

PARATHORMONE LEVELS AND VITAMIN D METABOLISM IN FEMALE PATIENTS WITH VARIOUS GRADES OF FECAL ELASTASE 1 DEFICIENCY

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Abstract

Background: There are still too few conclusive reports about conspicuous parathormone (PTH) and Vitamin D metabolism in patients with fecal elastase 1 deficiency or any connection of the calcium metabolism to the severity of exocrine pancreas insufficiency.

Methods: Between March 1998 and September 2002, we investigated on 240 female patients with fecal elastase 1 deficiency at an average age of approx. 56.4 years and suffering from meteorism and weight loss as well as on age matched 80 healthy female controls. Serum levels of PTH, total calcium, D₃-vitamins, calcitriol and calcifediol, as well as the concentration of fecal elastase 1 were determined in patients and controls.

Results: In 240 female patients with deficiency of fecal elastase 1 only two patients show milder cases of new diagnosed primary hyperparathyroidism. Calcitriol was markedly decreased (14.3 ± 6.1 and 20.7 ± 9.4 pg/ml) compared to controls (41.8 ± 8.3 pg / ml) ($p < 0.01$). Calcifediol was not significantly different within the various elastase-groups ($p = 0.07$). Nevertheless, vitamin D₃ and fecal elastase 1 in patients correlated significantly ($p < 0.01$) and, compared to controls, both were extremely low (means in patients. Both D₃-vitamins in patients were significantly lower when elastase 1 in feces was under 200 µg/g compared to the others (for calcitriol $p < 0.05$, for calcifediol $p < 0.05$).

Conclusion: In female patients elastase 1 in feces confirm the grade of vitamin D supply, and thus show a vitamin D₃-deficiency, depending on the loss of stool content. There seems to be a connection here between the loss of exocrine function and may be even the characteristic of sterol-binding of elastase 1 in the pancreas, which seems to be relevant for vitamin D-supply.

Key words: Fecal elastase 1, exocrine pancreatic insufficiency, PTH, vitamin D₃

INTRODUCTION

Deficiency of elastase 1 in feces has previously been regarded to be revealed sensitivities of 14%, 87%, and 95% for the Cambridge-grades I, II, and III, and correlated significantly with this classification of severity of chronic pancreatitis [1]. Faecal elastase 1 is, compared to the "gold standard", the secretin caerulein test, a highly sensitive and specific tubeless pancreatic func-

tion test [2]. In the diagnosis of chronic pancreatitis there is a parallelism between exocrine function and ERCP results [3], even using faecal elastase 1 for description of pancreatic insufficiency [4, 5]. One field which has until now received little attention are the changes of vitamin D₃ serum levels subjected to the different severity grades of pancreatic exocrine insufficiency. The consequences of exocrine insufficiency might be relevant for serum levels of lipid soluble vitamin D₃. However, conspicuous vitamin D-deficiency in patients with chronic pancreatitis has only been described by very few authors until now [6-10]. Accordingly, one of the most obvious cause of elevated PTH serum levels, impaired and lowered vitamin D₃, exocrine insufficiency with consecutive malassimilation and resulting insufficient vitamin D-supply should be further investigated.

MATERIAL AND METHODS

PATIENTS

Between March 1998 and September 2002, 240 female outpatients (aged from 56.47 ± 15.31 years) with lowered faecal elastase 1 were included in our studies. They were admitted to hospital for work up of weight loss resulting from pain related food intake, meteorism and/or maldigestion syndrome. Exclusion criteria were: male sex, age under 17 or over 80 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), altered kidney function and chronic or severe concomitant diseases. Based on the assumption of an interaction between exocrine and endocrine pancreatic function we excluded patients with a diabetes mellitus [11]. Controls: 80 healthy female persons between 39 and 60 years of age served as controls.

BIOCHEMICAL MEASUREMENTS

Blood examples were taken from all participants every morning at the same fixed time. The specific serum parameters of this study were PTH ("intact PTH 1 – 84 IRMA Kit from Nichols Institute Diagnostics, San Juan Capistrano, Californien, U.S.A., calcitriol ("1,25 (OH)₂ Vitamin D"-kit from Immun Diagnostik, Bensheim, Germany; competitive radio receptor assay) and calcifediol ("25 (OH)₂ Vitamin D"-kit from Im-

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mun Diagnostik, Bensheim, Germany; competitive protein-binding-assay). Pancreatic elastase 1 ("Pancreatic Elastase 1"-kit from ScheBo Biotech, Giessen, Germany; double-sided enzyme immuno-assay) was determined in the feces of all participants.

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 Welch's correction. The Pearson's correlation coefficient and also the non-parametric Spearman correlation coefficient were applied for investigating any connections [12, 13].

RESULTS

In 240 female patients with deficiency of fecal elastase 1 below the lowest reference of 200 µg/g feces only two patients (62 and 67 years) show milder cases of

new diagnosed primary hyperparathyroidism. At diagnosis of primary hyperparathyroidism events involving gastric disorders e.g. gastric ulcers, were prevalent in history of both patients. However there was no evidence of an acute or chronic pancreatitis in case history or ultrasound examination.

Furthermore, the vitamin D metabolism did not differ significantly within the various subgroups: Fecal elastase < 100 mg/g (N = 112) and 100 < 200 mg/g (N = 128) as well as extremely decreased compared to the controls (means in patients: 74.2 ± 22.7 and 158.5 ± 41.3µg/g; versus controls: 665.9 ± 117.4 µg/g; (p < 0.01; Table 1 and Table 3): Calcitriol in patients with deficiency of fecal elastase 1 was decreased (14.3 ± 6.1 and 20.7 ± 9.4 pg/ml) compared to controls (41.8 ± 8.3 pg / ml) (p < 0.01), but did not differ significantly within the various fecal elastase 1 -groups (p > 0.05; Table 4). Calcefediol was not significantly different within the various fecal elastase 1 -groups (p = 0.07). Nevertheless, both D₃-vitamins were lower in female patients with deficiency of fecal elastase 1 below the lowest reference of 200 µg/g feces more clearly for calcitriol than for calcefediol. Additionally, fecal elastase 1 in patients correlated significantly with both D₃-

Table 1. Age, fecal elastase 1, calcitriol and calcefediol (means ± standard deviation) in patients with fecal elastase 1 deficiency and controls. p < 0.05 indicates a significant difference between the patient-collectives allotted by the fecal elastase 1 deficiency

Parameters	Controls	Fecal elastase		p
	(N = 80)	< 100 mg/g (N = 112)	100 < 200 mg/g (N = 128)	
Age (years)	54.8 ± 12,4	56.0 ± 17.5	57.1 ± 13.4	n.s.
Fecal elastase 1 (mg/g)	665.9 ± 117.4	74,2 ± 22.7	158.5 ± 41.3	/
Calcitriol (pg/ml)	41.8 ± 8.3	14.3 ± 6,1	20.7 ± 9.4	p < 0.05
Calcefediol (nmol/l)	50,2 ± 14.7	21.8 ± 7.2	32.3 ± 10.8	p < 0.05
PTH (pg/ml)	48 ± 10.7	47 ± 23,7	42.1 ± 17	n.s.

Table 2. Comparison of serum PTH, calcitriol and calcefediol between different patient-collectives allotted by the fecal elastase 1 content and controls. p < 0.05 indicates a significant difference between patients with fecal elastase 1 deficiency and controls.

Parameters	Comparison of error probabilities of variation between patients and controls (N = 80)		
	controls (N = 80)	Fecal elastase deficiency	
		< 100 mg/g (N = 112)	100 < 200 mg/g (N = 128)
PTH	n.s.	n.s.	n.s.
Calcitriol	p < 0.01	p = 0.01	p < 0.01
Calcefediol	p < 0.01	p = 0.01	p < 0.01

Table 3. Correlation between vitamin D₃ and elastase 1 in feces in female patients with fecal elastase 1 deficiency. p < 0.05 indicates a significant correlation.

Parameter	Vitamin D ₃	
	Calcitriol	Calcefediol
Elastase 1 in feces		
Correlation Pearson	0.730	0.647
p	p < 0.01	p < 0.01

Table 4. Calcitriol and calcefediol (means \pm standard deviation) within the two subgroups according to elastase 1 in female patients with fecal elastase 1 deficiency. $p < 0.05$ indicates a significant difference between these two groups.

Parameters	Subgrouping for elastase 1 in feces		p
	< 100 mg/g (N = 112)	100 < 200 mg/g (N = 128)	
Calcitriol	14,3 \pm 6,1	20.7 \pm 9,4	n.s
Calcefediol	21.8 \pm 7.2	32.3 \pm 10.8	n.s.

vitamins ($p < 0.01$; Table 3). The higher elastase 1 in feces was, the higher were the D₃-vitamins calcitriol and calcefediol. If fecal elastase 1 in patients was below 200 mg/g, then vitamin D₃ also was significantly decreased compared to the others. Concerning estimation of PTH levels in serum, there was no correlation both between the fecal elastase 1 and the D₃-vitamins calcitriol and calcefediol.

DISCUSSION

We found a low prevalence of hyperparathyroidism in female patients with reduced fecal elastase 1 content. Only two patients (62 and 67 years) show milder cases of new diagnosed primary hyperparathyroidism with elevated PTH levels and hypercalcemia. At diagnosis the patients did not present previous fractures, myocardial infarction, stroke, psychiatric disorders, painful muscle disorder and kidney stones. We expected in hypercalcemic hyperparathyroidism a correlation with a history of pancreatitis, but case history and ultrasonography without pancreatic calcifications/cysts did not demonstrate this. Therefore, we are not able to support the link between primary hyperparathyroidism and induction of acute or chronic pancreatitis. Hyperparathyroidism is a rare but treatable cause of pancreatitis [14]. In the diagnosis of chronic pancreatitis there is a parallelism between exocrine function and ERCP results [5], even using fecal elastase 1 for description of pancreatic insufficiency [1, 2, 3]. Until now, very little has been published about deficiency of lipid soluble vitamins, especially vitamin D, in patients with chronic pancreatitis [7-10, 15]. The aim of the present study was to get an information about the PTH level and vitamin D status in patients with deficiency of fecal elastase 1 below the lowest reference and reduced exocrine pancreatic function. Both D₃-vitamins could be recognized to be lower in patients with deficiency of fecal elastase 1 more clearly for calcitriol than for calcefediol. Furthermore, calcitriol as well as calcefediol were extremely low in both subgroups: fecal elastase < 100 mg/g (N = 112) and 100 < 200 mg/g (N = 128) compared to the controls. These observations enhance statements already made by Dibble et al., Nakamura et al., Moran et al., as well as Haaber et al. [7 -10]. As described by these authors, the frequent presence of decreased vitamin D in patients with chronic pancreatitis is already confirmed by our own results comparing patients with controls. Hence, the confirm statement of distinctly decreased vitamin D-levels could be associated with the severity grade of the disease according to the fecal elastase 1. The reduction of serum concentration, as described by Scharla et al. [16], especially of

calcitriol during a chronically inflammatory process, could explain its retreat due to an increasing inflammatory destruction of the pancreas. Apart from leading a less burdened way of life with stronger bonds to home and thus reduced exposition to the sun, described by Poskitt et al. [17] as the essential cause for a depletion of vitamin D-storage, could also be relevant. Nevertheless, the increasing pathomorphological pancreas alterations accompanied by exocrine functional restriction with corresponding absorption disturbance in higher severance grades of chronic pancreatitis seem to be the most important reason for decreased vitamin D in patients. This respective occurrence of decimating vitamin D-pool, represented by calcefediol, would also explain the predominant constellation of decreased calcitriol in our patient study and those of Nakamura et al. [8], almost exclusively in all those with also low calcefediol.

To our knowledge, this is the first study dealing with the link between fecal elastase 1 and the respective serum levels of vitamin D₃. Assuming that elastase 1 in feces is the representative marker for an exocrine insufficiency during a chronic pancreatitis, Dutta et al. [6] already described a frequent existing lack of lipid soluble vitamins, even vitamin D, in patients with chronic pancreatitis and exocrine insufficiency. Accordingly, the present study showed a highly significant correlation between fecal elastase 1 and vitamin D₃, which was more pronounced for calcitriol than for calcefediol. However, dividing the patients into two subgroups, those with fecal elastase < 100 mg/g values and those with 100 < 200 mg/g values did not result in significant differences for calcitriol as well as for calcefediol between these two collectives. Thus, decreased elastase 1 in feces was accompanied by reduced serum concentrations of vitamin D₃, more pronounced for calcitriol than for calcefediol. This connection finally leads to distinct differences between patients with fecal elastase 1 of under 200 μ g/g compared to those with higher values, but no differences within the subgroups below 200 μ g/g fecal elastase 1 content.

Under the aspect of an exocrine pancreas insufficiency with resulting malabsorption for vitamin D in patients with chronic pancreatitis, elastase 1 in feces gains significance hereby as a pancreas function test. Therefore, vitamin D₃-deficiency would be very dependent upon the severity grade of exocrine insufficiency, represented here by the fecal elastase 1 in patients. If it is assumed that steatorrhea is the obvious symptom of exocrine insufficiency in patients with chronic pancreatitis, as reported by Twersky et al. [18], that its existence as well as occurrence is dependent

upon the severity of exocrine dysfunction and fat supply in food, the results from Dutta et al., Dibble et al. and also Nakamura et al. [6-8] contradict the above mentioned statement. Dutta et al. [6] could not find any connection between measured lipid soluble vitamins (including calcefediol) and severity of steatorrhea in patients with chronic pancreatitis. Likewise, Dibble et al. [7] obtained the same results by applying calcefediol only, and Nakamura et al. [8] by applying all lipid soluble vitamins (including calcitriol and calcefediol), except vitamin E, in all patients. Also, Haaber et al. [10] described the lack of difference for calcitriol and calcefediol depending on the exocrine insufficiency as well as on the duration of the disease in patients with chronic pancreatitis. Nevertheless, all these observations are not suitable to invalidate the link of elastase 1 values in feces, severity of disease and vitamin D-deficiency in patients with exocrine insufficiency. According to Twersky et al. [18] and Di Magno et al. [19], the parameter of steatorrhea is too variable for a precise description of exocrine function of the pancreas, and therefore, statements by Dutta et al., Dibble et al. and Nakamura et al. [8-10] are in this sense less representative. The results from Haaber et al. [10] also lose their significance, because enzymes were substituted in patients with exocrine pancreatic insufficiency. On the basis that under normal circumstances 80-90% of experimentally applied, radio-actively labelled vitamin D₃ is absorbed by the intestines, although only 40% in patients with pancreatic insufficiency [20], exocrine pancreatic function gains significance and supports our own results with corresponding evaluation of elastase 1 in feces. Furthermore, it is conceivable that elastase 1 plays an independent role with regard to vitamin D₃-supply in the organism. Since by passing the intestines, elastase 1 changes to a complete protein sterol complex by loading neutral steroids [21], and vitamin D₃ is also a sterol molecule, there is a hypothetical cross-link here. Therefore, there are still queries regarding the importance of sterol linking in elastase 1 in interaction with its excretion status for vitamin D₃-supply. As vitamin D deficiency and primary hyperparathyroidism are relatively common, a coexistence of these conditions must be considered. Vitamin D deficiency may increase the severity of primary hyperparathyroidism (presence of larger adenomas, higher PTH levels, and greater bone turnover). Nevertheless, some of the biochemical features of primary hyperparathyroidism can be masked by the coexisting vitamin D deficiency leading to an inappropriate therapeutic management of these patients [22]. 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 [23].

In summary, female patients with deficiency of fecal elastase 1 show alterations of the vitamin D metabolism. These resulted from the impaired exocrine pancreas function as compared to indirect test method: estimation of fecal elastase 1. The primary

hyperparathyroidism is a rare observation in patients with impaired pancreatic exocrine function and is not suitable to link hypercalcaemic hyperparathyroidism and acute or chronic pancreatitis. The estimation of fecal elastase 1 is a well founded indirect test for determination of vitamin D supply.

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