






Can pancreatic steatosis affect exocrine functions of pancreas?

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ABSTRACT

Background/Aims: Pancreatic steatosis (PS) is a generally used term to define accumulation of fat in the pancreas. In theory PS may be able to affect the exocrine function of pancreas. In this study we aimed to determine the effect of PS on exocrine pancreas function.

Materials and Methods: Forty-three patients with PS determined by 3 tesla magnetic resonance imaging (MRI) and 48 patients without PS were included in this study. Patients with PS were classified as group 1 and control patients were classified as group 2. Fecal elastase-1 levels were determined. Fecal elastase-1 levels <200 µg/g were defined as exocrine pancreatic insufficiency (EPI). Patients with PS were further grouped according to severity and anatomic distribution of steatosis based on findings of 3 tesla MRI.

Results: Fecal elastase-1 levels was significantly lower in group 1 compared to group 2 (319.76±45.7 vs 549.31±69.4, respectively, $p=0.003$). Proportion of patients with EPI was significantly higher in group 1 than group 2 (35.5% vs 12% $p=0.042$). There were no significant differences in terms of severity or the anatomic distribution of PS in patients with PS with EPI based on MRI ($p=0.052$, $p=0.198$, $p=0.405$)

Conclusion: Current study demonstrates that PS can cause EPI.

Keywords: Exocrine pancreatic insufficiency, magnetic resonance imaging, intra-abdominal fat

INTRODUCTION

Ectopic accumulation of fat can be seen in a variety of non-adipose tissues, such as liver, heart, kidney, striated muscles, and pancreas (1). There are multiple studies regarding the steatosis of non-adipose tissues and its clinical effects. Although defined as early as in 1926 by Schaefer (2), studies about the pathophysiology and clinical importance of fat accumulation in the pancreas are limited.

Pancreatic fat accumulation is a general term used for pancreatic steatosis (PS), pancreatic lipomatosis, and fatty pancreas (3). PS is generally preferred over these terms. It is associated with advanced age; diabetes; hemochromatosis; viral hepatitis B; or congenital syndromes, such as Cystic Fibrosis or Shwachman-Diamond syndrome (4-8). Pancreatic fat accumulation is thought to be a negative prognostic factor in pancreatitis, and it is postulated to play a role in the etiology of pancreatic cancer (9). This hypothesis is based on the fact that liver

and pancreas have similar embryological origins; hence, PS could act in a similar way in carcinogenesis as in the case of nonalcoholic fatty liver disease (NAFLD) (10). No relationship can be found between fatty infiltration of the pancreas and beta cell function (11).

Exocrine pancreatic insufficiency (EPI) can be defined as insufficient pancreatic enzyme activity due to insufficient enzyme production, insufficient enzyme activation, or premature enzyme destruction (12). A variety of conditions, such as chronic pancreatitis, celiac disease, pancreas cancer, surgery, and diabetes can cause EPI through different pathways (13). In theory, PS can affect the exocrine function of pancreas (14). However, to our knowledge, no study supporting this theory has been performed yet except for case reports (15-18). In a study performed by Terzin et al. (19), patients with type 2 diabetes were evaluated in terms of pancreatic exocrine function, and no relationship could be found between pancreatic volume and PS and impaired pancreatic exocrine function.

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Theoretically, PS can impair pancreatic exocrine function by 3 mechanisms: lipotoxicity in the acinar cells, adipocyte-mediated negative paracrine effect, and direct destruction of the acinar cells (14). This study aimed to explore if the theoretical effect of PS on pancreatic exocrine function is important in clinical practice. The main aim of the study was to evaluate the presence of EPI in PS. With this being the primary goal, we also aimed to determine the frequency of NAFLD in PS.

MATERIALS AND METHODS

Study population

In total, 43 patients with PS and 48 without PS detected using a 3-tesla magnetic resonance imaging (MRI) between 2014 and 2016 were included in this study. Patients were evaluated clinically and in terms of biochemical variables and fecal elastase-1 levels. Patients with chronic pancreatitis, chronic ethanol abuse, diabetes mellitus, gastric or pancreatic surgery history, inflammatory bowel disease, celiac disease, and pancreatic atrophy in imaging tests were excluded.

Blood sampling and analyses

Venous blood samples were taken after an overnight fast for biochemical measurements. Fasting plasma glucose (FPG), triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and amylase and lipase levels were measured us-

ing commercially available assay kits (Roche Diagnostics GmbH; Mannheim, Germany) with an auto-analyzer (cobas 501 Roche-Hitachi; Germany).

Evaluation of PS and NAFLD

The presumed diagnosis of PS and NAFLD were evaluated using a 3-Tesla MRI machine (Skyra, Siemens; Erlangen, Germany) with multi-channel body coil. All patients were scanned in a supine position without pre-imaging preparation. Pregnant women and the patients with cardiac pacemaker/metallic implant or claustrophobia were excluded from the study. After 3-plane localizer images, coronal/axial T1- and T2-weighted (W) and three-dimensional (3D) Dixon images were obtained. Sequence parameters and details of the MRI protocol are presented in Table 1. The total imaging time for the 3 Tesla MRI was approximately 20 minutes.

Evaluation of MRI images

All of the MRI scans were transferred and evaluated using a Leonardo workstation (Siemens; Erlangen, Germany) by experienced radiologists (O.A.) who were blinded to the patient's clinical information, previous imaging data, and/or surgical findings. The evaluation and diagnosis of steatosis was performed by techniques previously described (20-23). The anatomical distribution of steatosis and localization of dominant steatosis, if present, was recorded in the steatosis group. For determining the severity of PS, the percentage steatosis area with respect to total pancreatic volume was measured using the T1W and T2W sequences

Table 1. 3-Tesla Magnetic Resonance Imaging protocol used for the study

Sequences/ Parameters	T1-VIBE	T2-HASTE	T1-VIBE-DIXON	T2-HASTE
TR/TE (ms)	4/1.74	1000/99	4.21/1.34	1000/95
TR/TE (ms)	4/1.74	1000/99	4.21/1.34	1000/95
Fat-saturation	+	+	-	+
Slice thickness (mm)	2.2	5	1.5	5
FOV (mm)	400	400	450	380
Acquisition time (min)	0.13	0.38	0.14	0.56
NEX	1	1	1	1
Number of slices	64	26	96	38
Flip angle (°)	-	139	9	-
Distance factor (%)	20	10	20	20
PAT factor	3	3	6	2
Voxel size (mm)	1.3x1.3x2.2	1.2x1.3x4	1.4x1.4x1.5	1.2x1.2x5

TE: echo time; TR: repetition time; VIBE: volumetric interpolated breath-hold examination; HASTE: half-fourier-acquisition single-shot turbo spin-echo; FOV: field of view; NEX: number of excitations; PAT: parallel acquisition technique

and classified in a 3-point scale: Score 1: 0%-33% steatosis of the whole pancreatic tissue, Score 2: 34%-66% steatosis of the whole pancreatic tissue, Score 3: 67%-100% steatosis of whole pancreatic tissue. Figure 1 illustrates the an MRI scan of a patient with grade-3 steatosis.

Fecal elastase-1 assessment

Stool samples with solid consistency were collected and immediately stored at -80°C until further analysis. Fecal elastase-1 concentration of all samples were measured at the same time using the commercially available enzyme-linked immunosorbent assay (ELISA) kit (BIOSERVE Diagnostics GmbH; Rostock, Germany) according to the manufacturer's instructions. All samples were thawed and then extracted overnight at $2-8^{\circ}\text{C}$ using the extraction buffer provided in the kit. The basic principle of the test is a solid phase ELISA based on the double sandwich

technique. The ELISA microplate is coated with antibodies directed against human pancreatic elastase binding the pancreatic elastase contained in the patient samples. Thereafter, the biotin-labeled secondary antibody, which binds to the immobilized pancreatic elastase, is added to the microplate. To visualize the bound pancreatic elastase, streptavidin-labeled horseradish-peroxidase is added. The peroxidase then oxidizes the substrate 3,3',5,5'-tetramethylbenzidine (TMB). The reaction is stopped by the addition of $0.25\text{ mol/L H}_2\text{SO}_4$. Oxidized TMB can be measured photometrically at 450 nm . The intra and inter-assay variation coefficients of the test were 5.2% and 7.9%, respectively. Measurements were defined as $\mu\text{g/g}$ stool. Fecal elastase-1 levels $>200\text{ }\mu\text{g/g}$ were defined as normal, fecal elastase-1 levels $<200\text{ }\mu\text{g/g}$ were defined as EPI, with levels between 100 ve $200\text{ }\mu\text{g/g}$ defined as mild EPI and $<100\text{ }\mu\text{g/g}$ defined as severe EPI (24).

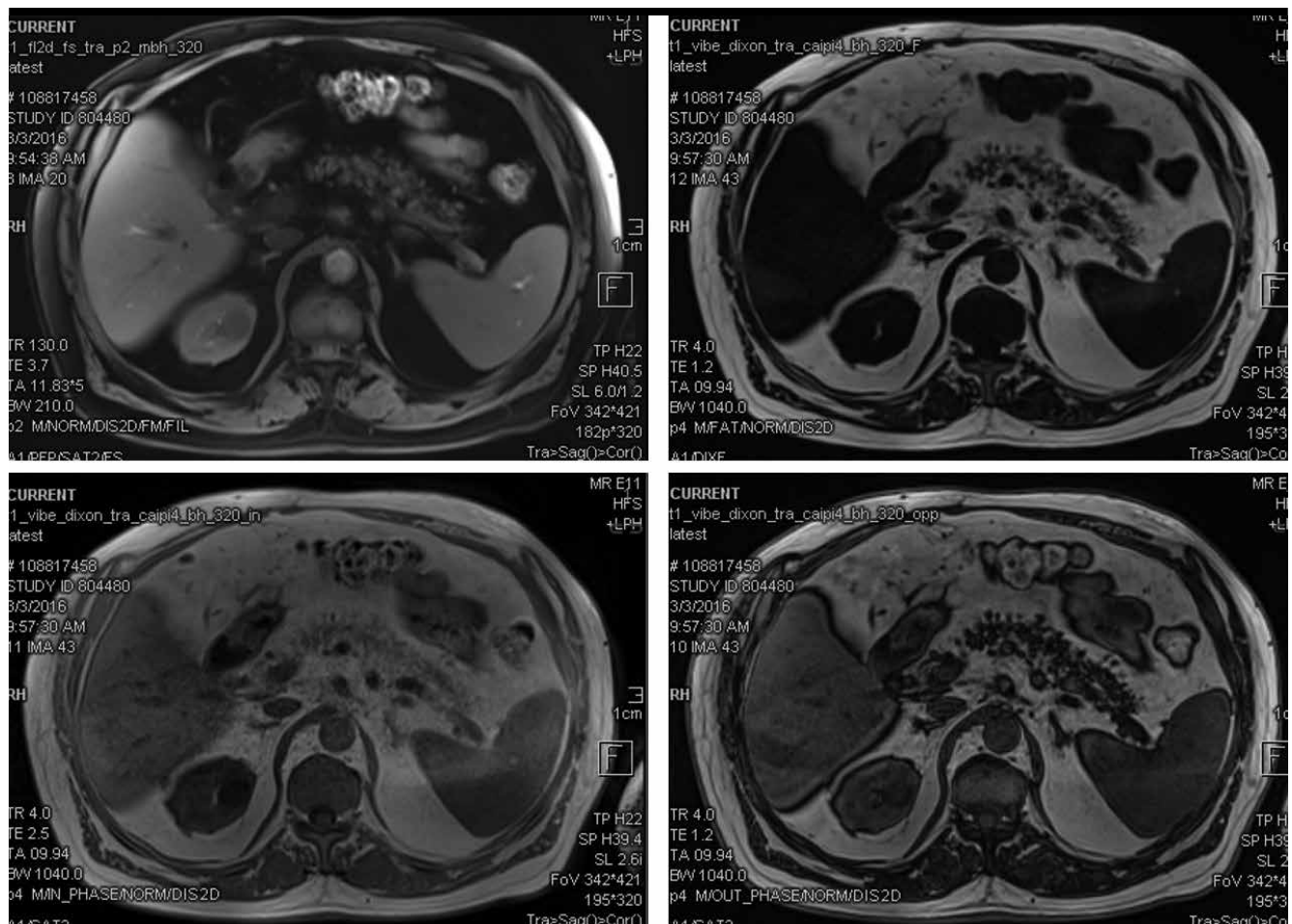


Figure 1. MRI scan of a patient with grade-3 steatosis

Statistical analysis

The preliminary analyzes were completed for frequencies, mean, standard errors (SE), and percentages as applicable. Categorical variables were analyzed using the Chi-square test. Continuous variables were analyzed using the Mann-Whitney U-test. The statistical significance was set at $P < 0.05$ for all analyzes. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc.; Chicago, IL, USA).

Written informed consent was obtained from patients who participated in this study. Ethics committee approval was received for this study from the ethics committee of the School of Medicine (Date: November 12, 2014, Approval Number: 193).

RESULTS

Patient characteristics

Overall, 43 patients with PS and 48 without PS detected via 3 Tesla MRI were included in the study. Twelve patients were excluded from the PS group and 23 patients from the control group because of the aforementioned exclusion criteria. Therefore, the data of 31 patients with pancreatic fat accumulation and 25 controls were analyzed. Patients with PS were classified as group 1, and the control patients were classified as group 2. The percentage of female patients and the mean age of the patients (year \pm SE of mean) in groups 1 and 2 were 43.7%, 65.96 \pm 1.6 and 60%, 65.76 \pm 1.6 respectively. There were no statistically significant differences between the groups in terms of gender and mean age ($p > 0.05$).

Biochemical parameters and fecal elastase-1

In both the groups, the mean FPG, triglyceride, HDL, LDL, total cholesterol, AST, ALT, amylase, and lipase were similar ($p > 0.05$). The mean fecal elastase-1 level was significantly lower in group 1 compared with that of group 2 (319.76 \pm 45.7 vs 549.31 \pm 69.4, respectively, $p = 0.003$). The proportion of patients with EPI was significantly higher in group 1 than group 2 (35.5% vs 12%, respectively, $p = 0.042$). There were no differences regarding the severity of EPI (mild or moderate) between the groups ($p = 0.082$; $p = 0.392$), respectively (Table 2).

PS and NAFLD

The proportion of patients with NAFLD was not significantly different ($p = 0.436$). In patients with PS, the percentage of those with NAFLD was not different irrespective of the presence of EPI ($p = 0.200$). The severity of steatosis upon T1W and T2W sequences in PS pa-

tients did not differ between patients with or without EPI ($p = 0.198$; $p = 0.405$). In PS patients with or without EPI, the severity of steatosis on T1 sequences were not statistically different regarding scores 1, 2, or 3 ($p = 0.577$; $p = 0.289$; $p = 0.281$), respectively. In PS patients with or without EPI, the severity of steatosis on T2 sequences are not statistically different regarding scores 1, 2, or 3 ($p = 0.284$; $p = 0.537$; $p = 0.573$), respectively. PS was classified as diffuse, diffuse and head, body, tail, diffuse, and involving more than 2 areas according to anatomical distribution. In PS patients with or without EPI, there were no significant differences in the anatomic distribution of steatosis ($p = 0.645$; $p = 0.490$; $p = 0.254$; $p = 0.409$; $p = 0.645$), respectively (Table 3).

DISCUSSION

Despite the important role in energy, metabolism studies about the fat accumulation in pancreas are limited (25). Studies about fat accumulation in the pancreas are mostly about imaging techniques and beta cell function. The net effect of pancreatic fat accumulation on the exocrine function of pancreas is unclear. This study shows that pancreatic fat accumulation can cause EPI.

Table 2. Comparison of demographic, biochemical, and Magnetic resonance imaging characteristics with PS patients and the control group

	PS (n=31)	Controls (n=25)	p
Female/male	14/17	15/10	0.403
Age (years)	65.96 \pm 1.6	65.76 \pm 1.6	0.843
FPG (mg/dL)	97.70 \pm 3.34	98.08 \pm 3.45	0.824
LDL (mg/dL)	112.5 \pm 5.3	124.73 \pm 6.7	0.076
HDL (mg/dL)	50.69 \pm 2.74	51.16 \pm 3.3	0.650
Triglyceride (mg/dL)	127.72 \pm 10.17	143.72 \pm 11.6	0.269
Total cholesterol (mg/dL)	189.29 \pm 7.56	202.88 \pm 8.6	0.119
AST (U/L)	22.61 \pm 2.41	20.32 \pm 0.8	0.503
ALT (U/L)	24.45 \pm 3.63	21.4 \pm 1.4	0.443
Fecal elastase-1	319.76 \pm 45.7	549.31 \pm 69.4	0.003
Total EPI n (%)	11(35.5)	3(12)	0.042
Mild EPI n (%)	8(25.8)	2(8)	0.082
Severe EPI n (%)	3(9.7)	1(4)	0.392
NAFLD n (%)	18(58.1)	11(44)	0.436

Parameters were expressed as mean with standard error; the bold values indicate that there was a significant difference

FPG: fasting plasma glucose; LDL: low-density lipoprotein; HDL: high-density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; EPI: Exocrine pancreatic insufficiency; NAFLD: Nonalcoholic fatty liver disease; PS: pancreatic steatosis

Table 3. Comparison of magnetic resonance imaging findings of PS patients according to EPI status

	PS (n=31)	Controls (n=25)	p
Steatosis scoring with T1W n (%)			
Score 1	7 (63.6)	12 (60)	0.577
Score 2	2 (18.2)	7 (35)	0.289
Score 3	2 (18.2)	1 (5)	0.281
Steatosis scoring with T2W n (%)			
Score 1	1 (9.1)	5 (25)	0.284
Score 2	7 (63.6)	9 (45)	0.537
Score 3	3 (27.3)	6 (30)	0.573
Anatomical distribution of steatosis n (%)			
Diffuse	11 (100)	19 (95)	0.645
Diffuse and Head	3 (27.3)	7 (35)	0.490
Body	0(0)	3 (15)	0.254
Tail	0(0)	2 (10)	0.409
Diffuse and more than 2	0(0)	1 (5)	0.645
NAFLD n (%)	8 (72.7)	10 (50)	0.200

Parameters were expressed as n (%)

T1W: T1 weighted; T2W: T2 weighted; NAFLD: Nonalcoholic fatty liver disease; PS: pancreatic steatosis; EPI: exocrine pancreatic insufficiency

As we excluded patients with disorders such as diabetes, which potentially cause EPI, our results show that PS may cause EPI independent of other causes.

Pancreatic fat accumulation can be named as pancreatic lipomatosis, PS, fatty replacement, fatty infiltration, fatty pancreas, lipomatous pseudohypertrophy, and nonalcoholic fatty pancreas disease (NAFPD) (3). The term fat replacement defines death of pancreatic acinar cells with subsequent replacement with adipocytes. The term best defining the situation of fat accumulation without fat replacement is accepted to be PS (26). We preferred the term PS, as it is not currently known whether fat accumulation in the pancreas is reversible or causes acinar cell injury.

Studies about fat accumulation of pancreas have shown that the chance of steatosis increases with advancing age (27,28). Despite the fact that our PS patients were old, they were not older than those in the control group. Fat accumulation seen during the degeneration of pancreas is thought to be responsible for the increased prevalence of steatosis with advancing age (27).

Although a histologic examination remains the most sensitive way to detect pancreatic fat accumulation, its inva-

sive nature limits its use. PS can be evaluated by imaging techniques, such as endoscopic ultrasound, computed tomography, or MRI. Despite endosonography being an invasive technique, it is quite sensitive for the evaluation of pancreatic pathologies such as chronic pancreatitis (29). The sensitivity of endosonography for the evaluation of PS should be explored further (30). MRI appears to be the most valuable noninvasive technique due to its high resolution, accuracy, and lack of ionizing radiation (28). Different techniques are defined in the determination of pancreatic fat. The MRI Dixon technique is a highly sensitive technique commonly used for fat quantification in the liver (31). Despite the fact that it is commonly employed for liver evaluation, studies evaluating the pancreas are limited (28). We diagnosed PS using a 3-tesla MRI, which also employed this technique.

NAFPD defines the accumulation of fat associated with obesity and metabolic syndrome. NAFLD is postulated to be related to NAFPD (32). We could not detect any significant differences between PS and control groups. This may be due to NAFPD representing a different group among patients with PS.

Chronic ingestion of a diet rich in lipids by Zucker diabetic fatty rats has been shown to result in intralobar fat accumulation and increased lipid droplets in the acinar cells of the pancreas; these changes lead to acinar cell injury and fibrosis (33). Fat in pancreas is associated with adipocyte infiltration and altered lipid composition (34). Main lipids that accumulate in PS are triglycerides (35). Despite this observation, no significant correlation could be found between the amount of pancreatic fat and serum triglyceride levels (36). In our study, we could not find any significant correlation between serum triglyceride levels and PS consistent with literature.

Studies that have investigated the effect of PS on pancreas function mostly focused on the endocrine function of pancreas. There are conflicting results about the relationship of PS and beta cell function (37). In the study by Terzin V et al. (19), which evaluated exocrine function of pancreas in diabetics with poor glycemic control, PS was not correlated with fecal elastase-1 levels. In this study, PS was detected by abdominal ultrasonography, which is a subjective method (13). We found that EPI was significantly more common in PS patients. PS is thought to impair pancreatic exocrine function through lipotoxicity in acinar cells, adipocyte-mediated negative paracrine effect, and direct destruction of acinar cells (14). Lipids are long known to impair beta cell function (38). Same situation may be true for

the pancreatic acinar cells. The absence of endocrine dysfunction in the PS group, while the exocrine dysfunction is evident, can imply that lipotoxicity may not be playing an important role. Lipid peroxidation of cellular membrane may be important in the free fatty acid-mediated pancreatic cellular injury (39). In PS patients, exocrine dysfunction may cause lipid accumulation eventually causing direct injury of the acinar cells. Adipocytes are capable of affecting multiple tissues through adipokines (40). Leptin, which is an adipokine, has been shown to inhibit pancreatic secretion (41). PS may cause adipokine-mediated dysfunction. In our study, the extent of steatosis rather than its severity has been significantly different in steatosis patients. Although the proposed mechanisms of exocrine dysfunction in PS are lipotoxicity in the acinar cells, adipocyte-mediated negative paracrine effect, and direct destructions of acinar cells, further studies are needed to clarify why it did not cause endocrine dysfunction.

There are certain limitations of our study: (1) Due to the broad exclusion criteria, the number of patients was low in both the groups. This may cause a statistical problem in subgroup analyzes for representation of the general population. (2) Fecal elastase-1 measurements used for diagnosis of EPI have high sensitivity for detection of severe EPI, while the sensitivity is significantly lower for mild EPI (42). This may affect the number of patients with EPI within the groups. (3) Although we excluded diabetic patients, our patients were not evaluated regarding prediabetes. Nevertheless, prediabetes has not been reported to cause EPI.

In conclusion, PS is a clinical entity with multiple unknown issues, both in description and in pathophysiology. Our study demonstrates that PS can cause EPI. Lipids are believed to act in different pathways on acinar cells causing exocrine dysfunction. Further studies are needed to determine the circumstances in which PS can cause EPI.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yıldırım Beyazıt University School of Medicine (Decision Date: 12 November 2014; Decision Number: 193).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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