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Fecal Elastase 1 and Vitamin D_3 in Patients with Osteoporotic Bone Fractures

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Abstract

Background and Aims: The aim of the present study was to clarify if patients with osteoporotic bone fractures have exocrine pancreatic insufficiency, especially reduced fecal elastase 1, connected with lowered serum levels of vitamin D_3 that could be relevant for predominant osteoporosis.

Methods: Between October 1999 and September 2001, we investigated on 167 patients with an average age of approx. 69 years suffering from typical osteoporotic bone fractures, as well as 20 healthy controls with an average age of 53 years. A standardized osteodensitometry via dual energy X-ray absorptiometry (DEXA) was performed in all participants. Levels of PTH, $1,25(OH)_2$Vitamin D_3, 25(OH)Vitamin D_3, calcium and phosphate in serum, elastase 1 in feces as well as the body mass index were determined in all patients and controls.

Results: In patients $25(OH)D_3$ was more than 60% and $1,25(OH)_2D_3$ was more than 53% decreased compared to controls. Fecal elastase 1 was lower than the lowest reference of 200 μg/g feces in more than 34% of the patients and it was more than 65% reduced in comparison to healthy controls (fecal elastase 1 patients: 240.7 ± 96.3 μg/g; controls 694.9 ± 138.6 μg/g). Separation of the patients in accordance with the elastase 1 contend in feces into four groups (below 100 μg/g, between 100 and 200 μg/g, between 201 and 300 μg/g and above 300 μg/g) resulted in significant variations for $25(OH)D_3$, $1,25(OH)_2D_3$, calcium and PTH between these groups ($p < 0.01$). Furthermore $25(OH)D_3$, $1,25(OH)_2D_3$, calcium and PTH correlated significantly with elastase 1 in feces ($p < 0.01$) the way, that lower fecal elastase 1 was connected with lower levels of the other parameters. BMI shows no relevant differences within the patients or between patients and controls.

Conclusion: Exocrine pancreatic insufficiency, especially lowered fecal elastase 1, may be much more frequent in patients with osteoporotic bone fractures than suggested so far. Lowered exocrine pancreatic function with lowered fecal elastase 1 seems to be relevant as a reason for reduced levels of circulating vitamin D_3 metabolites being an appropriate additional cause for predominant osteoporosis.

Key words: fecal elastase 1, vitamin D_3, osteoporosis, bone-fracture, bone metabolism.

Introduction

Fracture risk is a function of trauma sustained (e.g. in falls) and bone strength (which depends on both, the quantity of bone and its architecture). Osteoporotic bone fractures, commonly of the hip, spine or forearm, are typically sustained with little or no antecedent trauma. The combined lifetime risk for hip, forearm and vertebral fractures coming to clinical attention is around 40% [1]. Thus Osteoporosis and its consequences as osteoporotic bone fractures is a major public health problem with serious consequences in terms of mortality, morbidity and economic costs [2-6]. Beside other reasons for osteoporosis vitamin D_3 gains a special relevance. The basic importance of vitamin D_3 for calcium homeostasis, bone mineralisation, osteoblastic differentiation, and bone matrix snythesis is still irrefutable [7]. 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. and Chapuy et al. [8, 9] have already described the extensive consequences of a sub-clinical deficiency with values within the "normal" references. Vitamin D_3 and Calcium have been shown in some randomised clinical trials to reduce hip fractures and other non vertebral fractures in men and woman as much as over 40% [10-12]. Poskitt et al. [13] reported, that a depletion of vitamin D storage is mainly caused by a reduced exposition to the sun, but altogether serum levels of lipid soluble vitamin D_3 depends on photosynthesis in the skin as well as on direct intestinal resorption. In our further studies we could demonstrate a connection between reduced exocrine pancreatic function, especially reduced fecal elastase 1, lowered levels of vitamin D_3 and loss of skeletal mass in patients with chronic pancreatitis [14, 15]. The aim of the present study is to clarify, if patients with osteoporotic bone fractures and without chronic pancreatitis although have reduced fecal elastase 1 connected with reduced serum levels of vitamin D_3, that could be relevant for predominant osteoporosis.

Material and Methods

Patients

Between October 1999 and September 2001 we investigated on patients with typical osteoporotic bone

fractures such as forearm, hip and spine. A standardized osteodensitometry via dual energy X-ray absorptiometry (DEXA) was performed on all patients. If DEXA revealed T-scores lower than –2,5 SD (accordingly to actual WHO-definition [16] this means severe osteoporosis) patients matched our criteria and finally 167 could be included in our study. Exclusion criteria were: ages under 40 or over 86 years; steatorrhea; pancreatic-biliary obstructions; actual and relevant alcohol consumption; medication with influence on osteological and/or endocrine parameters (heparin, ketoconazol, glucocorticoids, thiacide-diuretics, psychopharmacological agents, carbamazepin); chronic or severe concommitant diseases.

Controls

Twenty healthy persons between 40 and 60 years of age served as controls.

Biochemical Measurements

Blood samples were taken from all participants once at a fixed time in the morining. The specific study parameters were parathormone ("INTACT PTH"-kit from Nichols Institute Diagnostics, San Juan Capistrano, California; double-sided immuno-radiometric assay), 1,25$(OH)_2$ Vitamin D_3 ("1,25$(OH)_2$ Vitamin D"-kit from Immun Diagnostik, Bensheim, Germany; competitive radio receptor assay), 25(OH)Vitamin D_3 ("25(OH) Vitamin D"-kit from Immun Diagnostik, Bensheim, Germany; competitive protein-binding-assay), calcium and phosphate from serum as well as pancreatic elastase 1 ("Pankreatic Elastase 1"-kit from ScheBo Biotech, Giessen, Germany; double-sided enzyme-immuno assay) from feces of patients and controls. The body mass index (BMI) was also determined in all.

Osteodensitomerty

Standardized osteodensitometry via dual energy X-ray absorptiometry (DEXA) was carried out in all participants. A Lunar DPX densitometer (LUNAR Radiation Corporation, Madison, Wisconsin) was used for measurement of BMD. The three scan regions included lumbar vertebra 2 to 4 ap and lateral as well as Ward`s triangle in the neck of the left femur. The results were determined as T-score of a normal reference collective of young healthy persons of approx. 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 non-parametric 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 non-parametric Spearman correlation coefficient were applied for finding any connections [17, 18].

Results

All over in patients with osteoporotic bone fractures 25$(OH)D_3$ was more than 60% and 1,25$(OH)_2D_3$ was more than 53% decreased compared to controls (Table 1). Fecal elastase 1 was lower than the lowest reference of 200 μg/g feces in more than 34% of the

Table 1. 25$(OH)D_3$, 1,25$(OH)_2D_3$, Calcium, PTH and BMI (means ± standard deviation) in patients with osteoporotic bone fractures and controls. $p < 0.05$ indicates a significant difference between patients with different fecal elastase 1 ranges.

		Patients					
		Fecal elastase 1 ranges (mg/g)					
Parameters	**Controls** (N=20)	**<100** (N=7)	**100-200** (N=50)	**201-300** (N=41)	**>300** (N=69)	**p**	**Total** (N=167)
Age (years)	52.6 ± 6.4	73.4 ± 8.6	70.4 ± 7.4	72.1 ± 8.3	64.9 ± 11.2	P = 0.24	68.7 ± 9.2
25$(OH)D_3$ (nmol/l)	69.5 ± 13.5	13.2 ± 3.7	21.6 ± 8.7	25.7 ± 5.3	34.3 ± 7.7	p < 0.01	27.5 ± 7.2 (N=126)
1,25$(OH)_2D_3$ (pg/ml)	67.5 ± 4.3	22.3 ± 16.9	26.1 ± 12.4	32.3 ± 10.8	36.2 ± 12.4	p < 0.01	31.6 ± 12.2 (N=97)
Calcium (mmol/l)	2.4 ± 0.15	2.23 ± 0.17	2.25 ± 0.16	2.27 ± 0.15	2.35 ± 0.14	p < 0.01	2.30 ± 0.15
PTH (pg/ml)	37.8 ± 4.8	21.8 ± 4.0	28.6 ± 14.5	35.2 ± 14.6	42.0 ± 12.5	p < 0.01	35.5 ± 13.3 (N=140)
BMI (kg/m2)	25.2 ± 1.5	25.0 ± 1.4	25.7 ± 1.8	25.4 ± 1.6	25.0 ± 1.4	P = 0.141	25.3 ± 1.6

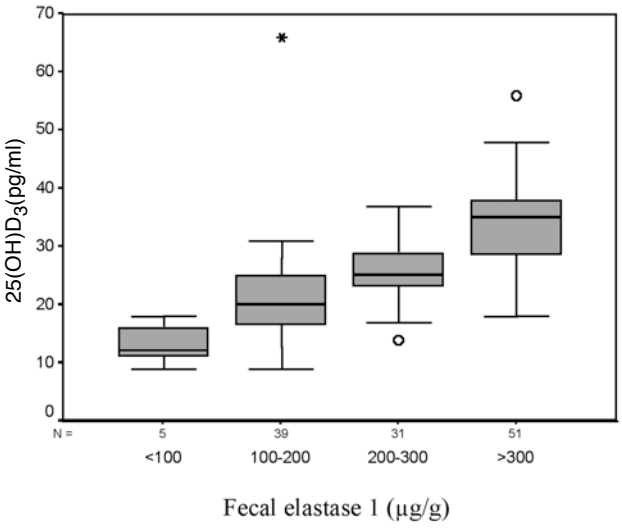

Fig. 1. $25(OH)D_3$ within the different ranges of fecal elastase 1.

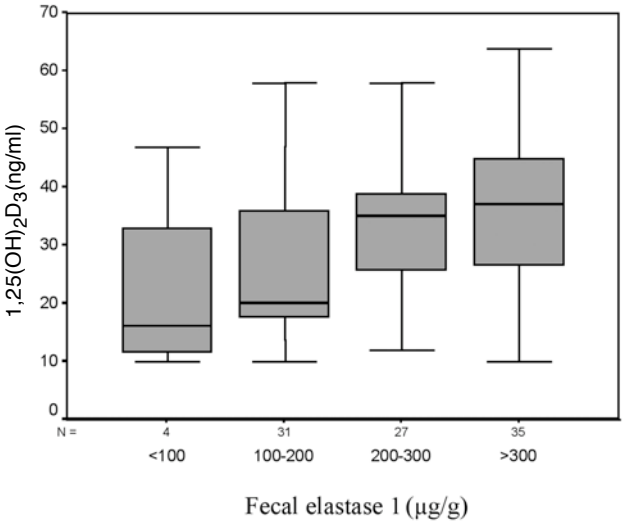

Fig. 2. $1,25(OH)_2D_3$. within the different ranges of fecal elastase 1.

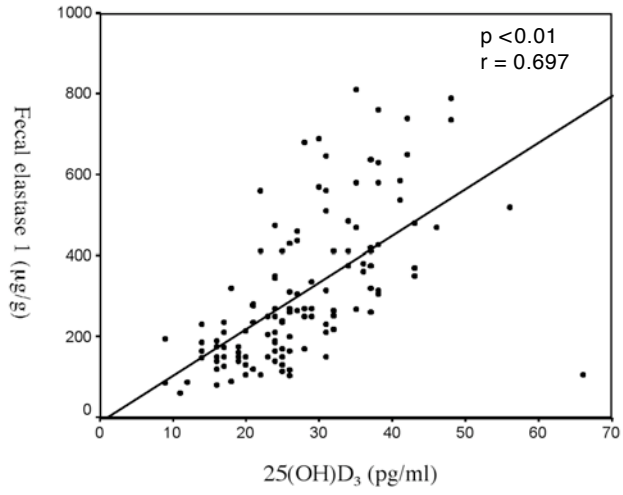

Fig. 3. $25(OH)D_3$ in patients with osteoporotic bone fractures depending on fecal elastase 1.

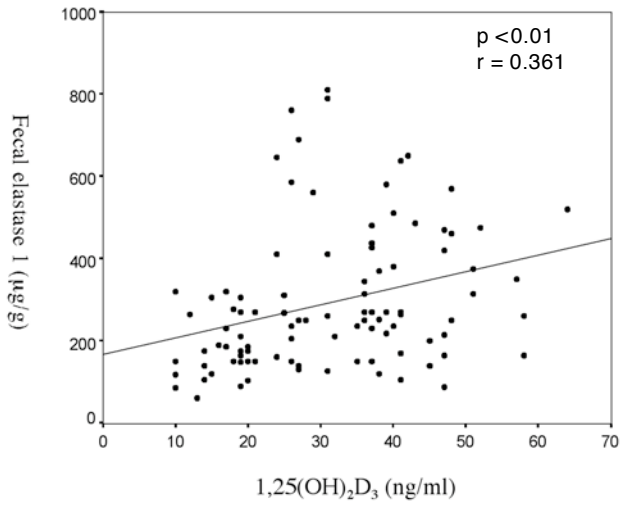

Fig. 4. $1,25(OH)_2D_3$ in patients with osteoporotic bone fractures depending on fecal elastase 1.

patients and it was more than 65% reduced in comparison to healthy controls (fecal elastase 1 patients: 240.7 ± 96.3 µg/g; controls 694.9 ± 138.6 µg/g). Separation of the patients in accordance with the elastase 1 contend in feces into four groups (below 100 µg/g, between 100 and 200 µg/g, between 201 and 300 µg/g and above 300 µg/g) resulted in significant variations for $25(OH)D_3$, $1,25(OH)_2D_3$, calcium and PTH between these groups ($p < 0.01$; Table 1; Figures 1-2). $25(OH)D_3$ decreases significantly from group with fecal elastase 1 of above 300 µg/g to all other groups ($p < 0.01$) and also from group with between 201 and 300µg/g to group with below 100 µg/g ($p < 0.01$). For $1,25(OH)_2D_3$ there is a significant decrease between group with above 300µg/g to group with between 100 and 200 µg/g ($p = 0.013$). Calcium and PTH was markedly decreased from group with fecal elastase 1 of above 300 µg/g to group with between 100 and 200 µg/g (calcium $p = 0.006$; PTH $p = 0.001$) as well as to group with below 100 µg/g ($p = 0.021$) only for PTH. Furthermore the parameters $25(OH)D_3$, $1,25(OH)_2D_3$, calcium and PTH correlated significantly with elastase 1 in feces of patients ($p < 0.01$; Table 2; Figures 3-4). Lower fecal elastase 1 therefore is connected with lower vitamin D_3 together with lowered PTH and calcium levels. BMI shows no relevant differences within the patients or between patients and controls (Table 1).

Discussion

Until now there are no studies dealing with the link between reduced circulating vitamin D_3 metabolites and lowered fecal elastase 1 in patients with osteoporotic bone fractures. In the present study fecal elastase 1 in patients with osteoporotic bone fractures is lower than the lowest reference of 200 µg/g feces in more than 34% of the patients and it is more than 65% reduced in comparison to healthy controls. Re-

Table 2. Correlation between fecal elastase 1 and $25(OH)D_3$, $1,25(OH)_2D_3$, Calcium, PTH and BMI. $p < 0.05$ indicates a significant correlation.

Parameter	$25(OH)D_3$	$1,25(OH)_2D_3$	Calcium	PTH	BMI
Fecal elastase 1					
Correlation Pearson	**0.620**	**0.300**	**0.256**	**0.423**	-0.114
p	**p < 0.01**	**p < 0.01**	**p < 0.01**	**p < 0.01**	p= 0.141
N	126	97	167	140	167
Fecal elastase 1					
Correlation Spearman	**0.697**	**0.361**	**0.236**	**0.490**	-0.137
p	**p < 0.01**	**p < 0.01**	**p < 0.01**	**p < 0.01**	p=0.079
N	126	97	167	140	167

duced fecal elastase 1 is connected with lowered vitamin D_3 and this could be demonstrated by comparison between patient groups with different severance grades of fecal elastase 1 deficiency as well as by direct correlation. In our further studies we could demonstrate a similar connection between fecal elastase 1, vitamin D_3 and BMD [14, 15], but no one of the patients had osteoporotic bone fractures and all had chronic pancreatitis. Nevertheless our present results are consistant with the observations we made at our patients with exocrine insufficiency caused by chronic pancreatitis. The fact of reduced BMD in our pancreatic patients with this way reduced vitamin D_3 serum levels allows the conclusion, that osteoporosis in our patients with osteoporotic bone fractures could be additional caused by vitamin D deficiency in consequence of occult exocrine pancreatic insufficiency. Poskitt et al. [13] reported, that a depletion of vitamin D storage is mainly caused by a reduced exposition to the sun, but altogether serum levels of lipid soluble vitamin D_3 depends on photosynthesis in the skin as well as on direct intestinal resorption. Since only 40% of experimentally administrered, radio-actively labeled vitamin D_3 is absorbed by the intestines of patients with pancreatic insufficiency [19], contrary to 80-90% 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. Upon passing through the intestines, elastase 1 complexes with neutral steroids [20]. Since 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. In the present study it is evident, that vitamin D_3 serum levels are more than 53% respectively more than 60% reduced in patients in comparison to controls. Therefore, as described by Scharla et al. and Chapuy et al. [8, 9], even low normal serum concentrations of vitamin D can lead to osteopenia due to increased bone loss. The prevalence of exocrine pancreatic insufficiency or lowered fecal elastase 1 in patients with osteoporotic bone fractures is jet unknown, because, to our knowledge, no data were published until now. But results of the present study make it highly probable that previous unknown exocrine pancreatic insufficiency, especially lowered fecal elastase 1, in patients with osteoporotic bone fracture is much more prevalent than suggested so far.

Even when other authors describe that BMI is, of all anthropometric factors, the strongest predictor of BMD [21, 22], our data do not support the relevance of BMI because no one of the patients had a low BMI but all had osteoporotic bone fracture.

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