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Importance of pancreatic exocrine dysfunction in patients with type 2 diabetes: A randomized crossover study

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ABSTRACT

Background: Levels of faecal elastase-1 (FE-1), a marker of exocrine pancreatic function, are lower in patients with type 2 diabetes than without diabetes. We aimed to investigate the association between FE-1 and nutritional status, gastrointestinal symptoms, and lipid absorption.
Methods: This randomized, open-label, crossover study included 315 patients with type 2 diabetes aged 18–70 years treated with oral antidiabetics, with HbA_{1c} 6.5–9.0% and BMI 18–40 kg/m^2. Assessments included levels of FE-1 and blood biomarkers of nutrition, and Bristol Stool Scale and Gastrointestinal Symptom Rating Scale (GSRS) scores. Plasma exposure of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) after oral administration of free omega-3 carboxylic acids or ethyl esters with breakfast was investigated in patients with low, intermediate, and normal FE-1 levels.
Results: The prevalence of low and intermediate FE-1 levels was 5.2% and 4.9%, respectively. Bristol Stool Scale scores and mean values of GSRS Diarrhoea and Indigestion domain symptoms were similar across groups, but patients with low FE-1 were heavier and reported lower stool frequency. FE-1 levels correlated positively with plasma levels of amylase, lipase, 25-hydroxy vitamin D, and albumin. Mean EPA + DHA exposure was similarly higher after intake of free vs. esterified omega-3 fatty acids in all FE-1 groups.
Conclusions: The prevalence of low FE-1 (<100 μg/g) as a measure of pancreatic exocrine insufficiency was infrequent in type 2 diabetes. Except for low plasma concentrations of EPA and 25-hydroxy vitamin D, type 2 diabetes patients with low FE-1 had no other signs of malabsorption or gastrointestinal disorders. Plasma levels of EPA and DHA after the intake of esterified versus free EPA and DHA did not correlate with FE-1 levels.
Trial registration: ClinicalTrials.gov NCT02370537.

1. Introduction

Type 2 diabetes is a common, complex, and chronic illness associated with obesity and sedentary lifestyle that may result in life-threatening complications. Apart from micro- and macrovascular complications, type 2 diabetes is associated with abnormalities of the exocrine pancreatic gland, including a reduced size of the pancreas, fibrosis and exocrine dysfunction [1–14], and a high prevalence of gastrointestinal (GI) symptoms [15].

Faecal elastase-1 (FE-1) is a digestive enzyme expressed and secreted from acinar cells in the exocrine pancreas. FE-1 is highly stable during passage through the intestine and can be measured in stool samples [16]. The concentration of FE-1 correlates with the results of sensitive, but low-throughput tests of pancreatic exocrine function [16,17], as well as with morphologic characteristics of chronic pancreatitis [1,18,19]. As measurement of FE-1 is simple, it has been used to estimate pancreatic exocrine function in large cohort studies of patients with diabetes [7,13]. Exocrine dysfunction, defined as low or intermediate levels of FE-1, is more common in patients with type 2 diabetes than in the general population, but the prevalence reported differs considerably [3,7,8,20,21]. A high prevalence of low FE-1 level and chronic pancreatitis has been regarded as a diabetes complication [22], but it has recently been shown that pancreatic exocrine dysfunction is also associated with pre-diabetes [23].

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Despite the large body of evidence indicating an increased prevalence of pancreatic exocrine dysfunction in type 2 diabetes, associations between changes in FE-1 level and clinical signs of maldigestion and malnutrition have not been fully explored. Coefficients of fat absorption for the exact determination of fat maldigestion in patients with type 2 diabetes indicate that exocrine dysfunction in these individuals is modest [14] and does not progress over time [24].

Pancreatic exocrine insufficiency (PEI) in chronic pancreatitis is associated with decreased levels of several nutritional markers in blood, including fat-soluble vitamins, magnesium, retinol-binding protein, prealbumin, and albumin [25], but the link between FE-1 concentration and nutritional blood biomarkers has not been fully investigated in type 2 diabetes.

Hypertriglyceridemia is a risk factor for cardiovascular events in patients with type 2 diabetes and oral treatment with eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA), in the form of esters such as ethyl esters or as free fatty acids, is an approved therapy for severe hypertriglyceridaemia. Hydrolysis by pancreatic lipases is important for the uptake of esterified EPA and DHA [26–28], and reduced pancreatic lipase activity, manifested as decreased fat absorption, is an early sign of reduced exocrine function of the pancreas [29]. We therefore considered characterization of how FE-1 levels influence uptake of esterified and free omega-3 carboxylic acids an important research topic with potential relevance for treatment of hypertriglyceridemia in patients with type 2 diabetes. We hypothesized that reduced pancreatic exocrine function, reflected by low or intermediate FE-1 levels, is associated with decreased uptake of esterified EPA and DHA, but not free EPA and DHA.

This two-part study was designed to investigate the functional significance of low FE-1 levels in type 2 diabetes. The aim of the observational first part was to assess the association between FE-1 level and maldigestion-related GI symptoms, and clinical and biochemical signs of malnutrition in patients with type 2 diabetes. The second part was an open-label, two-way crossover, non-therapeutic pharmacokinetic (PK) study; its primary aim was to estimate systemic uptake of DHA and EPA from single doses of free omega-3 carboxylic acids (OM-3 CA) and omega-3 ethyl esters (OM-3 EE) in three groups of patients with type 2 diabetes (with low, intermediate, and normal levels of FE-1) recruited from the first part of the study.

2. Methods

2.1. Ethics

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice and applicable regulatory requirements. Written informed consent was provided by all patients. The final clinical study protocol and the informed consent form were approved by an independent ethics committee or institutional review board in each participating centre.

2.2. Study design and patient population

This was a two-part (A and B) study in patients with type 2 diabetes. Part A was a cross-sectional, observational study, and part B was an open-label, randomized, crossover, multicentre, non-therapeutic study. Patients were enrolled at 23 centres across Europe (Denmark, 3 centres; Hungary, 4; Latvia, 3; Poland, 4; Slovakia, 3; and Sweden, 6). The first patient was enrolled on 7 April 2015, and the last patient's last visit was on 17 November 2015. Patients eligible to participate were men and women aged 18–70 years with a BMI of 18–40 kg/m^2 who had had clinically diagnosed type 2 diabetes, according to current American Diabetes Association guidelines, for at least 3 months, were treated with oral antidiabetic drugs for at least 3 months, and had HbA_{1c} levels between 6.5% and 9.0% (47 and 75 mmol/mol). Patients were excluded from the study if they were receiving pancreatic enzyme replacement therapy, insulin or glucagon-like peptide (GLP)-1 receptor agonists. Patients receiving insulin treatment were excluded to reduce the risk of including patients with type 1 diabetes, and patients receiving insulin and pancreatic enzyme replacement therapy were excluded to reduce the risk of including patients with type 3c diabetes. GLP-1 treatment was an exclusion criterium because of the perceived risk of adverse effects on the pancreas at the time of writing the protocol. Furthermore, patients were excluded if they were treated with bile acid sequestrants, fish oil or other EPA- or DHA-containing supplements or fortified food within 4 weeks before the study entry, and were not allowed *anti*-hyperlipidaemic treatments including fibrates or niacin. A stable dose of a statin was allowed.

Part A of the study served as screening of patients for part B, with the purpose of finding individuals with type 2 diabetes who had different degrees of reduced pancreatic exocrine function based on FE-1 measurements. Part A consisted of three visits to assess eligibility criteria, and to obtain demographic details, blood biomarker information and GI symptom data, including Bristol Stool Scale scores [30]. Patients were asked to collect two stool samples during 1 week (between visits 2 and 3) for measurements of FE-1 concentration. Dietary counselling with respect to dietary fat intake was given according to the Therapeutic Lifestyle Changes diet [31], starting at the first visit. No study drug was given during part A.

Patients who completed part A of the study were eligible to participate in part B. Based on results of FE-1 measurements in part A, patients were stratified into three groups: low (<100 μg/g FE-1), intermediate (100–200 μg/g FE-1), and normal (>200 μg/g FE-1) pancreatic exocrine function. Part B was a single-dose, randomized, open-label, two-way crossover study with administration of a single, oral 4 g dose of OM-3 CA (a mixture of free fatty acids containing mainly EPA and DHA) on one occasion and a single, oral 4 g dose of OM-3 EE (containing mainly ethyl esters of EPA and DHA) on another occasion, separated by a wash-out period of 10–14 days. The highest approved dose for both formulations is 4 g. Patients were randomly assigned (1:1) to each of the two treatment sequences by a centralized randomization system using computer-generated numbers.

The primary objective was to compare plasma exposure of EPA + DHA from single 4 g doses of OM-3 CA and OM-3 EE. The contents of EPA and DHA differ between OM-3 CA and OM-3 EE. One gram of OM-3 CA contains approximately 550 mg of EPA and 200 mg of DHA in free form; 1 g of OM-3 EE contains approximately 465 mg of EPA and 375 mg of DHA in ethyl ester form. The molar content of the sum of EPA and DHA is nearly identical in OM-3 CA (2.44 mmol) and OM-3 EE (2.46 mmol), thereby proposing exposure comparisons based on the sum of EPA and DHA.

Study drugs were administered 30 min after the start of a Therapeutic Lifestyle Changes diet breakfast (25–35% of energy from fat). Blood samples were collected three times within 1 h before the intake of study drug (to generate a baseline value) and were repeated thereafter up to 48 h after the intake of test medication for plasma exposure measurements of total EPA and DHA.

2.3. Study assessments

Following enrolment in part A (visit 2), patients were asked to

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