Vitamin D Status and Per-oral Vitamin D Supplementation in Patients Suffering from Chronic Pancreatitis and Pancreatic Cancer Disease

S. KLAPDOR[1,2], E. RICHTER[2] and R. KLAPDOR[1]

[1]*Internal Medicine, ZeTDT GmbH and* [2]*Compound and Care Pharma GmbH, Hamburg, Germany*

Abstract. *Exocrine pancreatic insufficiency due to chronic pancreatitis may result –depending on the degree of insufficiency–, in a decrease in serum 25-hydroxyvitamin D (25(OH)D) level. However, the data in the literature concerning the rate and extent of vitamin D deficiency in pancreatic cancer with or without previous pancreas resection, are very rare, in particular regarding the question how to supplement these patients with vitamin D. In recent years, vitamin D is increasingly being discussed as one factor involved not only in musculo-skeletal diseases but also in cardiovascular and autoimmune diseases, cancer development, diabetes mellitus and overall mortality. Patients and Methods: In all, 248 ambulatory patients (n=140 patients suffering from exocrine pancreatic insufficiency due to chronic pancreatitis, pancreatic cancer with/without previous resections of the pancreas n=108 patients without pancreatic disease), we measured the serum 25(OH)D concentrations by the chemoluminescence method. In addition, in 91 of these patients (n=65 pancreatic patients, n=26 controls), we started supplementation with oral vitamin D in combination with dietary advice and adequate substitution with pancreatic enzyme preparations, followed by subsequent serum 25(OH)D determinations. The oral vitamin D doses varied from 1000 IU per day over 1× 20000 IU per week, or 2-3 times 20000 IU per week up to 20000 IU per day in single patients, depending on the underlying disease and the estimated degree of maldigestion/malassimilation. In addition, in a pilot trial vitamins A and E were measured in the serum from 121 and 105 of these patients respectively (resp.) (HPLC method). Results: Serum 25(OH)D concentrations were <30 ng/ml in 93% of the patients with pancreatic diseases ,<20 ng/ml in 77.9%, <10 ng/ml in 32.1% and <4 ng/ml in 9.3%. The results were comparable to those in patients suffering from chronic pancreatitis and those with pancreatic tumor disease, with or without a previous tumor resection (n=51 Whipple procedure, n=11 left resection, n=9 total duodeno-pancreatectomy). Similar data were also found in the controls, only slightly higher. In contrast to the vitamin D data, however, determination of vitamins A and E in the serum resulted in values within the normal range for the majority of the patients of both groups, suggesting a diminished vitamin D uptake as being at least one reason to explain the low serum vitamin D concentrations in the patients with pancreatic diseases. Individual supplementation with oral vitamin D in all patients studied (n=91) resulted in an increase of the serum 25(OH)D concentrations into the normal range (14.2±5.8 up to 42.3±12 in controls, 11.9±7.4 up to 46.6±15.7 in patients with pancreatic diseases). The data of a subgroup of patients with continuous long-term supplementation, however, suggest that some patients with pancreatic diseases may need a significantly higher vitamin D supplementation, up to 20000 IU per day in single patients, compared to the controls. Conclusion: The results demonstrate that vitamin D deficiency is a common problem in patients suffering from exocrine pancreatic insufficiency from various reasons as well as in our controls. Apart from insufficient sun exposure, exocrine pancreatic insufficiency, as well as a too low vitamin D uptake with food seem to represent the main causes of low serum 25(OH)D. In nearly all patients, the serum 25(OH)D concentrations could be normalized by oral supplementation of vitamin D in the case of individual therapy based on routine serum controls.*

Exocrine pancreatic insufficiency due to chronic pancreatitis, pancreatic cancer and/or pancreatic surgery may result, depending on the degree of insufficicency, in reduced serum 25-hydroxyvitamin D [25(OH)D] concentrations. Fat soluble vitamin D is known to have effects on bone metabolism. In recent years, it is also increasingly being discussed as one factor involved in cardiovascular diseases, autoimmune diseases, cancer development, diabetes mellitus type 1 and type 2 and overall mortality (1-8).

Correspondence to: Prof. Dr. R. Klapdor, Internal Unit, Rothenbaumchaussee 5, 20148 Hamburg, Germany. E-mail: Prof.Klapdor@t-online.de

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In the literature, there are only very few articles focussing on this topic. Most of them report on single observations or small groups of patients. The results differ to some extent, some authors report normal serum 25(OH)D concentrations, some on reduced levels in pancreatic patients, to some extent also in correlation to decreased levels of pancreatic elastase in the stool as an indicator of exocrine pancreatic insufficiency (9-14). Some physicians therefore try to prevent or to treat vitamin D deficiency in pancreatic patients by recommending vitamin D supplementation. Although some case reports, as well as findings in patients suffering from cystic fibrosis (15,16), might suggest that it might be possible to supplement vitamin D in these patients by oral supplementation, most physicians in Germany generally recommend parenteral application of vitamin D in the form of so-called ADEK preparations (10,000 IU vitamin D per injection) (17), in addition to the advice to prevent vitamin D insufficiency by increased exposure to sunlight and by increasing the vitamin D intake via consumption of *e.g.* fish, known to have a relatively high vitamin D content.

However, our recent pilot determinations of serum 25(OH)D in patients suffering form chronic pancreatic diseases suggested that intramuscular (i.m.) injections of commercially available ADEK preparations were not able to raise the serum 25(OH)D concentrations into the normal range if given every 2 to 4 weeks in these patients (meaning 10,000 IU or 2× 10,000 IU per month) (18).

Therefore we started a prospective study into the rate and extent of reduced serum 25(OH)D concentrations in patients suffering from exocrine deficiency due to chronic pancreatitis and pancreatic cancer with/without preceding pancreatic surgery. In the second part of this study, we looked into the possibility of increasing the serum levels into the normal range by per-oral vitamin D supplementation in addition to dietary advice and adequate application of pancreatic enzymes for meals. The primary aim in this connection was to answer the question as to what extent and in how many patients the serum levels could be normalized without risk of undesired side- effects. The question of the lowest dose required to reach a normalization of the serum levels was not the aim of our the present study.

Patients and Methods

Patients. The patients, all of them ambulatory, were classified according to their diagnosis into two main groups: a) patients suffering from exocrine pancreatic insufficiency: n=103 due to pancreatic cancer (n=51 after previous Whipple or pylorus-preserving Whipple resection; n=9 after previous total duodenopancreatectomy; n=11 after cauda resection; n=22 of these patients without signs of tumor since previous tumor resection), n=37 suffering from chronic pancreatitis. All these patients were treated with so-called pancreatic enzyme drugs in order to ameliorate their clinical signs of exocrine pancreatic insufficiency (proven decrease in pancreatic elastase in the stool) such as loss of body weight, diarrhea and meteorism. b) n=108 patients without signs of exocrine pancreatic insufficiency and without known pancreatic disease in their history (so-called controls).

In 14 of these patients, it was also possible to measure the serum 25(OH)D concentrations in the course of a previous treatment with intramuscularily applied ADEK preparations (in most patients at monthly intervals) containing: 10,000 IU vitamin D, 100,000 IU vitamin A, 100 IU vitamin E and 10 mg vitamin K per injection.

Serum 25(OH)D determinations. Serum 25(OH)D was determined in: group I, in all of these patients in a state without oral and/or intramuscular vitamin D supplementation; group II, in n=65 of the patients with exocrine pancreatic insufficiency (n=51 pancreatic cancer group, n=14 chronic pancreatitis group) as well as in n=26 of the patients of the control group after per-oral vitamin D supplementation in order to investigate the possibility of increasing the serum 25(OH)D concentration into the normal range (>30 ng/ml serum) in these patients by oral supplementation of vitamin D; group III, in n=46 of these patients (n=36 suffering from exocrine pancreatic insufficiency (n=24 pancreatic cancer group, n=12 chronic pancreatitis) and n=10 controls) over a longer period of supplementation in order to analyse the serum 25(OH)D concentrations during a 'steady state' in relation to the applied per-oral supplementation of vitamin D.

Additional pilot determinations of the fat acid soluble vitamins A and E. When we found vitamin D deficiency to be a common problem in our patients suffering from exocrine insufficiency and that these deficiencies could be effectively treated by oral vitamin D supplementation, we simultaneously determined the serum concentrations of other fat soluble vitamins, namely vitamin A and E, in these patients as a pilot study for planning future investigations. Within this article, we report on these data in so far as these results may contribute to answer the question as to whether the vitamin D deficiency in our pancreatic patients can be explained by a low oral intake of vitamin D, reduced intestinal digestion/resorption due to exocrine pancreatic insufficiency, or due to a combination of both factors.

Oral vitamin D supplementation. For oral supplementation with vitamin D, we used commercially available vitamin D preparations (Vigantoletten® 1000 IU, Merck Pharma GmbH, Germany; Dekristol® 20,000 IU, mibe GmbH, Germany). The vitamin D amount was given orally during breakfast in relation to the measured serum concentrations during supplementation in order to increase the serum levels to more than 30 ng/ml in group II and in the patients of subgroup III in order to reach stable serum 25(OH)D concentrations in the normal range. The oral doses varied from 1,000 IU per day over 1× 20,000 IU per week, or 2-3 times 20,000 IU per week up to 20,000 IU per day in single patients, depending on the underlying disease and the estimated degree of maldigestion/malassimilation. With increasing clinical experience, we often started in the patients with an initial bolus of 100,000 IU vitamin D at day one of the first week or with 20,000 IU daily for the first week.

Laboratory determinations. Serum 25(OH)D was determined using a chemoluminescence method (Liaison®, normal range 30-100 ng/ml); vitamins A and E were determined using HPLC (normal

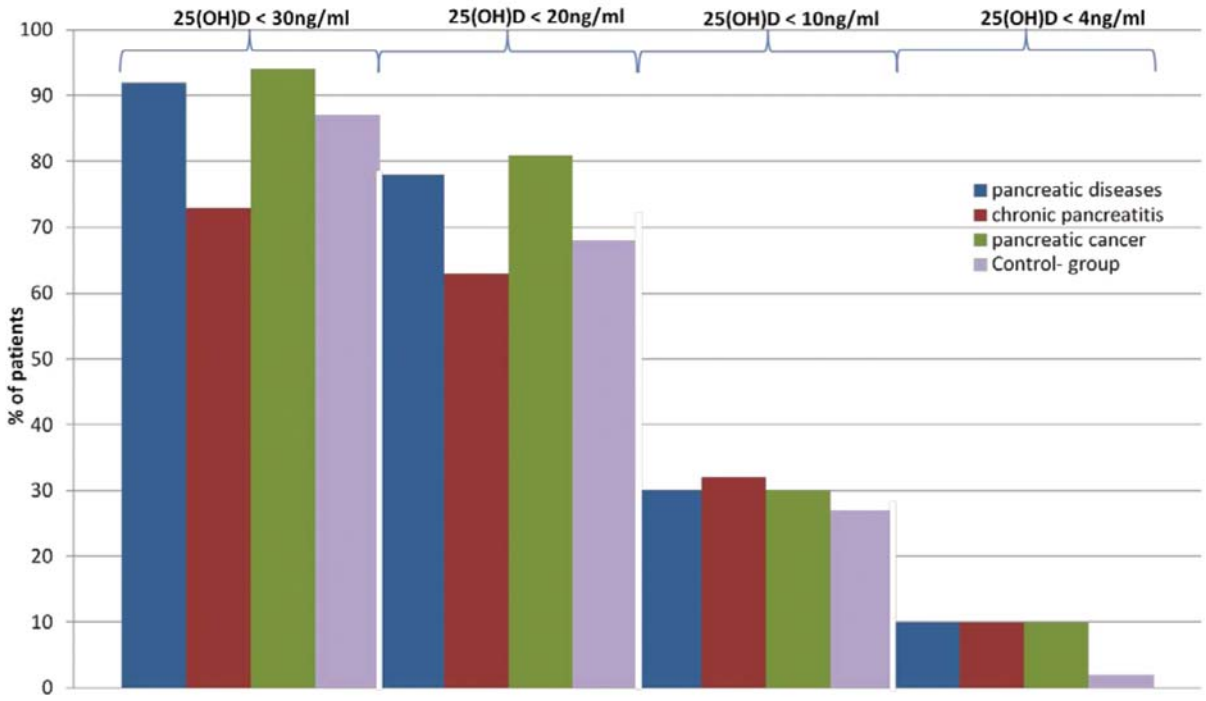

Figure 1. *Percentage of patients with serum 25(OH)D concentrations <30 ng/ml, <20 ng/ml, <10 ng/ml and <4 ng/ml respectively in the different groups of patients studied: n=140 patients with pancreatic diseases (n=103 patients with pancreatic cancer, n=37 patients with chronic pancreatitis), n=108 patients of the control group.*

range for vitamin A 0.2-1.2 mg/l, for vitamin E 5-18 mg/l) (Thermo HPLC Spectra Systems (Thermo Fischer Scientific Inc., USA), column Machery+Nagel Nr. 720051.30 (GmbH &Co, Düren, Germany), reagents Chrom Systems Inc., Boynton Beach, USA). All methods have been routinely used for determination of these vitamins in the laboratory of Drs Fenner and Partner at Hamburg.

Results

The results are presented in relation to the patient groups studied.

Group I) Basal serum 25(OH)D concentrations in patients with pancreatic disease and in the controls (n=248). According to Figure 1 serum 25(OH)D concentrations were found to be lower than normal in the majority of the patients suffering from pancreatic cancer as well as from chronic pancreatitis. Depending on the cut-off used, serum 25(OH)D was <30 ng/ml in 94.2% and <10 ng/ml in 30.1% of patients with pancreatic cancer and 86.5 % and 37.8 % respectively in the group of patients with chronic pancreatitis. Surprisingly, however, in our controls without clinical signs of pancreatic disease we found a rather similar situation. In 87% we found serum 25(OH)D concentrations <30 ng/ml and in 26.9% <10 ng/ml. The median values are only slightly higher in the controls compared to the patients with pancreatic disease: 17.5±9.7 in the controls *vs*. 14.0±7.7 and 15.6±13.6 for the pancreatic cancer and the chronic pancreatitis groups respectively.

Group II) Normalization of serum 25(OH D concentration by oral vitamin D supplementation. According to Figure 2 it was possible to normalize the serum 25(OH)D concentration by individually adjusting the oral vitamin D intake in nearly all of the supplemented patients and controls (mean values: 14.2±5.8 ng/ml to 42.3±12.0 ng/ml in the controls, and 11.9±5.4 ng/ml to 46.6±15.7 ng/ml in the pancreatic patients). This was also possible in the patients operated by Whipple-resection or total duodenopancratectomy (Figure 3). Clinical side-effects of supplementation have not been reported and were not detected by serum calcium determinations or other routine laboratory determinations. Four typical examples for normalization of serum 25(OH)D concentrations by oral vitamin D supplementation over winter and summer periods are demonstrated in Figure 4.

Group III) Oral vitamin D intake in relation to steady state serum 25(OH)D concentrations. According to Figure 5, demonstrating the results in patients and controls already treated for a longer period with oral vitamin D in order to maintain serum 25(OH)D concentrations in a normal range

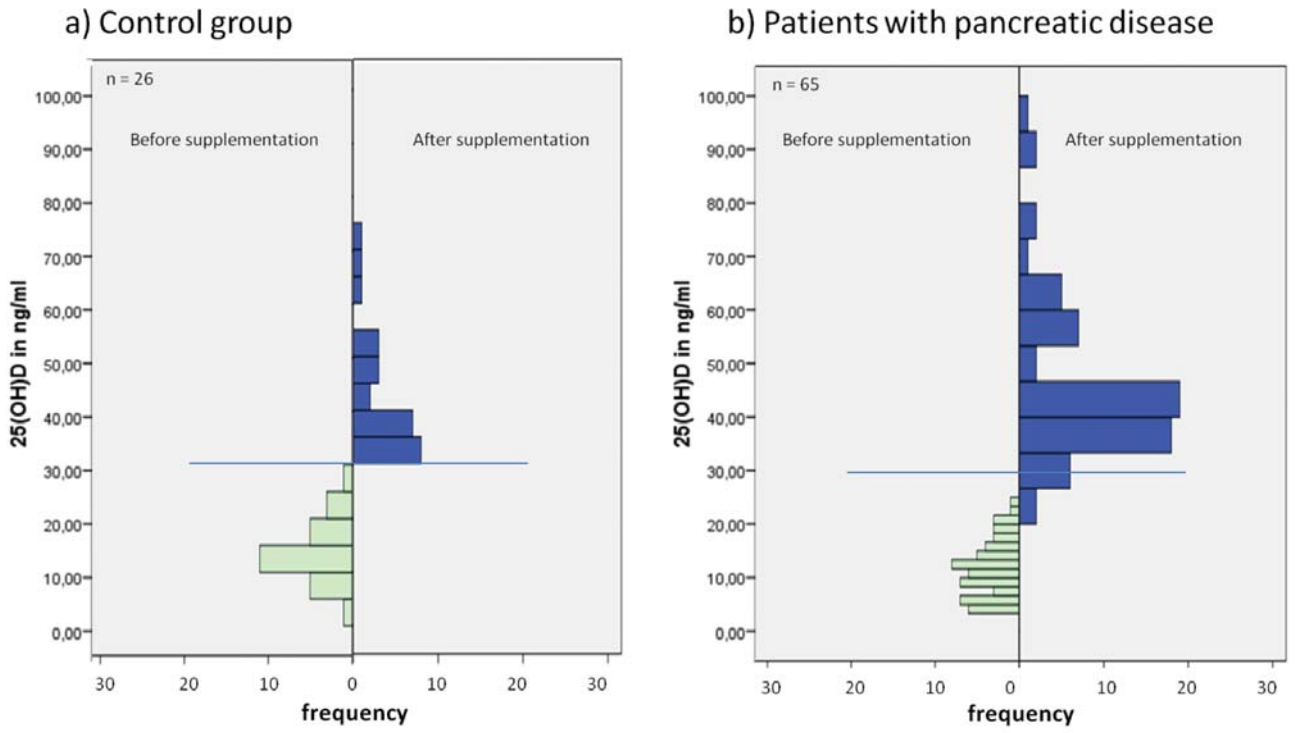

Figure 2. *Normalization of serum 25(OH)D concentrations by oral vitamin D supplementation in the control group (n=26) (a) and in patients suffering from pancreatic diseases (n=65) (b).*

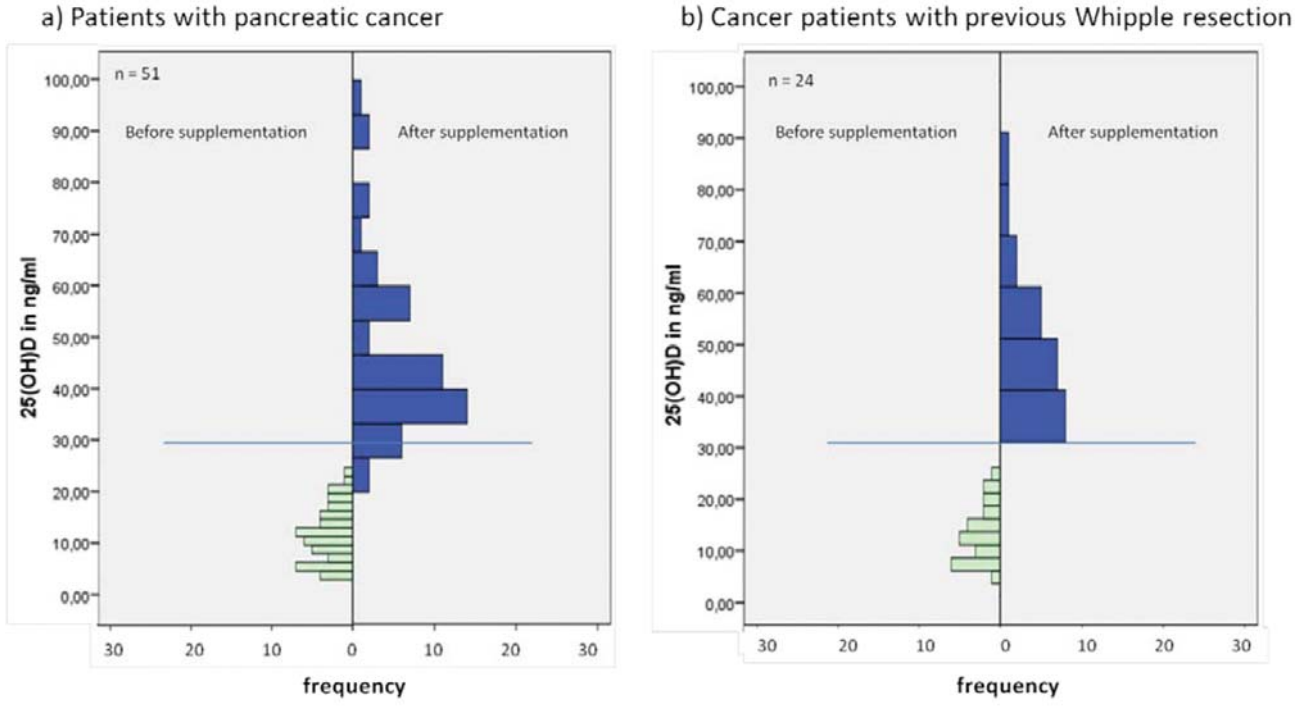

Figure 3. *Normalization of serum 25(OH)D concentrations by oral vitamin D supplementation in patients with pancreatic cancer diseases (n=51) (a) and in a subgroup of these patients with a preceding Whipple surgery in their history (n=24) (b).*

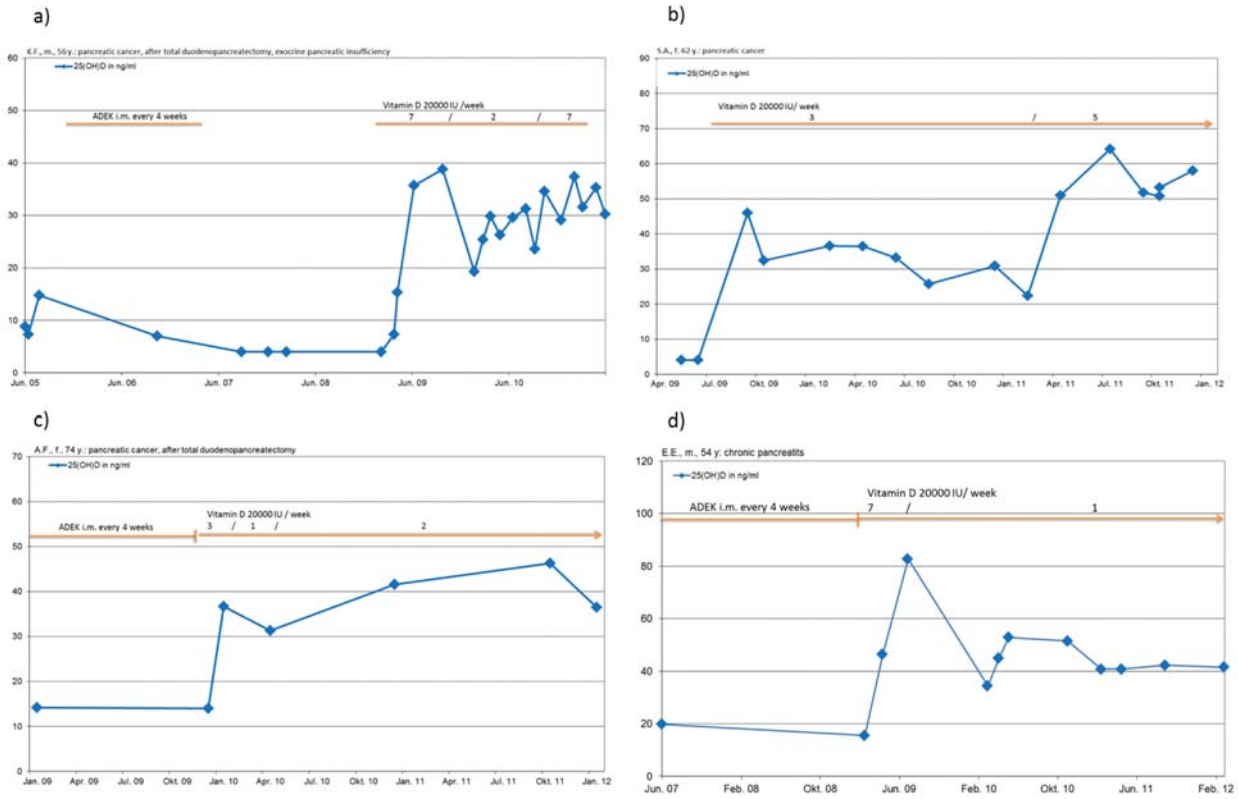

Figure 4. *Four typical examples for a long-term normalization of serum 25(OH)D concentrations by individualized oral vitamin D supplementation: a and c: after total duodenopancreatectomy; b: in advanced pancreatic cancer under chemotherapy; d: chronic pancreatitis.*

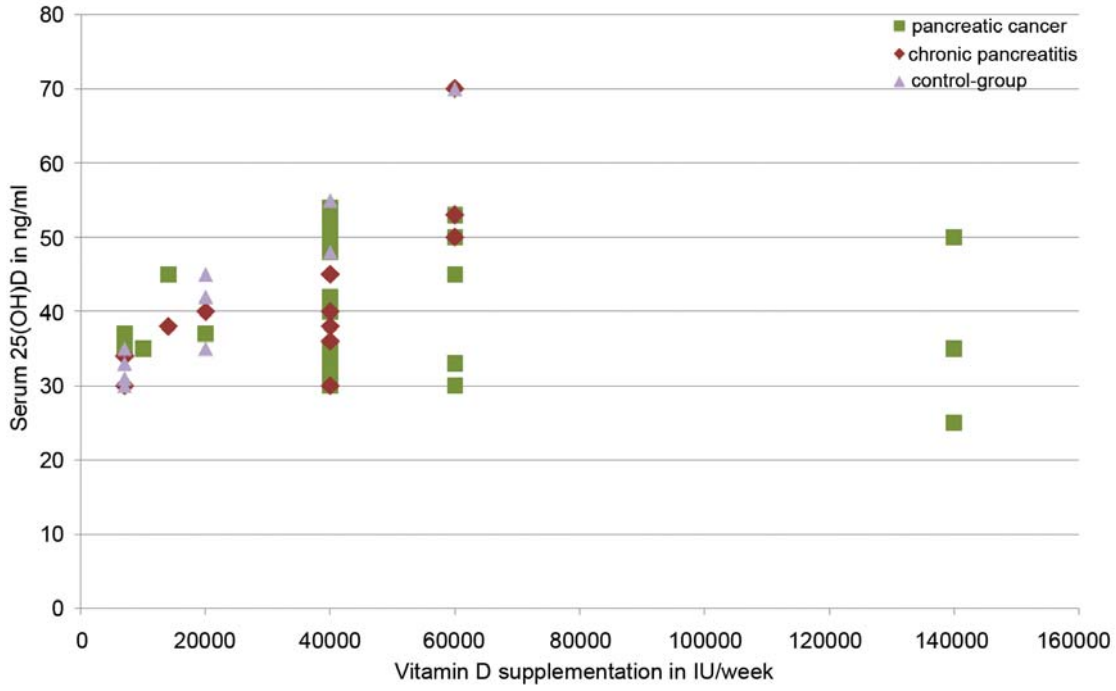

Figure 5. *serum 25(OH)D concentrations in relation to long-term oral vitamin D supplementation (weekly doses) in controls as well as in patients with chronic pancreatitis and pancreatic cancer.*

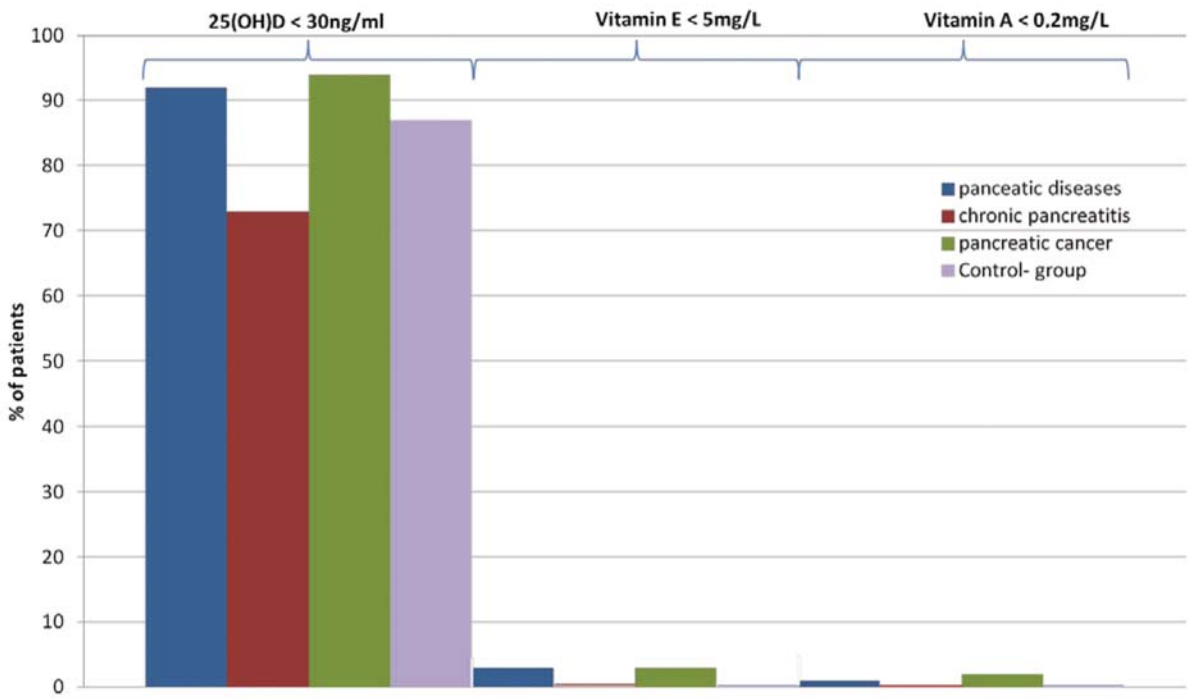

Figure 6. *Percentage of patients with serum 25(OH)D, vitamin A and vitamin E concentrations below reference values in the different groups of patients studied.*

between 30-50 ng/ml, the data in the control group suggest a positive correlation between oral vitamin D intake of between 7,000 and 60,000 IU per week (1,000 up to 8,570 IU/day) and steady state serum 25(OH)D concentrations of between 30-35 ng/ml up to 70 ng/ml under long-term supplementation. These data correlate to published data from an interventional study (19). With respect to the patients suffering from chronic pancreatitis and pancreatic cancer, the data of Figure 5 suggest that higher amounts of oral vitamin D supplementation seem to be necessary for at least some of the patients with pancreatic disease compared to the controls in our study and to the data of Hathcock *et al*. (19): in three of our patients with pancreatic cancer we needed up to 140,000 IU per week (20,000 IU per day) in order to obtain serum concentrations between 30-50 ng/ml 25(OH)D.

Serum vitamin A and E concentrations in patients with pancreatic disease and controls – a pilot study. Figure 6 clearly demonstrates that the serum vitamin A, as well as the serum vitamin E concentrations were in the normal range in the controls and in 99% and in 98% patients with pancreatic disease, in contrast to the very high rate of decreased serum level for the other fat soluble vitamin, the serum 25(OH)D, in both groups. The mean serum concentrations were 13.8±6.8 ng/ml for vitamin D in these patients and 0.49±0.2 mg/l for vitamin A and 8.6±4.3 mg/l for vitamin E.

Consequently, looking for correlations between the serum concentrations of the three fat soluble vitamins A, D and E we were unable to detect any correlation between them.

A similar situation with respect to the serum concentrations of the vitamins A, D and E we also found in 14 patients with a preceding period of intramuscular ADEK supplementation: decreased concentrations for serum 25(OH)D in more than 90% of the patients, in contrast to serum concentrations of vitamin A in the normal range and lowered vitamin E concentrations in no more than 25% (Figure 7).

Discussion

Vitamin D metabolism is increasingly discussed not only in musculo-skeletal diseases, but increasing evidence also suggests associations with respect to immunology, tumor prevention and oncology, depressive illness, heart diseases, as well as insulin resistance in diabetes mellitus type 1 and 2 (1-8). Sunlight and dietary intake represent the main sources of vitamin D. Precondition for a physiological intestinal uptake of the so-called fat soluble vitamin D is a normal digestion of fat, requiring bile acids and a physiological pancreatic exocrine function. In spite of some contradictory data in the 1980s and 1990s concerning patients with chronic pancreatitis or single patients after total duodenopancreatectomy (9-11,14), more recent studies suggest lower serum 25(OH)D concentrations in

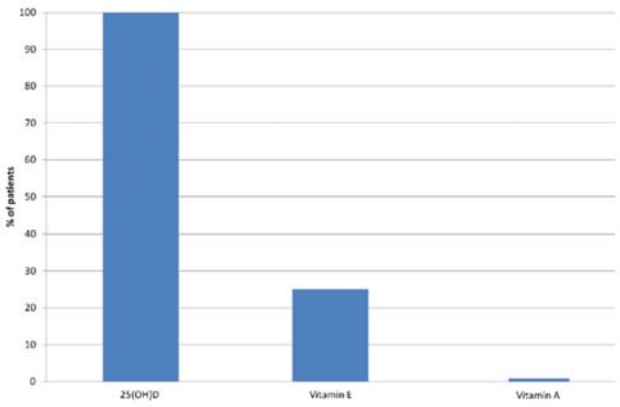

Figure 7. *Percentage of patients with serum 25(OH)D, vitamin A and vitamin E concentrations below reference values during a period of regular intramuscular injections of commercially available ADEK preparations (10,000 IE vitamin D per injection) (n=14).*

patients with chronic pancreatitis compared to controls and that exocrine pancreatic insufficiency seems to represent a contributing factor (12, 13). Although case reports highlight the possibility of increasing serum 25(OH)D concentrations into the normal range in single patients, the general recommendation was to supplement vitamin D by intramuscular injections if necessary. In Germany during past decades, clinicians favoured so-called commercially available ADEK preparations (17), even if there was not even a single clinical study using ADEK and therefore also no study demonstrating a significant effect on the serum 25(OH)D concentrations of the commercially available ADEK preparations given to these patients.

Moreover, the commercially available ADEK preparations to date did not contain more than 10,000 IU vitamin D per intramuscular injection. 10,000 IU every four or also every two weeks seem to be a rather low dose, as recent studies in patients suffering from cystic fibrosis for example demonstrated that oral supplementation with 800 IU daily was not able to increase low serum 25(OH)D concentrations in these patients (20), moreover, for normal adults, nowadays a daily supplementation with 800 IU (21) is proposed. Doses of 2,000-4,000 IU vitamin D daily are also increasingly being discussed.

Consequently it is not astonishing that we found low serum 25(OH)D concentrations in most of our patients supplemented with intramuscular ADEK injection every four weeks (in some cases also every two weeks) [see (18) and Figure 7].

This situation motivated us to investigate the possibility of effective oral supplementation in our patients with exocrine pancreatic insufficiency due to chronic pancreatits or pancreatic cancer with/without preceding pancreatic resective surgery and to compare these results with those of our control group, namely ambulatory patients without signs of exocrine pancreatic dysfunction and without diseases of the pancreas in their history.

On the one hand, our data confirm that serum 25(OH)D concentrations are lower than normal in the majority of our patients with pancreatic diseases to a more or less extent. As serum 25(OH)D concentrations in the controls were also low, nearly comparable to those in the patients with pancreatic disease, our data suggest that the levels in the patients cannot be explained by maldigestion/malabsorption alone, but also must result from other factors, such as a low dietary vitamin D uptake and/or a low exposure to sunshine (21). However, according to Figure 5, our results also suggest that a low dietary uptake and/or a low exposure to sunshine will not explain the low serum 25(OH)D concentrations by themselves alone. The results in Figure 7 suggest that patients suffering from chronic pancreatitis or pancreatic exocrine dysfunction due to pancreatic cancer and/or pancreatic resection seem to need higher amounts of oral vitamin D supplementation to reach serum 25(OH)D concentrations in a range between 30-50 ng/ml compared to the controls, up to the 20th fold. This conclusion that low serum vitamin D levels in the serum may also be related to the degree of exocrine dysfunction is supported by data in the literature suggesting a relation between the rate of decreasing serum concentrations of vitamin D and the extent of exocrine pancreatic insufficiency (13).

On the other hand, our results demonstrate that in the subgroup of patients with oral supplementation of vitamin D, the oral intake was able to increase the serum 25(OH)D concentrations in all of the controls, as well as in nearly all of the patients with pancreatic disease to above the lower value of the reference range (Figure 2), except for two patients in which the supplementation dose was not yet adjusted according to the serum levels at time of evaluation of the present data. With the aim of normalization of the serum levels, supplementation of oral vitamin D intake was combined with an adequate nutritionary advice by dieticians, with adequate dosage of pancreatic enzyme preparations, orientated to the patient's complaints of stool behaviour, flatulence and bodyweight, and with an adjustment of the initial dosage of vitamin D supplementation according to the following serum assays.

In individual patients with pancreatic diseases a daily vitamin D supplementation with up to 20,000 IU was certainly required (Figure 5). However, we did not notice any side-effects in our patients on the one hand, and on the other hand there is enough evidence in the literature indicating that vitamin D supplementation with up to more than 20,000 IU vitamin D daily will not result in side-effects in normal adults, and that side-effects also represent very rare events in the case of vitamin D supplementation up to 40,000 IU daily (18).

Finally, our results demonstrate that per-oral vitamin D supplementation resulted in normalization of the serum 25(OH)D concentrations not only in patients with chronic pancreatitis or pancreatic cancer, but also in the subgroup of

pancreatic cancer patients with pancreas resection in their history, both in the patients after Whipple or pylorus preserving Whipple surgery and in patients after total duodenopancreatectomy (Figure 3b).

Summarizing, our data indicate that oral vitamin D supplementation seems to be practicable in nearly all patients suffering from exocrine pancreatic insufficiency, without side-effects. On the basis of these data and the recent literature suggesting increasing evidence for a relevant role of vitamin D in areas other than musculo-skeletal diseases, it should be discussed whether vitamin D determinations in the serum as well as subsequent vitamin D supplementations should be included in the routine work in pancreatology and especially in the field of pancreatic oncology.

References

1 Holick MF: Vitamin D deficiency. N Engl J Med *357(3)*: 266-281, 2007.

2 DeLuca H: Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr *80(suppl.)*: 1689-1696, 2004.

3 Davis C and Milner J: Nutrigenomics, vitamin D and cancer prevention. J Nutrigen Nutrigenom *4*: 1-11, 2011.

4 Bertone-Johnson ER, Powers SI, Spangler L, Brunner RI, Michael LY, Larson JC, Millen AE, Bueche MN, Salmoirago-Blotcher E, Liu S, Wassertheil-Smoller S, Ockene JK, Ockene I and Manson JE: Vitamin D intake from foods and supplements and depressive symptoms in a diverse population of older women. Am J Clin Nutr *94*: 1104-1112, 2011.

5 Llewellyn DJ, Lang IA, Langa KM, Muniz- Terrera G, Phillips CI, Cherubini A, Ferrucci I and Melzer D: Vitamin D and risk of cognitive decline in elderly persons. Arch Intern Med *170*: 1135-1141, 2010.

6 Woloszynska- Read A, Johnson C, Trump D: Vitamin D and cancer: Clinical aspects. Best Pract Res Clin Endocrinol Met *25*: 605-615, 2011.

7 Mitri J, Muraru MD and Pittas AG: Vitamin D and type 2 diabetes: a systematic review. Eur J Clin Nutr *65(9)*: 1005-1015, 2011.

8 Hyppönen E, Läärä E, Reunanen A, Järvelin MR and Virtanen SM: Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet *358*: 1500-1503, 2001.

9 Dutta SK, Bustin MP, Russel RM and Costa BS: Deficiency of fat- soluble vitamins in treated patients with pancreatic insufficiency. Ann Intern Med *97(4)*: 549-552, 1982.

10 Nakamura T, Takebe K, Imamura K, Tando Y, Yamanda N, Arai Y, Terada A, Ishii M, Kikuchi H and Suda T: Fat-soluble vitamins in patients with chronic pancreatitis (pancreatic insufficiency). Acta Gastroenterol Belg *59(1)*: 10-14, 1996.

11 Haaber AB, REsenfalck AM, Hansen B, Hilsted J and Larsen S: Bone mineral metabolism, bone mineral density, and body composition in patients with chronic pancreatitis and pancreatic exocrine insufficiency. Int J Pancreatol *27(1)*: 21-27, 2000.

12 Mann STW, Stracke H, Lange U, Klör HU and Teichmann J: Alterations of bone mineral density and bone metabolism in patients with various grades of chronic pancreatitis. Metabolism *52(5)*: 579-585, 2003.

13 Mann ST, Stracke H, Lange U, Klör HU and Teichmann J: Vitamin D3 in patients with various grades of chronic pancreatitis, according to morphological and functional criteria of the pancreas. Dig Dis Sci *48(3)*: 533-538, 2003.

14 Armstrong T, Walters E, Varshnex S and Johnson CD: Deficiencies of micronutrients, altered bowel function, and quality of life during late follow-up after pancreaticoduodenectomy for malignancy. Pancreatology *2*: 528-534, 2002.

15 Dodge JA and Turck D: Cystic fibrosis: nutritional consequences and management. Best Pract Res Clin Gastroenterol *20(3)*: 531-546, 2006.

16 Bang UC, Matzen P, Benfield T and Jensen JEB: Oral cholecalciferol *vs*. ultraviolet radiation B: effect on vitamin D metabolites in patients with chronic pancreatitis and fat malabsorption-a randomized clinical trial. Pancreatology *11*: 176-182, 2011.

17 Delbrück H: Bauchspeicheldrüsenkrebs. Rat und Hilfe für Betroffene und Angehörige. 2. Auflage. Kohlhammer Verlag, Stuttgart, 2010.

18 Klapdor S, Denecke A and Klapdor R: Untersuchungen zur adäquaten oralen Substitutionstherapie eines Vitamin-D-Mangels bei Patienten mit Pankreaserkrankung. Proc Germ Nutr Soc (Abstract) *15*: 99, 2011.

19 Hathcock JN, Shao A, Cieth R and Heaney RP: Risk assessesment for vitamin D. Am J Clin Nutr *85*: 6-18, 2007.

20 Rowner AJ, Stallings VA, Schall JI, Leonard MB and Zemel BS: Vitamin D insufficiency in children, adolescents, and young adults with cystic fibrosis despite routine oral supplementation. Am J Clin Nutr *86*: 1694-1699, 2007.

21 Hintzberger B, Mensink GB, Thierfelder W, Müller MJ and Scheidt-Nave C: Vitamin D status and health correlates among German adults. Eur J Clin Nutr *62*: 1079-1089, 2008.

22 Deutsche Gesellschaft für Ernährung (Hrsg.): D-A-CH Referenzwerte für die Nährstoffzufuhr. 1. Auflage. 4. Korrigierter Nachdruck. Umschau Verlag, Bonn, 2012.

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