXA LV l (% of normal)	102.5 ± 3.2	103.7 ± 3.9	100.5 ± 3.7	99.9 ± 4.7	.14	100.8 ± 4.4
DEXA WARD (% of normal)	97.1 ± 3.1	97.3 ± 4.4	93.1 ± 4.9	89.8 ± 4.3	<.01	92.2 ± 5.2
Fecal elastase 1 (μg/g)	694.9 ± 138.6	243.1 ± 43.5	151.5 ± 52.7	96.7 ± 61.1	<.01	140.7 ± 75.7
1,25(OH)$_2$D$_3$ (pg/mL)	67.5 ± 4.3	38.0 ± 10.5	26.7 ± 7.7	27.6 ± 9.0	<.05	29.0 ± 9.5
25(OH)D$_3$ (nmol/L)	69.5 ± 13.5	34.1 ± 13.1	24.4 ± 7.6	25.8 ± 9.0	.07	26.7 ± 9.7

NOTE. Data are means ± SD.

P < .05 indicates a significant difference between the patient groups allotted by the Cambridge classification.

diseases. Twenty healthy male persons between 35 and 60 years of age served as controls.

Endoscopic Investigations

A standard ERCP was performed exclusively in patients to verify the diagnosis. Based on the ERCP results, the pathomorphologic alterations of the pancreatitis were classified into 3 grades according to the Cambridge classification of 1984[3]: Cambridge I (equivocal), Cambridge II (mild to moderate), and Cambridge III (severe), respectively.

Biochemical Measurements

Blood samples were taken from all participants once at a fixed time in the morining (before ERCP in patients). The specific study parameters were parathyroid hormone (PTH) ("INTACT PTH" kit; Nichols Institute Diagnostics, San Juan Capistrano, CA; double-sided immunoradiometric assay), osteocalcin (OC) ("Human Osteocalcin" kit; Nichols Institute Diagnositcs; double-sided immunoradiometric assay), carboxy-terminal propeptide of type I procollagen (CICP) ("Prolagen-C-IEMA" kit; Metra Biosystems, Osnabrück, Germany; double-sided enzyme immunoassay), bone-specific alkaline phosphatase (BAP) ("Alkphase-B" kit; Metra Biosystems; enzyme immunoassay), 1,25(OH)$_2$ vitamin D$_3$ ("1,25(OH)$_2$ Vitamin D" kit; Immun Diagnostik, Bensheim, Germany; competitive radio receptor assay), and 25(OH)vitamin D$_3$ ("25(OH) Vitamin D" kit; Immun Diagnostik; competitive protein-binding assay) from serum, as well as pancreatic elastase 1 ("Pankreatic Elastase 1" kit; ScheBo Biotech, Giessen, Germany; double-sided enzyme immunoassay) from feces of patients and controls.

Osteodensitomerty

Standardized osteodensitometry via DEXA was performed on all participants. A Lunar DPX densitometer (LUNAR Radiation, Madison, WI) was used for measurement of BMD. The scan regions included the lumbar vertebra 2 to 4 anterior/posterior (DEXA LV ap), lateral (DEXA LV l), and Ward's triangle in the neck of the left femur (DEXA WARD). The results were determined as a percentage of a normal reference collective of young healthy persons of approximately 30 years of age, therefore, at a time of "peak bone mass."

Statistical Analysis

Results are presented by mean values and standard deviation. The following methods were applied for statistical analysis: a single-factor variance analysis, the Scheffé test, the nonparametric Kurskal-Wallis test with subsequent Dunn test, as well as the *t* test for independent random samples with and without the Welche's correction. The Pearons's correlation coefficient and also the nonparametric Spearman correlation coefficient were applied for finding any connections.[15,16]

RESULTS

Separation of the patients in accordance with the Cambridge classification resulted in significant variations for DEXA LV ap, DEXA WARD, fecal elastase 1, as well as for 1,25(OH)$_2$D$_3$ between the different severance grades of chronic pancreatitis (Table 1, Figs 1-4). Furthermore, the BMD, fecal elastase 1, and both D$_3$ vitamins of patients were markedly decreased compared with controls (Tables 1 and 2). There were significant correlations between BMD and the Cambridge grades (Table 3) in patients. Fecal elastase 1 values were below the lowest reference of 200 μg/g feces in 14% (1 of 7 patients), 87% (13 of 15 patients), and 95% (19 of 20 patients) of the patients with Cambridge grades I, II, and III, respectively.

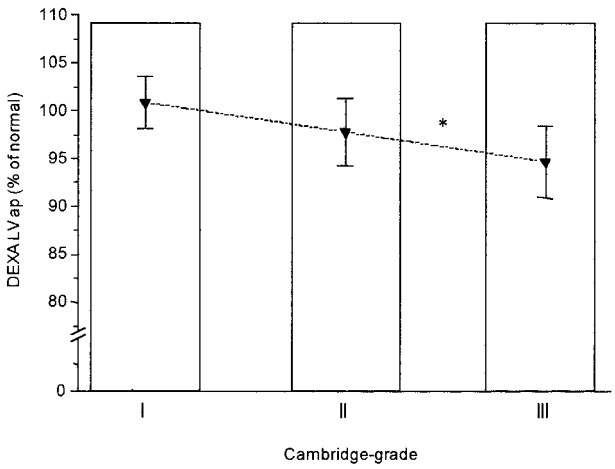

Fig 1. DEXA LV ap within the different grades of chronic pancreatitis according to the Cambridge classification (*P < .01).

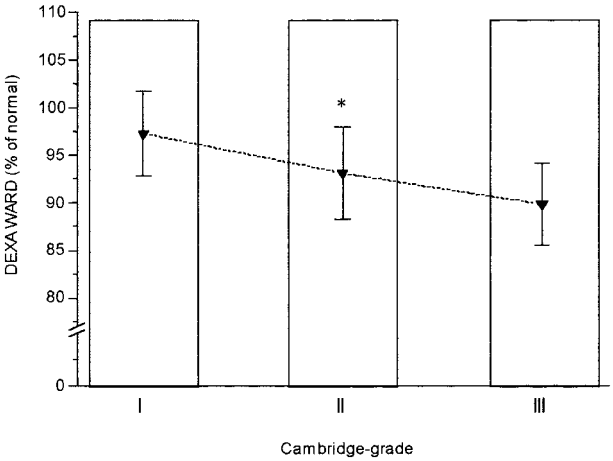

Fig 2. DEXA WARD within the different grades of chronic pancreatitis according to the Cambridge classification (*$P < .01$).

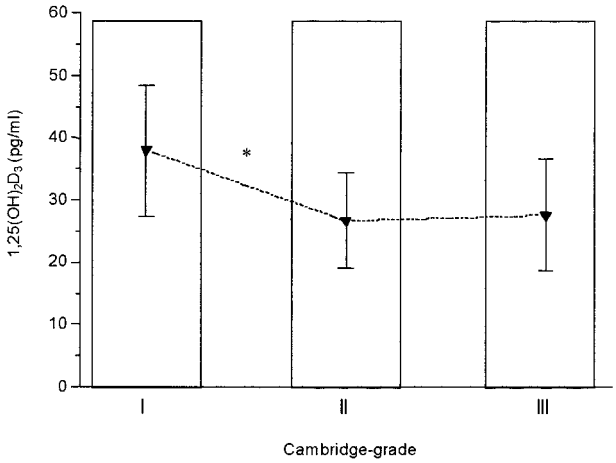

Fig 4. $1,25(OH)_2D_3$ within the different grades of chronic pancreatitis according to the Cambridge classification (*$P < .05$).

Furthermore, fecal elastase 1 in patients was significantly different within the various Cambridge groups ($P < .01$), and its average quantity was more than 79.5% decreased compared to controls (Tables 1 and 2). Also, fecal elastase 1 in patients correlated significantly with both D_3 vitamins (Table 4, Figs 5 and 6), as well as with all parameters of BMD (Table 5). A comparison of the 2 subgroups, those with values below the lowest reference of 200 μg/g for fecal elastase 1 and those above, showed significant differences for BMD and vitamin D_3 between these 2 groups. Therefore, if fecal elastase 1 was below 200 μg/g in patients, then the BMD and vitamin D_3 values were also significantly decreased compared to those with fecal elastase 1 above 200 μg/g (Table 6 and Fig 7). On the other hand, the D_3 vitamins correlated significantly with the BMD parameters (Table 4). $1,25(OH)_2D_3$ in patients with Cambridge grades II and III was markedly decreased compared with those with Cambridge grade I (between I and II, $P = .027$; between I and III, $P = .033$), and differed significantly within the various Cambridge groups (Table 1 and Fig 4). $25(OH)D_3$ was not significantly different within the various Cambridge groups ($P = .07$). Nevertheless, both D_3 vitamins were lower in patients with morphologic changes classified as Cambridge grades II and III, respectively, than in those with Cambridge grade I (Table 1), more clearly for $1,25(OH)_2D_3$ than for $25(OH)D_3$. All of the other parameters, such as PTH, OC, CICP, and BAP showed no relevant differences within the patients or between patients and controls.

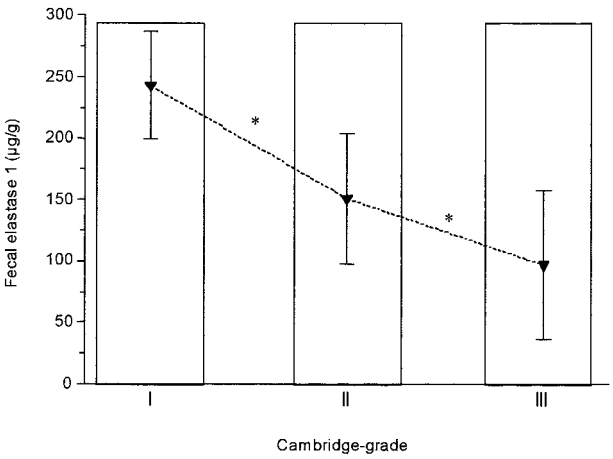

Fig 3. Fecal elastase 1 within the different grades of chronic pancreatitis according to the Cambridge classification (*$P < .01$).

DISCUSSION

In the past, chronic pancreatitis had been defined mainly by functional criteria of the exocrine pancreas. In recent years, it has been recognized that morphologic changes of the pancreas are also relevant for a correct grading of the disease, as stated by the Cambridge classification from 1984.[3] Diagnosis of chronic pancreatitis shows a parallel between exocrine function and ERCP results,[5] even using fecal elastase 1 to determine

Table 2. Comparison of PTH, OC, CICP, BAP, BMD, Fecal Elastase 1, $1,25(OH)_2D_3$, and $25(OH)D_3$ Between Different Patient Groups Allotted by the Cambridge Classification and Controls

	Error Probabilities of Variation in Comparison to Patients and Controls (N = 20)			
	Groups of Patients With Chronic Pancreatitis			
Parameters	Total (N = 42)	Cambridge I (n = 7)	Cambridge II (n = 15)	Cambridge III (n = 20)
PTH	$P = .0985$	$P = .3843$	$P = .0256$	$P = .6801$
OC	$P = .2036$	$P = .5319$	$P = .3872$	$P = .4741$
CICP	$P = .3614$	$P = .2311$	$P = .1240$	$P = .8775$
BAP	$P = .1201$	$P = .4211$	$P = .3555$	$P = .1394$
DEXA LV ap	$P = .0470$	$P = .0991$	$P = .4309$	$P = .0007$
DEXA LV l	$P = .0911$	$P = .4826$	$P = .1054$	$P = .0489$
DEXA WARD	$P < .0001$	$P = .9143$	$P = .0111$	$P < .0001$
Fecal elastase 1	$P < .0001$	$P < .0001$	$P < .0001$	$P < .0001$
$1,25(OH)_2D_3$	$P < .0001$	$P = .0004$	$P < .0001$	$P < .0001$
$25(OH)D_3$	$P < .0001$	$P = .0001$	$P < .0001$	$P < .0001$

NOTE. $P < .05$ indicates a significant difference between patients with chronic pancreatitis and controls.

Table 3. Correlation Between Cambridge Grade and BMD, as well as Fecal Elastase 1

Parameters	Cambridge Grade
DEXA LV ap	
Spearman correlation	−0.554
P	<.01
DEXA LV I	
Spearman correlation	−0.262
P	.093
DEXA WARD	
Spearman correlation	−0.498
P	<.01
Fecal elastase 1	
Spearman correlation	−0.652
P	<.01

NOTE. N = 42.
P < .05 indicates a significant correlation.

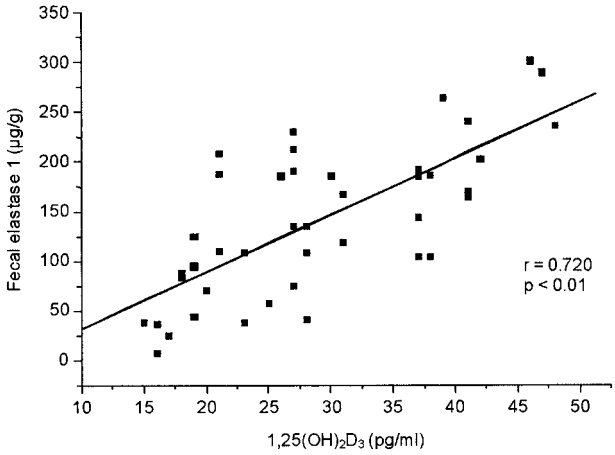

Fig 5. $1,25(OH)_2D_3$ in patients ith chronic pancreatitis depending on fecal elastase 1 ($r = .720$, $P < .01$).

pancreatic insufficiency.[6,7] Compared with the "gold standard," the secretin caerulein test, fecal elastase 1 is a highly sensitive and specific noninvasive pancreatic function test.[4] In the present study, fecal elastase 1 showed a highly significant negative correlation with pathomorphologic changes in patients, according to the Cambridge classification. This means distinctly lower levels of fecal elastase 1 in higher severity grades of chronic pancreatitis. In general, the average quantity of fecal elastase 1 in patients with chronic pancreatitis had decreased more than 79.5% compared to controls. Based on the lowest reference at 200 μg/g for fecal elastase 1 during diagnosed chronic pancreatitis, the results of sensitivities ranged from 14% to 87% and 95% for Cambridge grades I, II, and III, respectively. These results confirm the statements made by Dominguez-Muñoz et al[6] and Glasbrenner et al[7] by verifying the usefulness of fecal elastste 1 in diagnosis of chronic pancreatitis.

The present study showed highly significant differences of BMD between the different Cambridge severity grades of chronic pancreatitis, which were strongly marked by negative correlations. Therefore, the increasing severity grade of chronic pancreatitis also determined the decrease of BMD. These observations are new and enhance the statements made by Moran et al[13] and Haaber et al.[14] In their investigations, they used the pathomorphologic criteria for chronic pancreatitis only to establish a diagnosis in order to describe the frequency of loss of BMD in pancreatic patients. Complementary to this, we found that the loss of BMD depends on the severity grade of chronic pancreatitis, according to the Cambridge classification. There are various theories, which can be considered as a cause for loss of BMD in patients with chronic pancreatitis. Apart from the consequences of limited mobilization,[17] the results of malassimilation and chronic inflammation also have to be taken into consideration. Animal experiments were able to demonstrate that chronic unspecific inflammations through bone metabolism-influencing tissue factors lead to ostopenia in the trabecular, as well as compact bone by inhibiting osteoblast function.[18,19] Also, Scharla et al[20] discovered a simultaneous decrease of serum concentration of $1,25(OH)_2D_3$ in similar investigations, whereby an equivalent substitution was suitable

Table 4. Correlation Between D_3 Vitamins and BMD, as well as Fecal Elastase 1 in Patients With Chronic Pancreatitis

	Vitamin D_3	
Parameters	$1,25(OH)_2D_3$	$25(OH)D_3$
DEXA LV ap		
Pearson correlation	0.444	0.473
P	<.01	<.01
DEXA LV I		
Pearson correlation	0.145	0.237
P	.360	.131
DEXA WARD		
Pearson correlation	0.296	0.326
P	.057	.035
Fecal elastase 1		
Pearson correlation	0.720	0.623
P	<.01	< .01

NOTE. N = 42.
P < .05 indicates a significant correlation.

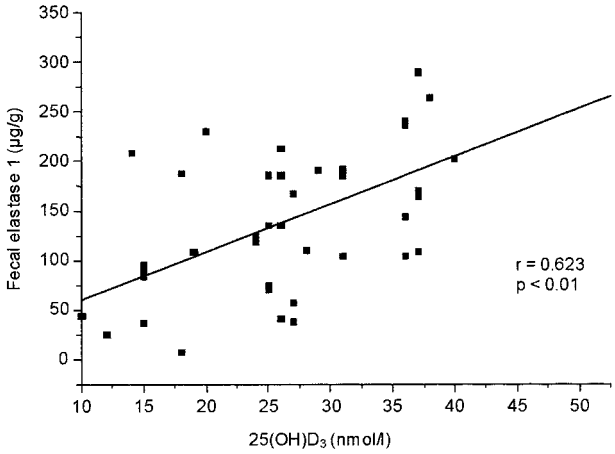

Fig 6. $25(OH)D_3$ in patients with chronic pancreatitis depending on fecal elastase 1 ($r = .623$, $P < .01$).

Table 5. Correlation Between Fecal Elastase 1 and BMD

Parameters	Fecal Elastase 1
DEXA LV ap	
Pearson correlation	0.641
P	<.01
DEXA LV I	
Pearson correlation	0.415
P	<.01
DEXA WARD	
Pearson correlation	0.552
P	<.01

NOTE. N = 42.
$P < .05$ indicates a significant correlation.

for preventing loss of skeletal mass, as well as preserving bone formation.

Until now, very little has been published about deficiency of lipid soluble vitamins, especially vitamin D, in patients with chronic pancreatitis.[11-14] The aim of the present study was to obtain information about the vitamin D status in patients with chronic pancreatitis and to see whether the deficiency depends on the severity grade of the disease. There were less amounts of both D_3 vitamins detected in patients with morphologic changes classified as Cambridge grades II and III than in those with Cambridge grade I, more clearly for $1,25(OH)_2D_3$ than for $25(OH)D_3$. Furthermore, both D_3 vitamins were extremely low in all Cambridge groups of patients with chronic pancreatitis compared with controls. These observations enhance statements made by Dibble et al,[11] Nakamura et al,[12] Moran et al,[13] as well as Haaber et al.[14] These investigators only found a difference in lipid soluble vitamins between patients with chronic pancreastitis and the control group. In addition, we were able to demonstrate a dependency between vitamin D_3 deficiency and the severity of chronic pancreatitis, according to the Cambridge classification. Possibly, the reduction of serum concentration, as described by Scharla et al,[20] especially of $1,25(OH)_2D_3$ during a chronically inflammatory process, could explain this phenomena. On the other hand, Poskitt et al[21] reported that a depletion of vitamin D storage is mainly caused by reduced exposition to the sun. Nevertheless, the increasing pathomorphologic pancreas alterations accompanied by restricted exocrine function in higher severance grades of chronic pancreatitis seem to be the most important reason for decreased vitamin D_3 in patients.

There are still no studies dealing with the link between fecal elastase 1 and the respective BMD or serum levels of vitamin D_3. Assumming that fecal elastase 1 is the representative marker for an exocrine insufficiency during a chronic pancreatitis, Dutta et al[10] described a frequent lack of lipid soluble vitamins, including $25(OH)D_3$, in patients with chronic pancreatitis and exocrine insufficiency. Accordingly, in the present study, fecal eleastase 1 showed a highly significant correlation to vitamin D_3, as well as to BMD. Therefore, vitamin D_3 deficiency, as well as BMD loss, depends very much on the severity grade of exocrine insufficiency, represented here by the fecal elastase 1 in patients. Twersky et al[22] reported that steatorrhea is the most obvious symptom of exocrine insufficiency in patients with chronic pancreatitis, and that its existence, as well as its frequency, depends on how severe exocrine dysfunction is and how much fat is supplied in food. Based on this, Dutta et al,[10] Dibble et al,[11] and also Nakamura et al[12] reported that steatorrhea does not influence the store of lipid soluble vitamins. Also, Haaber et al[14] described the lack of difference for $1,25(OH)_2D_3$ and $25(OH)D_3$ depending on the exocrine insufficiency, as well as on the duration of the disease in patients with chronic pancreatitis. Nevertheless, all of these observations are not suitable to invalidate the link with fecal elastase 1, severity of exocrine insufficiency, and vitamin D_3 deficiency in patients with chronic pancreatitis. According to Twersky et al[22] and DiMagno et al,[23] the parameter of steatorrhea is too variable for a precise description of exocrine function of the pancreas and, therefore, statements by Dutta et al,[10] Dibble et al,[11] and Nakamura et al[12] are less representative. The results from Haaber et al[14] also loose their significance, because enzymes were substituted in patients with exocrine pancreatic insufficiency. Because only 40% of experimentally administrered, radioactively labeled vitamin D_3 is absorbed by the intestines of patients with pancreatic insufficiency,[24] contrary to 80% to 90% in healthy persons, exocrine pancreatic function gains in significance and supports our own results with corresponding evaluation of fecal elastase 1. It is conceivable that fecal elastase 1 plays an independent role with regard to vitamin D_3 supply in the organism. On passing through the intestines, elastase 1 complexes with neutral steroids.[25] Because vitamin D_3 is also a sterol molecule, there is a hypothetical mechanism by which reduced vitamin D_3 absorption at reduced fecal elastase 1 could be linked.

Altogether the BMD loss, as well as vitamin D_3 deficiency, seems to be dependent on the severity of chronic pancreatitis and exocrine insufficiency, according to fecal elastase 1. This

Table 6. BMD, $1,25(OH)_2D_3$ and $25(OH)D_3$ Within the Two Subgroups According to Fecal Elastase 1 in Patients With Chronic Pancreatitis

Parameters	Subgrouping for Fecal Elastase 1		*P*	Total
	< 200 μg/g (n = 33)	> 200 μg/g (n = 9)		(N = 42)
DEXA LV ap (% of normal)	95.8 ± 3.7	100.3 ± 3.8	<.01	96.8 ± 4.2
DEXA LV I (% of normal)	100.0 ± 4.2	103.2 ± 4.2	=.056	100.8 ± 4.4
DEXA WARD (% of normal)	91.3 ± 5.0	95.6 ± 4.8	<.05	92.2 ± 5.2
$1,25(OH)_2D_3$	26.6 ± 8.0	37.6 ± 10.0	<.01	29.0 ± 9.5
$25(OH)D_3$	24.8 ± 8.0	33.8 ± 12.5	<.05	26.7 ± 9.7

NOTE. Data are means ± SD.
$P < .05$ indicates a significant difference between these 2 groups.

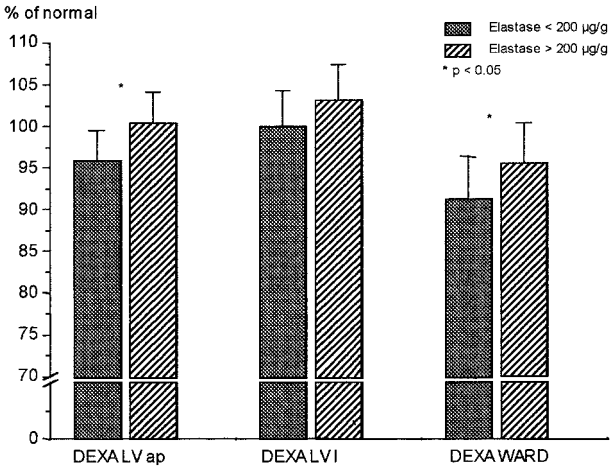

Fig 7. BMD depending on the subgrouping for fecal elastase 1 (*$P < .05$).

tendency finally leads to a distinctly reduced BMD and vitamin D_3 in patients with fecal elastase 1 values of below 200 μ g/g compared to those with higher values. Our own investigations of decreased BMD during decreasing values for fecal elastase 1 are plausible because it is irrefutable that vitamin D_3 is very important for calcium homeostasis, bone mineralization, osteoblastic differentiation, and bone matrix synthesis. Apart from the consequences of an extreme vitamin D_3 deficiency, such as rickets (infants), osteomalacia (adults), or fibrotic changes (osteitis fibrosa Recklingshausen), Scharla et al[26] and Chapuy et al[27] have already described the significant consequences of a subclinical deficiency with levels within the "normal" references. Therefore, even low normal serum concentrations of vitamin D can lead to osteopenia due to increased bone loss. While both groups found reduced serum levels of vitamin D_3 in patients with chronic pancreatitis, a finding which complements our results, neither Moran et al[13] nor Haaber et al[14] were able to confirm an association between low serum concentrations of vitamin D_3 and BMD. Even this connection, which neither was able to demonstrate (in the case of Moran et al[13] maybe due to an insufficient number of patients), was clearly confirmed by our results. According to Prost et al,[28] the loss of skeletal mass seems to be the result of a moderately decreased vitamin D level, as described by Scharla et al[26] and Chapuy et al.[27] In our studies, there were no significant differences between either patient groups or patients and controls with respect to PTH, OC, CICP, or BAP. Therefore, we did not find any evidence of an increase in bone turnover, which one would expect to find, for example, in the hyperparathyroidism associated with osteomalacia.

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