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Pancreatic cyst fluid glucose: rapid, inexpensive, and accurate diagnosis of mucinous pancreatic cysts

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ABSTRACT

Background. The most widely accepted biochemical test for preoperative differentiation of mucinous from benign, nonmucinous pancreatic cysts is cyst fluid carcinoembryonic antigen. However, the diagnostic accuracy of carcinoembryonic antigen ranges from 70% to 86%. Based on previous work, we hypothesize that pancreatic cyst fluid glucose may be an attractive alternative to carcinoembryonic antigen.
Methods. Pancreatic cyst fluid was collected during endoscopic or operative intervention. Diagnoses were pathologically confirmed. Glucose and carcinoembryonic antigen were measured using a patient glucometer and automated analyzer/enzyme-linked immunosorbent assay. Sensitivity, specificity, accuracy, and receiver operator characteristic analyses were performed.
Results. Cyst fluid samples from 153 patients were evaluated (mucinous: 25 mucinous cystic neoplasms, 77 intraductal papillary mucinous neoplasms, 4 ductal adenocarcinomas; nonmucinous: 21 serous cystic neoplasms, 9 cystic neuroendocrine tumors, 14 pseudocysts, 3 solid pseudopapillary neoplasms). Median cyst fluid glucose was lower in mucinous versus nonmucinous cysts (19 vs 96 mg/dL; $P < .0001$). With a threshold of ≤ 50 mg/dL, cyst fluid glucose was 92% sensitive, 87% specific, and 90% accurate in diagnosing mucinous pancreatic cysts. In comparison, cyst fluid carcinoembryonic antigen with a threshold of >192 ng/mL was 58% sensitive, 96% specific, and 69% accurate. Area under the curve for glucose and CEA were similar at 0.91 and 0.92.
Conclusion. Cyst fluid glucose has significant advantages over carcinoembryonic antigen and should be considered for use as a routine diagnostic test for pancreatic mucinous cysts.

Introduction

Pancreatic cancer will be diagnosed in 53,670 Americans and will take the lives of 43,090 in 2017.[1] Current available treatment strategies offer little chance for cure and a limited extension of life. In light of the low long-term survival rates after pancreatic cancer diagnosis, optimal clinical management should include prevention strategies. A unique opportunity for prevention of pancreatic cancer exists in specific high-risk populations such as patients with precancerous pancreatic cysts. Although as many as 2% to 3% of American adults are found to have pancreatic cysts on routine cross-sectional imaging, not all cysts have malignant potential and undergo malignant transformation.[2,3] Patients known to have cysts with a high risk for malignant transformation will optimally be managed surgically. Those with lower-risk cysts may be followed with more or less intensive surveillance programs depending on risk stratification. Avoidance of unnecessary, highly morbid surgery balanced with prevention of pancreatic cancer hinges on accurate preoperative diagnosis and malignant risk stratification.

Diagnostic tools for pancreatic cysts are limited by variable accuracy and reliability. Although cross-sectional imaging can detect

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the vast majority of pancreatic cysts, its accuracy in differentiating cyst types is lacking.[4] Differentiation of cyst types is key because this, in part, will determine their malignant potential. Mucinous pancreatic cystic lesions include intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN), *both of which can undergo* malignant progression.[5] Conversely, nonmucinous cysts include serous cystic neoplasms (SCN) and pseudocysts with virtually no propensity for malignancy and cystic pancreatic neuroendocrine tumors (NET) and solid pseudopapillary neoplasms (SPN), which are rare and almost always identified accurately on cytology. To aid in risk stratification, endoscopic ultrasound with fine needle aspiration is often performed in order to obtain cyst fluid for biomarker, cytologic, and genetic analysis.[5] Cyst fluid carcinoembryonic antigen (CEA) is the standard biomarker currently used to differentiate mucinous from nonmucinous pancreatic cysts.[6] However, CEA is not perfect. A recent multi-institutional retrospective study found CEA sensitivity and specificity of only 61% and 77%, respectively, at the accepted 192 ng/mL threshold for detection of mucinous cystic lesions.[7] Previous meta-analysis reported similar findings of 63% and 88% sensitivity and specificity of CEA.[8] Furthermore, CEA measurement requires specific laboratory capabilities that are costly and relatively time consuming.

We hypothesize that an alternative cyst fluid biomarker may offer improved diagnostic accuracy and efficiency over the standard CEA test for determination of mucinous versus nonmucinous cysts. Two previous studies from a single institution reported the potential of pancreatic cyst fluid glucose for the diagnosis of mucinous cysts.[9,10] The studies included 45 and 65 patient samples and found sensitivities and specificities ranging from 81% to 95% and 57% to 78% for detection of mucinous pancreatic cysts using thresholds of <66 and 50 mg/dL, respectively. We aim to independently validate these findings with a larger patient cohort and to compare the diagnostic utility of cyst fluid glucose and CEA.

Methods

Pancreatic cyst fluid samples were collected prospectively at the time of endoscopic ultrasound-guided fine needle aspiration ($n = 41$) or pancreatic resection ($n = 112$) at Indiana University Health University Hospital between June 2003 and June 2016. All patients provided informed consent in accordance with the Indiana University institutional review board. After procurement, pancreatic cyst fluid aliquots were placed immediately on ice and then stored at –80° C. Pancreatic cyst diagnosis was confirmed on surgical pathology by a University Hospital staff pathologist and then reconfirmed by a pancreatic pathologist. Demographic and clinical data were prospectively collected as patient samples were gathered. Additional or missing variables were obtained from retrospective review of electronic medical records.

Glucose and CEA analysis

Pancreatic cyst fluid (2 µl) *was thawed on ice and assayed within 1 hour.* Glucose was analyzed using a standard patient glucometer: the OneTouch Verio IQ Blood Glucose Monitoring System. The OneTouch glucometer measures glucose levels between 20 mg/dL and 600 mg/dL.[11] No pancreatic cyst fluid sample had a glucose reading of >600 mg/dL. All samples with glucose readings <20 mg/dL were recorded and analyzed as 19 mg/dL. A subset of patient samples had adequate fluid for concomitant CEA analysis. CEA was determined by Beckman Coulter DxI 800 analyzer or, in cases of low fluid volume, by enzyme-linked immunosorbent assay (ELISA) (Sigma-Aldrich, St. Louis, MO). CEA values obtained by ELISA were converted to the Beckman automated analyzer scale using linear regression.

Table
Patient demographic/clinical data for those with mucinous versus nonmucinous pancreatic cysts.

	n	Mucinous	Nonmucinous	*P* value
Sex (%male)	153	31.7%	27.7%	0.7
Age [Median (IQR)]	153	65.0 (55.0–73.0)	58.0 (42.0–68.0)	0.006
DM (% with DM)	153	23.8%	27.7%	0.7
Insulin use	153	9.4%	8.5%	0.5
Ha1c	74	5.9 (5.7–6.6)	5.8 (5.3–6.0)	0.06
Cyst size (cm)	151	2.8 (2.1–4.3)	3.6 (2.5–5.3)	0.08

DM, Diabetes mellitus; Ha1c, Hemoglobin a1c.

Statistical analysis

Descriptive statistics, including mean, median, standard deviation, interquartile range, and frequencies, were calculated as appropriate. Demographic and clinic-pathologic data were compared between patients with mucinous and nonmucinous pancreatic cysts using the Mann-Whitney *U* test for continuous data and chi square for categorical data. The Pearson correlation coefficient was calculated to determine the association of glucose with other variables. The diagnostic utility of glucose as a biomarker for mucinous cystic lesions was ascertained using sensitivity/specificity calculations and receiver operator characteristic (ROC) analyses. Analyses were repeated for cyst fluid CEA and compared with glucose analyses.

Results

A total of 153 pancreatic cyst fluid samples were collected and analyzed for study inclusion. Of these, 106 were pathologically confirmed as mucinous (25 MCNs, 77 IPMNs, 4 ductal adenocarcinomas) and 47 as nonmucinous cysts (21 SCNs, 9 cystic neuroendocrine tumors, 14 pseudocysts, and 3 solid pseudopapillary neoplasms). Although patient sex did not differ between those with mucinous and nonmucinous cysts (31.7% vs 27.7% male; $P = .7$), median age (interquartile range, IQR) was significantly younger in the nonmucinous cyst group at 65 (55–73) years versus 58 (42–68) years (Table). Frequency of diabetes mellitus (23.8% vs 27.7%), insulin use (9.4% vs 8.5%), median serum hemoglobin a1c (Ha1c) (5.9 vs 5.8), and median cyst size (2.8 cm vs 3.6 cm) were also not different between mucinous and nonmucinous cyst groups (Table). *None of these patient demographic or clinical variables* correlated with pancreatic cyst fluid glucose or CEA.

Median pancreatic cyst fluid glucose level [IQR] measured using a standard patient glucometer was significantly lower in mucinous cysts than in nonmucinous cysts (19 [19–29] vs 96 [66–114] mg/dL; $P < .0001$) (Fig 1). *Blood glucose levels on the day of the collection procedure did not correlate with cyst fluid glucose levels (data not shown).* Fig 2 displays the scatter plot dividing mucinous and nonmucinous cyst categories into cyst types comprising each category. Median and IQR values are shown under the scatter plot. All median values for mucinous cyst types (MCN, IPMN, and pancreatic ductal adenocarcinoma [PDAC]) fall below the previously published cutoff value (50 mg/dL) for detection of mucinous cysts.[9] With a threshold of <50 mg/dL, cyst fluid glucose was 92% sensitive, 87% specific, and 90% accurate in diagnosing mucinous pancreatic cysts. ROC analysis was performed, revealing an area under the curve (AUC) of 0.91 (95% CI: 0.85–0.96) (Fig 3). Pancreatic cyst fluid glucose was unable to differentiate invasive disease from noninvasive disease or invasive IPMN from noninvasive IPMN. Additionally, no association was found between cyst fluid glucose levels and *indications for surgery such as IPMN dysplasia grade or main duct involvement (data not shown).*

Of the 153 patients analyzed for glucose, 120 had sufficient pancreatic cyst fluid volume available for CEA measurement. Median