European Journal of Internal Medicine 68 (2019) 18–22

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Pancreatic exocrine insufficiency in diabetes mellitus - prevalence and characteristics

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ARTICLE INFO

Keywords:
Pancreatic exocrine insufficiency
Diabetes mellitus
Faecal elastase-1
Mixed ^{13}C-triglyceride breath test

ABSTRACT

Background: The prevalence of pancreatic exocrine insufficiency (PEI) in diabetes mellitus (DM) varies widely between studies, which may be explained by methodological problems. We aimed to establish the prevalence of PEI in DM using the faecal elastase-1 (FE-1) assay as a screening test, and to further investigate these patients by the mixed ^{13}C-triglyceride (^{13}C-MTG) breath test.

Methods: One hundred and thirty-three consecutive type 1 or type 2 DM patients without known exocrine pancreatic disorders were recruited. Demographic parameters, stool consistency, stool frequency, routine laboratory tests, and the presence of DM complications were registered. An FE-1 value < 200 μg/g was used as the screening cut-off for PEI, and patients with FE-1 values below this level were referred for a ^{13}C-MTG breath test.

Results: One hundred and two patients returned faecal samples. The prevalence of PEI as measured by low FE-1 was 13%. Insulin usage, type 1 DM, and DM duration were associated with low FE-1. Stool habits were unaffected by low FE-1. Twelve out of 13 patients with low FE-1 performed the breath test, which was normal in all cases.

Conclusions: The prevalence of PEI defined by FE-1 was low in our mixed cohort of type 1 and 2 DM patients. Furthermore, there was a discrepancy between FE-1 and the breath test. Hence, the role of FE-1 in evaluating pancreatic exocrine function in DM should be evaluated in larger studies in order to clarify the association between low FE-1 and clinically relevant PEI.

1. Introduction

Diabetes mellitus (DM) is a chronic condition in which the insulin-secreting capacity of the endocrine pancreas is inadequate compared to metabolic demands, leading to hyperglycaemia. Some DM aetiologies, such as diabetes of the exocrine pancreas or several types of MODY (Maturity Onset Diabetes of the Young), are strongly associated with *combined exo-* and endocrine pancreatic dysfunction [1–3]. In type 1 and 2 DM, on the other hand, the degree of association with pancreatic exocrine insufficiency (PEI) is a topic of considerable ambiguity, with reported prevalences of PEI varying between 14 and 74% [4,5].

Most previous studies used the faecal elastase-1 concentration (FE-1) for assessment of PEI. FE-1 has the advantage of being easy to perform, affordable, and widely available. Levels of FE-1 above 200 μg/g exclude PEI with a high negative predictive value, however, FE-1 levels below this cut-off are associated with false-positive rates as high as 11%

Abbreviations: BMI, body mass index; ^{13}C-MTG, mixed ^{13}C-triglyceride; CO_2, carbon dioxide; DM, diabetes mellitus; ELISA, enzyme-linked immunosorbent assay; FE-1, faecal elastase-1; HbA_{1c}, haemoglobin A_{1c}; IQR, interquartile range; MODY, maturity onset diabetes of the young; OR, odds ratio; PEI, pancreatic exocrine insufficiency; SD, standard deviation

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https://doi.org/10.1016/j.ejim.2019.07.021
Received 12 June 2019; Received in revised form 22 July 2019; Accepted 23 July 2019
Available online 08 August 2019

[6]. Consequently, there is a lack of consensus in terms of the appropriate FE-1 cut-off levels, with < 15, 50, 100, and 200 μg/g all currently in use [7].

FE-1 is a marker of pancreatic enzyme secretion and not PEI per se. It does not allow differentiation of primary from secondary PEI (i.e. to differentiate pancreatic acinar cell dysfunction from exocrine pancreatic dysfunction secondary to other conditions) [8,9]. Examples of such conditions include any small bowel damage or villous atrophy due to coeliac disease, cow milk protein enteropathy, or even transient intestinal damage resulting from enteric pathogens or small intestinal bacterial overgrowth [8,10,11]. In DM, autonomic neuropathy may lead to the impaired activation of the otherwise intact exocrine pancreas [12]. Finally, other extra-pancreatic parameters such as the dilution factor due to watery stool is highly associated with false low FE-1 [6]. Therefore, the FE-1 assay has limitations in terms of specificity [6].

Another method to evaluate pancreatic exocrine function is to measure intraduodenal lipase activity using the mixed ^{13}C-triglyceride (^{13}C-MTG) breath test. Exocrine pancreatic secretion is stimulated by way of a test meal (bread and butter), with added ^{13}C-labelled triglycerides. The amount of exhaled ^{13}C-labelled carbon dioxide is an indirect measure of lipolysis due to the activity of pancreatic lipase within the small intestine [13,14]. Although the test has limitations in terms of specificity (such as false positive results in non-pancreatic fat malabsorption), it is considered reliable and valid [14]. When using the secretin-pancreazymin test as gold standard on patients with a variety of pancreatic diseases, the sensitivity was reported at 63% and specificity 85% [13].

Hence, we aimed to establish the prevalence of PEI in type 1 and type 2 DM patients by using the FE-1 test as a screening test, and subsequently to further investigate the pancreatic exocrine function further using the ^{13}C-MTG breath test.

2. Materials and methods

This was a cross-sectional multicentre study, with consecutive recruitment at the diabetes outpatient clinics at Aalborg University Hospital, Denmark and Haukeland University Hospital, Bergen, Norway. Inclusion criteria were: age 18–75 years and a diagnosis of type 1 or 2 DM according to the American Diabetes Association's classification [15]. Exclusion criteria were: any previous gastrointestinal disease or surgery that might interfere with the study results, intake of orlistat or acarbose, excessive alcohol consumption, and a history of acute or chronic pancreatitis.

2.1. Assessment variables and investigations

Following patient consent, demographic parameters, body mass index, stool frequency, stool consistency by Bristol Stool Form Scale, and the most recent level of glycated haemoglobin (HbA1c) were registered [16]. Furthermore, we recorded the current antidiabetic therapy, duration of disease, and the presence of DM late complications in the patient history. Lastly, patients were instructed on how to collect faeces samples at home. Estimation of FE-1 was performed on ScheBo® Pancreatic Elastase 1 Stool Test (Biotech AG, Germany), which is an enzyme-linked immunosorbent assay (ELISA) method. Levels < 200 μg/g were considered abnormal, and these participants were referred for a ^{13}C-MTG breath test. Upon an overnight fast, the breath test was performed in accordance with previously published procedures [14]. In short, 10 mg metoclopramide was ingested to ensure optimal gastric emptying, then a baseline breath sample was taken 20 min after ingestion of metoclopramide followed by a standardized test meal (250 mg ^{13}C-MTG, 16 g of fat on a piece of toasted bread, and a glass (200 mL) of water). Breath samples were subsequently taken in 30-min intervals for six hours. The amount of ^{13}C-carbon dioxide (CO_2) and $^{12}CO_2$ was measured by mass spectrometry on an IRIS-3 breath analyzer (Wagner Analysen Tecknik GmbH, Bremen, Germany), and the $^{13}CO_2/^{12}CO_2$ quotient was calculated for each breath sample. A cumulative value of < 29% was considered to be abnormal [17].

2.2. Ethics

Prior to enrolment, all participants were informed about the study orally and in written form. Consent forms were signed ahead of any study-related procedures. The project was approved by the Ethical Committee for North Denmark Region (N-20130059) and Haukeland University Hospital (Western Norway Regional Committee for Medical and Health Research Ethics – REK Vest 2013/2333).

2.3. Statistical analysis

The data is presented as number of patients (%), means (standard deviation - SD), or medians (interquartile range – IQR) unless otherwise indicated. Assumption of normal distribution was tested by the Shapiro-Wilks test. Comparisons of assessment variables between patients with a normal and low FE-1 were made using the unpaired Student's *t*-test or the Kruskal-Wallis test as appropriate. Linear correlations were estimated by Pearson's r. For testing differences in proportions, we used Pearson's χ^2. The level of statistical significance was set at 5%.

All statistics were performed on STATA version 15.1 (StataCorp LLC, Texas, USA) or Analyse-it for Microsoft Excel version 5.30 (Analyse-it Software Ltd., United Kingdom).

3. Results

In total, 133 patients were enrolled in the study. Faecal samples were returned by 102 patients who were included for further analysis. The median age of enrolled patients was 54 (IQR 15) years and 56 were males – see Table 1 for clinical characteristics and results. An abnormal FE-1 value was seen in 13 patients (12.7%), and the distribution of FE-1 levels in this group is depicted in Fig. 1. Further, we found that the group with an FE-1 below the cut-off value had a significantly longer DM duration, $p = .005$.

Linear regression demonstrated a highly significant association between DM duration and FE-1 concentration, $r = -0.27$, $p = .009$ (Fig. 2).

Additionally, type 1 DM patients had a higher likelihood of low FE-1 when compared to patients with type 2 DM, Odds ratio 4.1 (95% CI 1.12–14.7), $p = .03$. Finally, all patients with low FE-1 were insulin treated, compared to 73% in the group with FE-1 ≥ 200 μg/g, $p = .04$.

Table 1
Clinical characteristics and results.

Variables	All participants	FE-1 < 200 μg/L	FE-1 ≥ 200 μg/L
n	102 (133[§])	13	89
Age	54 (15)	54 (12)	57 (13)
Gender (M/F)	56/47	5/8	51/39
BMI	27.3 (8.0)	26.3 (7.1)	27.7 (8.1)
FE-1 level (μg/g)	398 (222)	121 (124)*	433 (188)*
Diabetes duration	13.0 (17.0)	27.5 (32.8)*	13.0 (14.1)*
Diabetes type (1/2)	49/51%	77/23%*	45/55%*
Insulin treatment	76%	100%*	73%*
HbA1c (mmol/mol)	61 (15)	60 (15)	61 (15)
Stool frequency (/day)	1.0 (0.5)	1.0 (1.2)	1.0 (0.5)
Bristol score	4.0 (1.0)	3.0 (1.3)	4.0 (1.0)
Neuropathy	24%	8%	26%
Retinopathy	31%	31%	31%
Nephropathy	4%	8%	3%
Microalbuminuria	14%	15%	14%

The data is provided as medians (IQR) or proportions (%).

* $p < .05$.

§ 31 participants did not return faecal sample, data from these participants are not included.

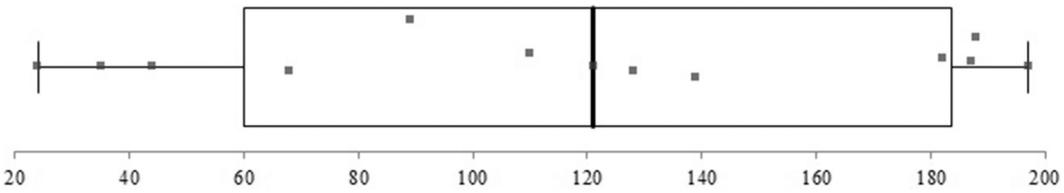

Fig. 1. The distribution of individual FE-1 in the cohort with FE-1 < 200 µg/g.

MTG breath tests were performed on 12 patients with low FE-1, all of which were within the normal range, cumulative $^{13}CO_2$ values 48 (14) %.

4. Discussion

In the present study on patients with both type 1 and type 2 diabetes mellitus, we found a relatively low PEI prevalence of 13% as measured by FE-1. However, all patients with abnormal FE-1 had normal pancreatic exocrine function evaluated by ^{13}C-MTG breath test. Patients with abnormal FE-1 levels had longer DM duration, and were more likely to have type 1 DM and be insulin treated. We could not detect any differences in terms of stool frequency, stool consistency, BMI, or late diabetic complications between patients with normal and abnormal FE-1 levels.

The apparent lack of clinical correlate to the low FE-1 is a bit surprising, since studies involving other conditions associated with PEI seem to indicate a clearer link between low FE-1 and BMI, stool habits, etc. [18]. Data on DM patients, on the other hand, is limited, and available studies concur with our results in terms of no impact on BMI [19].

The low PEI prevalence (by FE-1) in our study was intriguing, and clearly lower than in most previous studies [4]. This could be because we included patients prospectively at two tertiary centres in Norway and Denmark, with careful exclusion of patients with other causes of PEI, including pancreatitis, alcohol abuse, and other types of pancreatogenic DM. Hence, differences in patient populations or selection bias may explain the discrepancy in PEI prevalence. Moreover, two recent studies found prevalences more consistent with the present study, with estimates of 16.8% and 14.4% [20,21]. Finally, another study with similar exclusion criteria but which only included patients with more than five years duration of DM found an even lower prevalence of 5.4% [22]. All of these studies used FE-1 levels below 200 µg/g as the sole diagnostic cut-off, and two of them included pancreatic imaging studies to exclude post-pancreatitis DM [20,22]. A limitation to our study is that we did not perform such imaging studies. Consequently, we can not rule out some cases with low FE-1 due to other diseases of the exocrine pancreas

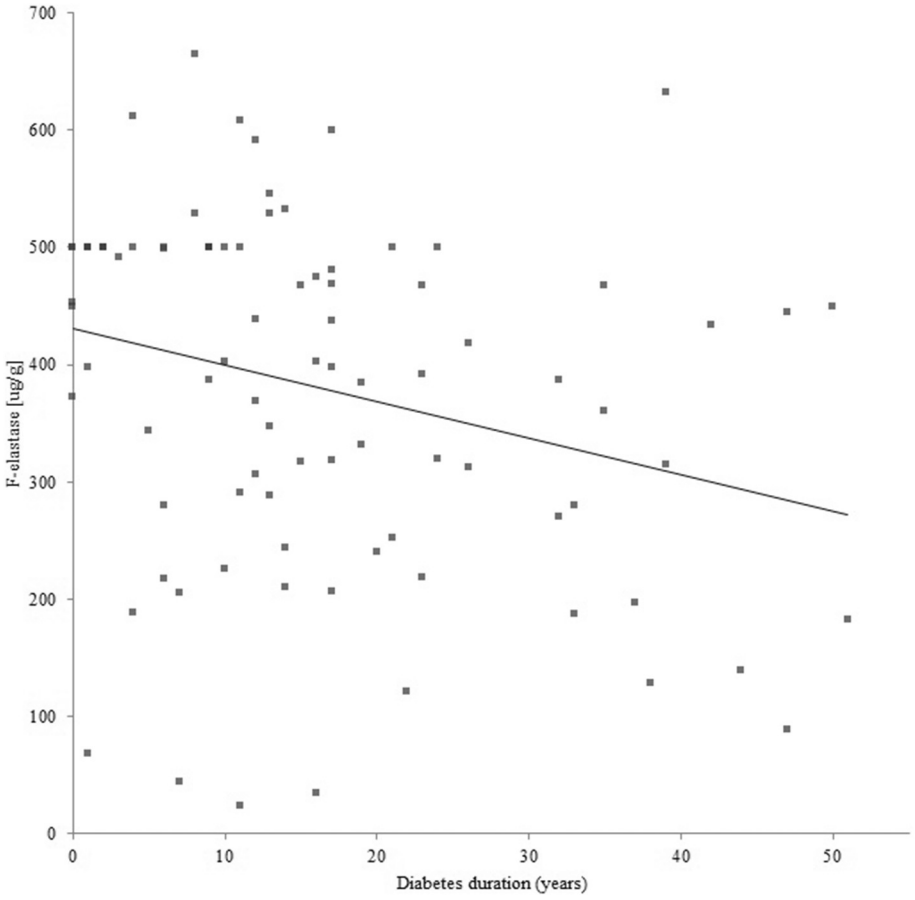

Fig. 2. Negative association between DM duration and FE-1 levels, $r = -0.27$, $p = .009$.

Another – somewhat speculative – explanation of the lower PEI prevalences in recent studies could be that the finding reflects an actual decline. Recent decades have witnessed improved control of several risk factors of DM complications, such as glycaemia and hyperlipidaemia, which might – in turn – result in less PEI [23].

In line with our findings, DM duration seems to be a risk factor for low FE-1 level in most studies [19]. The findings may add further weight to the hypothesis that PEI could be a late DM complication, with autonomic neuropathy likely being a contributing factor. We could not detect any statistically significant difference in the prevalence of neuropathy in this cohort, however the study was not designed to evaluate this question. Presence of neuropathy was defined based on anamnestic information. In practice, this means the presence of either an impaired monofilament test or pathological nerve conduction velocity studies. These tests assess the function of large myelinated nerves, however the innervation of the exocrine pancreas is primarily by small, unmyelinated autonomic nerve fibres [24]. Thus, we cannot exclude the impact of small fibre/autonomic neuropathy in our cohort.

Consistent with previous studies, we found a higher risk of low FE-1 levels in type 1 vs. 2 DM [19]. The risk was even higher when looking at patients who were on insulin treatment vs. no insulin treatment. All patients with low FE-1, including those with type 2 DM, were on insulin. Although the sample size is small, these results support the hypothesis that impaired insulin secretion into the insular-acinar portal system could be involved in the pathomechanism of PEI (as defined by FE-1) in DM [19].

In our study, we did not find any association between HbA_{1c}-levels and FE-1. A limitation of this study is that we did not investigate glycaemia in greater detail. PEI has been shown to be associated with the impaired secretion of the incretin hormones - glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) [25,26]. Incretin hormones have a stabilizing effect on post-prandial glucose excursions, hence we cannot rule out the impact of PEI on glucose variability in spite of unaffected HbA_{1c} [27]. Future studies, using continuous glucose monitoring, should evaluate this question.

At least one alternative hypothesis could address the lack of clinical correlate in the participants with low FE-1. A longer DM disease duration increases the risk of diabetic enteropathies such as dysregulated and delayed gastric emptying, intestinal dysmotility, and bacterial overgrowth [28–30] and might contribute to a false positive FE-1. To investigate this, we performed a second test of pancreatic exocrine function. Unexpectedly, there was a discrepancy between FE-1 and the mixed ^{13}C-triglyceride breath test, which was normal in all patients with abnormal FE-1 levels. Our study was not constructed to differentiate between primary and secondary PEI or to differentiate between causes of false positive FE-1 results, however, the low concordance between the two tests may indicate that such alternative explanations are involved. A larger study, including relevant markers of small bowel damage, is warranted to further elaborate on this issue. Additionally, using a lower FE-1 cut-off in a larger cohort could have increased the concordance between FE-1 and the breath test.

4.1. Methodological considerations

This study has some limitations. We only performed a single FE-1 test, meaning that it was not repeated to avoid water interference (i.e. samples from a watery part of the stool) nor did we dry the faeces (lyophilization) to prevent false positives [9,31]. On the other hand, stool consistency (Bristol score) was identical in patients with normal vs. low FE-1, so the impact of water interference was likely minimal. By repeating the test, even fewer instances of low FE-1 could be expected, meaning that we could have false positives in our cohort. Also, the FE-1 test was validated in patients with existing signs and symptoms of PEI, and therefore may be poorly suited for population-based screening studies [32]. This is supported by the confirmatory second test in our study, the ^{13}C-MTG breath test, which was negative in all the FE-1 positive patients. In our opinion, this could indicate that the pancreatic acinar cells are responsive after a high-fat meal stimulation, thus excluding primary PEI.

A relatively small study population, exacerbated by the unexpectedly low prevalence of subnormal FE-1, also limits the statistical power of the study. Nevertheless, a clearly significant impact of DM duration, DM type, and insulin treatment on the risk of low FE-1 was demonstrated. The biological plausibility of these factors in the pathophysiology of PEI in DM, as well as their biological interaction, increases the robustness of our findings. However, both significant and non-significant differences in the subgroup analyses should be interpreted with caution due to a small subgroup sample size.

5. Conclusion

In a mixed cohort of type 1 and 2 DM, low FE-1 levels were found in only 13% of participants. Insulin use, type 1 DM, and DM duration were risk factors for low FE-1. The ^{13}C-MTG breath test was normal in all patients with low FE-1. Our results indicate that FE-1 might not be an ideal marker of PEI in DM. We suggest that the discrepancy between FE-1 and the breath test should be further investigated in prospective interventional studies, in order to ensure pancreatic enzyme replacement therapy to the right patients. Furthermore, low FE-1 levels in DM patients may be caused by impaired enteropancreatic signalling induced by conditions such as neuropathy, dysmotility, or dysbiosis (i.e. “secondary PEI”). To decide whether detection of low FE-1 is of value in DM, future studies should include a more detailed investigation of the extra-pancreatic factors, nutritional and metabolic consequences, as well as the impact of pancreatic enzyme replacement therapy.

Funding

This work was supported by an unrestricted grant from Mylan A/S Copenhagen, Denmark.

Declaration of Competing Interest

The authors declare no relevant conflicts of interest.

References

[1] Tjora E, Wathle G, Engjom T, Erchinger F, Molven A, Aksnes L, et al. Severe pancreatic dysfunction but compensated nutritional status in monogenic pancreatic disease caused by carboxyl-ester lipase mutations. Pancreas 2013;42:1078–84. https://doi.org/10.1097/MPA.0b013e3182920e9c.

[2] Vesterhus M, Ræder H, Johansson S, Molven A, Njølstad PR. Pancreatic exocrine dysfunction in maturity-onset diabetes of the young type 3. Diabetes Care 2008;31:306–10. https://doi.org/10.2337/dc07-1002.

[3] Ewald N, Bretzel RG. Diabetes mellitus secondary to pancreatic diseases (Type 3c)—are we neglecting an important disease? Eur J Intern Med 2013;24:203–6. https://doi.org/10.1016/j.ejim.2012.12.017.

[4] Singh VK, Haupt ME, Geller DE, Hall JA, Diez PMQ. Less common etiologies of exocrine pancreatic insufficiency. World J Gastroenterol 2017;23:7059–76. https://doi.org/10.3748/wjg.v23.i39.7059.

[5] Capurso G, Traini M, Piciucchi M, Signoretti M, Arcidiacono PG. Exocrine pancreatic insufficiency: prevalence, diagnosis, and management. Clin Exp Gastroenterol 2019;12:129–39. https://doi.org/10.2147/CEG.S168266.

[6] Vanga RR, Tansel A, Sidiq S, El-Serag HB, Othman MO. Diagnostic performance of measurement of fecal elastase-1 in detection of exocrine pancreatic insufficiency: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018;16:1220–1228.e4. https://doi.org/10.1016/j.cgh.2018.01.027.

[7] Löhr JM, Dominguez-Munoz E, Rosendahl J, Besselink M, Mayerle J, Lerch MM, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United Eur Gastroenterol J 2017;5:153–99. https://doi.org/10.1177/2050640616684695.

[8] Schäppi MG, Smith VV, Cubitt D, Milla PJ, Lindley KJ. Faecal elastase 1 concentration is a marker of duodenal enteropathy. Arch Dis Child 2002;86:50–3. https://doi.org/10.1136/adc.86.1.50.

[9] Stein J, Jung M, Sziegoleit A, Zeuzem S, Caspary WF, Lembcke B. Immunoreactive elastase I: clinical evaluation of a new noninvasive test of pancreatic function. Clin Chem 1996;42:222–6.

[10] Walkowiak J, Herzig KH. Fecal elastase-I is decreased in villous atrophy regardless of the underlying disease. Eur J Clin Invest 2001;31:425–30. https://doi.org/10.

1046/j.1365-2362.2001.00822.x.
[11] Salvatore S, Finazzi S, Barassi A, Verzelletti M, Tosi A, Melzi D'Eril GV, et al. Low fecal elastase: potentially related to transient small bowel damage resulting from enteric pathogens. J Pediatr Gastroenterol Nutr 2003;36:392–6. https://doi.org/10.1097/00005176-200303000-00018.
[12] Hardt PD, Ewald N. Exocrine pancreatic insufficiency in diabetes mellitus: a complication of diabetic neuropathy or a different type of diabetes? Exp Diabetes Res 2011;2011:1–7. https://doi.org/10.1155/2011/761950.
[13] Weaver LT, Amarri S, Swart GR. 13C mixed triglyceride breath test. Gut 1998;43(Suppl. 3):S13–9.
[14] Domínguez-Muñoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. J Gastroenterol Hepatol 2011;26(Suppl. 2):12–6. https://doi.org/10.1111/j.1440-1746.2010.06600.x.
[15] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37(Suppl. 1):S81–90. https://doi.org/10.2337/dc14-S081.
[16] Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920–4. https://doi.org/10.3109/00365529709011203.
[17] Domínguez-Muñoz JE, Iglesias-García J, Vilariño-Insua M, Iglesias-Rey M. 13C-mixed triglyceride breath test to assess oral enzyme substitution therapy in patients with chronic pancreatitis. Clin Gastroenterol Hepatol 2007;5:484–8. https://doi.org/10.1016/j.cgh.2007.01.004.
[18] Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. World J Gastroenterol 2013;19:7258–66. https://doi.org/10.3748/wjg.v19.i42.7258.
[19] Zsóri G, Illés D, Terzin V, Iványi E, Czakó L. Exocrine pancreatic insufficiency in type 1 and type 2 diabetes mellitus: do we need to treat it? A systematic review. Pancreatology 2018;18:559–65. https://doi.org/10.1016/j.pan.2018.05.006.
[20] Terzin V, Várkonyi T, Szabolcs A, Lengyel C, Takács T, Zsóri G, et al. Prevalence of exocrine pancreatic insufficiency in type 2 diabetes mellitus with poor glycemic control. Pancreatology 2014;14:356–60. https://doi.org/10.1016/j.pan.2014.07.004.
[21] Demir K, Karaca C, Ahishali E, Mestanzade M, Celik S, Gul N, et al. A cross-sectional study to assess the prevalence of pancreatic exocrine insufficiency among diabetes mellitus patients in Turkey. Pancreas 2016;45:e39–40. https://doi.org/10.1097/MPA.0000000000000626.
[22] Vujasinovic M, Zaletel J, Tepes B, Popic B, Makuc J, Lenart ME, et al. Low prevalence of exocrine pancreatic insufficiency in patients with diabetes mellitus. Pancreatology 2013;13:343–6. https://doi.org/10.1016/j.pan.2013.05.010.
[23] Bakke Å, Cooper JG, Thue G, Skeie S, Carlsen S, Dalen I, et al. Type 2 diabetes in general practice in Norway 2005–2014: moderate improvements in risk factor control but still major gaps in complication screening. BMJ Open Diabetes Res Care 2017;5:e000459https://doi.org/10.1136/bmjdrc-2017-000459.
[24] Chandra R, Liddle RA. Modulation of pancreatic exocrine and endocrine secretion. Curr Opin Gastroenterol 2013;29:517–22. https://doi.org/10.1097/MOG.0b013e3283639326.
[25] Ebert R, Creutzfeldt W. Reversal of impaired GIP and insulin secretion in patients with pancreatogenic steatorrhea following enzyme substitution. Diabetologia 1980;19:198–204.
[26] Knop FK, Vilsbøll T, Larsen S, Højberg PV, Vølund A, Madsbad S, et al. Increased postprandial responses of GLP-1 and GIP in patients with chronic pancreatitis and steatorrhea following pancreatic enzyme substitution. Am J Physiol Endocrinol Metab 2007;292:E324–30. https://doi.org/10.1152/ajpendo.00059.2006.
[27] Nicolaus M, Brödl J, Linke R, Woerle HJ, Göke B, Schirra J. Endogenous GLP-1 regulates postprandial glycemia in humans: relative contributions of insulin, glucagon, and gastric emptying. J Clin Endocrinol Metab 2011;96:229–36. https://doi.org/10.1210/jc.2010-0841.
[28] Du YT, Rayner CK, Jones KL, Talley NJ, Horowitz M. Gastrointestinal symptoms in diabetes: prevalence, assessment, pathogenesis, and management. Diabetes Care 2018;41:627–37. https://doi.org/10.2337/dc17-1536.
[29] Farmer AD, Pedersen AG, Brock B, Jakobsen PE, Karmisholt J, Mohammed SD, et al. Type 1 diabetic patients with peripheral neuropathy have pan-enteric prolongation of gastrointestinal transit times and an altered caecal pH profile. Diabetologia 2017;60:709–18. https://doi.org/10.1007/s00125-016-4199-6.
[30] George NS, Sankineni A, Parkman HP. Small intestinal bacterial overgrowth in gastroparesis. Dig Dis Sci 2012;44:8–13. https://doi.org/10.1007/s10620-012-2426-7.
[31] Kampanis P, Ford L, Berg J. Development and validation of an improved test for the measurement of human faecal elastase-1. Ann Clin Biochem 2009;46:33–7. https://doi.org/10.1258/acb.2008.008123.
[32] Dominguez-Muñoz JE. Diagnosis and treatment of pancreatic exocrine insufficiency. Curr Opin Gastroenterol 2018;34:349–54. https://doi.org/10.1097/MOG.0000000000000459.