Oxyntomodulin May Distinguish New-Onset Diabetes After Acute Pancreatitis From Type 2 Diabetes

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OBJECTIVE: New-onset diabetes is an important sequela of acute pancreatitis, but there are no biomarkers to differentiate it from the much more common type 2 diabetes. The objective was to investigate whether postprandial circulating levels of gut hormones can serve this purpose.

METHODS: This was a case-control study nested into a prospective longitudinal cohort study that included 42 insulin-naive cases with new-onset prediabetes/diabetes after acute pancreatitis (NODAP) and prediabetes/diabetes followed by acute pancreatitis (T2D-AP), sex matched with 21 healthy controls. All individuals underwent a standardized mixed-meal test, and blood samples were assayed for gut hormones (glucose-dependent insulinotropic peptide, glucagon-like peptide-1, oxyntomodulin, and peptide YY). Analysis of variance and linear regression analysis were conducted in unadjusted and adjusted models (accounting for age, homeostatic model assessment of β-cell function, and magnetic resonance imaging–derived body fat composition).

RESULTS: Oxyntomodulin levels were significantly lower in NODAP compared with T2D-AP and healthy controls ($P \leq 0.027$ and $P \leq 0.001$, respectively, in the most adjusted model). Glucagon-like peptide-1 and peptide YY were significantly lower in NODAP compared with T2D-AP ($P \leq 0.001$ and $P \leq 0.014$, respectively, in the most adjusted model) but not compared with healthy controls ($P \geq 1.000$ and $P \geq 0.265$, respectively, in the most adjusted model). Glucose-dependent insulinotropic peptide levels were not significantly different between NODAP and T2D-AP.

DISCUSSION: Oxyntomodulin is a promising biomarker to guide the differential diagnosis of new-onset diabetes after acute pancreatitis. However, external validation studies are warranted before it can be recommended for routine use in clinical practice.

INTRODUCTION
Postpancreatitis diabetes mellitus is the second most common type of new-onset diabetes in adults (1). Yet, it is often misdiagnosed. A population-based study from the United Kingdom showed that nearly 90% of postpancreatitis diabetes mellitus cases are incorrectly labeled as type 2 diabetes (2). A series of population-based studies from New Zealand (the NORMA project) demonstrated that individuals with postpancreatitis diabetes mellitus are at significantly higher risks of hospitalization and mortality from gastrointestinal diseases, cancer, and infectious diseases compared with type 2 diabetes individuals (3). It also showed that the benefit–risk balance for insulin and metformin is markedly different in postpancreatitis diabetes mellitus vs type 2 diabetes (4,5). Identification of biomarkers that distinguish postpancreatitis diabetes mellitus from the much more common type 2 diabetes is important with a view to optimal managing of individuals with these types of diabetes (6). However, to date, such biomarkers have never been reported.

Abnormal glucose metabolism is a common sequela of acute pancreatitis (AP). A 2014 comprehensive meta-analysis showed that the risk of developing new-onset diabetes increases 2-fold in the 5 years after AP, with nearly 40% of patients developing new-onset prediabetes or diabetes after acute pancreatitis (NODAP) (7). Acute pancreatitis is one of the most common gastrointestinal disorders (8), and it is characterized by an acute inflammatory state, which was previously believed to be self-limiting and reversible. However, emerging evidence demonstrates the perpetuation of low-grade inflammation long after hospital discharge. The exact pathophysiological mechanisms underlying NODAP are yet to be fully elucidated, but a series of cross-sectional studies in fasting state from New Zealand (the DORADO project) clearly showed that they involve alterations in gut function (9–15).
The gastrointestinal tract secretes various hormones (e.g., glucose-dependent insulinotropic peptide [GIP], glucagon-like peptide-1 [GLP-1], oxyntomodulin, and peptide YY) in response to nutrients and efferent luminal stimulation to regulate satiety, gastric emptying, and control glucose metabolism (16). Glucagon-like peptide-1 and oxyntomodulin are derivatives of the proglucagon peptide and are secreted mainly from the intestinal L cells. While peptide YY is also released from the L cells, the proglucagon peptide and are secreted mainly from the intestinal K cells (17). Studies in type 2 diabetes have shown that gut hormones stimulate the release of proinflammatory cytokines (18), establishing a strong cross-link between the gut and immune system in both fasting and postprandial states. Although the fasting gut hormone profile has been shown to be significantly associated with elevated levels of proinflammatory cytokines in individuals after AP in our earlier study (15), the interplay between postprandial gut hormones and proinflammatory cytokines has never been studied in this setting.

The primary aim was to investigate whether gut hormone responses to mixed-meal test are different in NODAP, type 2 diabetes, and health. The secondary aim was to investigate the associations between postprandial gut hormones and proinflammatory cytokines in the study groups.

**METHODS**

**Study design**

The study was a case-control study nested into a prospective longitudinal study of individuals after AP as a part of the MENSA project. From the prospective cohort, 2 case groups were identified—NODAP and type 2 prediabetes or diabetes before acute pancreatitis (T2D-AP). Individuals with fasting plasma glucose ≥100 mg/dL (≥5.6 mmol/L) and/or glycated hemoglobin A1c (A1c) ≥5.7% (39 mmol/mol) beyond 3 months of hospital discharge for AP constituted the NODAP group, in line with the published recommendations (1,19). Individuals with A1c ≥5.7% (39 mmol/mol) before, during hospitalization for AP, or within 3 months after it constituted the T2D-AP group. Fasting plasma glucose ≥100 mg/dL (≥5.6 mmol/L) during hospitalization might reflect stress hyperglycemia (20) and, hence, was not considered in selecting individuals for the T2D-AP group. All cases were at least 18 years old, gave informed consent, had a primary diagnosis of non-severe AP established prospectively at the hospital of AP according to the international guidelines (21), met the American Diabetes Association criteria for prediabetes or diabetes (22), and were insulin-naive.

Individuals were excluded from the study if they did not have their A1c measured during hospitalization for AP, had chronic pancreatitis during hospitalization or follow-up, had type 1 diabetes during hospitalization or follow-up, had postendoscopic retrograde cholangiopancreatography pancreatitis, had pancreatic or gastrointestinal surgery, had one or more pancreatic cysts, were hospitalized for AP within 3 months before study visit, had malignancy, had cognitive impairment; received steroids, or were pregnant.

The control group was matched on sex with the 2 case groups and included healthy volunteers. All of them were at least 18 years old, gave informed consent, had no personal and family history of diseases of the exocrine pancreas and diabetes, had no family history of cystic fibrosis or coeliac diseases, had no upper abdominal symptoms in the 12 months preceding the study, had no history or evaluation for infectious or inflammatory diseases in the 6 months preceding the study, and had no history of cancer.

**Study protocol**

All participants visited the COSMOS clinic after an overnight fast (≥8 hours) to undergo a mixed-meal test. A venous catheter with stopcock apparatus was inserted into each participant’s arm to collect the fasting blood samples (t = 0 minute). Participants then consumed a commercially available mixed-meal drink (BOOST Original, Nestlé Health Science, Bridgewater, NJ) providing 61.5 g carbohydrates, 15 g protein, and 6 g fat. Blood samples were drawn at t = 15, 30, 45, 60, 75, and 90 minutes. All blood samples were centrifuged at 4,000g for 5 minutes; serum was separated and stored at −80 °C until batch analysis. Given that excess visceral and ectopic fat is implicated in the development of hyperglycemia (23–25) and could affect the studied associations, all participants underwent a comprehensive body composition analysis. They visited the Centre for Advanced Magnetic Resonance Imaging (University of Auckland, New Zealand) to undergo abdominal magnetic resonance imaging using a 3.0-Tesla MAGNETOM Skyra scanner (Siemens, Erlangen, Germany).

**Laboratory measurements**

Glycated hemoglobin A1c was measured using boronate affinity chromatography assay (Trinity Biotech, Wicklow, Ireland)—a method certified by the National Glycohemoglobin Standardization Program and standardized to the Diabetes Control and Complications Trial reference assay. Plasma glucose was measured using enzymatic colorimetric assay (E.Hoffmann-la Roche Ltd, Basel, Switzerland). Both plasma glucose and A1c were analyzed at LabPlus (International Accreditation New Zealand accredited laboratory) at Auckland City Hospital (New Zealand). Homeostatic model assessment of β-cell function (HOMA-β) was calculated using the HOMA2 calculator (v2.2.3 β, Diabetes Trials Unit, University of Oxford).

The following 4 gut hormones were studied—oxyntomodulin, GIP, GLP-1, and peptide YY. Before analyzing the blood samples for the gut hormones, sigma protease (Merck LGAa, Gernsheim, Germany) and dipeptidyl peptidase IV inhibitor (Merck KGAa, Gernsheim, Germany) were added to each sample. Oxyntomodulin was analyzed using a commercially available enzyme-linked immunosorbent assay (Phoenix Pharmaceuticals, Burlingame, CA). Results were measured using a Rayto Microplate Reader (V-2100C; Rayto, Santa Fe, Spain) with an absorbance of 450–630 nm. Values for oxyntomodulin were reported in pg/mL. GIP, GLP-1, and peptide YY were analyzed using the MILLIPLEX MAP human metabolic hormone bead panel based on the Luminex xMAP technology (Luminex Corporation, Northbrook, IL). The results were measured based on the fluorescent reporter signals recorded by the Luminex xPONENT software (MILLIPLEX analyst 5.1). All values were reported in pg/mL. The same panel was used to analyze interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNF-α), and insulin. The intra-assay and interassay variables were <10% and 15%, respectively.
**Table 1. Characteristics of the sex-matched study groups**

| Characteristic                          | Healthy controls (n = 21) | T2D-AP (n = 21) | NODAP (n = 21) | P       |
|----------------------------------------|---------------------------|----------------|----------------|---------|
| Age (yr)                               | 49 ± 20                   | 53 ± 15        | 62 ± 15        | 0.046   |
| Time since last episode of pancreatitis (mo) | N/A                      | 20 ± 10        | 21 ± 12        | 0.914   |
| Etiology                               |                           | 2              | 6              | 0.291   |
| Biliary                                |                           | 10             | 8              |         |
| Alcohol-related                        |                           | 2              | 6              |         |
| Other                                  |                           | 9              | 7              |         |
| Pancreatic necrosis                    | N/A                       | 20             | 20             | 0.317   |
| No                                     |                           | 5              | 8              |         |
| Yes                                    |                           |                |                |         |
| Recurrent pancreatitis                 |                           |                |                |         |
| No                                     |                           | 16             | 13             |         |
| Yes                                    |                           |                |                |         |
| Fasting plasma glucose (mmol/L)        | 4.7 (3.7–5.1)             | 5.3 (4.3–7.1)  | 5.3 (4.6–6.5)  | 0.027   |
| Glycated hemoglobin (mmol/mol)         | 34.0 (31.0–35.0)          | 41.0 (38.0–56.0)| 39.0 (37.0–45.7)| <0.001 |
| Fasting insulin (pmol/L)               | 96.2 (64.5–125.6)         | 148.5 (106.2–250.4)| 114.2 (77.6–201.4)| 0.139   |
| HOMA %β                                | 183.5 (106.0–263.8)       | 164.3 (123.5–265.4)| 133.5 (96.7–203.9)| 0.404   |
| Subcutaneous fat volume (cm³)          | 1710.0 (1,410.9–2,483.4)  | 3,011.3 (2,530.9–4,066.6) | 2,455.2 (2034.8–3,786.7) | 0.003   |
| Visceral fat volume (cm³)              | 720.7 (542.0–1,399.6)     | 2,458.6 (1,525.5–3,512.1)| 2,177.5 (1,514.9–3,206.2) | <0.001  |
| Pancreatic fat (%)                     | 7.3 (6.3–9.1)             | 9.7 (8.9–10.9)  | 9.7 (9.1–10.6)  | <0.001  |
| Liver fat (%)                          | 5.3 (2.2–10.8)            | 5.1 (2.8–13.5)  | 8.9 (6.3–21.0)  | 0.199   |

Data are presented as mean ± SD and median (interquartile range). Baseline characteristics were compared using one-way analysis of variance, χ² test, and independent samples t test, as appropriate. P values < 0.05 are shown in bold. NODAP, new-onset prediabetes/diabetes after acute pancreatitis; N/A, not applicable; T2D-AP, type 2 prediabetes/diabetes before acute pancreatitis.

**Measurements of body fat composition**

Magnetic resonance imaging–derived body fat composition measurements were performed as described elsewhere (25–30). Subcutaneous fat volume (cm³) and visceral fat volume (cm³) were quantified using the ImageJ software (National Institutes of Health). Pancreatic fat percentage (%) was measured using the “MR-opsy technique,” and liver fat % was measured using the single-voxel spectroscopy technique. Measurements were done independently by 2 raters in a blinded fashion. The average values from the 2 independent set of measurements were used for the statistical analyses.

**Statistical analyses**

All statistical analyses were conducted using SPSS for Windows 25 (IBM Corp.). A χ² test and an independent samples t test were used to investigate the differences in categorical and continuous characteristics, respectively, between the study groups. Data were presented as frequency or median (interquartile range). The total area under the curves (AUC) for cytokines (IL-6, MCP-1, and TNFa) and gut hormones (GIP, GLP-1, peptide YY, and oxyntomodulin) were calculated using the trapezoidal rule. Outliers (standardized residuals greater than ±3 SDs) were excluded from all analyses (31). The subsequent analyses were conducted in 2 steps.

First, the analysis of variance was conducted to compare the differences in means of total AUC of gut hormones (log-transformed) between the 3 groups in 5 models. Model 1 was unadjusted model; model 2 was adjusted for age; model 3 was adjusted for subcutaneous fat volume, visceral fat volume, pancreatic fat%, and liver fat%; model 4 was adjusted for HOMA-%β; and model 5 was adjusted for all the covariates used in models 2, 3, and 4.

Second, the linear regression analysis was conducted to investigate the associations between total AUC of postprandial cytokines (IL-6, MCP-1, and TNFa) and total AUC of postprandial gut hormones (GIP, GLP-1, peptide YY, and oxyntomodulin). Both the cytokines and gut hormones were log-transformed to account for violation of the assumption of normality. Each cytokine was investigated as a dependent variable in one unadjusted and 4 adjusted models. Model 1 was unadjusted model; model 2 was adjusted for age and sex; model 3 was adjusted for subcutaneous fat volume, visceral fat volume, pancreatic fat%, and liver fat%; model 4 was adjusted for HOMA-%β; and model 5 was adjusted for all the covariates used in models 2, 3, and 4.
RESULTS

Characteristics of participants
Each of the 3 study groups included 21 sex-matched participants. The 42 participants in the 2 case groups were studied, on average, in 21 months since their last episode of AP. Most participants (43%) had biliary etiology of AP, and none had hypertriglyceridemia-induced AP. A total of 24 participants had prediabetes and 18—diabetes, with no significant difference between the groups. The fasting levels of oxyntomodulin were 11.27 ± 7.70 pg/mL in the NODAP group, 18.65 ± 9.12 in the T2D-AP group, and 17.50 ± 5.82 pg/mL in the healthy control group. The differences were statistically significant between the NODAP and T2D-AP groups (P = 0.008), and between the NODAP and healthy control groups (P = 0.028). The fasting levels of GIP, GLP-1, and peptide YY did not differ significantly between the groups. Other characteristics of the study participants are presented in Table 1.

Postprandial gut hormone responses
The total area under the GIP response curve in the NODAP group was 10.32 ± 0.13 pg/mL × minutes compared with 10.41 ± 0.12 pg/mL × minutes in the T2D-AP group and 9.82 ± 0.14 pg/mL × minutes in the healthy control group in the most adjusted model (P = 0.014) (Figure 1a). The total area under the GLP-1 response curve in the NODAP group was 9.44 ± 0.13 pg/mL × minutes compared with 10.13 ± 0.13 pg/mL × minutes in the T2D-AP group and 9.56 ± 0.15 pg/mL × minutes in the healthy control group in the most adjusted model (P = 0.001) (Figure 1b). The total area under the peptide YY response curve in the NODAP group was 9.05 ± 0.10 pg/mL × minutes compared with 9.45 ± 0.09 pg/mL × minutes in the T2D-AP group and 9.34 ± 0.11 pg/mL × minutes in the healthy control group in the most adjusted model (P = 0.015) (Figure 1c). The total area under the oxyntomodulin response curve in the NODAP group was 6.43 ± 0.10 pg/mL × minutes compared with 6.79 ± 0.10 pg/mL × minutes in the T2D-AP group and 7.09 ± 0.01 pg/mL × minutes in the healthy control group in the most adjusted model (P = 0.001) (Figure 1d). Other models and pairwise comparisons are presented in Table 2.

Associations between gut hormones and proinflammatory cytokines
NODAP group. TNFα was significantly associated with peptide YY in all the models (Table 3). For every unit change in peptide YY, TNFα changed the most in model 3 with a β coefficient (95% confidence interval [CI]) of 0.78 (0.42–1.14), (P < 0.001). TNFα was significantly associated with GIP in one model (Table 3). For every unit change in GIP, TNFα changed the most in model 3 with a β coefficient (95% CI) of 0.26 (0.05–0.47), (P = 0.014). TNFα was not significantly associated with GLP-1 or oxyntomodulin in any of the studied models (Table 3).

IL-6 was significantly associated with GIP in one model (Table 3). For every unit change in GIP, IL-6 changed the most in
The present study has investigated, for the first time, the circulating postprandial levels of gut hormones in individuals with NODAP, T2D-AP, and healthy controls. To obtain the most robust estimates, we conducted the analyses in unadjusted and adjusted models, accounting for possible confounders such as model 5 with a β coefficient (95% CI) of $-0.57$ ($-1.09$ to $-0.05$), ($P = 0.012$). IL-6 was not significantly associated with GLP-1, oxyntomodulin, or peptide YY in any of the studied models (Table 3).

MCP-1 was not significantly associated with GIP, GLP-1, oxyntomodulin, or peptide YY in any of the studied models (Table 3). The results of the interaction analysis of the relationship between the gut hormones and cytokines in the NODAP group are presented in Table 4.

### DISCUSSION

The present study has investigated, for the first time, the circulating postprandial levels of gut hormones in individuals with NODAP, T2D-AP, and healthy controls. To obtain the most robust estimates, we conducted the analyses in unadjusted and adjusted models, accounting for possible confounders such as model 5 with a β coefficient (95% CI) of $-0.57$ ($-1.09$ to $-0.05$), ($P = 0.012$). IL-6 was not significantly associated with GLP-1, oxyntomodulin, or peptide YY in any of the studied models (Table 3). The results of the interaction analysis of the relationship between the gut hormones and cytokines in the NODAP group are presented in Table 4.
Table 3. Associations between gut hormones and cytokines after mixed-meal test in the study groups

| Cytokine | Gut hormone | Healthy controls (n = 21) | T2D-AP (n = 21) | NODAP (n = 21) |
|----------|-------------|--------------------------|----------------|----------------|
|          |             | β (95% CI) | P    | q | β (95% CI) | P    | q | β (95% CI) | P    | q |
| IL-6     | GIP         |            |      |    |            |      |    |            |      |    |
| Model 1  | 0.26 (−0.82 to 1.34) | 0.641      | 0.992 |    | −0.27 (−1.09 to 0.54) | 0.509 | 0.509 | −0.38 (−0.91 to 0.15) | 0.157 | 0.628 |
| Model 2  | 0.21 (−0.76 to 1.20) | 0.667      | 0.667 |    | 0.05 (−0.72 to 0.81) | 0.904 | 0.904 | −0.32 (−0.88 to 0.24) | 0.258 | 0.791 |
| Model 3  | 0.97 (−0.07 to 2.02) | 0.068      | 0.136 |    | −0.26 (−0.90 to 0.38) | 0.425 | 0.425 | −0.59 (−1.15 to −0.02) | 0.041 | 0.164 |
| Model 4  | −0.37 (−1.18 to 0.44) | 0.366      | 0.732 |    | −0.34 (−1.12 to 0.44) | 0.393 | 0.393 | −0.47 (−1.05 to 0.11) | 0.116 | 0.464 |
| Model 5  | 0.06 (−0.85 to 0.98) | 0.895      | 0.895 |    | −0.12 (−0.75 to 0.52) | 0.717 | 0.717 | −0.57 (−1.09 to −0.05) | 0.012 | 0.048 |
| GLP-1    |             |            |      |    |            |      |    |            |      |    |
| Model 1  | −0.05 (−1.10 to 1.00) | 0.929      | 0.992 |    | 0.72 (0.27 to 1.16) | 0.002 | 0.004 | −0.22 (−0.98 to 0.54) | 0.575 | 0.863 |
| Model 2  | 0.49 (−0.56 to 1.55) | 0.357      | 0.667 |    | 0.57 (0.15 to 1.00) | 0.002 | 0.004 | −0.12 (−0.88 to 0.65) | 0.765 | 0.791 |
| Model 3  | −0.56 (−1.69 to 0.56) | 0.325      | 0.325 |    | 0.47 (0.04 to 0.89) | 0.045 | 0.045 | −0.29 (−1.03 to 0.44) | 0.435 | 0.870 |
| Model 4  | −0.22 (−0.97 to 0.54) | 0.574      | 0.749 |    | 0.77 (0.37 to 1.18) | 0.001 | 0.002 | −0.32 (−1.13 to 0.49) | 0.441 | 0.882 |
| Model 5  | −0.28 (−1.14 to 0.58) | 0.523      | 0.697 |    | 0.55 (0.15 to 0.94) | 0.006 | 0.008 | −0.15 (−0.92 to 0.62) | 0.703 | 0.729 |
| Oxyntomodulin |             |            |      |    |            |      |    |            |      |    |
| Model 1  | −0.01 (−1.87 to 1.85) | 0.992      | 0.992 |    | 0.63 (0.01 to 1.25) | 0.048 | 0.064 | 0.13 (−1.31 to 1.56) | 0.863 | 0.863 |
| Model 2  | −0.44 (−2.19 to 1.31) | 0.625      | 0.667 |    | 0.54 (−0.02 to 1.09) | 0.057 | 0.076 | 0.19 (−1.21 to 1.58) | 0.791 | 0.791 |
| Model 3  | 1.42 (−0.68 to 3.53) | 0.186      | 0.248 |    | 0.74 (0.32 to 1.16) | 0.001 | 0.002 | −0.13 (−1.77 to 1.50) | 0.874 | 0.874 |
| Model 4  | 0.22 (−1.12 to 1.55) | 0.749      | 0.749 |    | 0.73 (0.15 to 1.31) | 0.013 | 0.017 | 0.06 (−1.40 to 1.53) | 0.932 | 0.932 |
| Model 5  | 0.74 (−0.72 to 2.20) | 0.319      | 0.638 |    | 0.76 (0.38 to 1.15) | 0.001 | 0.002 | −0.39 (−2.60 to 1.82) | 0.729 | 0.729 |
| Peptide YY |             |            |      |    |            |      |    |            |      |    |
| Model 1  | 1.41 (0.65 to 2.18) | <0.001     | 0.004 |    | 1.33 (0.94 to 1.71) | <0.001 | 0.004 | −0.12 (−1.35 to 1.11) | 0.845 | 0.863 |
| Model 2  | 1.39 (0.74 to 2.04) | <0.001     | 0.004 |    | 1.23 (0.83 to 1.62) | <0.001 | 0.004 | −0.16 (−1.36 to 1.03) | 0.791 | 0.791 |
| Model 3  | 1.44 (0.41 to 2.48) | 0.006      | 0.024 |    | 1.12 (0.64 to 1.60) | <0.001 | 0.002 | −0.21 (−1.40 to 0.98) | 0.731 | 0.874 |
| Model 4  | 0.83 (0.11 to 1.55) | 0.024      | 0.096 |    | 1.39 (0.97 to 1.82) | <0.001 | 0.002 | −0.28 (−1.57 to 1.01) | 0.670 | 0.893 |
| Model 5  | 0.66 (−0.19 to 1.51) | 0.131      | 0.524 |    | 1.20 (0.71 to 1.68) | <0.001 | 0.002 | −0.39 (−1.55 to 0.76) | 0.503 | 0.729 |
| MCP-1    | GIP         |             |      |    |            |      |    |            |      |    |
| Model 1  | 0.62 (0.27 to 0.97) | <0.001     | 0.002 |    | 0.23 (−0.53 to 0.98) | 0.557 | 0.997 | 0.38 (−0.36 to 1.13) | 0.316 | 0.632 |
| Model 2  | 0.62 (0.27 to 0.96) | <0.001     | 0.002 |    | 0.35 (−0.45 to 1.15) | 0.391 | 0.776 | 0.60 (−0.15 to 1.34) | 0.117 | 0.468 |
| Model 3  | 0.82 (0.50 to 1.13) | <0.001     | 0.004 |    | 0.21 (−0.51 to 0.92) | 0.570 | 0.754 | 0.30 (−0.52 to 1.12) | 0.472 | 0.581 |
| Model 4  | 0.56 (0.20 to 0.92) | 0.002      | 0.004 |    | 0.21 (−0.54 to 0.97) | 0.583 | 0.865 | 0.46 (−0.36 to 1.28) | 0.273 | 0.663 |
| Model 5  | 0.84 (0.45 to 1.23) | <0.001     | 0.004 |    | 0.21 (−0.50 to 0.92) | 0.564 | 0.890 | 0.37 (−0.32 to 1.05) | 0.293 | 0.593 |
### Table 3. (continued)

| Cytokine | Gut hormone | Healthy controls (n = 21) | T2D-AP (n = 21) | NODAP (n = 21) |
|----------|-------------|--------------------------|-----------------|----------------|
|          |             | β (95% CI) P q           | β (95% CI) P q  | β (95% CI) P q |
| Cytokine | Gut hormone |             | Model 1 | 0.61 (0.27 to 0.95) <0.001 0.002 | 0.25 (0.74 to 0.24) 0.317 0.997 | -0.22 (1.27 to 0.84) 0.685 0.913 |
|          |             |             | Model 2 | 0.70 (0.34 to 1.07) <0.001 0.002 | 0.33 (0.83 to 0.17) 0.190 0.760 | -0.05 (1.10 to 1.01) 0.929 0.929 |
|          |             |             | Model 3 | 0.62 (0.20 to 1.03) 0.004 0.008 | 0.28 (0.79 to 0.23) 0.281 0.754 | -0.28 (1.27 to 0.71) 0.581 0.981 |
|          |             |             | Model 4 | 0.58 (0.27 to 0.89) <0.001 0.004 | 0.24 (0.73 to 0.25) 0.336 0.865 | -0.38 (1.49 to 0.72) 0.497 0.663 |
|          |             |             | Model 5 | 0.64 (0.22 to 1.06) 0.003 0.006 | 0.20 (0.71 to 0.30) 0.428 0.890 | 0.01 (0.93 to 0.95) 0.980 0.980 |
| Oxyntomodulin |             | 0.34 (1.08 to 0.40) 0.362 0.362 | 0.00 (0.62 to 0.62) 0.997 0.997 | -0.07 (2.03 to 1.89) 0.945 0.945 |
| Peptide YY |             | 0.44 (0.09 to 0.79) 0.013 0.017 | 0.08 (0.71 to 0.55) 0.808 0.997 | 0.90 (0.76 to 2.56) 0.289 0.632 |
| TNFa |             | 0.13 (0.55 to 0.80) 0.711 0.711 | 0.16 (0.25 to 0.57) 0.438 0.438 | 0.23 (0.02 to 0.45) 0.034 0.068 |
| GIP |             | 0.12 (0.55 to 0.80) 0.723 0.723 | 0.39 (0.05 to 0.74) 0.026 0.035 | 0.26 (0.05 to 0.47) 0.014 0.028 |
| GLP-1 |             | 0.42 (0.06 to 0.92) 0.087 0.116 | 0.11 (0.67 to 0.90) 0.779 0.890 | 0.63 (0.76 to 2.02) 0.372 0.593 |
Table 3. (continued)

| Cytokine | Gut hormone | Healthy controls (n = 21) | T2D-AP (n = 21) | NODAP (n = 21) |
|----------|-------------|---------------------------|-----------------|---------------|
|          | β (95% CI)  | P            | q            | β (95% CI)  | P            | q            | β (95% CI)  | P            | q            |
| Oxyntomodulin |             |              |              |              |              |              |
| Model 1  | −1.75 (−2.63 to −0.86) | <0.001       | 0.001         | 0.28 (−0.04 to 0.60) | 0.087       | 0.116         | −0.11 (−0.73 to 0.51) | 0.733       | 0.733          |
| Model 2  | −1.84 (−2.76 to −0.92) | <0.001       | 0.001         | 0.22 (−0.07 to 0.51) | 0.133       | 0.133         | −0.18 (−0.77 to 0.41) | 0.544       | 0.544          |
| Model 3  | −1.39 (−2.11 to −0.66) | <0.001       | 0.002         | 0.29 (0.02 to 0.56) | 0.032       | 0.043         | −0.06 (−0.74 to 0.61) | 0.851       | 0.851          |
| Model 4  | −1.67 (−2.43 to −0.91) | <0.001       | 0.001         | 0.27 (−0.05 to 0.60) | 0.101       | 0.135         | −0.21 (−0.74 to 0.33) | 0.448       | 0.595          |
| Model 5  | −1.67 (−2.18 to −1.17) | <0.001       | 0.002         | 0.22 (−0.02 to 0.45) | 0.067       | 0.067         | −0.28 (−1.04 to 0.47) | 0.465       | 0.465          |
| Peptide YY |            |              |              |              |              |              |
| Model 1  | 1.26 (0.98 to 1.54) | <0.001       | 0.001         | 0.50 (0.23 to 0.78) | <0.001     | 0.002         | 0.78 (0.36 to 1.19) | <0.001     | 0.004          |
| Model 2  | 1.26 (0.99 to 1.53) | <0.001       | 0.001         | 0.40 (0.12 to 0.68) | <0.005     | 0.010         | 0.77 (0.40 to 1.13) | <0.001     | 0.004          |
| Model 3  | 0.97 (0.66 to 1.27) | <0.001       | 0.002         | 0.43 (0.10 to 0.76) | <0.010     | 0.020         | 0.78 (0.42 to 1.14) | <0.001     | 0.004          |
| Model 4  | 1.26 (0.94 to 1.58) | <0.001       | 0.001         | 0.67 (0.41 to 0.92) | <0.001     | 0.002         | 0.66 (0.27 to 1.06) | 0.001       | 0.004          |
| Model 5  | 0.95 (0.61 to 1.29) | <0.001       | 0.002         | 0.55 (0.29 to 0.81) | <0.001     | 0.004         | 0.72 (0.47 to 0.97) | <0.001     | 0.004          |

Model 1: unadjusted analysis; model 2: adjusted for age and sex; model 3: adjusted for subcutaneous fat volume, visceral fat volume, pancreatic fat%, and liver fat%; model 4: adjusted for homeostatic model assessment of β-cell function; and model 5: all the covariates used in models 2, 3, and 4. Data are presented as unstandardized β coefficients and 95% confidence intervals, and P value. Q value represents the minimum false discovery rate at which a result can be considered significant. P values with corresponding q values < 0.05 are shown in bold.

CI, confidence interval; NODAP, new-onset prediabetes/diabetes after acute pancreatitis; IL-6, interleukin-6; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; MCP-1, monocyte chemoattractant protein-1; TNFα, tumor necrosis factor α; and T2D-AP, type 2 prediabetes/diabetes before acute pancreatitis.
age, magnetic resonance imaging–derived body fat parameters, and β-cell function. In addition, the study investigated the role of postprandial gut hormones in modulating the inflammatory response. Given that individuals after AP often have low-grade inflammation (that may or may not result in abnormal glucose metabolism), the second case group purposely included individuals not merely with type 2 diabetes but with type 2 diabetes that had been followed by an episode of AP. In addition, all AP participants were purposely constrained to nonsevere (predominantly, mild) course of the disease and did not undergo any intervention on the pancreas—this virtually rules out the role of β-cell destruction in the pathogenesis of new-onset diabetes in our study population. A novel important finding of the present study is that the postprandial levels of oxyntomodulin, GLP-1, and peptide YY were significantly lower in the NODAP group compared with the T2D-AP group, in both unadjusted and adjusted models. Another notable finding is that the incretins (i.e., GIP and GLP-1) appeared to have a differential effect on proinflammatory cytokines in NODAP vs T2D-AP. Although GIP (but not GLP-1) was significantly inversely associated with IL-6 in NODAP, GLP-1 (but not GIP) showed a significant positive association with IL-6 in T2D-AP. These findings suggest that disturbances of the gut-immune axis underlie the pathogenesis of NODAP and may have translational implications.

The finding of significant differences in gut hormone concentrations between the NODAP, T2D-AP, and healthy control groups is not only important in characterizing postprandial states in the groups but may also have important implications for

Table 4. Interaction between the study groups for the relationship between gut hormones and cytokines

| Cytokine | Model | Group | GIP         | GLP-1        | Oxyntomodulin | Peptide YY |
|----------|-------|-------|-------------|--------------|---------------|------------|
|          |       |       | T2D-AP      | NODAP        | T2D-AP        | NODAP      | T2D-AP    | NODAP      | T2D-AP    | NODAP    |
| IL-6     | 1     | Control | 0.442       | 0.298        | 0.188        | 0.797       | 0.525     | 0.910      | 0.838     | 0.037     |
|          |       | T2D-AP  | —           | 0.829        | —            | 0.037       | —         | 0.530      | —         | 0.028     |
|          | 2     | Control | 0.791       | 0.350        | 0.890        | 0.358       | 0.298     | 0.531      | 0.678     | 0.025     |
|          |       | T2D-AP  | —           | 0.444        | —            | 0.122       | —         | 0.744      | —         | 0.030     |
|          | 3     | Control | 0.049       | 0.010        | 0.094        | 0.694       | 0.532     | 0.253      | 0.576     | 0.040     |
|          |       | T2D-AP  | —           | 0.455        | —            | 0.081       | —         | 0.313      | —         | 0.043     |
|          | 4     | Control | 0.954       | 0.852        | 0.020        | 0.799       | 0.023     | 0.856      | 0.189     | 0.140     |
|          |       | T2D-AP  | —           | 0.797        | —            | 0.013       | —         | 0.018      | —         | 0.016     |
|          | 5     | Control | 0.754       | 0.239        | 0.086        | 0.827       | 0.976     | 0.878      | 0.278     | 0.151     |
|          |       | T2D-AP  | —           | 0.278        | —            | 0.115       | —         | 0.205      | —         | 0.013     |
| MCP-1    | 1     | Control | 0.347       | 0.565        | 0.004        | 0.143       | 0.487     | 0.797      | 0.158     | 0.597     |
|          |       | T2D-AP  | —           | 0.722        | —            | 0.958       | —         | 0.948      | —         | 0.281     |
|          | 2     | Control | 0.547       | 0.964        | 0.001        | 0.186       | 0.614     | 0.695      | 0.109     | 0.626     |
|          |       | T2D-AP  | —           | 0.656        | —            | 0.630       | —         | 0.879      | —         | 0.244     |
|          | 3     | Control | 0.126       | 0.249        | 0.009        | 0.127       | 0.800     | 0.692      | 0.400     | 0.640     |
|          |       | T2D-AP  | —           | 0.865        | —            | 0.961       | —         | 0.591      | —         | 0.387     |
|          | 4     | Control | 0.421       | 0.834        | 0.006        | 0.101       | 0.504     | 0.909      | 0.205     | 0.699     |
|          |       | T2D-AP  | —           | 0.663        | —            | 0.817       | —         | 0.855      | —         | 0.364     |
|          | 5     | Control | 0.128       | 0.242        | 0.011        | 0.229       | 0.517     | 0.670      | 0.506     | 0.786     |
|          |       | T2D-AP  | —           | 0.753        | —            | 0.691       | —         | 0.495      | —         | 0.524     |
| TNFα     | 1     | Control | 0.929       | 0.765        | 0.099        | 0.023       | <0.001    | 0.003      | <0.001    | 0.058     |
|          |       | T2D-AP  | —           | 0.762        | —            | 0.205       | —         | 0.275      | —         | 0.278     |
|          | 2     | Control | 0.485       | 0.697        | 0.020        | 0.011       | <0.001    | 0.003      | <0.001    | 0.034     |
|          |       | T2D-AP  | —           | 0.528        | —            | 0.507       | —         | 0.229      | —         | 0.121     |
|          | 3     | Control | 0.225       | 0.174        | 0.692        | 0.293       | <0.001    | 0.008      | 0.018     | 0.450     |
|          |       | T2D-AP  | —           | 0.985        | —            | 0.310       | —         | 0.335      | —         | 0.163     |
|          | 4     | Control | 0.446       | 0.349        | 0.104        | 0.006       | <0.001    | 0.002      | 0.005     | 0.022     |
|          |       | T2D-AP  | —           | 0.909        | —            | 0.059       | —         | 0.134      | —         | 0.987     |
|          | 5     | Control | 0.861       | 0.388        | 0.165        | 0.100       | <0.001    | 0.003      | 0.065     | 0.027     |
|          |       | T2D-AP  | —           | 0.267        | —            | 0.591       | —         | 0.216      | —         | 0.366     |
differentiating between type 2 diabetes and NODAP. Our 2017 study showed that, although the fasting levels of GLP-1 and peptide YY did not change significantly, the fasting levels of oxyntomodulin were significantly lower in individuals with abnormal glucose metabolism after AP (compared with individuals with normoglycemia after AP) (9). However, their levels were not investigated in either type 2 diabetes or healthy controls in that study. In the present study, the postprandial levels of GLP-1 and peptide YY were significantly lower in the NODAP group than in the T2D-AP group (and did not change significantly in comparison with the healthy control group). At the same time, the postprandial levels of oxyntomodulin were significantly lower in the NODAP group compared with both the T2D-AP group and the healthy control group. Importantly, these held true after adjustment for age, β-cell function assessed by the HOMA model, and magnetic resonance imaging–derived body fat parameters. Given the above findings, oxyntomodulin may be considered a biomarker of NODAP. Although the absolute difference in the levels of oxyntomodulin between the NODAP and T2D-AP groups was small, this does not take away from the importance of our study but rather highlights the need to optimize the nutritional load given to stimulate the secretion of gut hormones in future studies. Oxyntomodulin has the potential to be used for the differential diagnosis of type 2 diabetes vs NODAP, if our findings are confirmed in external validation studies.

Findings from the present study also justify the need to explore the possible therapeutic potential of oxyntomodulin in NODAP. Oxyntomodulin is derived from post-translational cleaving of proglucagon and comprises a 29-amino acid sequence of glucagon with an 8 amino-acid C-terminal extension (34). Oxyntomodulin is cosecreted with GLP-1 at an equimolar ratio and binds with equal potency to both glucagon and GLP-1 receptors (34). Historically, studies of the pharmacological effects of oxyntomodulin were limited to obesity. It was shown that the subcutaneous administration of oxyntomodulin in obese people suppresses appetite, increases energy expenditure, and leads to weight loss (35–37). However, a 2018 randomized placebo-controlled trial of obese individuals showed that the beneficial effects of oxyntomodulin were not ascribed to weight reduction alone (38). The study found that a single dose of native oxyntomodulin improves insulin secretion rate and glucose metabolism in participants with type 2 diabetes. Furthermore, the glucose-lowering effect of oxyntomodulin was identical to that of a GLP-1 analog (used as a positive comparator) (38). Furthermore, a 2019 randomized placebo-controlled trial investigated the effects of triple hormone (oxyntomodulin, GLP-1, and peptide YY) infusion in obese individuals with prediabetes/diabetes over 4 weeks (39). The three-hormone combined infusion significantly lowered the glucose levels compared with saline infusion. Purposely designed studies are now warranted to investigate the effect of oxyntomodulin analogs (or hormone combination therapies that include oxyntomodulin) specifically in individuals with NODAP.

Another noteworthy finding of our study is the differential effect of incretins on cytokines in the study groups. The pathogenesis of NODAP involves, at least in part, changes in the GIP-cytokine-GLP-1 signaling pathway (9,11,15). Our earlier study investigating the fasting gut hormones demonstrated that GIP is significantly associated with nearly 30% increase in IL-6 levels (15). The present study showed that, in contrast to the fasting state, the postprandial GIP levels are inversely associated with IL-6 in NODAP. For every unit change in the total concentration of GIP, the IL-6 levels decrease by 57% in the most adjusted model ($P = 0.012$). At the same time, GLP-1 is not significantly associated with IL-6, and this finding is similar to our earlier finding in the fasting state. Although the associations between GIP and IL-6 in the fasting and postprandial states are diametrically opposite, both findings support the importance of a compromised GIP-cytokine-GLP-1 signaling pathway in the pathogenesis of NODAP. GIP regulates the postprandial glucose metabolism by binding to specific G-protein-coupled receptors on a cells to activate the adenylyl cyclase/cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) pathway (40). A study using isolated islets found that IL-6 secretion is stimulated by pancreatic α cells (41). Interleukin-6, a pleiotropic cytokine, facilitates the communication between GLP-1, pancreatic islets, and insulin-sensi live tissues (16). As GIP stimulates GLP-1 in the presence of IL-6 (41), it is conceivable that, in the presence of high circulating levels of GIP, desensitization of the GIP receptors (42) causes disruption in the downstream signaling of cAMP/PKA pathways, further affecting secretion of IL-6 and GLP-1. It is worth noting that peptide YY is also implicated in persistence of inflammation in NODAP (15). Peptide YY measured in the fasted state in our earlier study was significantly associated with IL-6 and MCP-1 but not associated with TNFα (15). However, postprandial levels of peptide YY in the present study were significantly associated with TNFα (but not IL-6 or MCP-1) in NODAP. The mechanism underlying the association between postprandial levels of peptide YY and TNFα in NODAP needs to be investigated in future studies.

The present study has several limitations. First, we did not quantify the size of the incretin effect using an isoglycemic clamp (43). However, we used a mixed-meal test to evaluate the incretin response to fat and protein. Second, we did not adjust for the use of antidiabetic medications (4,5). However, all study participants were insulin-naive and only 10 participants received oral glucose lowering medications. Third, we did not account for smoking in the studied associations. Future studies should investigate the impact of smoking on postprandial gut hormone levels in NODAP vs T2D-AP. Fourth, the study sample size was rather limited. However, this was a pilot study that will inform the design and sample size calculation of future studies. Fifth, gut motility and gastric emptying (16,44) may affect the secretion of some gut hormones (especially, GIP). However, a recent study showed that gastric emptying does not have a significant effect on the circulating levels of gut hormones in NODAP (24). Last, we did not investigate some other gut hormones with glucoregulatory properties (e.g., cholecystokinin, gastrin, and secretin). However, the associations between them and abnormal glucose metabolism were found to be nonsignificant in the postpancreatitis setting (9).

In conclusion, individuals with NODAP are characterized by low circulating levels of oxyntomodulin, which may serve as a biomarker to distinguish NODAP from type 2 diabetes. The therapeutic potential of oxyntomodulin-based therapies in NODAP may need to be explored in future studies.

**CONFLICTS OF INTEREST**

**Guarantor of the article:** Max Petrov, MD, MPH, PhD.

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Acquisition of data: S.H.B., C.E.S., J.C., J.K.

Analysis and interpretation of data: Max Petrov, MD, MPH, PhD.
S.H.B., J.C. Drafting of the manuscript: S.H.B. Critical review of the manuscript: C.E.S., J.C., J.K., G.C.A.R., M.S.P. Study supervision: M.S.P. All authors approved the final version of this manuscript.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN
- New-onset diabetes is the most common sequela of AP.
- New-onset diabetes after AP is often misclassified as type 2 diabetes.
- There are no biomarkers to differentiate new-onset diabetes after AP from type 2 diabetes.

WHAT IS NEW HERE
- Circulating levels of oxyntomodulin are significantly lower in new-onset diabetes after AP than type 2 diabetes or health.
- This finding is independent of age, sex, β-cell function, and body composition.
- GLP-1 and GIP have differential effects on proinflammatory cytokines in new-onset diabetes after AP vs type 2 diabetes.

TRANSLATIONAL IMPACT
- This study opens up an avenue to further oxyntomodulin as a diagnostic biomarker for new-onset diabetes after AP.
- Oxyntomodulin may have a therapeutic potential in new-onset diabetes after AP.
- GIP-cytokine-GLP-1 signaling pathway is compromised in new-onset diabetes after AP and could be targeted therapeutically.

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