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Comparison of Fasting Human Pancreatic Polypeptide Levels Among Patients With Pancreatic Ductal Adenocarcinoma, Chronic Pancreatitis, and Type 2 Diabetes Mellitus

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Abstract

Objectives: Human pancreatic polypeptide (HPP) is a hormone secreted by the ventral pancreas. While postprandial HPP levels have been studied in chronic pancreatitis (CP) and pancreatic ductal adenocarcinoma (PDAC), there are limited data on fasting HPP in these diseases.

Methods: Fasting serum HPP was measured in the following groups of patients: CP with diabetes mellitus (DM) (n = 16), CP without DM (n = 34), PDAC with new-onset DM (n = 50), PDAC without DM (n = 49), new-onset type 2 DM (n = 50), and controls without DM (n = 49). Sixty-six had type 3c DM (CP with DM, n = 16; PDAC with new-onset DM, n = 50).

Results: Median fasting HPP levels (in picograms per milliliter) were similar among all groups. Median (interquartile range) HPP levels in new-onset type 2 DM (n = 50; 288.3 [80.1–1072.1]) were similar to those in type 3c DM (n = 66; 242.3 [64.9–890.9]) ($P = 0.71$). In PDAC (n = 99), HPP values were similar in pancreatic head (n = 75) versus body/tail (n = 24) tumors (245.3 [64.3–1091.3] vs 334.7 [136.1–841.5]; $P = 0.95$), regardless of DM.

Conclusions: Fasting HPP levels are similar in CP, PDAC, and controls regardless of glycemic status.

Keywords

chronic pancreatitis; pancreatic cancer; pancreatic polypeptide; type 3c diabetes mellitus

The term type 3c diabetes mellitus (type 3c DM) has been increasingly used to describe diabetes resulting from disorders of the exocrine pancreas. The term mirrors the use of type 1 and type 2 to describe the more common forms of diabetes. In an earlier version of etiologic classification of DM by the American Diabetes Association, other disorders of the exocrine pancreas causing diabetes (pancreatogenous diabetes) listed in section IIIC include

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pancreatitis, trauma/surgery, neoplasia, cystic fibrosis, and so on.[1] Clinically, chronic pancreatitis (CP) (78%) and pancreatic ductal adenocarcinoma (PDAC) (8%) constitute the 2 leading causes of type 3c DM.[2] Although this nomenclature groups all causes of pancreatogenous diabetes together, the pathophysiology of diabetes resulting from these conditions may be different.[3] Whereas new-onset diabetes secondary to PDAC is believed to be a paraneoplastic phenomenon that manifests 2 to 3 years prior to cancer diagnosis, patients with CP have progressive insulin deficiency with pancreatic endocrine and exocrine function worsening concurrently.[3,4] Because, type 2 DM (T2DM) is much more prevalent, type 3c DM is often misdiagnosed as T2DM.[5] This can have a particularly significant impact for those with type 3c DM secondary to PDAC as early detection is the only reliable means of achieving a good outcome. Therefore, it is critical to distinguish not only type 3c DM from T2DM overall but also new-onset DM (T2NOD) associated with PDAC (PDAC-NOD) from DM associated with CP (CP-DM).

Human pancreatic polypeptide (HPP) is a hormone predominantly secreted by the F cells in the pancreatic islets[6,7] and has been studied in patients with CP and PDAC.[6–11] It has also been proposed as a biomarker for pancreatogenous DM.[12] Studies have not compared HPP in patients with PDAC, CP, and T2DM. Moreover, there are limited data on the comparison of fasting HPP levels in these conditions. Therefore, we aimed to compare fasting levels of HPP in patients with CP and PDAC, stratified by DM status with patients with new-onset T2DM and healthy controls. We also compared fasting HPP levels in patients with type 3c versus T2DM.

MATERIALS AND METHODS

The study was approved by Mayo Clinic Institutional Review Board. A total of 250 patients were included in the study. All subjects were enrolled in the database of the Mayo Clinic Specialized Program of Research Excellence in pancreas cancer. The patients belonged to one of the following groups: CP (n = 50), PDAC with new-onset DM (PDAC-NOD) (n = 50), PDAC without DM (PDAC-noDM; n = 50), new-onset T2DM (NOD; n = 50), and controls without DM (Ctrl; n = 50). Patients with CP were further divided into those with DM (CP-DM; n = 16) and without DM (CP-noDM; n = 34). Pancreatic ductal adenocarcinoma was histo-logically confirmed in 94% of subjects. Fasting HPP levels were measured using the EZ-HPP 40 K ELISA kit (EMD Millipore, Burlington, Mass). In 21 samples (2 CP, 5 NOD, 1 Ctrl, 11 PDAC-NOD, and 2 PDAC), HPP levels fell below the lower detection threshold of the assay and were reported as “<15.6.” The intra-assay coefficient of variability was 2.91%. For the purpose of analysis, these samples were recorded as a numeric variable with a value of 15.599. Type 2 DM was defined by the American Diabetes Association criteria.[8] Patients with PDACNOD and CP-DM were classified as type 3c DM. Age, body mass index, and fasting blood glucose are summarized using mean (standard deviation [SD]). A 2-sample t-test was used for comparisons between groups. Sex and medication use are summarized using frequency and percent, with a χ^2 test used for comparisons between groups. Human pancreatic polypeptide levels across groups are summarized with median (interquartile range [IQR]), and a Wilcoxon rank sum test was used to compare levels between groups. Analyses were performed using an institutionally licensed copy of JMP Pro 10.0.0 (SAS Institute, Cary, NC; 2012).

RESULTS

Patient Characteristics

Mean age (SD) of patients with CP without DM (CP-noDM) was lower (53.03 [16.28]) than that of patients with CP-DM (63.12 [15.97]), PDAC-NOD (64.58 [9.47]), PDAC-noDM (63.98 [10.37]), T2NOD (65.26 [7.67]), and controls (65.46 [9.82]) ($P < 0.001$). There was no significant difference in the sex distribution between the groups. All patients were white. Pancreatic ductal adenocarcinoma was histologically confirmed in 94%. Details of demographics and diabetes medication use among the study subjects are detailed in Table 1.

Comparison of HPP Levels in Patients With PDAC, CP, Type 2 DM, and Controls

Median (IQR) fasting HPP levels (in picograms per milliliter) were similar among the groups and are as follows: PDAC-NOD: 242.31 (32.38–797.12), PDAC–noDM: 253.23 (136.52–1342.05), CP–DM: 303.78 (142.63–2295.75), CP–noDM: 235.04 (94.58–816.77), T2NOD:288.32(80.12–1072.06), and controls:493.26(193.90–2129.44) ($P = 0.73$) (Fig. 1).

Comparison of HPP Levels in Patients With Type 3c Versus Type 2 DM

There were 66 subjects with type 3c DM (CP-DM 16 and PDAC-NOD 50) and 50 with T2DM. Human pancreatic poly-peptide levels were not significantly different in patients with type 3c DM versus T2NOD (252.23 [64.71–925.31] vs 288.32 [80.12–1072.06], respectively; $P = 0.9351$). The corresponding receiver operating characteristic curves demonstrate that HPP levels are not able to reliably distinguish (*a*) patients with PDAC from patients with new-onset T2DM and healthy controls (Fig. 2) and (b) patients with PDAC from those with CP (Fig. 3).

Effect of Tumor Location on HPP Levels

In patients with PDAC (n = 99), median (IQR) HPP values were not significantly different in patients with head (n = 75) versus body/tail (n = 24) tumors (245.30 [64.29–1091.63] vs 334.74 [136.13–841.46], respectively; $P = 0.95$). This remained true for PDAC patients with and without new-onset DM. The proportion of patients with HPP levels below the detection threshold (ie, 15.599) was not different in those with head versus body/tail tumors (11/75 [14.67%] for head tumors vs 2/24 [8.33%] for body/tail tumors; $P = 0.7288$).

DISCUSSION

In this large single-center study, we compared fasting levels of HPP among patients with PDAC with and without new-onset DM, CP with and without DM, new-onset T2DM, and healthy controls. Our data show that fasting HPP levels cannot reliably distinguish among these patients.

Human pancreatic polypeptide secretion is increased by nutrients; hormones such as gastrin, secretin, and cholecystokinin; gastric distension; insulin-induced hypoglycemia; and vagal stimulation, whereas hyperglycemia, somatostatin, and vagal inhibition reduce HPP secretion.[11] We have previously demonstrated that the postprandial HPP response to a mixed meal administration is blunted in patients with PDAC with head tumors. This was thought to

be secondary to destruction or disruption of the ventral pancreas, where HPP is predominantly secreted.[9] Skrha et al[10] have also demonstrated lower mean values of fasting HPP in patients with PDAC as compared with those with T2DM. However, in this larger subset of patients, fasting values of HPP did not differ in patients with PDAC from those with T2NOD. Moreover, there was no difference in HPP values among patients with head versus body/tail tumors. Human pancreatic polypeptide levels were also similar between patients with PDAC-NOD and T2NOD, which argues in favor of PDAC-NOD having an overall pathophysiology similar to T2DM, despite being a subtype of type 3c DM. Also in support of this argument is the fact that in PDACNOD both decreased beta cell function and increased insulin resistance have been demonstrated, and these are also seen in T2DM at advanced stages.[13,14] Mediators such as adrenomedullin have been proposed to have a role in PDAC-NOD, and adrenomedullin from exosomes has been found to interact with its receptors on beta cells, leading to their dysfunction.[15–17] However, why PDAC-NOD continues to worsen despite ongoing weight loss is not clear, as opposed to T2DM where in general weight loss improves glucose tolerance.

Even though the precise physiologic effects of HPP have not been elucidated, HPP is known to be associated with modulation of body weight. In a study by Ueno et al,[18] transgenic mice that overexpressed HPP showed reduced weight gain and decreased fat mass due to reduced appetite leading to markedly decreased oral intake. These phenotypic changes were seen to be reversed upon immunoneutralization with anti-PP serum.[18] Considering the possible role of HPP in inducing weight loss, long-acting analogs of HPP have been proposed for the treatment of obesity.[19] Patients with CP and PDAC also have significant weight loss. While patients with CP have malabsorption, weight loss in patients with PDAC precedes diagnosis by approximately 1 year, at a stage when patients are otherwise asymptomatic.[20] This weight loss has been demonstrated to be a result of a preferential loss of subcutaneous adipose tissue over visceral adipose tissue.[21] However, whether HPP directly causes lipolysis or affects the subcutaneous adipose tissue and visceral adipose tissue compartments differentially has not been studied. Interestingly, Skrha et al[10] demonstrated that the lowest HPP values were found in patients who lost the most weight. This was thought to be related to increased expression of proteases such as fibroblast activation protein α and dipeptidyl peptidase 4 in pancreatic cancer tissue.[22] However, the authors also acknowledged that an increased expression of proteases in cancer tissue cannot explain the fact there was no difference in concentrations of GLP-1, PYY, and NPY in patients with PDAC as compared with T2DM, which were also studied on the same patients at the same time as HPP.

To our knowledge, this is the first study comparing values of fasting HPP in patients with CP-DM and PDAC-NOD, which are both subtypes of type 3c DM. Even though CP-DM is the most common etiologic factor for type 3c DM, it is crucial to distinguish these patients from those who develop NOD from underlying PDAC. Clinically, type 3c DM from underlying CP is usually accompanied by evidence of exocrine dysfunction as well.[3,4] In contrast, those with PDAC-NOD tend to be asymptomatic or have vague symptoms until they reach advanced stages. Therefore, it is crucial to identify mediators that can help detect PDAC-NOD early by distinguishing it from other forms of type 3c DM.

Our study has several limitations. Despite being the largest study comparing these subgroups, our study is limited by small numbers, especially in patients with CP, out of which only 16 had DM attributable to CP. A larger number of patients with CP-DM might be required to definitively compare CP-DM from PDAC-NOD. Our study was also limited by the detection threshold of the assay used; 21 patients had HPP levels below the measurable threshold. Thirteen of these 21 patients had PDAC (including 11 with PDAC-NOD). We compared the proportion of patients with head versus body/tail tumors that had HPP levels below the detection threshold of the assay and found no difference. However, it is still possible that if we had the true values of HPP available for these patients, differences between the comparison groups would become apparent. Finally, we measured fasting levels of HPP for the purpose of this study. Although a fasting state also affects levels of HPP, it is not known if the post-prandial levels or response to feeding would be different in these subgroups when compared with each other.

Therefore, we conclude that fasting levels of HPP cannot be used to distinguish PDAC-NOD from new-onset T2DM as well as type 3c DM. Pancreatic polypeptide response to mixed meal may be a better biomarker to help distinguish type 3c DM from underlying PDAC and CP, as well as from type 2 NOD, and act as the second “sieve” to enrich a population that can then be targeted for screening for PDAC.

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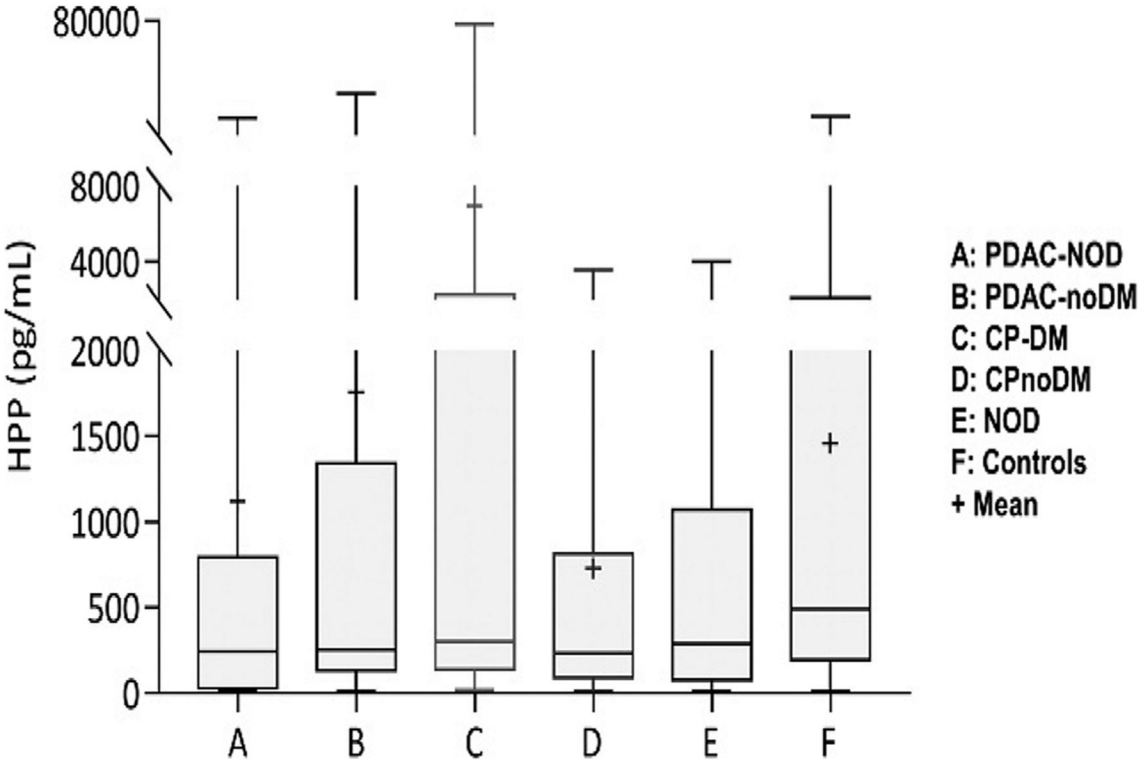

FIGURE 1.

Box-whisker plot comparing the values of fasting HPP (in picograms per milliliter) between groups (A = PDAC-NOD, B = PDAC-noDM, C = CP-DM, D = CPnoDM, E = NOD, and F = controls) ($P = 0.73$). Horizontal bars represent median.

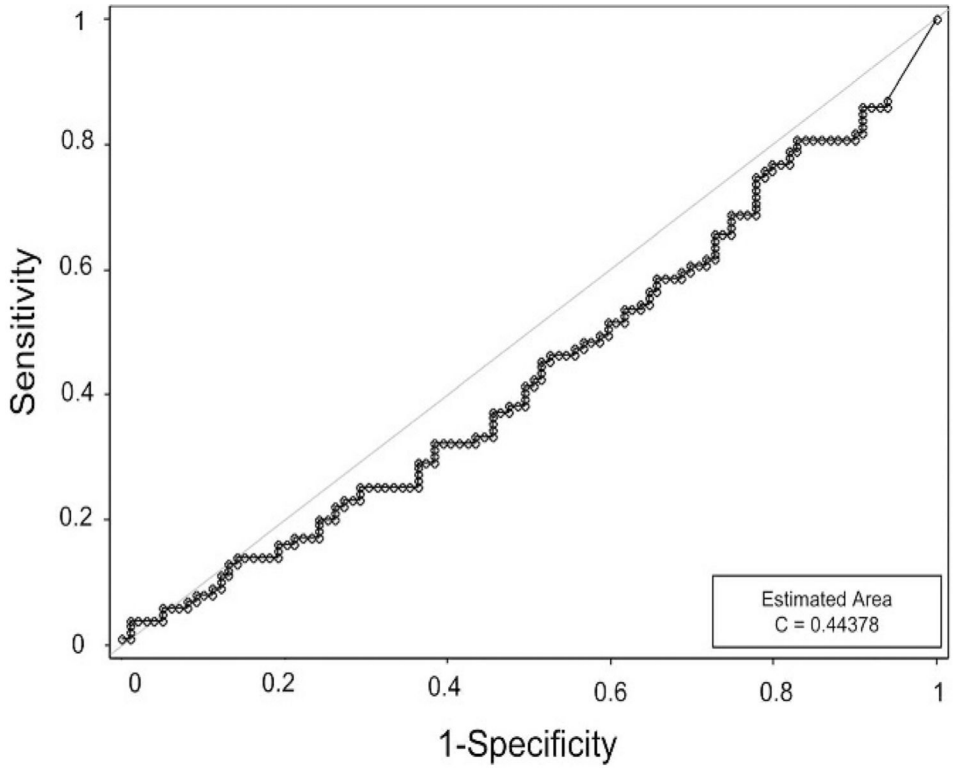

FIGURE 2.

Receiver operating characteristic curve demonstrating the accuracy of HPP in distinguishing patients with PDAC (n = 99; 49 with NOD and 50 without DM) from patients with type 2 NOD (n = 49) and controls (n = 50) (total n = 99).

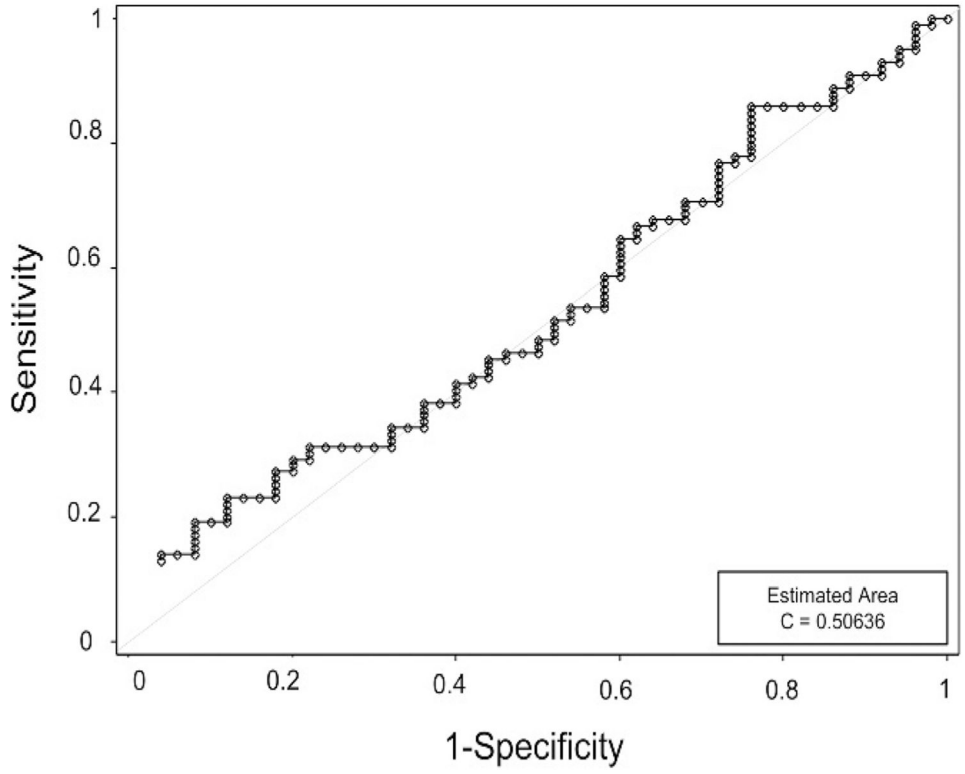

FIGURE 3.

Receiver operating characteristic curve demonstrating the accuracy of HPP in distinguishing patients with PDAC (n = 99; 49 with NOD and 50 with noDM) from patients with CP (16 with DM and 34 with noDM).

TABLE 1.

Demographic Characteristics and Medication Use of the Study Population

	PDAC-NOD n = 50	PDAC-noDM n = 50	CP-DM n = 16	CP-NoDM n = 34	Type 2 NOD n = 50	Controls n = 50	*P*
Age, mean (SD), y	64.58 (9.47)	63.12(15.97)	63.98 (10.37)	53.03 (16.28)	65.26 (7.67)	65.46 (9.82)	**<0.0001**
Body mass index, mean (SD), kg/m^2	26.72 (4.13)	26.07(5.18)	25.01 (4.50)	25.51 (5.13)	31.22(5.11)	26.22 (4.05)	**<0.0001**
Sex, male, n (%)	35/50 (70)	35/50 (70)	11/16(68.75)	17/34(50)	35/50 (70)	35/50 (70)	0.41
Fasting glucose, mean (SD), mg/dL	163.88 (58.39)	109.06(27.25)	177.75(70.12)	101.82(10.79)	150.98 (25.40)	82.94 (3.55)	**<0.0001**
Insulin use, n (%)	7/20 (35)	0/8 (0)	2/5 (40)	0/3 (0)	5/18(27.78)	0/3 (0)	0.08
OHA use, n (%)	12/23(52.17)	0/9 (0)	3/5 (60)	0/3/(0)	14/19(73.68)	0/4 (0)	**<0.001**

Bold font indicates statistical significance.

OHA indicates oral hypoglycemic agent.