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Pancreatic Function in Chronic Pancreatitis: A Cohort Study Comparing Three Methods of Detecting Fat Malabsorption and the Impact of Short-Term Pancreatic Enzyme Replacement Therapy

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Abstract

Objectives: Reliable pancreatic function tests in patients with chronic pancreatitis (CP) are needed. This cohort study identified malabsorption in people with CP compared to healthy people, then investigated short-term pancreatic enzyme replacement therapy (PERT) and fat malabsorption, nutritional status, and quality of life (QOL).

Methods: Subjects with CP were evaluated before and after PERT and compared to the healthy cohort using coefficient of fat absorption (CFA), stool bomb calorimetry, and the malabsorption blood test (MBT). Anthropometrics, micronutrients, and QOL data were collected. Group means at baseline and after PERT were analyzed.

Results: The 24 subjects with CP had greater stool energy loss (5668 cal/g [standard deviation {SD}, 753] vs 5152 cal/g [SD, 418], $P < 0.01$), reduced triglyceride absorption (MBT, 8.3 mg*h/dL [SD, 4.3] vs 17.7 mg*h/dL [SD, 10.3], $P < 0.001$), lower fat intake, and poorer QOL.

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Differences in CFA were not significant (90.9 % [SD, 12.8] vs 95.4 % [SD, 9.3]). After PERT, triglyceride absorption (= 1.7 [SD, 3], $P < 0.05$) and QOL increased.

Conclusions: The MBT detected changes in triglyceride absorption in the absence of CFA changes. The malabsorption blood test may be helpful in guiding PERT initiation in patients with CP before significant morbidity.

Keywords

fat absorption; fat-soluble vitamins; chronic pancreatitis; exocrine pancreatic insufficiency; pancreatic enzyme replacement therapy

Introduction

Reduced exocrine pancreatic function (RPF) and ultimately exocrine pancreatic insufficiency (EPI) contribute to poor clinical outcomes in patients with chronic pancreatitis (CP). CP is a disease of chronic inflammation in the pancreas that is progressive, leading to scarring and irreversible tissue damage that ultimately results in loss of endocrine and exocrine function.^{1–7} Patients initially experience chronic abdominal and back pain, nausea, vomiting, and decreased appetite, and then develop steatorrhea, increased stool frequency, weight loss, and even diabetes as the disease progresses.^{8,9} Symptoms may wax and wane in individuals over time, and the progression is insidious. As a result, the approach to diagnosis and clinical care is not well standardized.

The incidence and clinical implications of RPF in patients with CP is unclear, as patients are often diagnosed late in the disease course, after the sequela of poor pancreatic function have accrued. Weight loss is particularly in lean body mass, which can lead to increased fatigue, poorer physical performance and reduced quality of life.^{10,11} Patients frequently experience micronutrient deficiencies, and these include in particular deficiency of the fat-soluble vitamins A, D, E and K, magnesium, fatty acids, and zinc.^{11–19} Numerous studies have demonstrated significantly poorer quality of life (QOL) outcomes including multiple physical, pain, emotional, and social domains in patients with CP compared to healthy reference populations.^{9,20,21}

Systematic reviews and meta-analyses of the safety and efficacy of pancreatic enzyme replacement therapy (PERT) in subjects with CP and subjects with EPI in general have yielded mixed results.^{22–26} In general, randomized clinical trials have shown that PERT can safely improve fat absorption to some degree, reduce diarrhea and episodes of defecation and mitigate weight loss.^{27,28} The primary aim of this study was to compare three methods of characterizing fat and energy absorption in both healthy subjects and subjects with CP, who are at risk for RPF/EPI, and to use these methods to assess for changes in subjects with CP and RPF/EPI once PERT is initiated. Exploratory aims included association of these changes with markers of nutritional status and QOL.

Materials and Methods

This was a single-center, open-label cohort study to evaluate differences in dietary fat absorption between healthy subjects and subjects with chronic pancreatitis, as well as the efficacy of the PERT pancrelipase (Creon36™, Abbvie, Inc., North Chicago, Ill.) to alter fat absorption in subjects with CP. The trial was approved by the Children's Hospital of Philadelphia (CHOP) Institutional Review Board, conducted at the CHOP Center for Human Phenomic Science (CHPS), and registered with [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02849704) (NCT02849704).

The primary outcomes were the differences in fat absorption as indicated by the gold standard CFA, bomb calorimetry, and the malabsorption blood test (MBT) between healthy subjects and subjects with CP, as well as the change in these measures in subjects with CP before and after PERT. Exploratory outcomes included the relationship between changes in the primary outcomes and nutritional and QOL outcomes.

Subjects were recruited from academic medical centers in the Philadelphia region between August 2016 and November 2017. For the CP cohort, subjects were diagnosed with CP by a gastroenterologist based on criteria as recommended by the American Pancreatic Association (APA) Practice Guidelines.⁷ Subjects were considered at risk for fat malabsorption based on a history of unintended weight loss, fatty stools or increased stool frequency, or a history of PERT use. Subjects with CP were excluded for a history of intestinal obstruction, fibrosing colonopathy, gout, chronic kidney disease, or an allergy to pork products. Healthy subjects in the same age range were eligible if they did not have a chronic illness or medication affecting dietary or fat intake. For inclusion, all subjects were between 30–70 years of age, in their usual state of health in the previous two weeks with no changes in medications or medication doses, and be able to consume a moderate fat diet. Subjects were excluded from either group if they were taking medications affecting fat absorption or were pregnant or breastfeeding. Subjects who met inclusion criteria were invited to complete a screening and consent visit.

After consenting, all subjects underwent a baseline evaluation visit. Subjects with CP were prescribed a nine-day supply of enteric-coated capsules containing 36,000 units of pancrelipase (Creon36™). After taking the medication for a three-day period, subjects with CP returned for a follow-up visit to assess outcome measures. The schematic for the study visits is shown in Figure 1. All subjects took a standard dose of 72,000 lipase units with meals and 36,000 lipase units with snacks while on the medication.

At the baseline evaluation visit, all subjects provided a health history and demographic information and completed the outcome measures. Subjects with CP who were already prescribed PERT discontinued the medication 72 hours prior to this visit. Pancreatic function was assessed in subjects with CP at the baseline visit using fecal elastase-1 via quantitative enzyme-linked immunosorbent assay (ELISA, ARUP Laboratories, Salt Lake City, Utah).^{29,30} Fecal elastase was not assessed in healthy subjects, who were assumed to have normal pancreatic function. Subjects collected stool for 72 hours at home at both time points for both CFA and bomb calorimetry. Samples were homogenized in bags using a BagMixer™ (Interscience Laboratories, Woburn, Mass.) and an aliquot was extracted from the

homogenized stool for bomb calorimetry. The remaining stool sample was assessed for total fat content by nuclear magnetic resonance spectroscopy (Mayo Clinic Laboratories, Rochester, Minn.). The gold-standard CFA assessed dietary fat absorption and was derived from the total home stool collections and 3-day weighed food records.³¹ Three-day average calories and nutrient intake for North Americans was analyzed by Nutrition Data System 2012 (NCC, University of Minnesota, Minneapolis, Minn.). Coefficient of fat absorption was then calculated as grams of fat consumed per day minus grams of fat excreted per day, divided by total fat grams consumed.³² Total stool energy loss from the 72 hour stool collection was extrapolated after being assessed using bomb calorimetry on the aliquoted stool (NIDDK Research Unit, Phoenix Indian Medical Center, Phoenix, Ariz.). Heat of combustion (energy) was measured in a bomb calorimeter, with energy liberated quantified in cal/g stool.^{33,34}

All blood samples were obtained after a 12-hour fast. Serum 25-dihydroxyvitamin D, transthyretin, zinc, selenium, comprehensive metabolic panel, and complete blood count were assessed (Clinical Laboratories, CHOP). Plasma fatty acids were assessed via quantitative gas chromatography (ARUP Laboratories). Serum retinol and alpha- and gamma-tocopherol were assessed using high-performance liquid chromatography (Eurofins Craft Laboratories, Wilson, N.C.). The malabsorption blood test (MBT) was used to assess dietary fat absorption over eight hours using a simultaneous oral dose of pentadecanoic acid (PA), a free fatty acid, and triheptadecanoin (THA), a triglyceride with three heptadecanoic (HA) fatty acids that requires hydrolysis by pancreatic lipase for HA absorption.^{35,36} A non-compartmental analysis estimated the area under the curve (AUC) for PA and HA micromolar concentrations.

Anthropometrics were obtained in triplicate by CHPS research staff according to standardized techniques, and the mean was used for analysis.³⁷ Body mass index (BMI) was calculated (kg/m^2) from weight using a digital scale (Seca, Munich, Germany) and standing height using a stadiometer (Holtain, Crymch, U.K.). Triceps, biceps, subscapular and supra-iliac skinfold thicknesses were measured with a skinfold caliper (Holtain) to estimate subcutaneous fat stores. Mid-upper arm circumference was measured to the nearest 0.1cm with a non-stretchable fiberglass tape (McCoy, Maryland Heights, Mo.) and triceps skinfold thickness measures were used to calculate upper arm muscle and fat areas.³⁸ Resultant areas were compared with reference data to generate z-scores for upper arm muscle area (UAMA) and upper arm fat area (UAFA).³⁹ Total body composition, total fat-free mass (FFM) and fat mass (FM) were assessed by whole body dual x-ray absorptiometry (Delphi A, Hologic, Inc., Bedford, Mass.).

Quality of life was assessed using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), a standardized, validated healthy survey covering physical functioning, bodily pain, general health perception, vitality, social functioning, emotional, and mental health domains.^{40–45} Subjects also completed the NIH-developed Patient Reported Outcomes Medical Information System (PROMIS) short forms for the following domains: physical function, alcohol use, anxiety, depression, emotional support, fatigue, pain behavior, pain intensity, pain interference, social role participation, and sleep disturbance.

^{46–54} Adherence to PERT for subjects with CP was assessed, and adverse events for both CP and healthy participants were reported.

Sample size was determined for the CFA outcome. Variability in CFA exists in the literature for both CF and CP; based on this variability, we estimated that 21 subjects in each group would have 80% power to detect a CFA difference in means of 10% (difference in CFA% between healthy group mean of 95% and CP group mean of 85%) assuming that the common standard deviation (SD) was 11% using a t test with $\alpha = 0.05$.^{31,55–57} Our recruitment goal was 24 subjects with CP and 24 healthy subjects to account for a potential 10% attrition rate during the study.

Descriptive statistics were presented as frequency counts and percentages for categorical variables and mean (SD) for continuous variables. Differences at baseline between subjects with CP and healthy subjects were determined using unpaired (two-sample) t tests for continuous variables and χ^2 tests and Fisher exact tests for categorical variables. For subjects with CP, differences in outcomes over time from before to after PERT use are determined using paired (one-sample) t tests for continuous variables and χ^2 tests and Fisher exact tests for categorical variables. Longitudinal mixed-effects (LME) analysis was used to assess time trends (before and after PERT use) for the three major outcomes indicating level of fat absorption, CFA, bomb calorimetry and the MBT variable AUC HA. Subjects were divided into groups denoting poorer fat absorption vs. normal fat absorption using either CFA (CFA <93% vs. CFA $\geq$ 93%) or fecal elastase groups (either fecal elastase <100 μ g/g vs. 100 μ g/g stool, or fecal elastase <200 μ g/g vs. $\geq$ 200 μ g/g stool), and potential differences between these groups in change over time were evaluated by examining the interaction effects of group by time (group $\times$ time). Stata 12.1 (Stata Corporation, College Station, Texas) was used, and statistical significance level was set at $P = 0.05$ for all tests. Secondary and exploratory analyses were restricted to subjects who had valid measure with adequate data – for example, complete stool collections and diet records for CFA and bomb calorimetry, and complete sets of blood draws for the MBT.

Results

A total of 24 subjects with CP and 24 healthy subjects were recruited between November 2016 and September 2017. Two healthy subjects were excluded from analysis due to illnesses not disclosed at enrollment – one subject had a diagnosis of chronic pancreatitis, and one subject had significant liver disease and was taking medications that affected dietary fat absorption. Demographics, anthropometrics, and outcome measures for these two groups are presented in Table 1. The subjects with CP were similar to the healthy controls in respect to race; the CP group was on average six years older and a greater percentage of the healthy group were female. Body mass index only differed slightly between the two groups, with healthy subjects on average 1.7 kg/m² greater than subjects with CP. Of the subjects with CP, 46% had a history of PERT use prior to enrollment.

Primary Outcome Measures

Comparisons of mean dietary intakes and measures of fat absorption between groups at baseline are presented in Table 1, while changes after PERT in subjects with CP are

presented in Table 2. Dietary fat and energy intakes differed significantly between the two groups; on average, healthy subjects consumed an average of 652 more calories and 35 more grams of fat per day than their counterparts with CP. Of the subjects with CP, 63% had EPI as indicated by a fecal elastase <200 $\mu\text{g/g}$ stool. Six of the subjects with CP exhibited dietary fat malabsorption as indicated by a CFA $<93\%$; two healthy subjects had a CFA $<93\%$. The CP group, while providing a smaller mean stool volume, had significantly higher calorie losses in stool than healthy subjects as measured by bomb calorimetry. The MBT indicated that while the absorption of the free fatty acid PA was similar between groups, absorption of HA, the free fatty acid administered in a triglyceride, was significantly lower. After administration of PERT, there was no significant change in mean CFA or calories per gram of stool as measured by bomb calorimetry. Absorption of HA increased significantly after PERT in subjects with CP, while PA did not change.

Table 2 also presents the results of the longitudinal mixed-effects analysis for the fat absorption outcomes CFA, bomb calorimetry and the AUC HA from the MBT by fat absorption groups based upon CFA and fecal elastase. Subjects with poorer fat absorption based upon CFA ($<93\%$) at baseline showed a significant increase in CFA of 9.9% on PERT ($P < 0.001$) compared to no change for the subjects with normal CFA (93%) at baseline. The group $\times$ time interaction term was also highly significant ($P < 0.001$). These subjects also had significantly greater loss of calories in stool (852 more cal/g lost, $P < 0.001$) at baseline than those with normal CFA, although the decrease in this loss with PERT use was not significantly greater. AUC HA did not differ by CFA groups either at baseline or for change over time.

Subjects with EPI based upon a fecal elastase of <100 $\mu\text{g/g}$ stool at baseline had 13.2% lower CFA than those with fecal elastase 100 $\mu\text{g/g}$ stool at baseline ($P < 0.01$), and a significant increase of 6% in CFA compared to no change for the higher fecal elastase group ($P < 0.01$). The group $\times$ time interaction term also was significant ($P < 0.05$). These subjects also had significantly greater loss of calories in stool (888 more cal/g, $P < 0.001$) at baseline but a similar decrease in calories lost with PERT use as the higher fecal elastase group. Those with fecal elastase <100 $\mu\text{g/g}$ stool also had lower AUC HA at baseline and a significant increase in absorption of HA with PERT use compared to the higher fecal elastase group.

Subjects with EPI based upon a fecal elastase of <200 $\mu\text{g/g}$ stool at baseline had 8.9% lower CFA than those with fecal elastase 200 $\mu\text{g/g}$ stool at baseline and a significant increase of 4.2% in CFA compared to no change for the higher fecal elastase group ($P < 0.05$). These subjects also had a significantly greater loss of calories in stool (915 more cal/g, $P < 0.001$) at baseline but a similar decrease in calories lost with PERT use as the higher fecal elastase group. Those with fecal elastase <200 $\mu\text{g/g}$ stool had a significant increase in absorption of HA ($P < 0.05$) with PERT use.

Micronutrients

Serum micronutrient concentrations were not significantly different between the healthy subjects and those with CP. Secondary analysis of fat-soluble vitamins and selenium is presented in Table 3, further comparing healthy subjects to those with CP and EPI defined

by fecal elastase <200 µg/g and those who were pancreatic-sufficient. Subjects with EPI had significantly lower serum α-tocopherol concentrations than healthy subjects. The subjects who were pancreatic sufficient had significantly higher serum vitamin D concentrations than their counterparts with EPI. Figure 2 demonstrates individual values for vitamins D and E compared to indicators of pancreatic status.

Quality of Life

Differences in QOL between healthy subjects and subjects with CP off and on PERT are presented in Figure 3. Subjects with CP reported significantly higher (more undesirable) PROMIS symptom T-scores than healthy subjects in the domains of alcohol use, anxiety, depression, fatigue, pain behavior, pain intensity, pain interference, and sleep disturbance. Of these, five domains improved with administration of PERT: alcohol use, anxiety, depression, fatigue, and pain intensity. Healthy subjects reported significantly higher (desirable) PROMIS function T-scores than subjects with CP in global physical health and physical function. The global mental health T-score was higher in healthy subjects than those with CP but only approached significance.

Results were similar on the SF-36, with healthy subjects reporting higher scores in physical functioning, physical and emotional role function, energy/fatigue, emotional well-being, social functioning, pain, general health, and health change. Significant improvements were reported in subjects with CP in the domains of physical and emotional role functioning, emotional well-being, social functioning, and health change after PERT administration.

Dietary Intake

Mean dietary intake data for healthy subjects and subjects with CP was collected at both time points (see Table 1, Supplemental Digital Content, which reports mean dietary intakes). Subjects with CP reported significantly lower fat, carbohydrate, protein, and overall energy intakes compared to healthy controls. Subjects with CP reported suboptimal dietary intake of linoleic acid (an essential fatty acid), choline, vitamins C, D, and E, calcium, magnesium, potassium, and zinc. While healthy subjects reported inadequate intakes of choline, vitamins C, D, and E, calcium, and potassium, intakes of all but vitamins C, D, and A were significantly higher than in subjects with CP. Subjects in both the healthy and CP cohorts routinely consumed liquid or powdered nutrition supplements with similar frequency, 27% and 29% respectively, and multivitamin or mineral products, 29% and 36% respectively. Vitamin D-only supplements were used more commonly by subjects with CP, with 25% reporting supplementation vs 14% of healthy subjects. Use of a variety of other supplements including specific vitamins, minerals, or other bioactive food components was common in both groups (33% CP vs 32% healthy). Dietary intakes did not change significantly in the CP group with PERT administration.

Adverse Events

No serious adverse events (SAE) were reported in the cross-sectional portion of the study in healthy subjects or subjects with CP, and none occurred in subjects with CP during PERT administration (see Table 2, Supplemental Digital Content, which summarizes adverse events reported during the study). The majority of AE in subjects with CP were

gastrointestinal in nature and included abdominal pain, cramps, gas, bloating, constipation, diarrhea, acid reflux, and nausea. One subject reported abdominal discomfort after consuming the high-fat study meal. One subject with CP reported flank pain and hematuria, but evaluation including a CT scan was negative for nephrolithiasis. Healthy subjects also reported nausea, gas, cramping, constipation, diarrhea, and abdominal pain, as well as headaches attributed to not drinking coffee the morning of the study visit.

Discussion

In this study, we present differences in dietary intakes, dietary fat absorption, and quality of life between people with CP and healthy subjects; in addition, we demonstrate improvement in triglyceride absorption with PERT administration in subjects with CP.

Chronic pancreatitis results from a complex interplay between genetic and environmental factors, with no clear clinical definition or diagnostic criteria in the early stages of disease.²⁵ While recent progress has been made identifying genetic risk factors and improving imaging modalities in CP, there remain no reliable, non-invasive tests for assessing clinically-significant reduced pancreatic function before severe disease and malnutrition develops.^{58,59} The discordance in the percentage of subjects with CP in our study who had EPI as defined by a fecal elastase <200 µg/g (63%) and the number taking PERT prior to study initiation (46%) reflects undertreatment of existing EPI and the uncertainty surrounding the appropriate time in the disease course to test for and treat RPF/EPI in patients with CP.

Reliable, non-invasive screening or diagnostic tests with acceptable patient burden are not available for RPF/EPI. The gold-standard CFA has been used in clinical trials to describe fat malabsorption in CP and demonstrate a response to PERT. In a placebo-controlled trial in Indian adults with CP, Thorat et al noted an increase in CFA from 66.5 (SD, 14.1) to 86.1 (SD, 7.5)% in those taking PERT compared to an increase from 67.0 (SD, 14.0) to 72.9 (SD, 11.5)% for placebo.⁵⁷ In a similar study, Ramesh et al found an increase in CFA from 66.7 (SD, 14.0) before PERT to 88.9 (SD, 5.2)% after PERT, also in Indian adults with CP.⁵⁶ Others have detected similar improvements in absorption in PERT trials in people with CP living in the US and in Eastern Europe.^{60–63} There is no doubt that PERT has revolutionized CP care and improves dietary fat malabsorption in that group of patients; however, a large study of 224 subjects with cystic fibrosis found no relationship between the enzyme dosage and the degree of fat malabsorption.⁶⁴ While there was no significant difference in CFA with PERT use in our study, the average baseline CFA in our subjects was substantially higher than reported in other studies. In our secondary longitudinal mixed-methods analysis, the four subjects with CP with baseline CFA <93% and complete CFA assessments showed a significant improvement in CFA that was also significantly different from the improvement in subjects with baseline CFA >93%. Furthermore, two healthy subjects had a CFA that indicated fat malabsorption, despite no symptoms or medical history to suggest EPI. In fact, this is comparable to findings from other studies.⁶⁵ Due to its variability and unreliability of the test itself and the significant burden on the patient in its proper execution, the CFA is impractical and rarely used in clinical practice.⁶⁶ A dietary fat intake of 80 g/day (sometimes 100 g/day) has been the minimum recommendation for the CFA and was the protocol for this study, but the necessity of any increase in dietary fat intake has been

questioned, as has the utility of reporting CFA versus fecal fat.⁶⁵ Ultimately, the CFA remains an imprecise, difficult test to execute in clinical care.

Recently, Erchinger et al demonstrated calorimetric assessment of fecal energy loss in subjects with CP, and found a strong correlation between stool energy loss and fecal fat loss.⁶⁷ Similarly, we found that subjects with CP had significantly greater energy loss in stool than their healthy counterparts. In our subgroup analysis, those subjects with CP and EPI defined with either CFA <93% or fecal elastase <200 µg/g stool had significantly greater energy loss in stool than subjects with CP who had a normal CFA or fecal elastase ($P < 0.01$). When it has been used in for research purposes, bomb calorimetry has been executed with stool collections ranging from 24–72 hours along with diet records.^{34,68,69} Thus, it carries with it the same burden as the CFA, with the added caveat that the test may not be as useful in patients with carbohydrate or protein malabsorption disorders.

The ability of the MBT to detect changes in triglyceride absorption has been established previously in children and adults with cystic fibrosis as well as healthy adults.^{35,70,71} This is the first study to specifically examine triglyceride absorption in subjects with CP. As expected, triglyceride absorption was significantly higher in the healthy controls compared to the subjects with CP, and improved with PERT administration. The comparison groups were too small to demonstrate significant correlations between MBT triglyceride absorption, CFA, and stool energy loss, but in our subgroup analysis, changes in triglyceride absorption in subjects with EPI defined by fecal elastase were significant with PERT administration. It is likely that with more subjects the trends noted would be more robust. Studies are ongoing to improve the sensitivity and reduce the patient burden associated with the MBT.

While serum fat-soluble vitamin concentrations did not change significantly, differences were apparent on secondary analysis. Subjects with CP with EPI defined by fecal elastase <200 µg/g had significantly lower serum α-tocopherol concentrations. We further explored the effect of pancreatic status on serum vitamins, and found increased variability in vitamins E and D in subjects with EPI. Thus, rather than conclude that EPI correlates with low serum fat-soluble vitamin status, our data suggest that EPI alone cannot be used to predict fat-soluble vitamin status. This emphasizes the need to check and follow these vitamins in patients with EPI. Pancreatic lipases are at least partially responsible for hydrolyzing retinol esters and some forms of vitamin D, while vitamin E absorption is facilitated by hydrolases in the enterocyte.^{72–74} All require incorporation into a mixed micelle, which depends upon the presence of free fatty acids in the lumen. Changes in free fatty acid content in the gut lumen in EPI may also affect microbiome and bile acid composition, providing another mechanism contributing to inconsistent fat-soluble vitamin bioavailability. Further study is needed to clarify the relationship between dietary fat malabsorption, the gut microbiome, bile acid composition, and fat-soluble vitamin bioavailability.

While a recent study suggested that EPI was less associated with QOL in chronic pancreatitis than other factors, a previous trial of pancreatin in subjects with CP and EPI demonstrated improvement in a gastrointestinal QOL index at six months and one year.^{9,75} In our population, both the PROMIS and SF-36 questionnaires revealed statistically and clinically significant differences in QOL between subjects with CP and healthy subjects.

Furthermore, just three days of PERT administration led to significant improvement in the PROMIS domains of fatigue and pain intensity, as well as depressive and anxiety symptoms. Minimally important differences for PROMIS scales have been variously reported between 1.9–6.0 in diseases with chronic pain.^{76,77} Based on these estimates, the changes our subjects in the PROMIS domains of anxiety, depression, and fatigue were clinically significant as well. At the same time, improvement in emotional and physical role functioning, emotional well-being, and social functioning were noted on the SF-36 questionnaire. These improvements suggest that PERT initiation has a prompt impact on QOL in patients with CP.

As Zator and Whitcomb have described, the paradigm for approaching the diagnosis of CP is shifting toward more a personalized medicine framework, encompassing genetics and other biomarkers.⁵⁸ Understanding the genetic basis of pancreatic disease is one component of this approach, and may facilitate early and more efficient screening for and detection of dietary fat malabsorption in at-risk patients. To this end, the MBT was able to detect changes in triglyceride absorption and responsiveness to PERT that was not identified by the traditional CFA. Upon detection of dietary fat malabsorption, PERT administration at the appropriate time early in the disease course will likely improve fat absorption, nutritional status, and quality of life in patients with CP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1: Study protocol. All subjects underwent an assessment visit upon entry to the study (**Panel 1A**). Subjects with CP completed nine total days of PERT including the MBT and stool collection for CFA and bomb calorimetry (**Panel 1B**).

Figure 2:

Scatter plots demonstrating serum vitamin D and E concentrations plotted by indicator of pancreatic status. **Panel 2A:** Vitamin concentrations plotted against coefficient of fat absorption (EPI as <93%). **Panel 2B:** Vitamin concentrations plotted against fecal elastase (EPI as <200 µg/g stool). **Panel 2C:** Vitamin concentrations plotted against serum heptadecanoic acid (HA) concentrations (no defined cutoff; instead, the cutoff line corresponds to the 50th percentile HA for this study).

Figure 3:

Quality of life. Unpaired t-tests were used to compare scores between healthy and CP groups at baseline and between CP groups at baseline and on PERT. Dotted bars = Healthy Subjects; Crosshatched bars = CP subjects at baseline; Striped bars = CP subjects on PERT. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, Y $P < 0.10$. PROMIS t-scores are compared to a reference population with a mean of 50, and higher scores indicate more of the characteristic

being assessed. **Panel 3A:** PROMIS symptom t-scores. **Panel 3B:** PROMIS function t-scores. **Panel 3C:** SF-36 short form summary raw scores.

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Table 1:

Characteristics of Subjects With Chronic Pancreatitis Compared to Healthy Subjects at Baseline Measurement

	Healthy n = 22	Chronic Pancreatitis n = 24
Demographics		
Age, yr	43.4 (10.0)	50.7 (9.6)
Sex, % female	68	46
Race		
% White	55	54
% African American	41	38
% East Asian	5	8
Anthropometrics		
BMI, kg/m ²	25.6 (4.4)	23.9 (3.6)
UAMA, cm ²	56 (24)	47 (11)
UAMA Z score	1.9 (1.3)	0.6 (1.0)
UAFA, cm ²	22 (11)	19 (9)
UAFA Z score	-0.2 (0.9)	-0.2 (0.8)
Outcome Measures		
Total fat intake, g/24 hr *	106.6 (42.8)	71.2 (33.6) [†]
Total energy intake, kcal/day *	2366 (849)	1714 (641) [†]
%EER, low active *	101 (36)	74 (25) [†]
Stool weight, total g/24 hr ‡	433 (156)	372 (146)
Stool fat, g/24 hr ‡	4.9 (4.4)	5.3 (5.3)
Fecal Elastase		
µg/g stool	--	169 (172)
% subjects <200	--	63
% subjects ≥ 200	--	37
Coefficient of Fat Absorption ‡		
CFA, %	95.4 (9.3)	90.9 (12.8)
CFA <93%	9	25
Bomb Calorimetry §		
Energy, cal/g	5171 (393)	5728 (717) [†]
Malabsorption Blood Test ¶		
AUC: PA, mg *h/dl	22.0 (10.2)	19.9 (8.9)
AUC: HA, mg *h/dl	17.7 (10.3)	8.3 (4.3) [#]
AUC: HA/PA ratio	6.5 (1.3)	4.1 (2.0) [#]
AUC: HA < 8 mg *h/dl, %	15	59 [‡]
Micronutrients		
Selenium, µg/L	112 (17)	112 (21)
Retinol, µg/dl	57.4 (15.1)	52.0 (15.5)

	Healthy n = 22	Chronic Pancreatitis n = 24
α-Tocopherol, µg/ml	11.9 (2.0)	10.4 (3.3)
λ-Tocopherol, µg/ml	1.9 (0.9)	2.0 (1.3)
25(OH)D, ng/ml	30.9 (15.2)	28.9 (16.4)
Linoleic acid, nmol/mL	--	3269 (825)
α-Linolenic acid, nmol/mL	--	74 (34)
Docosahexaenoic acid, nmol/mL	--	144 (77)
Eicosapentaenoic acid, nmol/mL	--	79 (76)
Oleic acid, nmol/mL	--	2380 (897)
Arachidonic acid, nmol/mL	--	793 (175)

Data presented as mean (SD) or mean %, as indicated in the left column.

BMI: body mass index; UAMA: upper arm muscle area; UAFA: upper arm fat area; EER: estimated energy requirement; CFA: coefficient of fat absorption; AUC: area under the curve; PA: pentadecanoic acid; HA: heptadecanoic acid

*
n=22 Healthy, n=23 CP

†
Student's unpaired t test for differences between CP and Healthy subjects significant at $P < 0.01$

‡
n=22 Healthy, n=20 CP

§
n=19 Healthy, n=21 CP

¶
n=20 Healthy, n=22 CP

Student's unpaired t test for differences between CP and Healthy subjects significant at $P < 0.001$

Table 2:

Primary Outcome Measures in Subjects with Chronic Pancreatitis at Baseline and Follow-up on Pancreatic Enzyme Replacement Therapy, n = 23

	Chronic Pancreatitis Baseline	Chronic Pancreatitis On PERT	Change
Total fat intake, g/24 hr *	75 (32)	72 (25)	-3 (31)
Total energy intake, kcal/day *	1762 (630)	1714 (554)	-49 (449)
%EER, low active *	77 (25)	75 (24)	-1 (20)
Stool weight, total g/24 hr *	365 (149)	375 (217)	10 (154)
Stool fat, g/24 hr *	5.5 (5.7)	4.6 (4.9)	-0.9 (4.0)
Coefficient of Fat Absorption			
CFA, %, ALL †	90.5 (13.8)	93.0 (8.8)	2.6 (6.1)
CFA, % <93% †	24	24	-
If CFA<93% at baseline (n=4) †	72.5 (21.1) [§]	82.4 (23.9) [¶]	9.9 (9.2) [#]
If CFA 93% at baseline (n=13)	96.0 (1.9)	96.3 (2.6)	0.3 (2.3)
If fecal elastase <100 (n=7) †	82.7 (19.4) ^{**}	88.7 (12.6) ^{††}	6.0 (7.9) ^{‡‡}
If fecal elastase 100 (n=10)	95.9 (2.8)	96.1 (2.9)	0.0 (3.1)
If fecal elastase <200 (n=10) †	86.7 (17.2)	90.8 (11.1) ^{§§}	4.2 (7.2)
If fecal elastase 200 (n=7)	95.9 (3.0)	96.2 (2.3)	0.2 (3.4)
Bomb Calorimetry ¶¶			
Bomb calorimetry, cal/g	5761 (719)	5702 (691)	-58 (314)
If CFA<93% at baseline (n=4) †	6314 (633) ^{**}	6131 (585)	-183 (255)
If CFA 93% at baseline (n=12)	5462 (596)	5381 (118)	-81 (219)
If fecal elastase <100 (n=10) †	6205 (667) ^{**}	6115 (232)	-90 (404)
If fecal elastase 100 (n=10)	5317 (455)	5290 (304)	-27 (208)
If fecal elastase <200 (n=13) †	6081 (673) ^{**}	5964 (713)	-117 (372)
If fecal elastase 200 (n=7)	5166 (307)	5216 (269)	50 (124)
Malabsorption Blood Test ¶¶			
AUC: PA, mg*h/dl	19.1 (8.7)	19.3 (6.7)	0.2 (6.6)
AUC: HA, mg*h/dl	7.7 (3.7)	9.4 (4.2)	1.7 (3.0) ^{##}
AUC: HA/PA ratio	4.1 (2.1)	4.2 (1.6)	0.1 (2.4)
AUC HA, mg*h/dl by group			
If CFA<93% at baseline (n=4) †	8.6 (4.7)	10.5 (3.8)	1.9 (2.7)
If CFA 93% at baseline (n=13)	7.9 (3.8)	9.7 (4.5)	1.8 (3.3)
If fecal elastase <100 (n=8) †	6.2 (3.5)	9.2 (3.4) ^{††}	3.0 (3.7)
If fecal elastase 100 (n=12)	8.7 (3.7)	9.5 (4.7)	0.9 (2.2)
If fecal elastase <200 (n=11) †	7.2 (3.8)	9.1 (4.1) ^{§§}	1.9 (4.0)
If fecal elastase 200 (n=9)	8.3 (3.7)	9.8 (4.4)	1.5 (1.5)

Data presented as mean (SD) or mean %, as indicated in the left column.

CFA: coefficient of fat absorption; AUC: area under the curve; PA: pentadecanoic acid; HA: heptadecanoic acid

*
n=20 pairs

†
n=17 pairs

‡ Longitudinal mixed effects (LME) models for change over time (before and after PERT use) in CFA, bomb calorimetry and AUC HA by group (either CFA or fecal elastase groups) with group $\times$ time interaction in the model. Change over time in CFA, bomb calorimetry or AUC HA (before and after PERT use) within group (either CFA or fecal elastase groups).

§ Difference at baseline between groups, $P < 0.001$

¶ Change with PERT use within group, $P < 0.001$

group $\times$ time interaction significant at $P < 0.001$

** Difference at baseline between groups, $P < 0.01$

‡‡ Change with PERT use within group, $P < 0.01$

‡‡ group $\times$ time interaction significant at $P < 0.05$

§§ Change with PERT use within group, $P < 0.05$

¶¶ n=20 pairs

Paired t test for change over time significant $P < 0.05$

Table 3:

Baseline Serum Micronutrient Status for Healthy Subjects and Subjects With Chronic Pancreatitis by Exocrine Pancreatic Status

	Healthy n = 22	All Chronic Pancreatitis n = 24	CP, Pancreatic Insufficient n = 15	CP, Pancreatic Sufficient n = 9
Serum Retinol, µg/dl	57.4 (15.1)	52.0 (15.5)	51.3 (18.9)	53.2 (8.3)
% < 20 (deficient)	0	4	7	0
% 20–29 (insufficient)	5	0	0	0
% 30 (sufficient)	95	96	93	100
Serum α-Tocopherol, µg/ml	11.9 (2.0)	10.4 (3.4)	9.7 (3.8) *	11.4 (2.0)
% < 9.18 (deficient)	9	29	40	11
% 9.18 (sufficient)	91	71	60 *	89
Serum 25(OH)D, ng/ml	30.9 (15.2)	28.9 (16.4)	23.1 (14.8)	38.6 (14.9) †
% < 20 (deficient)	18	29	47	0
% 20–29 (insufficient)	37	21	20	33
% 30 (sufficient)	45	50	33	67 †
Selenium, µg/L (23–190 µg/L)	112 (21)	112 (17)	106 (14)	122 (28)

Data presented as mean (SD) or mean %, as indicated in the left column.

CP: chronic pancreatitis

* Significantly different from healthy subjects by unpaired t test or by Fisher's exact test $P < 0.05$.

† Significantly different from Pancreatic Insufficient group by unpaired t test or by Fisher's exact test, $P < 0.05$.