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The level of glucose in pancreatic cyst fluid is more accurate than carcinoembryonic antigen to identify mucinous tumors: A French multicenter study

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ABSTRACT

Background and Objectives: Pancreatic cyst fluid level of glucose is a promising marker to identify mucinous from nonmucinous tumors, but the glucose assay has not yet been recommended. The objective of this study is to compare the diagnostic performances of pancreatic cyst fluid level of glucose and carcinoembryonic antigen (CEA).

Methods: In this French multicenter study, data of consecutive patients who underwent fine-needle aspiration of pancreatic cyst with intracyst glucose assay between 2018 and 2022 were retrospectively reviewed. The area under the receiver operating characteristic curve (AUROC) of glucose and corresponding sensitivity (Se), specificity (Sp), accuracy (Acc), positive predictive value (PPV), and negative predictive value (NPV) were calculated and compared with those of CEA. The best threshold of glucose was identified using the Youden index.

Results: Of the 121 patients identified, 81 had a definitive diagnosis (46 mucinous, 35 nonmucinous tumors) and were included for analysis. An intracystic glucose level <41.8 mg/dL allowed identification of mucinous tumors with better diagnostic performances (AUROC, 93.6%; 95% confidence interval, 87.2%–100%; Se, 95.3%; Sp, 91.2%; Acc, 93.5%; PPV, 93.2%; NPV, 93.9%) compared with CEA level >192 ng/mL (AUROC, 81.2%; 95% confidence interval, 71.3%–91.1%; Se, 41.7%; Sp, 96.9%; Acc, 67.6%; PPV, 93.8%; NPV, 59.6%) (P = 0.035). Combining values of glucose and CEA did not offer additional benefit in terms of diagnosis.

Conclusion: Our results confirm previously published data and support the use of pancreatic cyst fluid glucose for the identification of mucinous tumors when the definitive diagnosis remains uncertain.

Keywords: Glucose; Carcinoembryonic antigen; Pancreatic cystic neoplasms; Mucinous tumors

INTRODUCTION

Pancreatic cystic neoplasms (PCNs) are common in the general population. Pancreatic cystic neoplasms are seen in approximately 5% of patients older than 50 years and in 10% of those older than 70 years.[1] The main issue at the time of diagnosis is to identify mucinous tumors, including intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystadenomas (MCAs). Both types of lesion carry a risk of malignant transformation of 5% and 10% within the 5 and 10 years following the diagnosis, respectively.[2] Nonmucinous tumors include numerous kinds of pancreatic cysts, such as pancreatic pseudocysts (PPCs) and serous cystadenomas (SCAs). No surveillance is required for these tumors because the risk of malignant transformation is nonexistent in theory, misdiagnosis aside.[2] Cystic pancreatic neuroendocrine tumors and solid pseudopapillary tumors are rare and constitute distinct entities.[3] Their diagnosis is often easy (imaging features, context).

In clinical practice, the identification of mucinous tumors is often based on clinical and radiological criteria. For instance, the occurrence of a PCN following a severe acute pancreatitis is consistent with a PPC; the honeycomb pattern is considered pathognomonic of SCA; the branch duct pattern without history of pancreatitis as well as multiple cysts (40% of cases) supports the diagnosis of IPMN. However, approximately two-thirds of pancreatic cysts are unilocular (<6 loci) and macrocystic (>2 cm), which is not specific.[4] In this case, the spectrum of differential diagnosis is wide (IPMN, MCA, PPC, SCA, etc). Therefore, EUS-FNA for biochemical

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and cytological analysis of the cystic fluid is recommended to help achieve definitive diagnosis.[1,2] The contribution of cytology is quite poor in this setting. The level of carcinoembryonic antigen (CEA) is, to this day, the most performing tool to identify mucinous tumors. A cystic CEA >192 ng/mL is 96% specific of a mucinous tumor. However, the sensitivity (Se) is of 56% only.[5] A CEA <5 ng/mL suggests an SCA or PPC (Se, 50%; specificity [Sp], 95%). A CEA >800 ng/mL strongly suggests MCA or MCA carcinoma (Se, 48%; Sp, 98%).[6] Recently, there has been growing interest in the diagnostic performances of the pancreatic cyst fluid level of glucose (cystic glucose). In 2013, a previous metabolomic study of pancreatic cystic fluid identified 2 discriminant biomarkers for mucinous PCN, including glucose (and kynurenine).[7] The glucose assay has been well established in various biological fluids (serum, plasma, urine, cerebrospinal) with a very good reproducibility. Conversely, CEA assay is in theory validated only in serum. Further, CEA value can vary across laboratories and assay kits. Finally, the cost of CEA assay is approximately 4-fold higher than that of glucose. Performances of glucose for the diagnosis of mucinous pancreatic cyst have been rarely compared with those of CEA. In a recent meta-analysis including 8 comparative studies,[5] the pooled Se of a glucose level ≤50 mg/dL for the diagnosis of mucinous tumors was 90%, and the Sp was 85%.[5] To date, there are no data in France regarding this biomarker in pancreatic cyst fluid. The aim of the present study is to compare diagnostic performances of glucose to those of CEA for the identification of mucinous pancreatic tumors.

METHODS

Patients

Medical records of all patients who underwent EUS-guided FNA of a pancreatic cyst between 2018 and 2022 in seven French centers were retrospectively reviewed. Fine-needle aspiration was performed either for therapeutic (PPC drainage) or diagnostic (undetermined pancreatic cyst) purposes. Pancreatic cyst fluid level of glucose was routinely evaluated in addition to CEA. This study was performed in accordance with the ethical standards of the declaration of the Helsinki. The study was approved by our local ethics committee (IRBN862022/CHUSTE).

Definition of the definitive diagnosis

Pancreatic cysts were classified as mucinous or nonmucinous. This classification was performed either prospectively by a senior gastroenterologist or retrospectively by 3 reviewers (a senior gastroenterologist, a radiologist, and a digestive surgeon) blinded for the glucose level. Only cases with a definitive diagnosis (ie, mucinous or nonmucinous) were included for the evaluation of the diagnostic performances of cyst fluid glucose level.

Definitive diagnosis of pancreatic cysts included (i) all pancreatic cysts with cytopathology diagnosis (surgical resection of IPMN and/or IPMN with malignant transformation); (ii) all cysts that were drained because of symptoms (PPCs, wall-off necrosis [WON]); and (iii) all pancreatic cysts for which the definitive diagnosis was performed after EUS-FNA, basing on clinical and radiological criteria by reviewers, or via needle-based confocal laser endomicroscopy performed during the follow-up. For (ii) and (iii), a minimum follow-up of 6 months was required to support the final diagnosis. Intraductal papillary mucinous neoplasm, malignant IPMN, and MCA were classified as mucinous. All the other pancreatic cysts were classified as nonmucinous tumors.

End point and statistical analysis

The primary objective was to compare cyst fluid glucose and CEA levels in terms of diagnostic performances to identify mucinous lesions. The primary end point was the area under the receiver operating characteristic curve (AUROC) to determine the Se, Sp, accuracy (Acc), positive predictive value (PPV), and negative predictive value (NPV). Glucose and CEA diagnostic performances were compared using the Delong method. $P < 0.05$ was considered as statistically significant. The optimal threshold of glucose for the diagnosis of mucinous tumors was identified using the Youden index. The threshold used for CEA was 192 ng/mL, in accordance with published data.[5]

Quantitative variables were reported as median value with their interquartile ranges (IQRs) from 25% to 75% and compared by using Mann-Whitney-Wilcoxon test. Qualitative variables were reported as numbers and percentages and compared by using χ^2 or Fisher exact test as appropriate. Factors associated with a high level of cystic fluid glucose were assessed by logistic regression. All statistical analyses were performed using RStudio software version 3.2.2 (R project, Auckland, New Zealand), version 1.3.1056, and the pROC package.[8]

RESULTS

Population study

During the 2018–2022 period, a total of 121 patients underwent EUS-guided FNA with cyst fluid glucose and CEA level measurement in 7 centers. This included 15 patients (12.4%) with PPC drainage. Pancreatic cystic neoplasms were located in the body ($n = 28$) or the tail ($n = 38$) of the pancreas in 54.5% of cases. Glucose and CEA level assay failed in 8 (6.6%) and 16 (13.2%) of cases, respectively ($P = 0.13$). Definitive diagnostic was certain in 81 cases (68.7%), as per our defined criteria, including 19 (23.4%) based on cytologic or pathological findings (12 surgical resections, 1 needle-based confocal laser endomicroscopy, 6 nonsurgical malignant IPMNs), 33 (40.7%) based on imaging findings at baseline, and 21 (25.9%) based on imaging findings during follow-up.

Hence, of 121 patients, 81 were included for the evaluation of glucose diagnostic performances and comparison with CEA. The main characteristics are reported in Table 1. There were 46 mucinous tumors, including 33 IPMNs (71.7%), 8 malignant IPMNs (17.4%), and 5 MCAs (10.9%). There were 35 other pancreatic cysts as considered in the nonmucinous tumor group, including 15 PPCs (42.9%), 13 SCAs (37.1%), and 7 rare cysts (20.0%; 2 simple cysts, 2 mesenteric cyst lymphangiomas, 1 cystic dystrophy in heterotopic pancreas, 1 WON, 1 cystic metastasis of kidney cancer). Patients' age (49 *vs.* 71.5 years old, $P < 0.01$), tail localization (42.9% *vs.* 17.4%, $P = 0.01$), and tumor median size (40.0 *vs.* 26.0 mm, $P < 0.001$) were statistically different between both groups (nonmucinous *vs.* mucinous). Conversely, there was no difference between the 2 groups in terms of sex ratio (approximately 1) and the macrocystic (67.9%), microcystic (24.7%), or mixed (7.4%) feature of the tumor.

Comparison glucose vs. CEA

Distribution of glucose and CEA values are reported in Table 1 and Figure 1. The median level of cystic glucose was lower in the mucinous group (5.1 mg/dL; IQR, 1.8–10.9 mg/dL) than in the nonmucinous group (77.3 mg/dL; IQR, 58.2–101.5 mg/dL; $P < 0.001$). Conversely, the median level of cystic CEA was higher in the mucinous group

Table 1

Comparison of main characteristics between mucinous and nonmucinous pancreatic tumors.

Variables	Mucinous tumors (*n* = 46)	Other pancreatic cysts (*n* = 35)	*P*
Age, y	71.5 [60.8–78]	49 [41–57]	<0.01
Sex, male, *n* (%)	22 (47.8)	18 (51.4)	0.82
Follow-up, median [IQR], mo	4.6 [0.3–17.8]	2.6 [0–11.5]	0.42
Tumor size, mm	26 [19.2–35]	40 [30–70]	<0.001
Unilocular tumors, *n* (%)	31 (67.4)	23 (65.7)	1
Loci features, *n* (%)			0.28
Macrocyst tumors	28 (60.9)	27 (77.1)	
Microcyst tumors	14 (30.4)	6 (17.1)	
Mixed tumors	4 (8.7)	2 (5.7)	
Tumor localization, *n* (%)			0.01
Head	11 (23.9)	13 (37.1)	
Uncus	5 (10.9)	1 (2.9)	
Isthmus	10 (21.7)	2 (5.7)	
Body	12 (26.1)	4 (11.4)	
Tail	8 (17.4)	15 (42.9)	
Surgical resection, *n* (%)	7 (15.2)	5 (14.3)	1
Need for nCLE: yes, *n* (%)	4 (8.7)	5 (14.3)	0.71
Glucose, median [IQR], mg/dL	5.1 [1.8–10.9]	77.3 [58.6–101.5]	<0.001
CEA, median [IQR], ng/mL	103.5 [31.4–676.1]	7.6 [0.5–43.3]	<0.001
Amylase, median [IQR], IU/L	1480 [125–37,311.8]	4277.5 [85–25,773.8]	0.99

CEA: carcinoembryonic antigen; IQR: interquartile range; nCLE: needle-based confocal laser endomicroscopy.

(103.5 ng/mL; IQR, 31.4–676.1 ng/mL) than in the nonmucinous group (7.6 ng/mL; IQR, 0.5–43.3 ng/mL; $P < 0.001$). Distribution of values for each type of cyst is reported in Supplementary Figure 1, http://links.lww.com/ENUS/A340.

Based on the AUROC and the Youden test, the optimal threshold of cystic glucose for the diagnosis of mucinous tumor was <41.8 mg/dL, with Se, Sp, Acc, PPV, and NPV of 95.3%, 91.2%, 93.5%, 93.2%, and 93.9%, respectively [Figure 2]. The corresponding diagnostic performances for CEA >192 ng/mL were an Se of 41.7%, an Sp of 96.9%, an Acc of 67.6%, a PPV of 93.8%, and an NPV of 59.6%, respectively. The AUROC of glucose was higher than that of the CEA: 93.6% (95% confidence interval [CI], 87.2%–100%) *versus* 81.2% (95% CI, 71.3%–91.1%) ($P = 0.035$).

There was no additional benefit in terms of diagnosis by combining values of glucose and CEA. Considering glucose <41.8 mg/dL or

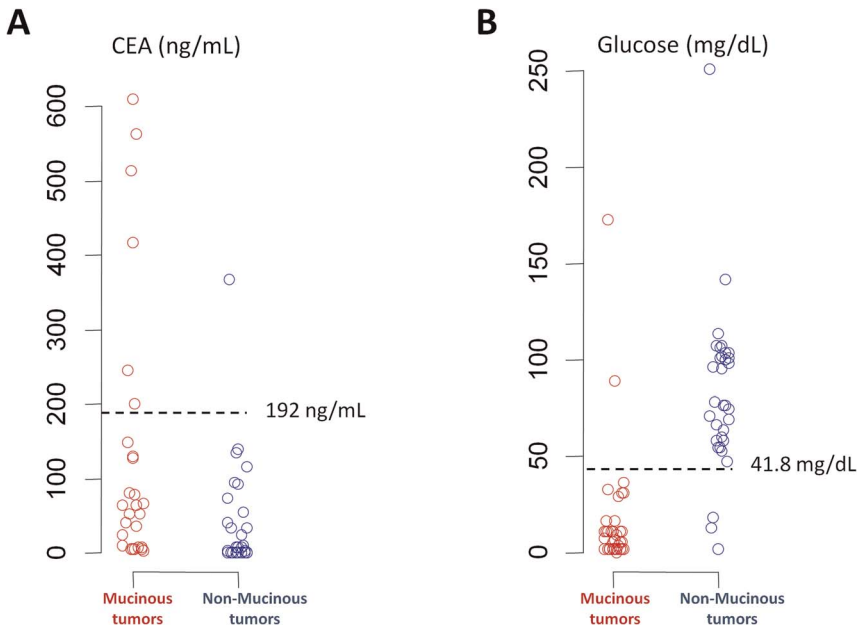

Figure 1. Levels of carcinoembryonic antigen (A) and glucose (B) in mucinous and nonmucinous pancreatic tumors.

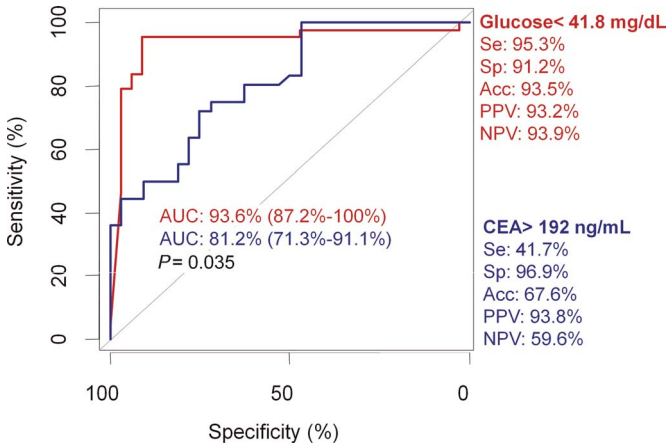

Figure 2. Comparison of glucose and carcinoembryonic antigen for their ability to identify mucinous tumors using the area under the receiver operating characteristic curve.

CEA >192 IU/L, the corresponding diagnostic performances were very close to those of glucose alone (Se, 95.3%; Sp, 87.5%; Acc, 92.0%; PPV, 91.1%; and NPV, 93.3%). Similarly, considering glucose <41.8 mg/dL and CEA >192 IU/L, the corresponding diagnostic performances were very close to those of CEA alone (Se, 41.7%; Sp, 100%; Acc, 70.0%; PPV, 100%; and NPV, 61.8%).

Factors associated with high level of cystic fluid glucose

In univariate analysis, nonmucinous tumors ($P < 0.001$), tail of pancreas lesion ($P = 0.023$), lesion size >30 mm ($P = 0.006$), age as continuous variable ($P < 0.001$), and CEA >192 ng/mL ($P = 0.005$) were associated with a cystic glucose level higher than 41.8 mg/dL. Blood contamination in fluid aspiration ($n = 10$) was not associated with high glucose level ($P = 0.65$). After multivariate analysis, nonmucinous lesion was the only factor significantly associated with a cyst glucose level higher than 41.8 mg/dL (odds ratio, 73.6; 95% CI, 8.6–1891.7; $P = 0.001$).

DISCUSSION

This is the first cohort reporting the performance of cystic glucose in the diagnosis of pancreatic mucinous tumors in France. In this multicenter study, our results concurred with previously published data. A low level of cystic glucose allows the identification of mucinous tumors with a very high Se (approximately 95%) and a good Sp (approximately 90%). Our results also show that the optimal threshold of cystic glucose ranges between 40 and 50 mg/dL. In a recent systematic review including 8 comparative studies, a low cystic glucose (<40 or 50 mg/dL according to studies) was associated with a higher pooled Se (91%) compared with CEA alone (56%; $P < 0.001$) with no difference in Sp (86% *vs.* 96%; $P > 0.05$).[5] The corresponding diagnostic Acc was significantly higher for cystic glucose *versus* CEA (94% *vs.* 85%; $P < 0.001$), which also concurs with our data.[5] Studies like ours are necessary to enhance scientific evidence. Our study, conducted across multiple expert centers, is the first of its kind in France. Previous cohort studies have mainly been conducted in Italy and the United States.[9–12] Through this study, we confirmed the high diagnostic Acc of glucose for identifying pancreatic mucinous tumors, as previously reported. However, we did not find any additional benefit of combining glucose with CEA for this purpose.

We additionally report outcomes in PPCs, rarely reported yet. Except one, all of these PPCs were associated with a high level of intracyst glucose. Finally, we assessed for the first time the potential impact of blood contamination on glucose and CEA levels in our samples. Although there were only a few samples with blood contamination ($n = 10$), we observed that the presence of a small amount of blood in the pancreatic sample did not appear to have an effect on the results (in univariate analysis: $P = 0.65$). Because these 10 patients were from a single center, it is possible that this feature of the cystic fluid was overestimated by clinicians, which could explain why the results were not affected by it.

Cystic glucose assay thus appears interesting in several ways: (i) its higher diagnostic performances, especially in terms of Se for mucinous tumors, compared with cystic CEA or the string-sign; (ii) its better reproducibility across laboratories and assay kits; and (iii) its lower cost compared with CEA assay.[13] Finally, according to the laboratory technicians, there is no potential impact on the glucose measurement results in pancreatic fluid as long as the sample is collected and sent to the laboratory within 4 hours at ambient temperature, which is the case in the vast majority of facilities. For instance, in France, the cost of CEA assay is close to 12.42 €, whereas glucose assays costs 2.7 €.[13] Finally, substantial data exist in favor of next-generation sequencing for the definitive diagnosis of pancreatic cysts,[14] especially in preoperative settings.[15] *KRAS*/*GNAS* mutations are detected in 100% of IPMNs but only in 30% of MCAs. However, next-generation sequencing of the pancreatic cyst fluid is not performed routinely in France. Hence, intracystic glucose could constitute an alternative. The feasibility of glucose level measure by a glucometer and its good correlation with values obtained by a laboratory assay have been reported.[9,10,16] However, the 2018 guidelines recommended intracyst CEA assay in addition to cytology.[1,2] Data on intracystic glucose were scarce when these guidelines were published. It is likely that the updated guidelines will support the use of cyst fluid glucose level to identify mucinous pancreatic tumors.[17] If cystic glucose were routinely used in clinical practice, a glucometer could allow rapid on site diagnosis, with a higher Se compared with the string sign.[9,10,16] However, further prospective studies are needed before this practice becomes routine.

There are no robust scientific data to explain that the mucinous lesions (MCNs, IPMNs, and malignant IPMNs) have lower cystic glucose content compared with the nonmucinous lesions. Previous studies evaluating the diagnostic performance of ^{18}F-FDG PET/CT in differentiating malignant from benign pancreatic cysts have suggested that glucose consumption is higher in IPMN with carcinoma than IPMN with adenoma lesions (maximum standard unit values were correlated with the histopathological types: Spearman rank correlation, 0.865; $P < 0.0001$).[18–20] However, the corresponding studies designed to differentiate mucinous from nonmucinous PCN have not yet been conducted, and it is unlikely that ^{18}F-FDG PET/CT was sensitive and specific enough for such nonmalignant lesions. The idea that glucose consumption may be higher in mucinous (preneoplastic) lesions than in nonmucinous lesions (normal cells) remains hypothetical and is based on glucose concentration levels in pancreatic cysts, as evaluated in the present study. This remains the most plausible explanation for this reliable finding to date. Like malignant lesions, it is widely accepted that infectious or inflammatory foci are associated with a high maximum

standard unit value on ^{18}F-FDG PET/CT, indicating high glucose consumption. However, there are no data regarding glucose levels in such pancreatic cysts. Although there were some PPCs that were drained in our study, the indication was to alleviate patients' pain or digestive discomfort. There were no infected pancreatic cysts in our cohort. Except one, all of these PPCs were associated with a high level of intracyst glucose. The only one inflammatory pancreatic cyst was the WON whose final diagnosis was obtained after surgical resection. The presentation of this WON was indeed unique, with no known history of acute pancreatitis, and its imaging features were suggestive of malignancy. Its glucose level was low (<41.8 mg/dL), which supports the hypothesis of overconsumption of glucose in an inflammatory pancreatic cyst.

One of the limitations of our study is its retrospective design in addition to the definition of the final diagnosis that is not exclusively based on pathologic analyses. Moreover, we included numerous cyst lesions that did not raise questions about their diagnosis, especially PPC that was endoscopically drained. However, the surgical series also have their limits (represents only a minority of cystic lesions, therefore risk of bias linked to the dropout). The ideal study design would be to prospectively include only unilocular macrocystic lesions of the pancreas and to obtain their definitive diagnosis by surgical resection analysis, which is not ethically acceptable, because most of them do not require surgery.

In conclusion, our study suggests that a low level of cystic glucose is an efficient marker of pancreatic mucinous tumors, with no major additional cost or additional risk compared with current practice. These results concur and add to the existing literature. Prospective studies are warranted. Future guidelines on the diagnosis of cystic pancreatic tumors will likely suggest cystic glucose assay as a useful tool.

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Conflicts of Interest

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Ethical Approval

The study was approved by the authors' local ethics committee (IRBN862022/CHUSTE).

Author Contributions

Nicolas Williet was responsible for conception of the study, study supervision, literature review, data collection, statistical analyses, and drafting the manuscript. Fabrice Caillol, David Karsenti, Einas Abou-Ali, Marine Camus, Arthur Belle, Ulriikka Chaput, Jonathan Levy, Jean-Philippe Ratone, Quentin Tournier, Rémi Grange, and Bertrand Le Roy performed data collection and critical review of the manuscript. Aymeric Becq did the data collection, critical review of the manuscript, and review of English Language. Jean-Marc Phelip was responsible for interpretation of data and critical review of the manuscript.

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