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ORIGINAL ARTICLE

Nutritional markers in patients with diabetes and pancreatic exocrine failure

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Abstract

Aims Altered pancreatic exocrine function can be observed in patients with type 1 or type 2 diabetes. In the present study, we evaluated the potential nutritional consequences of this dysfunction.

Methods Serum concentrations of nutritional markers, including albumin, cholesterol, triacylglycerol, vitamins A, D, and E, were assessed in a cohort of 468 patients (137 with type 1 diabetes and 331 with type 2 diabetes), after exclusion of the patients with a CRP > 10 mg/l. These patients were compared with 47 patients with diseases of the exocrine pancreas and diabetes (type 3c diabetes or pancreatogenic diabetes). Fecal elastase-1 and chymotrypsin concentrations were measured and patients with type 1 and type 2 diabetes were divided into three groups according to whether zero (group NN), one (group LN), or both (group LL) concentrations were decreased.

Results Several markers differed significantly between the groups of patients, including BMI, albumin, phosphorus, and fat-soluble vitamins. Patients with pancreatogenic diabetes had markedly more profound alterations than patients with type 1 or type 2 diabetes and altered exocrine function. However, patients with type 1 or type 2 diabetes and decreased concentrations of both elastase-1 and chymotrypsin had lower albumin, phosphorus, and vitamin A than patients with normal pancreatic exocrine function.

Conclusions Modest nutritional alterations were found in patients with type 1 or type 2 diabetes and altered exocrine function. Patients with type 1 or type 2 diabetes and altered exocrine function may thus deserve to be screened for nutritional deficiencies.

Keywords Diabetes · Nutrition · Pancreatic exocrine dysfunction · Fat-soluble vitamins · Fecal elastase

Introduction

Pancreatic exocrine function can be altered in patients with diabetes [1–6]: it has been recently rediscovered that the size of the pancreas is decreased in patients with T1D [7–12], including in patients with recent-onset diabetes [8, 11, 12]. This seems to indicate that the exocrine pancreas could be damaged early on in T1D natural history [13], given that the

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exocrine pancreas represents more than 95% of the pancreatic mass. Moreover, it has recently been shown that a leucocytic infiltration can be observed in the exocrine pancreas of patients with T1D [14–16], suggesting that the exocrine dysfunction can also be a consequence of an immune-mediated destruction of the exocrine pancreas. Likewise, T2D is associated with low-grade inflammation: macrophages can be observed in islets [17] and chronic pancreatitis has been frequently observed at autopsy since the seminal work of R. Cecil [18].

In patients with type 1 diabetes (T1D), pancreatic exocrine failure is associated with diabetes of long duration [1, 19–21], whereas in patients with type 2 diabetes (T2D), we showed that it is also associated with vascular diseases [1].

Malabsorption of fat-soluble vitamins is a well-established consequence of chronic pancreatitis and other diabetes-associated diseases of the pancreas. However, outside the context of chronic pancreatitis, pancreatectomy and other well defined diseases of the exocrine pancreas, nutritional consequences of pancreatic exocrine failure have seldom been described [22, 23], in part, because the exocrine deficiency is deemed to be mild in the context of T1D or T2D, and often occurs without steatorrhea [5, 24–27]. However, we and others [1, 21, 25] have shown that the BMI of patients with pancreatic exocrine dysfunction in the context of T2D is lower than that of patients with normal pancreatic exocrine function, and this observation raises the question of the nutritional consequences of this pancreatic exocrine failure. In the present study, we investigated several nutritional markers, including the serum concentrations of vitamins A, D, and E in relation with pancreatic exocrine status in patients with diabetes. The results were compared with those of patients with overt exocrine diseases of the pancreas and pancreatogenic diabetes (PD).

Materials and methods

Patients

From our cohort of 667 patients [1] who had an investigation of pancreatic exocrine function, 537 patients were assessed for vitamins A, D, and E, in addition to serum albumin. These patients were compared to 55 patients with PD. From this new cohort, we excluded all patients with a C-reactive protein > 10 mg/l, because inflammation can alter the serum concentration of several markers such as vitamin A [28], thus leaving 515 patients: 137 with T1D, 331 with T2D and 47 with PD. Among the 137 patients with T1D, plain abdominal radiography or CT scan was normal in all of the 101 patients in whom they were performed. Among the 331 patients with T2D, plain abdominal radiography or CT scan was normal in all of the 289 patients in whom they were performed.

The PD group included 37 patients with alcohol-induced pancreatitis, three with total or subtotal pancreatectomy (1 nesidioblastosis, 1 intraductal papillary mucinous neoplasm of the pancreas, and 1 unknown), three with genetic chronic pancreatitis including 1 fibro calculous diabetes, and four with idiopathic chronic pancreatitis. Diabetes was confirmed in all patients. All of the patients with alcohol-induced chronic pancreatitis had pancreatic calcifications on CT scan.

Pancreatic function assessment

Exocrine function of the pancreas was assessed by the measurement of fecal elastase-1 concentration and chymotrypsin activity performed on a sample of feces obtained in non-diarrheic patients. Samples were stored at − 20 °C until analysis. Pancreatic fecal elastase-1 concentration was determined using a "sandwich"-type enzyme immunoassay (Schebo-Biotech, Germany) and results were expressed as µg/g of stool. The normal cut-off value was defined as > 200 µg/g. Fecal chymotrypsin activity was measured using a colorimetric method using Succ–Ala–Ala–Pro–Phe-*p*-nitroanilin as substrate (Immundiagnostik, Germany). Results were expressed as U/g of stool at 25 °C and activity values > 6 U/g were considered normal.

Nutritional assessment included measurements of serum vitamin 25OH-D2 + D3, vitamin A and vitamin E, albumin, calcium, phosphorus, and serum lipids.

Vitamin A (retinol) and vitamin E (alpha-tocopherol) were assayed by HPLC as previously described in [29], with excellent intra and inter-assay reproducibility at all levels of retinol and for higher levels of alpha-tocopherol, but with lower precision when alpha-tocopherol was < 7.5 µmol/l. As this low level of alpha-tocopherol was only found in four patients in our whole cohort, we consider our method to be satisfactory.

Vitamin A deficiency was defined as a vitamin A concentration < 0.7 µmol/l and vitamin E deficiency was defined as a vitamin E concentration < 12 µmol/l. Vitamin D concentration was assayed as the sum of 25-hydroxy vitamin (D2 + D3) (Immunodiagnosticsystems, Paris, France). Vitamin D deficiency was defined as a vitamin D concentration < 75 nmol/l, severe vitamin D deficiency was defined as a vitamin D concentration < 25 nmol/l [30].

Statistical analysis

We classified the patients into three groups as previously described [1]:

- Group LL: patients with a fecal elastase-1 < 200 µg/g AND a fecal chymotrypsin activity < 6 U/g (both parameters decreased).
- Group LN: patients with a fecal elastase-1 < 200 µg/g OR a fecal chymotrypsin activity < 6 U/g (only one decreased parameter).
- Group NN: patients with NORMAL fecal elastase-1 AND fecal chymotrypsin activity.

We have previously shown that the patients of the LL group display more severe decreases in both fecal elastase-1 concentration and fecal chymotrypsin activity than those of the LN group [1]. Comparisons of groups were performed using non-parametric tests, i.e., ANOVA using the Kruskal–Wallis test. When the test was significant, three pairs of data, PD vs LL, LN vs LL, and NN vs LL were compared using the Tukey post-hoc test. Categorical parameters were compared using the Pearson's Chi-square test. Correlations between continuous parameters were assessed with the non-parametric Pearson's test. Independent parameters that correlated significantly with serum concentration of fat-soluble vitamins were analyzed in a multivariate analysis with adjustment for gender, age, BMI, duration of diabetes, HbA1c, serum cholesterol concentration, serum triacylglycerol concentration, eGFR, and either fecal elastase-1 or fecal chymotrypsin concentrations.

Statistical analyses were performed using Sigmastat version 3.5. Results are expressed as median and interquartile range. *P* values were considered significant if < 0.05.

Results

Clinical characteristics of the patients

The clinical characteristics of the patients are presented in Table 1. Patients of the different groups were of similar age. The patients included in the present study are a subpart of those described in a previous publication [1]. As previously reported in this former publication, the patients were divided with regard to the results of fecal elastase-1 and chymotrypsin into LL (78 patients), LN (94 patients), and NN (296 patients) groups, as described in "Methods".

As shown before in this cohort, altered pancreatic exocrine function was more frequent in patients with T1D than in patients with T2D (24% of patients with T1D belonged to

Table 1 Clinical characteristics of the patients

	PD (*n* = 47)	Type 1 or 2 diabetes (*n* = 468)	LL (*n* = 78)	LN (*n* = 94)	NN (*n* = 296)	Name of test, *P* value
Age (years, median [IQR])	55 [46–63]	58 [49–66]	57 [45–68]	58 [50–65]	57 [51–65]	Kruskal, $P = 0.62$
Males (*n*, %)	42 (89%)	272 (58%)	48 (61%)	51 (54%)	173 (58%)	Pearson, $P = 0.0003$
Type 1 Diabetes (*n*, %)[a]	–	137 (29%)	33 (42%)	40 (42%)	64 (22%)	Pearson, $P < 10^{-6}$[b]
Known duration of diabetes (years, median [IQR])	6 [1–14]	12 [6–20]	15 [5–25]	12 [7–21]	11 [6–19]	Kruskal, $P = 0.0021$ Post-hoc: PD vs LL**
Known duration of diabetes in patients with T1D (years, median [IQR])	–	15 [6–27]	19 [8–35]	18 [9–30]	13 [2–22]	Kruskal, $P = 0.042$
Known duration of diabetes in patients with T2D (years, median [IQR])	–	11 [6–19]	14 [4–22]	9 [5–19]	11 [6–19]	Kruskal, $P = 0.52$
HbA1c (%, median [IQR]) HbA1c (mmol/mmol)	8.2 [7.2–10] 66	8.8 [7.7–10.2] 73	8.8 [7.9–10.3] 73	8.9 [7.6–9.9] 74	8.9 [7.6–10.3] 74	Kruskal, $P = 0.62$
BMI (kg/m^2, median [IQR])	22.6 [20.1–25.4]	27.7 [24.5–32.4]	26.0 [23.8–28.6]	27.2 [24.4–32.1]	28.7 [24.8–33.7]	Kruskal $P < 10^{-6}$ Post-hoc: PD vs LL and NN vs LL**
BMI in patients with T1D (kg/m^2, median [IQR])	–	24.9 [22.6–27.9]	24.7 [23.1–26.4]	25.8 [22.7–28.5]	24.8 [21.9–28.3]	Kruskal, $P = 0.64$[b]
BMI in patients with T2D (kg/m^2, median [IQR])	–	29.1 [25.9–33.9]	27.1 [24.6–29.7]	29.2 [24.5–33.7]	30.1 [26.0-34.2]	Kruskal, $P = 0.0064$[b] Post-hoc: NN vs LL**
Insulin use (*n*, %)[c]	42 (89%)	196 (59%)	35 (78%)	25 (46%)	136 (58%)	Pearson, $P = 0.0061$

The *P* values indicated in the last column are the overall *P* values of the Kruskal–Wallis or Pearson Chi-square tests performed for each parameter. For the Kruskal–Wallis tests, if the *P* value was < 0.05, LL was compared to PD, LN and NN groups: *$P < 0.05$, **$P < 0.01$

[a]Only in patients with T1D or T2D

[b]Comparison of LL, LN and NN only

[c]Only in patients with PD and T2D

the LL group, vs only 13% of patients with T2D). In patients with T1D, pancreatic exocrine dysfunction was associated with a longer median duration of diabetes (19 years in the LL group vs 13 years in the NN group), this was not observed in patients with T2D. In patients with T2D, altered pancreatic exocrine function was associated with insulin use, as we already described [1].

Nutritional markers in patients with diabetes

BMI was significantly lower in the PD group than in the LL group, and in the LL group than in the NN group. Lower BMI in the LL subjects as compared to NN subjects was, however, only observed in patients with T2D, not in those with T1D (Table 1). Mean serum albumin and phosphorus concentrations were lower in the LL group (36.4 g/l and 1.15 mmol/l, respectively) as compared to the NN group (38 g/l and 1.22 mmol/l, respectively) (Fig. 1).

Although cholesterol and calcium concentrations differed significantly under ANOVA analysis, no significant difference was found between the LL group and the LN and NN groups.

Serum concentration of fat-soluble vitamins in patients with diabetes

As shown in Fig. 2, the serum concentrations of vitamins A, D, and E differed significantly between groups. Post-hoc analyses showed that vitamin D and vitamin E were lower in the PD group as compared to the LL group. Vitamin A was lower in the LL group than in the LN and NN groups.

The prevalence of vitamin D deficiency was extremely high in the whole study cohort: vitamin D concentration was < 75 nmol/l in 94% of the patients and was < 25 nmol/l (severe vitamin D deficiency) in 20% of the patients. In contrast, the prevalence of vitamin A and E deficiencies, defined, respectively, as a value below 0.7 µmol/l and 12 µmol/l, were very low, 1.2% and 4.4%, respectively. However, vitamins A and E deficiencies and severe vitamin D deficiency were more common in patients of the PD group

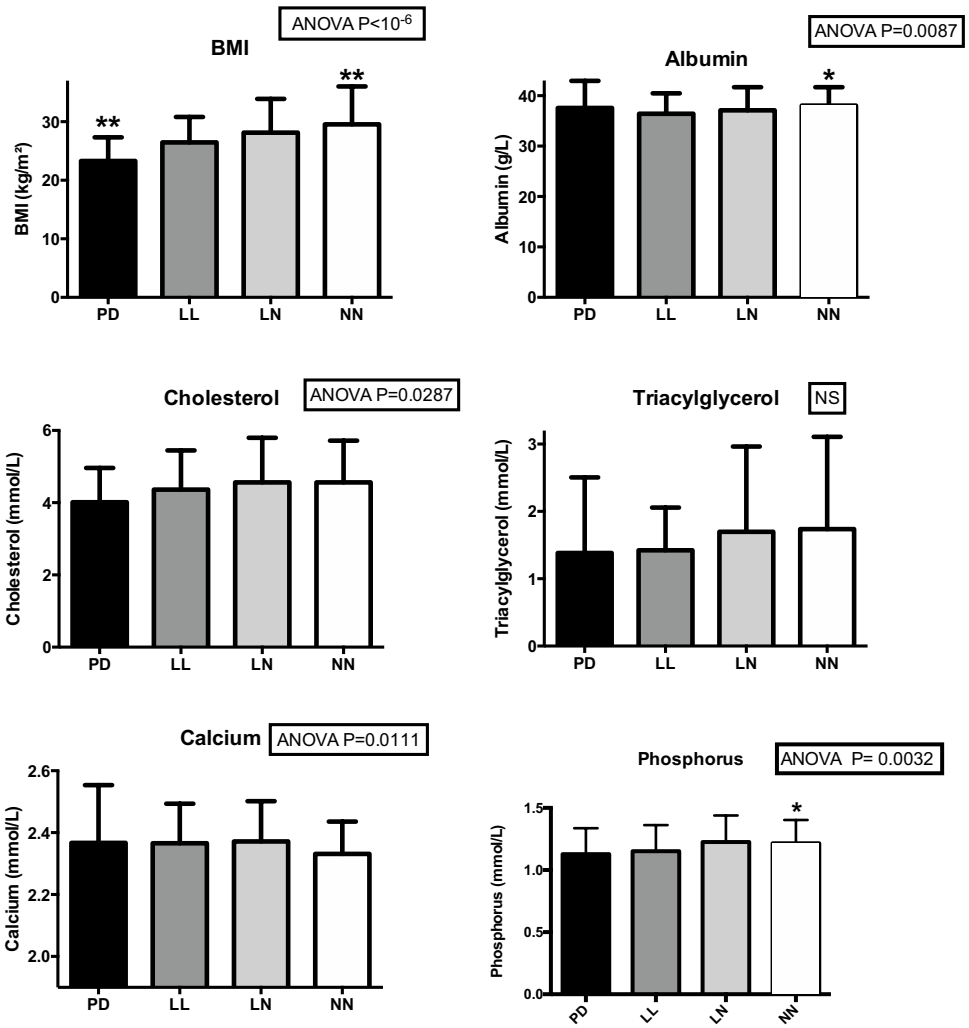

Fig. 1 BMI, albumin, cholesterol, triacylglycerol, calcium, and phosphorus concentrations in the PD, LL, LN, and NN groups. If the *P* value of ANOVA was < 0.05, LL group was compared to PD, LN, and NN groups: **P* < 0.05, ***P* < 0.01

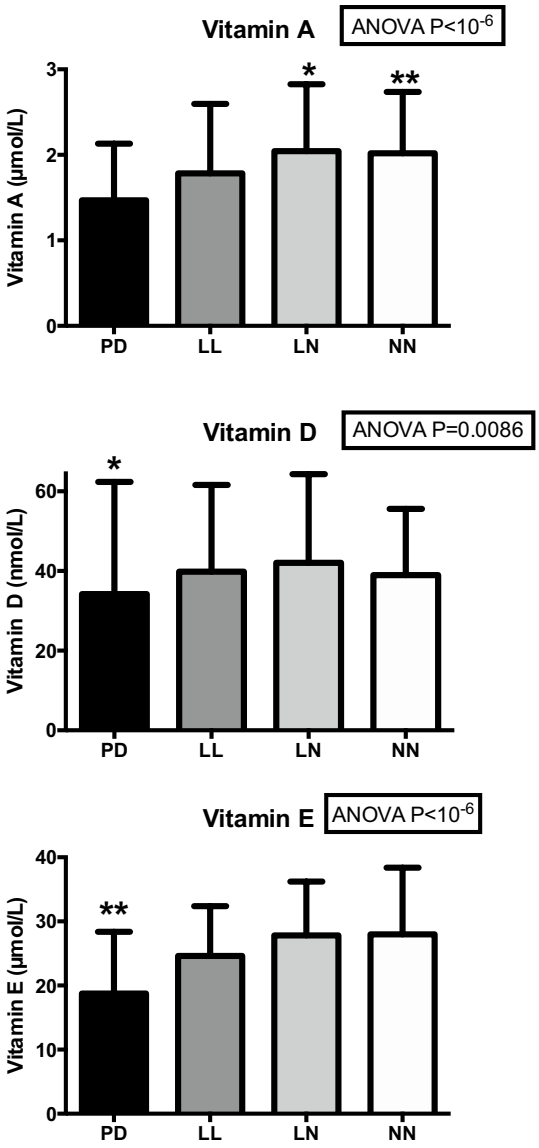

Fig. 2 Vitamins A, D, and E concentrations in the PD, LL, LN, and NN groups. If the *P* value of ANOVA was <0.05, LL group was compared to PD, LN, and NN groups: $*P<0.05$, $**P<0.01$

(6.7%, 22%, and 38.8%, respectively) and in patients of the LL group (2.6%, 9.2%, and 24.7%, respectively), than in patients of the LN (0%, 2.2%, and 20.2%, respectively) and NN groups (0.3%, 1.4%, and 16.6%, respectively) (Table 2).

Serum concentrations of fat-soluble vitamins were affected by several parameters, as listed in Supplementary Table 1. Multivariate analysis with adjustment for gender, age, BMI, duration of diabetes, HbA1c, serum cholesterol concentration, serum triacylglycerol concentration, Egfr, and either fecal elastase-1 or fecal chymotrypsin concentrations showed that serum lipids concentrations and BMI were independently associated with serum concentrations of vitamins A and E, whereas only serum cholesterol concentration was associated with vitamin D concentration. When the analysis was performed after exclusion of the PD patients, fecal elastase-1 concentration remained a significant independent determinant of vitamin E concentration, but not of vitamin A (data not shown).

Discussion

In the present study, we have investigated the nutritional consequences of impaired exocrine function in patients with diabetes. Patients with varying degrees of impairment of exocrine function tests and either T1D or T2D were compared with patients with PD. In patients with PD, nutritional defects were quite mild, with a median BMI of 22.6 kg/m^2 and a serum albumin concentration of 37.6 g/l, owing to the fact that 27 patients out of 47 (60%) already received pancreatic enzyme therapy at the time of study. In the patients with type 1 and type 2 diabetes, the patients in whom both fecal elastase concentration and fecal chymotrypsin activity were decreased (LL group) had an intermediate nutritional status between that of patients with PD and patients with normal exocrine function. BMI, phosphorus, and vitamin A were lower in patients of the LL group as compared to patients of the NN group. Fecal elastase concentration was positively associated with serum vitamin A and serum vitamin E in a multivariate analysis that also revealed a correlation between the serum concentration of vitamins A and E on one hand and BMI, GFR, and serum lipids concentration on the other hand. With regard to vitamin D concentration, the deficit was quasi-universal in all groups of patients, but severe deficiency was more frequent in patients of the LL group as compared to patients of the NN group. In patients with T1D or T2D and altered exocrine function, serum phosphorus concentration was lower in the LL group, suggesting that these patients might have lower phosphate intestinal absorption and secondary hyperparathyroidism as a consequence of more severe vitamin D deficiency, but serum PTH concentration was not measured in this study. However, it must be noted that patients with severe vitamin D deficiency did not have a significantly lower serum phosphorus concentration than the other subjects, even though diabetes is known to alter the parathormone increase in face of vitamin deficiency due to decreased magnesium concentration in patients with diabetes [31].

The patients with T2D and altered exocrine function tests had a lower BMI than the patients with normal exocrine function tests. It has already been observed that the weight of the patients with low fecal elastase is lower than that of patients with normal exocrine function tests [2, 20, 21]. We have shown that the weight gain after initiation of insulin was similar in patients with or without exocrine failure, suggesting that weight loss in these patients was mostly

Table 2 Prevalence of fat-soluble vitamins deficiencies in patients with diabetes

	PD	LL	LN	NN	*P* value
Vitamin D deficiency[a] (*n*, %)	42 (95.5%) *N* = 44	71 (92.2%) *N* = 77	79 (88.8%) *N* = 89	276 (95.2%) *N* = 290	0.16
Severe vitamin D deficiency[b] (*n*, %)	17 (38.6%) *N* = 44	19 (24.7%) *N* = 77	18 (20.2%) *N* = 89	48 (16.6%) *N* = 290	0.0058
Vitamin A deficiency[c] (*n*, %)	3 (6.7%) *N* = 45	2 (2.6%) *N* = 78	0 (0%) *N* = 94	1 (0.33%) *N* = 295	N/A
Vitamin E deficiency[d] (*n*, %)	9 (22%) *N* = 41	7 (9.2%) *N* = 76	2 (2.2%) *N* = 92	4 (1.4%) *N* = 291	0.0001

The *P* values indicated in the last column are the overall *P* values of the Chi-square tests. The test was not applicable for vitamin A deficiency, because the number of patients with deficiency was too small

[a]As defined by a vitamin D concentration < 75 nmol/l

[b]As defined by a vitamin D concentration < 25 nmol/l

[c]As defined by a vitamin A concentration < 0.7 µmol/l

[d]As defined by a vitamin E concentration < 12 µmol/l

due to more severe insulin deficiency, not to malabsorption secondary to exocrine failure [1]. We have, however, also shown that pancreatic exocrine deficiency is associated with lower insulin secretion [13]. This concurs with the higher prevalence of insulin use observed in patients with T2D and altered exocrine function.

In this study, only serum concentration of vitamin A was assessed, not the concentrations of retinol-binding protein (RBP) or transthyretin (TTR). We verified in a subset of this cohort that vitamin A was highly correlated with RBP and TTR ($n = 65$, correlation coefficient > 0.95, $P < 10^{-6}$, data not shown) and we confirmed that in patients with diabetes the relation of serum retinol, RBP and TTR are unchanged and occur in a 1:1:1 complex, as already described [32, 33]. Thus, in these patients, assessment of RBP and TTR gives no further information than that of retinol alone. Serum retinol reflects an individual's vitamin A status, particularly when the body's reserves are limited [34]. Serum retinol < 0.7 µmol/l is considered diagnostic of vitamin A deficiency [35]. In the present study, serum concentration of vitamin A correlated with multiple parameters, including gender, BMI, serum lipid concentration, and eGFR. Except for lipids [36], these parameters were not yet known to be associated with vitamin A concentration in patients with diabetes. Inflammation is known to influence serum concentration of vitamin A as is malnutrition. We excluded patients with a CRP > 10 mg/l from the present study.

To our knowledge, only a few studies have analyzed the nutritional consequences of altered exocrine function in patients with diabetes [22, 27]. In the study by Ewald et al., 80 patients with fecal elastase-1 concentration < 100 µg/g were randomized to either 40,000 U pancreatin per meal or to placebo for 16 weeks. At baseline, serum concentration of vitamins A, D, and E was normal in both groups and remained unchanged during the trial. However, the serum concentration of vitamins in these patients was not compared to reference values [22]. On the other hand, Lindkvist et al. showed that in patients with T2D, fecal elastase-1 concentration positively correlated with 25-hydroxy vitamin D [27]. Finally, one important point of discussion relates to the threshold of fecal elastase-1 concentration that defines pancreatic exocrine insufficiency. Traditionally, a concentration < 100 µg/g is said to be diagnostic of exocrine failure and values > 200 µg/g are considered normal [37, 38]. More recently, due to the lack of sensitivity and specificity of the test in certain conditions [39–41], the American guidelines have suggested that a concentration < 50 µg/g should be considered diagnostic of exocrine insufficiency [42], and a threshold of < 15 µg/g has even been suggested [43]. If these different thresholds were applied to our population, between 0.2 and 25% would be considered to have exocrine insufficiency, as compared to 67–93% of the patients with PD (Table 3). This may explain the relatively mild pattern of nutritional deficits in the patients with T1D or T2D and low elastase concentration. If a criterion of Elastase-1 < 50 µg/g is applied, about 10% of patients with diabetes would be considered to have exocrine insufficiency. This may be important to consider not only in the context of fat-soluble vitamin deficiency, but also with regard to hypoglycaemia [22].

Table 3 Percentage of patients with fecal elastase-1 concentration below several thresholds

	Pancreatogenic diabetes (*n* = 27) (%)	Type 1 or -2 diabetes (*n* = 467) (%)
Elastase-1 concentration		
< 200 µg/g	93	25
< 100 µg/g	81	15
< 50 µg/g	74	9
< 15 µg/g	67	0.2

Conclusion

In patients with type 1 or type 2 diabetes and exocrine dysfunction, modest nutritional alterations can be observed. Indeed, BMI was lower in patients presenting with type 2 diabetes, low fecal elastase-1 concentration, and low fecal chymotrypsin activity than in patients with type 2 diabetes and normal pancreatic exocrine function. Moreover, patients with diabetes and exocrine dysfunction presented more frequent vitamin A and E deficiencies and severe vitamin D deficiency than patients without pancreatic exocrine dysfunction. Hence, patients with type 1 or type 2 diabetes and altered pancreatic exocrine function should be screened for nutritional deficiencies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. All investigations were performed in the context of routine patient's care.

Ethical standard statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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