Fecal Elastase 1 and Vitamin D₃ in Patients with Osteoporotic Bone Fractures

Department of Internal Medicine, Medical Clinic III and Polyclinic of the Justus-Liebig-University Giessen, Germany

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 D₃, that could be relevant for predominant osteoporosis.

Methods: Between October 1999 and September 2001, we investigated 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)₂Vitamin D₃, 25(OH)Vitamin D₃, 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)Vitamin D₃ was more than 60% and 1,25(OH)₂Vitamin D₃ 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)D₃, 1,25(OH)₂D₃, calcium and PTH between these groups (p < 0.01). Furthermore 25(OH)D₃, 1,25(OH)₂D₃, 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 D₃ metabolites being an appropriate additional cause for predominant osteoporosis.

Key words: fecal elastase 1, vitamin D₃, 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]. Besides other reasons for osteoporosis vitamin D₃ gains a special relevance. The basic importance of vitamin D₃ for calcium homeostasis, bone mineralisation, osteoblastic differentiation, and bone matrix synthesis is still irrefutable [7]. Apart from the consequences of an extreme vitamin D₃-deficiency, such as rickets (infants), osteomalacia (adults) or fibrotic changes (osteitis fibrosa Recklinghausen), 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 D₃ 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 D₃ 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 D₃ 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 D₃ that could be relevant for predominant osteoporosis.

MATERIAL AND METHODS

Patients

Between October 1999 and September 2001 we investigated on 167 patients with typical osteoporotic bone
fractures such as forearm, hip and spine. A standard-
ized osteodensitometry via dual energy X-ray absorp-
tiometry (DEXA) was performed on all patients. If
DEXA revealed T-scores lower than −2.5 SD (accord-
ingly 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; pan-
creatic-biliary obstructions; actual and relevant alcohol
consumption; medication with influence on osteologi-
cal and/or endocrine parameters (heparin, ketocona-
zol, glucocorticoids, thiacide-diuretics, psychopharma-
cological 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 morning. The specific study para-
eters were parathormone ("INTACT PTH"-kit from
Nichols Institute Diagnostics, San Juan Capistrano,
California; double-sided immuno-radiometric assay),
1,25(OH)₂ Vitamin D₃ ("1,25(OH)₂ Vitamin D"-kit
from Immundagnostik, Bensheim, Germany; com-
petitive radio receptor assay), 25(OH)Vitamin D₃
("25(OH) Vitamin D"-kit from Immun Diagnostik,
Bensheim, Germany; competitive protein-binding-as-
say), calcium and phosphate from serum as well as
pancreatic elastase 1 ("Pankreatic Elastase 1"-kit from
ScheSp Biotech, Giessen, Germany; double-sided en-
zymo-immuno assay) from feces of patients and con-
trols. The body mass index (BMI) was also determined
in all.

OSTEODENSITOMETRY

Standardized osteodensitometry via dual energy X-ray
absorptiometry (DEXA) was carried out in all partici-
pants. A Lunar DPX densitometer (LUNAR Radiation
Corporation, Madison, Wisconsin) was used for mea-
surement 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 de-
viation. The following methods were applied for sta-
tistical 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 coeffi-
cient and also the non-parametric Spearman correla-
tion coefficient were applied for finding any connec-
tions [17, 18].

RESULTS

All over in patients with osteoporotic bone fractures
25(OH)D₃ was more than 60% and 1,25(OH)₂D₃ 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)D₃, 1,25(OH)₂D₃, 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.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls (N=20)</th>
<th>&lt;100 (N=7)</th>
<th>100-200 (N=50)</th>
<th>201-300 (N=41)</th>
<th>&gt;300 (N=69)</th>
<th>p</th>
<th>Total (N=167)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.6 ± 6.4</td>
<td>73.4 ± 8.6</td>
<td>70.4 ± 7.4</td>
<td>72.1 ± 8.3</td>
<td>64.9 ± 11.2</td>
<td>P = 0.24</td>
<td>68.7 ± 9.2</td>
</tr>
<tr>
<td>25(OH)D₃ (nmol/l)</td>
<td>69.5 ± 13.5</td>
<td>13.2 ± 3.7</td>
<td>21.6 ± 8.7</td>
<td>25.7 ± 5.3</td>
<td>34.3 ± 7.7</td>
<td>p &lt; 0.01</td>
<td>27.5 ± 7.2</td>
</tr>
<tr>
<td>1,25(OH)₂D₃ (pg/ml)</td>
<td>67.5 ± 4.3</td>
<td>22.3 ± 16.9</td>
<td>26.1 ± 12.4</td>
<td>32.3 ± 10.8</td>
<td>36.2 ± 12.4</td>
<td>p &lt; 0.01</td>
<td>31.6 ± 12.2</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.4 ± 0.15</td>
<td>2.23 ± 0.17</td>
<td>2.25 ± 0.16</td>
<td>2.27 ± 0.15</td>
<td>2.35 ± 0.14</td>
<td>p &lt; 0.01</td>
<td>2.30 ± 0.15</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>37.8 ± 4.8</td>
<td>21.8 ± 4.0</td>
<td>28.6 ± 14.5</td>
<td>35.2 ± 14.6</td>
<td>42.0 ± 12.5</td>
<td>p &lt; 0.01</td>
<td>35.5 ± 13.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2 ± 1.5</td>
<td>25.0 ± 1.4</td>
<td>25.7 ± 1.8</td>
<td>25.4 ± 1.6</td>
<td>25.0 ± 1.4</td>
<td>P = 0.141</td>
<td>25.3 ± 1.6</td>
</tr>
</tbody>
</table>
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 content 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)D₃, 1,25(OH)₂D₃, calcium and PTH between these groups (p < 0.01; Table 1; Figures 1-2). 25(OH)D₃ 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)₂D₃ 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)D₃, 1,25(OH)₂D₃, 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 D₃ 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 D₃ 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-
duced fecal elastase 1 is connected with lowered vitamin D, 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, and BMD [14, 15], but no one of the patients had osteoporotic bone fractures and all had chronic pancreatitis. Nevertheless our present results are consistent with the observations 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 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 D3 depends on photosynthesis in the skin as well as on direct intestinal resorption. Since only 40% of experimentally administered, radio-actively labeled vitamin D3 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 D3 supply in the organism. Upon passing through the intestines, elastase 1 complexes with neutral steroids [20]. Since vitamin D3 is also a sterol molecule, there is a hypothetical mechanism by which reduced vitamin D1 absorption at reduced fecal elastase 1 could be linked. In the present study it is evident, that vitamin D1 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 yet 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.

**REFERENCES**


**Table 2. Correlation between fecal elastase 1 and 25(OH)D3, 1,25(OH)2D3, Calcium, PTH and BMI.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>25(OH)D3</th>
<th>1,25(OH)2D3</th>
<th>Calcium</th>
<th>PTH</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal elastase 1 Correlation Pearson</td>
<td>0.620</td>
<td>0.300</td>
<td>0.256</td>
<td>0.423</td>
<td>-0.114</td>
</tr>
<tr>
<td>p</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p = 0.141</td>
</tr>
<tr>
<td>N</td>
<td>126</td>
<td>97</td>
<td>167</td>
<td>140</td>
<td>167</td>
</tr>
</tbody>
</table>

**Table 2. Correlation between fecal elastase 1 and 25(OH)D3, 1,25(OH)2D3**, Calcium, PTH and BMI. p < 0.05 indicates a significant correlation.

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Address for correspondence:
Dr. Sacha T.W. Mann
Klinik und Poliklinik für Orthopädie und Orthopädische Chirurgie
Universitätsklinikum Giessen und Marburg
Standort Giessen
Justus-Liebig-Universität Giessen
Paul-Meimberg-Strasse 3
35392 Giessen
Germany
Phone: +49641/99-42900
Fax: +49641/99-42999
E-mail: SachaTWMann@web.de