Early Alterations in Glycemic Control and Pancreatic Endocrine Function in Nondiabetic Patients With Chronic Pancreatitis

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Objectives: Diabetes mellitus is a frequent consequence of chronic pancreatitis (CP). Little is known about pancreatic endocrine function before the development of diabetes mellitus in CP, particularly in females, or those without calcific and/or alcoholic pancreatitis.

Methods: Twenty-five nondiabetic adult patients with CP (19 female; mean [SE] age, 34.2 [2.4] years) were compared with 25 healthy controls matched for age, sex, and body mass index. Subjects underwent frequent sample intravenous glucose tolerance testing (FSIVGTT) and mixed meal tolerance testing (MMTT).

Results: Mean (SE) fasting glucose was higher in patients with CP (89.5 [2.3] mg/dL) than in controls (84.4 [1.2] mg/dL, $P = 0.04$). On MMTT, patients with CP had a higher area under the curve (AUC) glucose and AUC glucagon compared with controls ($P \leq 0.01$). The AUC C-peptide was equivalent ($P = 0.6$) but stimulated C-peptide at 30 minutes was lower in patients with CP ($P = 0.04$). Mean insulin sensitivity index calculated from the FSIVGTT was lower in CP group, indicating reduced insulin sensitivity ($P \leq 0.01$). Disposition index (insulin secretion adjusted for insulin sensitivity on FSIVGTT) was lower in patients with CP ($P = 0.01$).

Conclusions: Patients with CP had higher fasting and MMTT glucose levels, without a compensatory increase in insulin secretion suggesting subtle early islet dysfunction. Our cohort had relative hyperglucagonemia and was less insulin sensitive than controls.

Key Words: β cell, pancreatitis, diabetes, total pancreatectomy and islet autotransplantation, pancreatectomy, islet

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Chronic pancreatitis (CP) is an inflammatory condition that causes permanent structural damage to the pancreas. Although it is severe abdominal pain that generally brings the disease to clinical attention, diabetes mellitus (DM) is an important and frequent consequence.[1–5] The lifelong risk of developing DM in the setting of CP is estimated at 25% to 75%[6–9] and depends in part on previous surgical resection, etiology of disease, and extent of pancreatic damage, with exocrine insufficiency and calcifications as important markers of the latter.[7–11]

Compared with type 1 and type 2 DM, very few clinical studies exist to characterize the pathophysiology and natural history of DM in CP. Impaired insulin responses to oral and intravenous (IV) secretagogues have been observed in those with DM and CP[6,10,12] and in a handful of patients with normal glucose tolerance and CP.[10] However, these studies included nearly all male patients, usually with alcohol-induced pancreatitis and with late calcific CP. More than half of CP cases are due to causes other than alcohol, and women are frequently affected.[13] This important demographic has been overlooked. Moreover, glucose homeostasis is regulated by multiple other factors; mixed data exist on the role of glucagon and prandial incretin responses as well as insulin sensitivity in metabolic control in this population.[4,6,14–20]

Little is known about the natural history of pancreatic endocrine function in CP before the onset of DM. It has been proposed that inflammation and an altered pancreatic milieu may cause β-cell dysfunction early in the disease course, with progressive loss of β cells leading to frank diabetic mellitus in a subset of patients.[21,22] The aim of this study was to advance our current understanding of the development of endocrine insufficiency in CP. Insulin secretion in response to oral and IV secretagogues, postprandial glucagon suppression, and the incretin axis were assessed in nondiabetic patients with CP and compared with the well-matched healthy controls. Moreover, we enriched our CP cohort with patients who have been underrepresented in earlier studies, including those with nonalcoholic disease, females, and patients who had not yet developed pancreatic calcifications. Better understanding of the progression from endocrine dysfunction to DM is critical to develop screening tools for early detection and intervention.

MATERIALS AND METHODS

Subjects

Twenty-five nondiabetic patients with CP and 25 healthy volunteers were studied in a matched case-control cross-sectional analysis. Patients with CP were recruited from a cohort of adult patients, aged 18 years or older, scheduled for total pancreatectomy and islet autotransplantation (TP-IAT) at the University of Minnesota from 2010 to 2012. All patients with CP were participants in a clinical trial, which included metabolic testing performed within 2 weeks before TP-IAT. Patients were considered ineligible for study participation if they had a previous diagnosis of DM, if they were using any antidiabetic medications at the time of study enrollment, if fasting blood glucose level was

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R.L. and M.D.B. constructed the design of the study, collected and analyzed data, and wrote the manuscript. G.J.B. constructed the design of the study and revised the manuscript. T.B.D., T.L.P., K.L.B., and P.E.P. participated in participant care, data collection for the study, and approval of final manuscript. M.L.F., R.P.R., and A.M. contributed to data interpretation, revised, and approved the manuscript. R.L. and M.D.B. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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greater than 115 mg/dL, or if hemoglobin A1c (HbA_{1c}) level was more than 6.0%.

All patients with CP were seen in consultation and clinical history was reviewed by a multidisciplinary team. The CP diagnosis before TP-IAT was based on at least one of the following, as previously described[1]: documented episodes of recurrent acute pancreatitis (amylase/lipase > 3 times upper limit of normal) with progression to characteristic chronic abdominal pain[2]; imaging or functional studies supporting CP (at least 2 tests abnormal among abnormal magnetic resonance cholangiopancreatography, ≥4 criteria on endoscopic ultrasound, or abnormal secretin-stimulated pancreatic function tests)[3]; pancreatic calcifications on computed tomography scan[4]; or histopathology-confirmed CP at time of previous surgery (if done).

Healthy control subjects were recruited from 2012 to 2013 through fliers and advertisements displayed around the community. Interested subjects were screened by phone or through e-mail for eligibility. Eligible healthy controls were matched to patients with CP on the basis of sex, age (±3 years), and body mass index (BMI) (±3 kg/m^2). Subjects were excluded if they had a history of any of the following: past or present use of insulin or oral antidiabetic mediation, DM, diagnosis of acute or CP, chronic unexplained abdominal pain, or use of corticosteroids in the past 6 months. Screening fasting glucose was obtained at time of informed consent.

The University of Minnesota Institutional Review Board (IRB) reviewed and approved the protocols (IRB Number 1006M83756 for CP group, IRB Number 1203M11602 for healthy control group). Informed consent was obtained from all participants.

Subject Demographics and Medical History

Basic demographic characteristics were collected for all participants. Additional data elements were obtained for all patients with CP including etiology of disease, duration of disease, presence of calcifications on imaging, previous pancreatic surgeries, previous endoscopic retrograde cholangiopancreatography procedures, and pancreatic enzyme supplementation status (as prescribed by managing physician). Height and weight were measured at time of enrollment of healthy controls to confirm BMI match before performing metabolic testing.

Metabolic Testing

Patients with CP and healthy controls underwent frequent sample intravenous glucose tolerance testing (FSIVGTT) and mixed meal tolerance testing (MMTT) on 2 mornings after an overnight fast of 10 hours or more. Subjects' weight and height (averaged on the basis of 3 measurements) were determined, and BMI (kg/m^2) was calculated.

Protocols for metabolic testing have been previously described.[23] On the morning of the FSIVGTT, 2 peripheral IVs were placed in antecubital fossa or large forearm vein 30 minutes before blood draws. Glucose, insulin, and C-peptide levels were measured at baseline fasting (in triplicate, with a mean value calculated for "time 0") and then measured at predefined intervals for 180 minutes. At time 0, dextrose 0.3 g/kg was given via IV push for 30 seconds. Immediately after the 20-minute draw, insulin, 0.025 U/kg, was given via IV push to augment glucose disposal. Insulin and C-peptide levels were then measured at 1, 2, 3, 4, 5, 7, and 10 minutes after dextrose injection. The acute C-peptide response to glucose (ACRglu) was calculated by the trapezoidal area under the curve (AUC) for the first 10 minutes after dextrose. The acute insulin response to glucose (AIRglu), insulin sensitivity index (SI), and disposition index (DI, AIRglu × SI) were calculated from insulin and glucose levels for the 180-minute period using MINMOD software.[24,25] Because adequate IV access was difficult to maintain in some patients with CP and hemolysis can compromise the accuracy of insulin immunoassay measures, we excluded patients with CP and their matched controls for respective analyses of AIRglu and/or SI if lacking adequate samples for insulin measures during necessary time points (resulting in matched pairs, n = 20 for AIRglu, n = 21 for SI).

The mixed meal tolerance test required placement of 1 peripheral IV 30 minutes before the first blood draw. At time 0, the patient consumed 6 mL/kg Boost HP to a maximum of 360 mL within 5 minutes. Patients on pancreatic enzyme therapy were instructed to take their usual dose with the Boost HP. Glucose, insulin, C-peptide, glucagon, gastric inhibitory peptide (GIP), and active glucagon-like peptide 1 (GLP-1) were measured at −1, +30, +60, +90, and +120 minutes. Area AUC for C-peptide (AUC C-peptide) and glucose (AUC glucose) were calculated using the trapezoidal method. One patient in the CP group was unable to complete the MMTT because of vomiting and was excluded from the MMTT analyses. The earliest 5 patients in our CP cohort did not have glucagon collected (n = 20 case-control pairs for AUC glucagon).

Plasma glucose levels were measured by glucose oxidase assay, and plasma C-peptide levels were measured by Siemen immunolite 2000 chemiluminescent immunoassay. Insulin levels were measured by 2-site immunoenzymometric assay on a TOSOH 2000 autoanalyzer.[26,27] Glucagon was measured by radioimmunoassay, active GLP-1 and GIP by ELISA fluorescent sandwich immunoassay (EMD Millipore Corp, Billerica, Mass). HbA_{1c} was obtained on day 1 of testing and analyzed by high-performance liquid chromatography.

Data Analysis

Data are presented as mean (SE). Statistical analysis was performed with SAS software version 9.2 (Cary, NC). Two-tailed paired Student *t* tests were used to compare matched case-control pairs. The DI was log adjusted to normalize for wide distribution of values in each group (46-fold difference in minimum vs maximal value). A subgroup analysis was performed for those with calcific versus noncalcific CP; nonparametric Wilcoxon rank sum test was used for subgroup analysis because of the small number of patients per group and nonpaired nature of the data. *P* values of 0.05 or less were considered statistically significant.

RESULTS

Patient Characteristics

Characteristics of the CP and control cohorts are displayed in Table 1. As expected by study design, sex, mean age, and mean BMI were similar in the 2 cohorts. Although BMI was equivalent, the patients with CP were on average shorter (165.7 [1.8] vs 170.9 [1.9] cm, $P = 0.02$) and weighed less (68.3 [3.2] vs 72.5 [3.0] kg, $P = 0.04$) compared with healthy controls. Seven patients (28%) with CP had calcific pancreatitis; the remaining patients were diagnosed with noncalcific CP on the basis of a combination of recurrent acute pancreatitis with clinical progression and/or supportive studies as described previously. Fourteen (56%) were on pancreatic enzyme replacement therapy.

Causes of pancreatitis were genetic (n = 10), idiopathic (n = 6), or obstructive (n = 9, congenital abnormality or sphincter of Oddi dysfunction). The patients with calcific CP all had genetic risk factors: 2 with protease serine 1, 3 with serine protease inhibitor Kazal type 1, and 2 with cystic fibrosis transmembrane conductance regulator mutations. Four patients (16%) had previous surgery, Puestow drainage procedure in 3, and pancreatic debridement and pseudocyst drainage in 1.

TABLE 1. Characteristics of the 25 Nondiabetic Patients With CP and the 25 Healthy Control Participants, Matched on the Basis of Age, Sex, and BMI

	CP (n = 25)	Healthy Control (n = 25)	*P*
Sex, female, n (%)	19 (76)	19 (76)	1.00
Age, y	34.2 (2.4)	34.3 (2.5)	0.74
BMI, kg/m^2	24.7 (0.9)	24.8 (0.9)	0.71
Weight, kg	68.3 (3.2)	72.5 (3.0)	0.04
Height, cm	165.7 (1.8)	170.9 (1.9)	0.02
Fasting blood glucose, mg/dL	89.5 (2.3)	84.4 (1.2)	0.04
HbA_{1c}, %	5.15 (0.06)	5.09 (0.04)	0.41
HbA_{1c}, mmol/mol	32.8 (0.66)	32.1 (0.44)	0.41

Data are presented as mean (SE), unless otherwise indicated.

Histopathology at the time of TP-IAT showed evidence of CP in 23 of 25 patients; in the remaining 2 cases, 1 had well-documented recurrent acute pancreatitis with progression to daily chronic pain and imaging findings suggesting CP (but normal pathology from head and tail biopsy), and the second had a grossly abnormal pancreas with pancreatic pseudocyst at surgery but pancreatic tissue was not captured in the biopsy sample for histopathology. Five patients had impaired fasting glucose by current American Diabetes Association criteria (≥100 mg/dL) but only 1 had a fasting glucose greater than 110 mg/dL (111 mg/dL on day of testing). As per study design, none had DM.

Mixed Meal Tolerance Tests

Although mean glucose levels were in the nondiabetic range in the CP cohort, the area AUC glucose from MMTT was significantly higher in the patients with CP compared with healthy controls (12,144 [412] vs 10,511 [306] mg/dL * min, $P = 0.009$). Mean glucose levels were greater than in controls at fasting baseline, 30, 60, and 120 minutes during testing (Fig. 1). In contrast, AUC C-peptide was no different in the CP cohort compared with controls (536 [53] vs 579 [45], $P = 0.6$). However, there was a notably lower stimulated C-peptide value at 30 minutes in the patients with CP (4.6 [0.6] ng/mL vs 6.2 [0.5] ng/mL, $P = 0.04$, Fig. 1).

Although the change in glucagon (peak minus baseline on MMTT) did not differ between the 2 groups (21.5 [5.1] vs 22.9 [2.2] ng/L, $P = 0.84$), overall glucagon levels were elevated both basally and throughout the MMTT in the patients with CP (Fig. 2), resulting in a greater AUC glucagon (including baseline) in the CP cohort (8956 [627] vs 6376 [263] ng/L × minute in controls, $P = 0.0009$).

The incretin hormones GLP-1 and GIP did not differ overall in the CP and control cohorts. Mean (SE) AUC GLP-1 was 1247 (263) pM per minute in CP and 860 (91) pM per minute in controls ($P = 0.2$). Mean (SE) AUC GIP was 32,121 (3197) pg/mL per minute in CP and 31,918 (1970)pg/mL per minute in controls ($P = 0.9$, Fig. 1).

Frequent Sample IV Glucose Tolerance Tests

The FSIVGTT were performed to assess the AIRglu, insulin SI, and DI (Fig. 2). There was no difference in AIRglu in the CP group and matched controls (340 [55] vs 359 [58] mIU/mL × min, $P = 0.9$, and supplemental Figure 1, http://links.lww.com/MPA/A415). However, mean (SE) SI was lower in the CP group (3.48 [0.04] vs 5.8 [0.73] in controls, $P = 0.004$) indicating that these

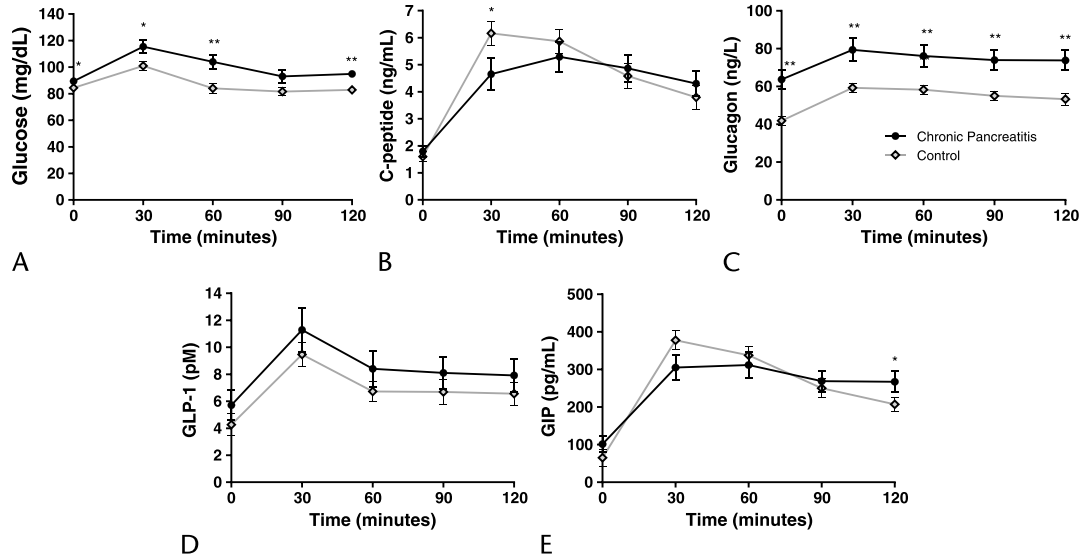

FIGURE 1. From mixed meal tolerance tests in CP (dark circle) and healthy control (grey diamonds): glucose (A), C-peptide (B), glucagon levels (C), GLP-1 (D), and GIP (E). The AUC glucose and AUC glucagon were significantly higher in the CP cohort, but AUC C-peptide, GLP-1, and GIP did not differ between groups. *$P \leq 0.05$. **$P \leq 0.01$.

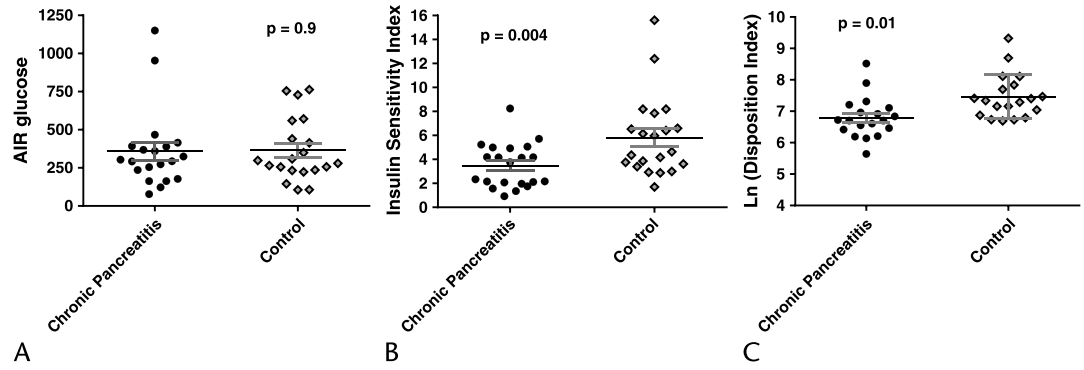

FIGURE 2. Results from the frequent sample IV glucose tolerance test in CP and matched control patients: acute insulin response to glucose (A, n = 20 pairs), insulin SI (B, n = 21 pairs), and natural log of the DI (C, n = 19 pairs).

patients were, on average, less insulin sensitive than healthy control patients. When insulin secretion was adjusted for insulin sensitivity, the mean DI was lower in CP compared with healthy controls (log-adjusted DI, 6.79 [0.15] vs 7.47 [0.16], $P = 0.01$) suggesting a defect in insulin secretion. For all parameters, there was a significant overlap between the 2 groups (Fig. 2).

We also calculated the ACRglu using C-peptide levels measured in the first 10 minutes after the IV dextrose bolus. The ACRglu did not differ between CP and control patients. However, when normalizing stimulated C-peptide to fasting baseline, only 63% of patients with CP had an at least a 2.5-fold increase in C-peptide (defined as peak divided by fasting baseline), compared with 84% of controls ($P = 0.08$).

Differences in Patients With Noncalcific and Calcific Pancreatitis Suggest Disease Progression

We performed a subgroup analysis to compare those patients with noncalcific pancreatitis (n = 18) to those with pancreatic calcifications, presuming that the latter represents a more severe stage of disease with potentially greater pancreatic damage (Fig. 3). Notably, the patients with calcific pancreatitis, on average, exhibited higher HbA_{1c} levels, greater AUC glucose on MMTT, and lower AIRg, ACRg, and DI from FSIVGTT (Table 2, online supplementary Figure 1, http://links.lww.com/MPA/A415). The mean DI was nearly 70% reduced for the calcific CP group compared with the group with noncalcific pancreatic disease. Although there was a trend toward lower AUC glucagon in the calcific pancreatitis group, this difference was not statistically significant in this small cohort.

DISCUSSION

In CP, progressive replacement of the pancreatic parenchyme with fibrosis can result in irreversible damage to the pancreatic islets and risk of DM.[3] This form of pancreatic diabetes (also called type 3c DM) may occur in more than half of patients with long-standing severe CP[7–9,28] and is characterized clinically by loss of islet mass.[6,20,22] However, most research to date has focused on small cohorts (often 10 or fewer patients per study group) with late-stage disease, often with DM already present or at least severe calcific CP on imaging.[10,12,20] Thus, our understanding of the natural history of progression from early stage CP to late disease with DM remains incomplete. In the current analysis, we performed metabolic testing in a cohort of patients with largely noncalcific "earlier" stages of pancreatic damage, who were scheduled for total pancreatectomy and islet autotransplant, and compared pancreatic endocrine function in these patients with healthy controls matched for important attributes of age, sex, and BMI. In our cohort of nondiabetic patients with CP due to obstructive, genetic, or idiopathic causes, we observed small but significant elevations in glucose fasting and after mixed meal challenge, a reduced early insulin secretory response to a meal, insulin resistance, and a state of relative hyperglucagonemia compared with healthy individuals. Those with more advanced disease, as represented by pancreatic calcifications, exhibited a more severe defect in insulin production.

In patients with pancreatogenous DM, insulin secretion in response to IV and oral secretagogues is abnormal.[6,10,12] We observed modestly higher glucose levels in the patients in our cohort afflicted with CP, with a blunted C-peptide response at 30 minutes after ingestion of the mixed meal. The first-phase insulin response (AIRglu) was not in and of itself different in the patients with CP but, when adjusted for insulin sensitivity using the DI, was lower on average in the patients with CP. These results taken together suggest that the earliest abnormalities in CP are subtle changes in glycemic control with blunted early insulin secretory response to a meal.

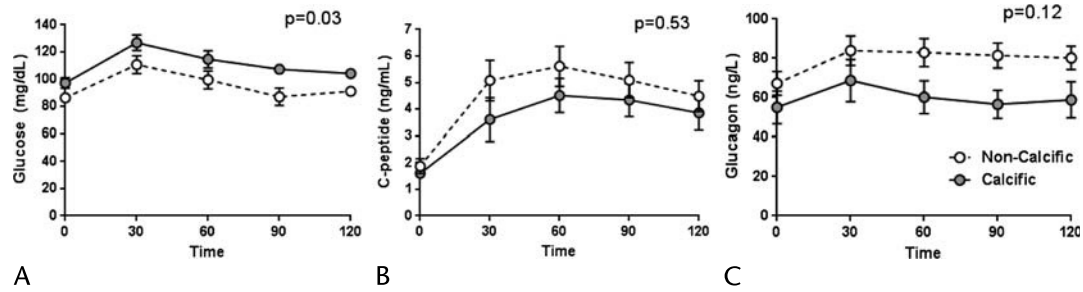

FIGURE 3. Mixed meal tolerance test glucose (A), C-peptide (B), and glucagon levels (C) in patients with noncalcific CP (n = 18, open circles with dashed line) and calcific pancreatitis (n = 7, grey circles, solid grey line). The AUC glucose was significantly higher in calcific CP, whereas differences in C-peptide and glucagon were not statistically significant. Data are graphically represented as mean (SE).

TABLE 2. Fasting Basal, Mixed Meal Tolerance Test, and Frequent Sample IV Glucose Tolerance Test Parameters in Those With Calcific Versus Noncalcific CP

	Healthy Controls (for Reference)	Noncalcific Pancreatitis (n = 18)	Calcific Pancreatitis (n = 7)	*P**
HbA_{1c}, %	5.09 (0.04)	5.03 (0.06)	5.45 (0.04)	0.002
HbA_{1c}, mmol/mol	32.1 (0.44)	31.5 (0.66)	36.1 (0.44)	0.002
Fasting blood glucose, mg/dL	84.4 (1.2)	86.4 (2.5)	97.3 (3.9)	0.07
Number with IFG, n (%)	0	2 (11)	4 (43)	0.07
Fasting C-peptide, ng/mL	1.60 (0.19)	1.87 (0.27)	1.60 (0.16)	0.81
Fasting glucagon, ng/L	41.8 (2.2)	67.2 (5.9)	55.0 (8.3)	0.25
AIRglu	359 (58)	339 (60)	187 (45)	0.02
ACRglu	44.8 (4.2)	50.5 (4.5)	28.2 (3.9)	0.006
DI	2349 (568)	1434 (283)	465 (65)	0.003
SI	5.8 (0.7)	3.7 (0.4)	3.5 (2.8)	0.49
AUC glucose, MMTT, mg/dL * min	10511 (306)	11588 (513)	13493 (321)	0.03
AUC C-peptide, MMTT, ng/mL * min	579 (45)	569 (68)	456 (67)	0.53
AUC glucagon, MMTT, ng/L * min	6379 (263)	9680 (723)	7267 (996)	0.12

Data are presented as mean (SE). The healthy control data are provided for reference.

**P* value for noncalcific versus calcific CP.

IFG indicates impaired fasting glucose.

Unexpectedly, we found an elevation of basal and postmeal glucagon levels in patients with CP. This, on the surface, seems in contrast to the classic picture of glucagon deficiency in advanced CP complicated by DM.[6,20] It also differs from another disease with partial fibrotic destruction of islets, cystic fibrosis, where both insulin and glucagon secretion are diminished.[29,30] Because this result was unanticipated, we first questioned whether this could be a technical or assay problem. However, all specimens were collected in aprotinin-containing tubes prepared by the same technician, were subjected to the same processing procedures, and run with an identical glucagon assay. In addition, there was overlap in the timeframes during which the CP and control glucagon assays were run making assay drift an unlikely cause.

Our data suggest that hypoglucagonemia may be a late finding, which is preceded by a period of hyperglucagonemia early in the course of the disease. Elevations in basal and alanine-stimulated glucagon have been previously observed in acute pancreatitis[20] and CP.[17,31] Kannan et al[31] reported a similar elevation in basal glucagon and after stimulation with oral glucose or IV arginine in 10 patients with CP. This latter cohort of patients was similar to ours in that only 20% (2 of 10 patients) had calcific pancreatitis, with strikingly similar differences in basal and postprandial glucagon levels compared with healthy controls to those we observed in the present study. We postulate that elevations in glucagon may result from chronic stress and inflammation, until the pancreas reaches a state where too many α cells have been lost to maintain high levels. Alternatively, slowly dying α cells may release stored glucagon leading to chronic elevation, or β-cell dysfunction may alter the normal β-cell–α-cell signaling for glucagon suppression and exaggerate such responses, as is observed in those with type 1 diabetes.[32,33] A progressive loss of glucose suppression of glucagon in response to an oral glucose load has been reported in patients with CP, because severity of disease progressed from normal to impaired glucose tolerance to diabetes.[17] Interestingly, in our cohort, the elevation in glucagon was present in the basal and postmeal measures, but the increment of change (ie, basal to postmeal) was similar between groups, suggesting a different "set point" in the glucagon secretion rather than a truly exaggerated meal response. Interestingly, it has been proposed that patients with CP have increased hepatic insulin resistance on the basis of clinical and preclinical models[4,34–36]; thus, one could postulate that hyperglucagonemia is contributing to the phenotype of hepatic insulin resistance. Regardless of the cause, the observed differences in glucagon levels between normal and patients with CP may be contributing to the higher glucose levels we observed in the latter during mixed meal testing.

In contrast to previous publications by Knop et al,[14–16] we did not observe any abnormalities in the incretin response to a meal. It has been previously postulated that malabsorption in CP may lead to abnormal secretion of small bowel incretin hormones GLP-1 and GIP, thereby contributing to insulin dysregulation and hyperglycemia in CP. However, our patients were instructed to take their pancreatic enzymes because they would with a meal if prescribed by their gastroenterologist (14 of our 25 participants with CP); thus, we were likely to avoid malabsorption in those who might have been at risk.

Insulin sensitivity was measured by FSIVGTT. Peripheral insulin sensitivity has been postulated to be enhanced in CP, although the data from hyperinsulinemic euglycemic clamp studies are mixed.[6,19,37] We observed that our cohort of patients with CP, who were clinically well at the time of testing, were less insulin sensitive than healthy controls. One might hypothesize that the chronic illness, chronic inflammation, and reduced physical activity state of these patients with CP lead to a state of reduced insulin sensitivity. However, cystic fibrosis patients, who also have lost islets to fibrosis and who experience chronic inflammation, compensate for insulin insufficiency with normal to increased insulin sensitivity, unless they are acutely ill, which leads to transient insulin resistance.[29,38] It is possible, however, that inflammation within the pancreas itself is greater in CP than in CF, because most of the exocrine tissue is destroyed and replaced by fibrosis and fat very early in the course of CF in most patients. Furthermore, the MINMOD model using FSIVGTT does not distinguish between total body or hepatic insulin resistance, so it is possible that there is a relative hepatic insulin resistance while retaining whole body insulin sensitivity, as has been proposed in this population previously.[4]

A potential important contributor to insulin resistance that is unexplored in our current study is pancreatic polypeptide (PP)

deficiency. Pancreatic polypeptide is absent in patients with type 3c (pancreatogenous) DM and those with pancreatic head resection.[1,4] Current data from clamp studies suggest that this deficiency of PP contributes to hepatic insulin resistance, and infusion of PP can reverse this insulin resistance.[4] Thus, future analyses in this population should include PP measures to determine progression to PP loss, if before diabetes onset, and the importance of PP deficiency in modulating the observed changes.

Although this is not the first study to evaluate endocrine function in patients with CP, we believe that there are several features of this study that distinguish it from previously published work. First, much of the early literature on CP focuses on those with diabetes or impaired glucose tolerance or with no diabetes but advanced pancreatic parenchymal damage as evidenced by calcifications on computed tomography. Our data from the calcific pancreatitis subgroup (7 patients) suggest that this represents a more severe stage of disease progression. Second, early studies generally focused on a specific population of patients—men, with alcohol-induced pancreatitis. Newer epidemiologic data in fact suggest that alcohol is not the causative factor in most patients with CP. Our cohort, in contrast, included more female participants and included idiopathic, anatomic, and genetic disease etiologies. We had histopathology from the TP-IAT procedure to aid in confirming the clinical/imaging diagnosis for most our participants, to validate this cohort. Lastly, and importantly, previous studies have largely not controlled for the healthy population. Glucose regulation and insulin secretion can depend on important attributes such as BMI and age. We attempted to better control for the variation in the normal population by matching our healthy control cohort to the CP cohort for sex, age, and BMI.

Chronic pancreatitis is a heterogeneous disease, with varying etiologies, but a similar endpoint of pancreatic fibrosis and loss of pancreatic function. Given the variability in disease course and causes, generalized conclusions are limited by our small cohort. However, our results do suggest that early changes may be detectable before frank diabetes onset. Future studies might consider using other measures of β-cell mass such as arginine stimulation and repeating studies on a routine basis to assess disease progression.[39] Progressive loss of pancreatic endocrine function has implications, particularly with when to intervene in the process of disease with a major procedure such as TP-IAT. Interestingly, our group of patients with calcific pancreatitis largely had genetic etiologies of disease; it is feasible that the progressive decrements in β-cell function that were observed with the calcific pancreatitis group were attributable to genetic disease more so that the calcific changes themselves. This would require further study with prospective longitudinal assessments.

In summary, the progression to diabetes in CP is poorly characterized, particularly within populations other than men with alcoholic disease. In our population of patients with CP due to nonalcohol etiologies, including both men and women, patients with CP had a reduced DI on FSIVGTT, modest but significant elevations in their glucose response to a meal, a lower early C-peptide response to mixed meal testing, basal and postmeal hyperglucagonemia, and reduced insulin sensitivity compared with healthy controls. Insulin deficiency is more pronounced in those with calcific CP, presumably representing a more advanced stage of fibrosis and islet destruction. Early deficits in glucose regulation in CP seem to result from small deficits in insulin production and abnormal glucagon elevations before the classic glucagon deficiency of severe late-stage CP complicated by "brittle" diabetes occurs.

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