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Original article

Association of faecal elastase 1 with non-fasting triglycerides in type 2 diabetes

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ABSTRACT

Aims: Intestinal absorption of esterified fatty acids depends on exocrine pancreatic function and influences plasma triglycerides levels. The aim was to investigate the association of reduced exocrine pancreatic function (low fecal elastase-1; FE1) with plasma triglycerides in type 2 diabetes and controls without diabetes.

Methods: FE1 (μg/g stool) and non-fasting plasma triglyceride measurements were undertaken in 544 type 2 diabetes patients (age: 63 ± 8 years) randomly selected from diabetes registers in Cambridgeshire (UK), and 544 matched controls (age, sex, practice) without diabetes. Linear regression models were fitted using FE1 as dependent and log-triglycerides as independent variable adjusting for sex, age, body mass index, alcohol consumption, serum lipase, HbA1c, and smoking.

Results: FE1 concentrations were lower (mean ± SD: 337 ± 204 vs. 437 ± 216 μg/g, $p < 0.05$) and plasma triglycerides were higher (geometric mean */: standard deviation factor: 2.2*/:1.9 vs. 1.6*/:1.8 mmol/l, $p < 0.05$) in type 2 diabetes compared to controls, respectively. Within the category of type 2 diabetes and controls separately, a 10% increase in plasma triglycerides was associated with 4.5 μg/g higher FE1 concentrations ($p < 0.01$) after adjusting for confounders. In contrast, in diabetes patients and controls with pathological FE1 (<100 μg/g), low FE1 levels were associated with high plasma triglycerides (significant only in controls).

Conclusions: Non-fasting triglycerides were positively related to FE1 in both type 2 diabetes and controls suggesting that impairment of exocrine pancreas function is influencing plasma triglycerides. Marked loss of exocrine pancreatic function had the opposite effect, resulting in higher levels of plasma triglycerides.

Introduction

Morphological alterations of the exocrine pancreas are observed in patients with diabetes and a considerable number show mild to moderate impairment of bicarbonate and enzyme secretion [1]. The pathophysiological mechanisms leading to impairment of exocrine pancreatic function in diabetes mellitus have not been elucidated, but may include imbalance of islet hormones, pancreatic fibrosis due to angiopathy, autoimmune mechanisms, autonomic neuropathy and altered release of gastrointestinal regulatory mediators [2].

Pancreatic elastase 1 is an enzyme that is highly stable during passage through the gastrointestinal tract [3]. The concentration of elastase 1 can be measured in faeces using an enzyme-linked immunosorbent assay [4]. Faecal elastase-1 (FE1) levels have been demonstrated to correlate with more sensitive tests of pancreatic secretion, such as the secretin-caerulein test and

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resulting duodenal lipase activity [4]. Low FE1 levels have also been shown to correlate with morphologic characteristics of chronic pancreatitis as detected with endoscopic retrograde pancreatography [5] and magnetic resonance cholangiopancreatography [6].

In patients with type 2 diabetes, the prevalence of pancreatic exocrine insufficiency (PEI) estimated by low FE1 measurements ranged between 12 and 73% in different studies [2]. However, most of these studies only included small numbers of highly selected patients and have limited statistical power. In the largest population-based study so far, we randomly selected 544 type 2 diabetic patients (age: 63 years) from local diabetes registers in Cambridgeshire (UK), and 544 individually matched controls without diabetes [7]. Low levels of FE1 (<100 μg/g) were found in 11.9% of cases and 3.7% of controls (age-sex-adjusted odds ratio (OR); 95% CI: 3.6; 2.2–6.2) [7].

The most accepted definition of PEI is a reduction of exocrine pancreatic function to a level that results in malabsorption, demonstrated as a decreased coefficient of fat absorption [8,9]. However, exocrine dysfunction in patients with diabetes defined by low FE1 is usually mild to moderate and does not lead to steatorrhea in the majority of cases. Thus, the clinical relevance of low fecal elastase in type 2 diabetes is questionable.

Although decreased lipase activity in the intestine is a hallmark for PEI, little is known about the impact of PEI on plasma triglycerides in general. Intestinal absorption of esterified fatty acids depends on exocrine pancreatic function and influences plasma triglycerides levels. In a recent study, chronic pancreatitis patients with PEI according to the 13C mixed triglycerides breath-test were unexpectedly observed to have higher triglyceride concentrations than to those without PEI [10]. Studies investigating the metabolic importance of mild and more severe impaired pancreatic exocrine function on triglyceride concentrations are lacking.

To the best of our knowledge, the association of FE1 concentrations with plasma triglycerides in type 2 diabetes has not been investigated. Therefore, our study aimed (i) to investigate the association between FE1 concentrations and non-fasting plasma triglycerides in type 2 diabetes and in controls without diabetes adjusting for potential confounders including age, sex, body mass index (BMI), HbA1c, smoking and alcohol intake and (ii) to evaluate the relationship of mild and more severe PEI (FE1 <100 μg/g) on plasma triglycerides.

Methods

Study population

We analyzed data from a case–control study in Cambridgeshire (UK) [7]. Five-hundred-and-forty-four randomly selected type 2 diabetic patients from general practitioner registers in South Cambridgeshire (UK) were individually matched with 544 controls (diabetes excluded by HbA1c measurement, cut-off 7.0%). The matching variables were sex, age and practice. The presence of type 2 diabetes was primarily based on clinical criteria, e.g. onset of diabetes after the age of 30 years, and no insulin therapy during the first year after diagnosis. Because of the high prevalence of previously undiagnosed diabetes in patients of this age (mean age: 63 years), diabetes was not only excluded in controls by medical record search but also by normal glycated hemoglobin measurement using a cut-point of <7% which was accepted at the time of the study.

The study was approved by the Cambridgeshire Local Research Ethics Committee. This analysis of the data was approved by the Ethical Committee of the Medical Faculty of the Heinrich Heine University Düsseldorf, Germany. All participants gave formal written consent after they had been instructed in detail about the study aims and investigations.

Measurements

FE1 measurements (μg/g stool) were performed centrally at ScheBo-Tech Institute in Wettenberg (Germany) blind to case–control assignation. Patients sampled a probe of their morning stool into a labeled stool tube that was collected by the investigators, frozen and dispatched to the laboratory on ice. Pathologically low levels of FE1 were defined as <100 μg/g stool.

Anthropometric measures were performed in light clothing using standardized methods. Detailed medical history was recorded by structured interviews and questionnaires. Current and historical alcohol consumption as well as smoking was assessed. Current alcohol intake was calculated as alcohol units per week. Among diabetic patients, diabetes duration and treatment was recorded.

Whole blood was collected and delivered to the central laboratory at Addenbrooke's Hospital, Cambridge, England, for measurement of HbA1c and plasma was collected for measurement of triglycerides using the RA 1000 analyzer (Bayer Diagnostics, Basingstoke, England). Other measurements were performed as previously described [7].

Statistical analyses

Demographic variables of the study population were stratified by diabetes depending on their distributions by frequency tables, means ± standard deviations (SD), geometric means */: standard deviation factors (SDF) or non-parametrically by medians (interquartile ranges). FE1 was analyzed as a continuous variable assuming an approximate normal distribution, fitting the data better than a log-normal distribution. An approximate log-normal distribution was assumed for triglycerides. Scatter plots of FE1 versus log-triglycerides were carried out. Linear regression models were fitted using FE1 as dependent variable and log-triglycerides as independent variable. Potential confounders were sex, age (continuous), BMI (continuous), alcohol consumption (heavy drinking: ever/never), current heavy drinking (men: ≥21 g/day; women: ≥14 g/day), lipase (continuous), HbA1c (continuous), smoking and in the diabetes sub-population, insulin treatment (yes/no), and diabetes duration (<5 years, 5–10 years, >10 years). In a first step, bivariate linear models were fitted using log-triglyceride and one confounder as independent variables in each model. Furthermore, a final model including all potential confounders was calculated using stepwise variable selection (log-triglycerides forced into the model). Analyses were also performed separately in the subgroup of subjects with pathological FE1 (<100 μg/g).

Finally, linear regression models with log-triglycerides as dependent and elastase as independent variable were fitted, separately for diabetes patients and non-diabetic controls. Sex, age, BMI, history of and current alcohol consumption, HbA1c, lipase, smoking, insulin therapy and diabetes duration were considered as potential confounders. Interaction variables between the subgroup indicator “elastase <100 μg/g” and elastase were included in univariate and in final multivariate models. To evaluate multicollinearity in the regression models, Pearson and Spearman correlation matrices of all variables were calculated. In addition, the variance inflation factor (VIF) was used to assess the extent to which the variances of the estimated coefficients were inflated. A variable with VIF >10 is considered as an indication of serious collinearity. Furthermore, a collinearity analysis estimating condition indices and proportions of variances was performed. Finally,

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