Secretion of the Human Exocrine Pancreas in Health and Disease

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I. Introduction

Secretion from the human exocrine pancreas is highly regulated and essential for nutrient digestion. Pancreatic secretions are coordinated with responses occurring in both digestive and interdigestive periods and vary with meal composition and patient-related factors. In diseases affecting the exocrine pancreas, the amount and/or composition of pancreatic secretion can change and lead to maldigestion. Although our understanding of pancreatic secretion in the healthy state has been well-characterized, knowledge of the changes that occur during disease states remains limited. Management of exocrine pancreatic insufficiency is primarily focused on replacement of digestive enzymes, particularly lipase, with exogenous pancreatic enzymes. There is renewed interest in the study of pancreatic secretion for studies of both pancreatic physiology and disease due to advances in its collection and analysis and the growing recognition that pancreatic insufficiency often follows acute pancreatitis, particularly when it's severe. In this chapter we review various aspects of human pancreatic secretion in health and disease.

II. Anatomy of the Exocrine Pancreas

The anatomy of the exocrine pancreas has been comprehensively reviewed (41). In brief, the functional exocrine unit of the pancreas consists of groups of acinar cells and a network of pancreatic ductules and ducts. The production of the vast majority of pancreatic juice proteins occurs in the acinar cells. Of the pancreatic enzymes, proteases (e.g., trypsin, carboxypeptidases, chymotrypsin, and elastase) are the most abundant (according to mass) and comprise around 90% of the enzymes found in human pancreas fluid; amylase, lipase, and nucleases are relatively less abundant (54). Following production and storage of inactive proenzymes (termed zymogens) and active enzymes in acinar cell zymogen granules, they are secreted into a network of pancreatic ductules and ducts in response to a meal. These conduits are lined with cuboidal ductal epithelial cells, which secrete a bicarbonate-rich fluid needed

solubilize proteins secreted from the acinar cell and carry them to the duodenum. Secretion from acinar and ductal cells is highly regulated, primarily in response to nutrient ingestion and neural stimulation (6). Diseases that interfere with either the function of the ductal cells or the continuity of the ductal network will lead to exocrine pancreatic insufficiency, as discussed below.

III. Normal Secretion of the Exocrine Pancreas

During the interdigestive (i.e., fasting) state, exocrine secretion is somewhat cyclic and associated with the three phases of gastrointestinal motility (30). Pancreatic secretion in the digestive period is much greater than the interdigestive period. This secretion is regulated by neurohormonal responses and occurs in three primary phases – cephalic, gastric, and intestinal (6, 31). The initial cephalic phase (stimulated by the sight, smell or taste of food) is primarily controlled by the vagal nerve and results in levels of enzyme secretion that account for 20-25% of the total elicited by a meal (31). Next, the gastric phase is activated by gastric distention, which only produces a small increase in pancreatic enzyme secretion. Finally, the intestinal phase is activated by chyme in the duodenum, resulting in the majority (50-80%) of the pancreatic stimulus associated with a meal (31). Together these responses cause a rapid increase in enzyme secretion to a maximal output about 1 hour after meal ingestion (11, 17). The enzyme output generally remains elevated for approximately 3-4 hours, but can vary depending on multiple factors (11, 17, 42). The cessation of pancreatic enzyme secretion is believed to be primarily the result of nutrient exposure to the distal small intestine based on experiments demonstrating the inhibition of endogenously stimulated secretion following

ileal perfusion of carbohydrates or lipids (36). Hormones believed to be involved in this feedback inhibition include peptide YY and glucagon-like peptide-1 (31).

Several meal-related factors influence exocrine pancreatic secretion, including caloric content, nutrient composition, and physical properties of the meal. In regards to caloric content, there appears to be a minimal and maximal threshold of pancreas stimulation, with the maximal enzyme response occurring after consumption of approximately 500 kcal (5). The meal composition of fats, carbohydrates, and proteins can also influence the relative and absolute levels of enzymes in pancreatic secretion. For example, healthy subjects exposed to a high fat diet for two weeks had an total enzyme output that was 2 to 4 times greater than those on a high carbohydrate diet in the immediate postprandial and interdigestive periods, respectively (4). Although temporary exposure to a high fat diet for 24 hours also increased enzyme output in this study, the observation was not replicated with intraduodenal infusion of different nutrient compositions (24). Another key observation is that ingestion of a solid meal results in a more sustained enzyme response than an identical homogenized meal (4, 42).

Pancreatic secretion of a bicarbonate rich fluid has a distinct mechanism and has important consequences. The transport of bicarbonate by duct cells into the pancreatic duct lumen is mediated by the cystic fibrosis transmembrane conductance regulator (CFTR). This transporter can either secrete chloride to drive a chloride-bicarbonate exchanger on duct cells or directly transport bicarbonate into the duct lumen. The relative levels of ion secretion depend on the amount of stimulation; at low rates, chloride predominates but at high secretory rates, bicarbonate is dominant. Reduced bicarbonate and fluid secretion are

seen in chronic pancreatitis, cystic fibrosis, and in some individuals with alcohol abuse possibly due to inhibition of CFTR function (discussed below). Duodenal pH is the primary driving force for ductal fluid and electrolyte secretion though nutrient digestive products can also enhance bicarbonate secretion. After ingestion of a meal in a healthy subject, the duodenal pH changes from a baseline near 7.0 to a nadir of 5.0-4.5 in the early postprandial phase (11, 42). When a threshold of about pH 4.5 is reached in the duodenum, secretin is released and secretion of bicarbonate-rich fluids into the duodenum follows. The alkaline fluid in the duodenum has several functions including: inactivating pepsin, increasing the solubility of fatty acids and bile acids, maintaining an optimal pH (>4.0) for pancreatic and brush border enzymes, and preventing intestinal mucosal damage.

IV. Alteration of Exocrine Secretion in Disease

Pancreatic enzyme secretion is a highly controlled process in health, so it is not surprising that its dysfunction is often observed with disorders of the exocrine pancreas. Although enzyme response to different nutrients has been well characterized in a healthy state, much less is known regarding the extent of change in disease. Rather, most studies have focused on the clinical ramifications of inadequate enzyme production and/or secretion.

A. Mechanisms of abnormal exocrine function

The multiple mechanisms whereby pancreatic disorders can lead to decreased pancreatic enzyme activity can be categorized as:
1. decreased enzyme production,
2. impaired enzyme secretion, and/or
3. impaired enzyme mixing with food.

Reduced acinar cell mass leads to decreased enzyme production and arises from disorders of primary and secondary exocrine pancreatic insufficiency (EPI). Primary disorders are illustrated by Shwachman-Diamond syndrome and Johanson-Blizzard syndrome; secondary causes include chronic pancreatitis, severe acute pancreatitis, or pancreatic surgical resection. Patients with impaired enzyme secretion can have impairment at the cellular (e.g., impaired duct cell function in cystic fibrosis) or macroscopic level (e.g., obstruction of the main pancreatic duct secondary to a stricture, intraductal stone, or mass). Impaired mixing of pancreatic enzymes with food often occurs in the postoperative setting, such as following a gastrojejunostomy. Additionally, impaired bicarbonate secretion by ductal cells can lead to impaired mixing, a suboptimal pH for enzyme activities, and reduced formation of micelles (2, 31).

B. Chronic pancreatitis

Chronic pancreatitis is one of the most common causes of exocrine pancreatic insufficiency (EPI), with insufficiency observed in 30 to 90% depending on the clinical severity of disease (37). In a study examining the natural history of chronic pancreatitis, the onset of EPI was often delayed 10-15 years after symptom onset (37). This delay is attributable to the dramatic functional reserve of the exocrine pancreas, requiring loss of more than 90% of exocrine pancreatic function before developing malabsorption. Whether or not the reduction of the various pancreatic enzymes occurs in parallel remains unclear. However, the clinical abnormalities are predominantly related to fat maldigestion. This is primarily a consequence of limited levels of lipase in the normal pancreas and minimal redundancy of lipase production from non-pancreatic sources. Further, other luminal conditions for fat digestion and absorption, especially the

formation of micelles needed for both optimal lipid hydrolysis and lipid delivery to mucosal cells, is disordered in chronic pancreatitis. In contrast, only 5% of normal amylase content is needed to maintain starch digestion; this amount can typically be reached by a combination of salivary gland and brush border oligosaccharidase production of amylase (38). Similar levels of pancreatic proteases are likely needed for efficient protein digestion. In a landmark study, DiMagno and colleagues demonstrated that steatorrhea (>7gram fat/24 hours) develops when the lipase output is <10% of normal (9). The reported lipase output in chronic pancreatitis may range from 1-60% of levels found in healthy controls (31). The wide variability is in part due to methodologic differences in the studies (e.g., method of pancreas stimulation and collection methods), but also likely reflects subjects studied at various stages of disease.

Chronic pancreatitis can alter all aspects of pancreatic enzyme synthesis and secretion, so EPI is typically multifactorial. First, parenchymal fibrosis can lead to acinar cell injury and loss of exocrine mass with a resultant loss of enzyme production. Second, duct cell function is impaired in chronic pancreatitis leading to decreased bicarbonate secretion (8). As a result, postprandial duodenal pH is lower in chronic pancreatitis than in healthy subjects, and can exceed the pH threshold for irreversible lipase inactivation (pH 4.5) (11). Obstruction of the main pancreatic duct can also occur due to fibrotic strictures and intraductal calculi and likely contributes to reduced duct pancreatic secretion. However, neither endoscopic nor surgical correction of main pancreatic duct obstruction has been convincingly demonstrated to restore pancreatic enzyme secretion. Since the functional and tissue loss found in chronic pancreatitis is currently not reversible with the possible exception of cystic fibrosis, clinical treatment of exocrine insufficiency is limited to oral supplementation with pancreatic enzyme replacement therapy.

C. Cystic fibrosis

The CFTR gene codes for a chloride channel, which is central to the production of fluid and electrolyte secretion in various exocrine glands. In the pancreas, the primary pathophysiologic result of CFTR mutations is decreased electrolyte and fluid secretion into the pancreatic duct lumen. The consequence of these changes is pancreas fluid that is more viscous and acidic than normal secretion. Although acinar cells may not be directly affected in early or mild disease, both pancreatic enzyme secretion and function are impaired. In addition to impaired flow, the acidic pancreatic duct lumen can result in precipitation of mucins, secretory protein aggregation, and premature activation of enzymes (47). Furthermore, the decreased bicarbonate secretion leads to a more acidic intraluminal pH in the duodenum. It has been observed that the pH is lower by 1-2 units in both the interdigestive and digestive periods in cystic fibrosis compared to controls (20). Collectively, EPI is prevalent in classic CF with estimates that 80% of patients with CF will develop EPI by 2 years of life (14). Importantly, EPI appears to be mostly limited to those subjects with two severe deleterious mutations, though pancreatic disease can rarely occur in those with less severe mutations (14). Recent studies reported that correction of EPI can occur with treatment using CFTR modulators (45, 46). How often this response is seen in CF patients and whether this class of drugs might impact EPI in those having other pancreatic diseases remains to be studied. There is also evidence that prominent levels of alcohol ingestion can rapidly reduce ductal CFTR function (Hegyi, P. The Pancreapedia, 2021).

As in other diseases, the EPI in CF and impaired lipase secretion may at least partially be compensated by increased activity of gastric lipase (3). Studies of pancreatic enzyme secretion in CF are limited. This is likely due to the multiple methodologic challenges to completing these studies, the greatest of which is that EPI manifests at a young age. This poses technical and ethical issues for research study design. In these patients with EPI, lifelong pancreatic enzyme replacement therapy is recommended and improvement in nutritional status has been associated with improvements in pulmonary function and overall survival (53).

D. Acute pancreatitis

In contrast to chronic pancreatitis and cystic fibrosis, which are chronic, progressive diseases, acute pancreatitis is a multiphasic disease. Thus, impairment of pancreas enzyme secretion is variable and depends on the clinical severity of acute pancreatitis and chronologic proximity to the inciting insult. Knowledge of pancreatic enzyme secretion during the early phase of acute pancreatitis is limited in part because of the belief that pancreatic stimulation in this setting may be harmful. Epidemiological studies have characterized EPI prevalence following acute pancreatitis. It is estimated that 62% of these patients have EPI during admission with persistent EPI in 35% of patients during follow-up (25). This prevalence trend suggests that transient exocrine pancreatic dysfunction is common after acute pancreatitis and that a smaller number will develop long-term EPI. Persistent EPI appears to be more common in patients with pancreatic necrosis or an alcohol etiology (25). This is a commonly overlooked sequela of acute pancreatitis, and additional understanding of the pathophysiology is needed.

E. Pancreatic cancer

The changes in pancreas enzyme secretion are not well characterized in pancreatic cancer. Although the prevalence of EPI in pancreatic cancer has not been characterized in a large clinical cohort, the pooled prevalence in a recent meta-analysis was over 70% (26). In addition to tumor-mediated parenchymal destruction, abnormal secretion can develop as a consequence of pancreatic duct obstruction and following surgical resection (61). The location of the tumor is an important factor in determining whether pancreatic secretion remains adequate. In one study involving direct PFTs, a shorter length of unaffected pancreatic duct (i.e., a tumor located closer to the pancreatic head) was associated with decreased bicarbonate and enzyme output in response to CCK stimulation (10).

F. Pancreatic surgery

Alterations in exocrine secretion following pancreatic surgery are influenced by the type of surgery, extent of resection, and health of the remnant pancreatic parenchyma. The exocrine function remains largely unchanged, and occasionally improves, in those undergoing a drainage procedure with or without minor resection of the parenchyma (27). Conversely, clinically diagnosed EPI is observed in approximately 25-50% of those following a pancreaticoduodenectomy (27, 28, 43, 58, 63). In patients undergoing surgery for a diffuse disease, such as chronic pancreatitis, the risk of developing EPI following surgery is increased. For example, in a clinical series limited to subjects with chronic pancreatitis, over 50% developed clinically overt steatorrhea following pancreaticoduodenectomy and up to 40% following distal pancreatectomy (16, 29, 58).

G. Non-pancreatic etiologies of impaired exocrine pancreatic function

In addition to the preceding pancreatic etiologies, there are other non-pancreatic diseases that can indirectly impair exocrine pancreatic function. For example, in those undergoing a partial or total gastrectomy there are multiple factors that decrease intraluminal enzyme activity. The greatest contributing factor is post-cibal asynchrony, which describes disordered mixing of meal contents and pancreatic enzymes in the small intestine (31). The asynchrony is further compounded by pancreatic denervation during surgical dissection and the loss of compensatory gastric lipase production. The dilution of pancreatic enzymes in the duodenal lumen that results from rapid delivery of an osmotic load also reduces nutrient digestion. Asynchrony is also a contributing factor to the EPI observed following pancreaticoduodenectomy. Although steatorrhea is not universally present in patients with Zollinger-Ellison syndrome (ZES), it is important to consider the effect on exocrine pancreatic function due to its unique pathophysiologic mechanism (52). In ZES there is excessive gastrin production which leads to inappropriate gastric acid secretion. This lowers the duodenal pH beyond the threshold at which normally secreted pancreatic enzymes are active and leads to inactivation of some, most importantly lipase (19). The relatively acidic duodenal pH in ZES also leads to bile salt precipitation. This reduces the effectiveness of lipase-dependent triglyceride hydrolysis as well as formation of micelles that are needed to carry lipids to enterocytes. Lastly, impaired exocrine function has been shown in patients without clinically evident pancreatic disease. For example, patients with type 2 diabetes mellitus can develop fibrosis that is histologically similar to chronic pancreatitis (44). This condition, currently referred to as diabetic exocrine pancreatopathy, differs from chronic pancreatitis in that chronic inflammatory cells are absent and overt EPI is rare. Exocrine pancreatic insufficiency may also occur in celiac disease (when measured using fecal elastase levels) despite the absence of structural changes in the pancreas (51, 60). The EPI in celiac disease is generally attributed with mucosal injury which may disrupt an enteric-mediated cholecystokinin stimulation of the pancreas and gallbladder emptying. In children, short-term support with oral pancreatic enzymes is often considered. Pancreatic secretion usually resolves with mucosal healing on a gluten free diet (51). EPI has also been reported to occur in patients with inflammatory bowel disease and following gastrointestinal surgeries, but, additional studies are needed to further characterize the potential mechanisms of exocrine dysfunction in these scenarios (55).

V. Measurement of Human Pancreatic Secretion (direct pancreatic function testing)

Our knowledge of normal human pancreatic secretion primarily comes from human studies using luminal tube(s) to collect intestinal fluids following pancreatic stimulation with either a standardized meal or an intravenous secretagogue such as secretin or cholecystokinin. The use of exogenous stimulation to measure pancreatic function is referred to as direct pancreatic function testing (PFT) (**Table 1**). Although different types of tubes have been used, one of the most recognized is the Dreiling tube, which permitted simultaneous aspiration from the gastric and duodenal lumens. One drawback of this approach was that the enzyme output could not be determined because the flow rate could not be calculated. To resolve this issue, a method

was developed using a second tube placed with ports in both proximal and distal duodenum. A non-absorbable marker (typically polyethylene glycol) was infused through the proximal port and aspirated with pancreatic secretions through the distal port (18). Using this marker-perfusion method permitted calculation of pancreatic enzyme output as well as a correction coefficient for the amount of fluid not collected distally. A variety of endogenous and exogenous stimuli were administered, and the changes in pancreatic secretions could be characterized. Significant drawbacks to these techniques included patient discomfort and prolonged fluoroscopy time to maintain proper tube location. Despite these challenges, the majority of the data related to human pancreatic secretory physiology were acquired using this technique.

Name	Sensitivity	Specificity	Advantages	Disadvantages	Cost
Direct Pancreatic Function Tests:					
CCK-stimulated pancreatic function test	High	High	• Provides the most direct measure of pancreatic enzyme output	• Tubes are no longer available to measure enzyme output • Invasive	$$$$
Secretin-stimulated pancreatic function test	High	Moderate	• Highly sensitive in early stages of disease • High negative predictive value to rule out chronic pancreatitis	• Invasive • False positives: CFTR mutations and cigarette smoking • Does not directly assess acinar cell function	$$$$
Indirect Pancreatic Function Tests:					
Coefficient of fat absorption (CFA)	High	Moderate	• Highly accurate for fat malabsorption • Can be used to monitor PERT • Noninvasive	• Requires 3 day stool collection • False positives: any cause of fat malabsorption (which must be excluded before diagnosing EPI)	$
Fecal elastase (FE-1)	Mild - Moderate	Moderate-High	• Convenient collection • Noninvasive	• Lower accuracy in those with mild EPI or history of pancreatic resection • Cannot be used to monitor PERT • False positives: bacterial overgrowth, watery stool	$
^{13}C-mixed triglyceride breath test (MTBT)	Moderate	Moderate	• Can be used to monitor PERT • Noninvasive	• Limited availability • Time consuming test	$$

EPI, exocrine pancreatic insufficiency; PERT, pancreatic enzyme replacement therapy

Table 1. Comparison of direct and indirect pancreatic function tests. Estimates of sensitivity and specificity are assigned semi-quantitatively due to extreme heterogeneity in study designs, which precludes accurate pooling (7, 22).

Further studies regarding the mechanisms of human pancreatic secretion became possible following adaptation of early work demonstrating the ability to isolate functioning pancreatic acini from rodents (62). The ability to isolate acini from human pancreases and study them in a controlled environment has led to further understanding of the cellular mechanisms of pancreatic secretion in health and disease, which are described elsewhere (40).

More than a decade ago, an endoscopic-based pancreatic function test (ePFT) was developed that greatly improved patient tolerance and eliminated the need for fluoroscopy (8). Although the stimuli for pancreatic secretion remained similar (i.e., cholecystokinin (CCK) and/or secretin), the method of fluid collection was through the suction channel of the endoscope rather than an enteric tube. Since there is only one "port" for collecting samples through the endoscope, this technique permits determination of enzyme and analyte

concentration, but not enzyme output (or flow rate). The most common use of the ePFT is for evaluation of suspected chronic pancreatitis. However, there is emerging use of this methodology for translational science, including the study of disease biomarkers (23).

Currently, the most commonly used measurement made using ePFT is the peak bicarbonate concentration following secretin stimulation. Although this measurement is more directly an assay of pancreatic duct-cell function than acinar-cell function, previous studies have demonstrated that peak bicarbonate corresponds to peak lipase concentrations in the pancreatic fluid of healthy subjects as well as chronic pancreatitis (56). For the evaluation of chronic pancreatitis, measurement of peak bicarbonate concentration (following secretin stimulation) has improved discrimination compared to peak lipase or amylase concentrations (following CCK stimulation) (35). Importantly, the negative predictive value (97%) of a normal bicarbonate response to secretin stimulation to exclude chronic pancreatitis is very high; however, the positive predictive value (45%) is much lower (33). Thus, the primary clinical use for endoscopic function tests is to "rule out" a diagnosis of chronic pancreatitis.

In addition to the previously mentioned electrolytes and pancreatic enzymes, there is a large number of other potential analytes in pancreatic fluid. During an ePFT there is typically an abundant volume of fluid collected, which provides the opportunity for other studies. Investigators have begun to explore various molecular targets in pancreas fluid, including: protein expression, cytokines, DNA methylation markers, microRNAs, and genetic mutations (23). Various markers are being examined for the purposes of identifying diagnostic or disease biomarkers, as well as observations that may lead to novel therapeutic approaches. Although early studies were primarily limited to proteomics, there has been a recent resurgence in other areas with exciting preliminary findings (48, 49). For example, Abu Dayyeh et al. demonstrated that prostaglandin E2 (PGE2) is a promising disease biomarker for the various stages of chronic pancreatitis (1). Levels are different in early and advanced chronic pancreatitis compared to healthy controls, with areas under the curve (AUC) of 0.62 and 0.9, respectively. When used in combination with the pancreatic fluid bicarbonate, the AUC for diagnosis of early and advanced chronic pancreatitis were 0.94 and 1.0, respectively. Another example of biomarker discovery includes the identification of DNA hypermethylation markers that identify patients with pancreatic cancer compared to controls with AUCs ranging from 0.62-0.92 (34).

VI. Indirect Pancreatic Function Testing

Tests measuring pancreatic function without the use of hormonal stimulation are referred to as indirect PFTs. Since the indirect tests are typically less accurate for detecting early stages of exocrine dysfunction, they are more helpful for quantifying the degree of insufficiency in those with known pancreatic disease, rather than diagnosis. Indirect PFTs are non-invasive and typically less expensive, so the selection of the pancreatic function test to be employed in the clinical setting requires considering the tradeoff between diagnostic test performance, invasiveness, and costs (**Table I**). For example, indirect PFTs are generally adequate to identify EPI in patients with overt morphological changes (e.g. calcifications and/or main pancreatic duct dilation). In contrast, a direct PFT would be preferred to identify EPI in a patient with clinical suspicion of chronic pancreatitis and normal or

equivocal imaging tests (7). Poorly studied indirect tests (including serum trypsin, fecal chymotrypsin, and qualitative fecal fat analysis) are not discussed here.

A. Coefficient of fat absorption

Among indirect testing methods, the coefficient of fat absorption (CFA) is considered the gold standard to diagnose fat malabsorption from any cause, and to document and quantify EPI in those with pancreatic disease (15, 50, 64). This test involves consumption of a high-fat diet (100 grams/day) for at least 5 days with stool collection during the final three days of the diet. The daily dietary fat intake is recorded, and factored into the final CFA calculation, using the following equation:

CFA (%) = 100 x [(mean daily fat intake – mean daily stool fat) / mean daily fat intake]

A CFA of <0.93 (which corresponds to >7 grams of stool fat per 24-hour period while on a 100 g fat diet) is considered abnormal (22). Although this test is accurate when carefully performed, the three-day collection period can be inconvenient for patients and errors may occur when performed in a non-controlled environment with either collection or processing. Since fat excretion is directly related to fat ingestion over a broad range of values (excretion ~7% of intake over a broad range of intakes), subjects must have an exact record of their intakes. Though this test is also useful to assess adequacy of PERT dosing, follow-up testing is rarely performed outside of the research setting.

B. Fecal elastase-1

In contrast to the CFA, a fecal elastase-1 (FE-1) level can be determined from a single formed stool sample. The test's convenience makes it the most widely used indirect PFT in clinical practice. Pancreatic elastase is resistant to degradation as it passes through the gut, so it can be measured in the stool (57). Although early studies demonstrated strong correlation with pancreatic enzyme output during direct PFT, more recent studies have demonstrated only fair accuracy in mild EPI (22). False positives occur in about 10% of patients with low pre-test probability for EPI (59). Similarly, levels are falsely low any time a liquid stool specimen is analyzed. Also, low levels are commonly observed in diabetes mellitus (both type 1 and type 2 diabetes), but it is uncertain if this truly represents EPI (21, 39). Lastly, since FE-1 levels detected by monoclonal (but not polyclonal) assays are unaffected by PERT this test is not useful for monitoring the adequacy of therapy.

C. ^{13}C-mixed triglyceride breath test

The ^{13}C-mixed triglyceride breath test (MTBT) is another indirect test that measures the intraluminal lipolytic activity as an estimate of exocrine pancreatic function. The test involves ingesting a standardized meal (including triglycerides with radiolabeled carbon tracers) (22). The triglycerides are hydrolyzed by pancreatic lipase releasing ^{13}C-fatty acid, which is absorbed, then transported to the liver. Lipolysis and beta-oxidation occur in the liver leading to the formation of $^{13}CO_2$. These molecules are exhaled by the lungs and measured in serial breath samples. A decrease in the recovery of $^{13}CO_2$ is associated with decreased pancreatic lipase secretion and fat malabsorption as measured by CFA (12, 13, 32). Although this is a non-invasive test it lasts approximately 6 hours and the radiotracers are not universally available, so the clinical utility of this test worldwide is limited.

VII. Summary

Pancreas exocrine secretion represents a complex response to a meal which involves the coordinated release and transport of enzymes

from acinar cells and fluid and electrolytes from duct cells into the pancreatic ductal system and then into the duodenal lumen where they are required for normal digestion. Essentially all pancreatic disorders may alter this process to different degrees and do so through a variety of mechanisms. There are various methods for determining enzyme output and bicarbonate secretion in response to endogenous and exogenous pancreatic stimulation. These tools have shaped our current understanding of pancreas physiology and hold significant potential for biomarker discovery and identification of novel therapeutic targets.

VIII. Acknowledgements

IX. References

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