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Pro-inflammatory cytokines after an episode of acute pancreatitis: associations with fasting gut hormone profile

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Abstract

Introduction Pro-inflammatory cytokines, such as interleukin (IL)-6, tumour necrosis factor (TNF)α, and monocyte chemoattractant protein (MCP)-1, are often elevated in individuals after acute pancreatitis but what determines their levels is poorly understood. Gut hormones have emerged as possible modulators of inflammatory response. The aim was to investigate the associations between pro-inflammatory cytokines and a comprehensive panel of gut hormones after an episode of acute pancreatitis.

Materials and methods Fasting blood samples were collected to measure cytokines (IL-6, TNFα, and MCP-1) and gut hormones (cholecystokinin, gastric inhibitory peptide (GIP), ghrelin, glicentin, glucagon-like peptide-1, oxyntomodulin, peptide YY, secretin, and vasoactive intestinal peptide). A series of linear regression analyses was conducted and four statistical models were used to adjust for patient- and pancreatitis-related covariates.

Results A total of 83 individuals were recruited. GIP and peptide YY were significantly ($p < 0.001$) associated with IL-6, TNFα, MCP-1, consistently in all the four models. Every 1 ng/mL change in GIP resulted in a 16.2, 3.2, and 50.8% increase in IL-6, TNFα, and MCP-1, respectively, in the most adjusted model. Every 1 ng/mL change in peptide YY resulted in a 7.0, 2.4, and 32.1% increase in IL-6, TNFα, and MCP-1, respectively, in the most adjusted model. GIP independently contributed 29.0–36.5% and peptide YY − 17.4–48.9% to circulating levels of the studied pro-inflammatory cytokines. The other seven studied gut hormones did not show consistently significant associations with pro-inflammatory cytokines.

Conclusions GIP and peptide YY appear to be involved in perpetuation of subclinical inflammation following an episode of acute pancreatitis, which is known to play an important role in the pathogenesis of blood glucose derangements. These findings advance the understanding of mechanisms underlying diabetes of the exocrine pancreas and have translational implications.

Keywords Acute pancreatitis · Chronic hyperglycaemia · Gastric inhibitory peptide · Interleukin-6 · Monocyte chemoattractant protein-1 · Peptide YY

Introduction

Acute pancreatitis has long been known as a classical acute inflammatory disease but recent evidence shows that subclinical low-grade inflammation often persists after hospital discharge and is associated with obesity, insulin resistance, and post-pancreatitis diabetes mellitus [1]. Diabetes of the exocrine pancreas has long been recognised as an important clinical entity, with up to 70% of all its cases attributable to post-pancreatitis diabetes mellitus [2–5]. Yet, its underlying mechanisms remain poorly understood. Mechanistic evidence to date stems largely from studies on type 1 and type 2 diabetes, both of which have clinically distinct characteristics to diabetes of the exocrine pancreas [6]. A sound understanding of the underlying pathophysiology of diabetes of the exocrine pancreas is thus essential to better understand impaired glucose homeostasis in individuals after acute pancreatitis, and to develop potential therapeutic treatments to prevent new-onset diabetes after acute pancreatitis [7].

The immune system plays a key role in the pathogenesis of diabetes, including the interaction between the gut and

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the pancreas [8]. However, the initiation of the detrimental cytokine cascade and possible pathways via which the cytokines are involved in the gut-pancreas interaction are not fully understood. Evidence from pre-clinical and clinical studies in the setting of type 2 diabetes suggests that glucoregulatory peptides derived from the gut [gastric inhibitory peptide (GIP), peptide YY] and pro-glucagon derived peptides [glucagon-like peptide-1 (GLP-1), oxyntomodulin, glicentin] induce an inflammatory response in the peripheral tissues, characterised by the induction of pro-inflammatory cytokines [more specifically, interleukin (IL)-6, tumour necrosis factor (TNF)α, and monocyte chemoattractant protein (MCP)-1] [9–15]. Further evidence suggests that these cytokines modify both endocrine and exocrine pancreatic functions in metabolically compromised individuals [10, 16]. Interleukin-6, TNFα, and MCP-1 up-regulate the secretion of counter-regulatory pancreatic hormones, in particular glucagon, by stimulating pancreatic α cells and activating hepatic gluconeogenesis, resulting in exacerbation of hyperglycaemia [17–19]. However, the evidence on the role of immune system in the interaction between the gut and the pancreas, although abundant, is derived largely from the setting of type 1 and type 2 diabetes [20–23]. Whether gut hormones are involved in the inflammatory response in post-pancreatitis setting has never been investigated.

The aim of this study was to investigate the association between a comprehensive panel of gut hormones and pro-inflammatory cytokines in individuals after acute pancreatitis, with a particular emphasis on glucose homeostasis.

Materials and methods

Study protocol

This was a cross-sectional study of individuals after acute pancreatitis, approved by the Health Disability Ethics Committee (13/STH/182).

Individuals who were at least 18 years of age, had a primary diagnosis of acute pancreatitis between January 1, 2010 and December 31, 2014 prospectively established in line with the current international guidelines [24], resided in Auckland at the time of the study, and provided informed consent, were invited to participate in the study.

Individuals who were pregnant, had malignancy, chronic pancreatitis, intraoperative diagnosis of pancreatitis, post-endoscopic retrograde cholangiopancreatography pancreatitis, prediabetes or diabetes prior to the first hospital admission due to acute pancreatitis, or cognitive disability were excluded from the study.

All individuals recruited into the study were divided into two groups—hyperglycaemia after acute pancreatitis and normoglycaemia after acute pancreatitis. Hyperglycaemia was defined as glycated haemoglobin A1c (HbA1c) ≥ 39 mmol/mol (5.7%) and normoglycaemia was defined as HbA1c < 39 mmol/mol, in line with the current American Diabetes Association recommendations [2, 25].

Blood sample acquisition and storage

All participants visited the COSMOS clinic at 8:00 a.m. and were fasted for at least 8 h. Venous blood was then collected by a certified phlebotomist at LabPlus, an International Accreditation New Zealand accredited medical laboratory (Auckland City Hospital, New Zealand). Appropriate inhibitors (mentioned below) were added to the collected blood samples before allowing the blood to clot for 30 min before centrifugation. Blood was centrifuged at 4000*g* for 7.5 min at 4 °C. Aliquots of separated plasma were stored at − 80 °C until use.

Laboratory assays

Glycated haemoglobin A1c and insulin were analysed at LabPlus (Auckland City Hospital, New Zealand). HbA1c was measured using the boronate affinity chromatography assay (Trinity Biotech, Ireland), while insulin was measured using the chemiluminescence sandwich immunoassay (Roche Diagnostics NZ Ltd.).

The MILLIPLEX® MAP Human metabolic hormone magnetic bead panel based on the Luminex xMAP® (Luminex Corporation, Austin, Texas, USA) technology was used to measure IL-6, MCP-1, TNFα, ghrelin, and peptide YY. Results were quantified based on fluorescent reporter signals recorded by the Luminex xPONENT® software (MILLIPLEX Analyst 5.1) and reported in ng/mL. All assays were performed in accordance with the user's manuals.

Cholecystokinin, GIP, glicentin, GLP-1, oxyntomodulin, secretin, and vasoactive intestinal peptide (VIP) were measured using the Merck-Millipore (MA, USA) ELISA kits as per the user's manuals. The Rayto Microplate Reader (V-2100C, Santa Fe, Granada, Spain) with an absorbance of 405–630 nm was used to read the results. Cholecystokinin, GIP, GLP-1, oxyntomodulin, secretin, and VIP results were reported in ng/mL, while results for glicentin were reported in pmol/L. Aprotinin inhibitor was added to all assays upon blood withdrawal except for GLP-1, to which the DPP-4 inhibitor was added.

Statistical analyses

The student's *t* test and Chi square test were used to investigate the differences in continuous and categorical baseline characteristics, respectively, between the two study groups. Data were presented as either mean ± standard

deviation (SD) or frequency. The subsequent statistical analyses were conducted in two steps.

First, a linear regression analysis was conducted to investigate the associations between gut hormones and pro-inflammatory cytokines. Each pro-inflammatory cytokine was investigated as a dependent variable in one unadjusted and three adjusted models. Model 1 was the unadjusted model. Model 2 was adjusted for age, sex, ethnicity, BMI, and smoking. Smoking status was recorded as yes or no based on the participants' response to a questionnaire asking whether or not they smoked tobacco or related products on a daily basis. Model 3 was adjusted for aetiology, recurrence, severity of acute pancreatitis, and time since acute pancreatitis. Aetiology was classified as biliary, alcohol-induced, or other. Individuals admitted with two or more episode of acute pancreatitis at the time of the study were determined as having recurrent acute pancreatitis. Severity of acute pancreatitis was determined based on the 2012 determinant-based classification [26]. Model 4 was adjusted for all the covariates in models 2 and 3. A main-effects model was fit for all four models to obtain the most conservative and robust estimates.

Second, a linear regression analysis was conducted to investigate the contribution of each gut hormone to the variance of each pro-inflammatory cytokine. Each gut hormone was investigated independently and in combination with every other gut hormone. The most robust R^2 value for each model was reported.

All analyses were conducted using SPSS for Windows Version 24 (IBM Corp., Armonk, New York, USA). p value < 0.05 was deemed to be statistically significant.

Results

Eighty-three individuals were recruited into the study (Fig. 1). Of these, 19 (23%) developed hyperglycaemia after an average of 32 months since an episode of acute pancreatitis while 64 did not. Individuals with hyperglycaemia had a significantly higher male:female ratio and were significantly older. Other baseline characteristics of the study participants are shown in Table 1.

Interleukin-6

Association with gut hormones

In the overall analysis, IL-6 increased with a change in concentration of GIP, ghrelin, peptide YY, and secretin in all four models (Table 2). For every ng/mL change in GIP, IL-6 increased most in model 4 with a β coefficient [95% CI] of 0.162 [0.116, 0.208] ($p < 0.001$), while for every ng/mL change in ghrelin, IL-6 increased most in model 3 with a β coefficient of 0.666 [0.187, 1.144] ($p = 0.006$). For every ng/mL change in peptide YY, IL-6 increased most in model 1 with a β coefficient of 0.082 [0.043, 0.121] ($p < 0.001$) while for every ng/mL change in secretin, IL-6 increased most in model 4 with a β coefficient of 44.238 [16.388, 72.088] ($p = 0.002$) (Table 2).

Interleukin-6 increased with a change in concentration of VIP in two models (Table 2). For every ng/mL change in VIP, IL-6 increased most in model 4 with a β coefficient of 26.089 [4.372, 47.806] ($p = 0.019$).

No change in IL-6 was observed with a change in concentrations of cholecystokinin, glicentin, GLP-1, and oxyntomodulin (Table 2).

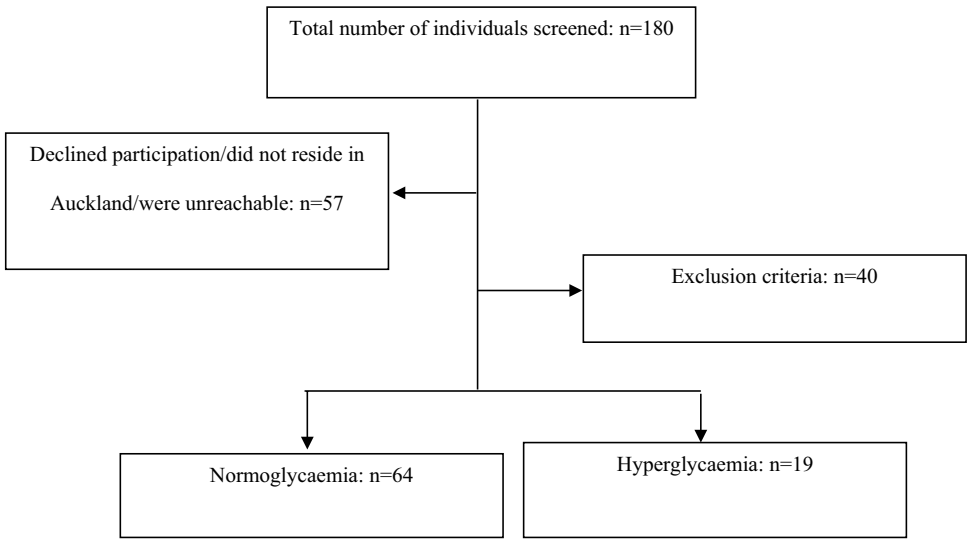

Fig. 1 Number of participants screened and recruited

Table 1 Baseline characteristics of study participants

Characteristic	Normoglycaemia ($n=64$)	Hyperglycaemia ($n=19$)	p
Age (years)[a]	48 ± 15	61 ± 12	**0.001**
Sex			**0.020**
Male	35	16	
Female	29	3	
Ethnicity			**0.024**
Europeans	35	12	
Maori	3	3	
Pacific Islanders	3	0	
Asian	5	4	
Other	18	0	
BMI (kg/m^2)[a]	27.42 ± 5.20	30.05 ± 6.51	0.072
Smoking			0.577
Yes	51	14	
No	13	5	
Aetiology			0.775
Biliary	28	9	
Alcohol	15	3	
Other	21	7	
Recurrence			0.776
No	45	14	
Yes	19	5	
Severity			**0.008**
Mild	57	11	
Moderate	5	6	
Severe/critical	2	2	

AP acute pancreatitis, *BMI* body mass index

p values < 0.05 are shown in bold

[a]Data are presented as mean ± standard deviation (SD)

The studied associations in the hyperglycaemia versus normoglycaemia groups are detailed in Table 2.

Contribution of gut hormones

The contribution of each gut hormone (independently and in combination with each other) to the variance of IL-6 is shown in Table 3. Of all the studied gut hormones, the three hormones independently contributing most to variance of circulating IL-6 were GIP (29.0%), peptide YY (17.4%), and secretin (8.1%). All the studied gut hormones cumulatively contributed 41.3% to the circulating IL-6 variance (Table 3).

Tumour necrosis factor α

Association with gut hormones

In the overall analysis, TNFα increased with a change in concentration of GIP, ghrelin, and peptide YY in all four models (Table 3). For every ng/mL change in GIP, TNFα increased most in model 3 with a β coefficient of 0.032 [0.023, 0.041] ($p<0.001$), while for every ng/mL change in ghrelin, TNFα increased most in model 1 with a β coefficient of 0.135 [0.045, 0.226] ($p=0.003$). For every ng/mL change in peptide YY, TNFα increased most in models 1 and 3 with a β coefficient of 0.026 [0.021, 0.032] ($p<0.001$) and 0.026 [0.020, 0.032] ($p<0.001$), respectively (Table 4).

Tumour necrosis factor α increased with a change in concentration of oxyntomodulin in one model only (Table 3). For every ng/mL change in oxyntomodulin, TNFα increased in model 4 with a β coefficient of 0.069 [0.002, 0.136] ($p=0.043$) (Table 4).

No change in TNFα concentration was observed with a change in concentration of cholecystokinin, glicentin, GLP-1, secretin, and VIP (Table 4).

The studied associations in the hyperglycaemia versus normoglycaemia groups are detailed in Table 4.

Contribution of gut hormones

The contribution of each gut hormone (independently and in combination with each other) to the variance of TNFα is shown in Table 5. Of all the studied gut hormones, the three hormones independently contributing most to variance of circulating TNFα were peptide YY (48.9%), GIP (35.4%), and ghrelin (9.6%). All the studied gut hormones cumulatively contributed 61.0% to the circulating TNFα variance (Table 5).

Monocyte chemoattractant protein-1

Association with gut hormones

In the overall analysis, MCP-1 increased with a change in concentration of GIP and peptide YY in all four models (Table 4). For every ng/mL change in GIP, MCP-1 increased most in model 3 with a β coefficient of 0.543 [0.402, 0.685] ($p<0.001$), while for every ng/mL change in peptide YY, MCP-1 increased most in model 1 with a β coefficient of 0.338 [0.230, 0.446] ($p<0.001$) (Table 6).

Monocyte chemoattractant protein 1 increased with a change in concentration of cholecystokinin in two models (Table 4). For every ng/mL change in cholecystokinin, MCP-1 increased most in model 1 with a β coefficient of 44.550 [1.766, 87.334] ($p=0.041$) (Table 6).

No change in MCP-1 concentration was observed with a change in concentration of ghrelin, glicentin, GLP-1, oxyntomodulin, secretin, and VIP (Table 6).

The studied associations in the hyperglycaemia versus normoglycaemia groups are detailed in Table 6.

Table 2 Associations between gut hormones and interleukin-6 in hyperglycaemia versus normoglycaemia

Gut hormone	Overall		Normoglycaemia		Hyperglycaemia	
	β [95% CI]	p	β [95% CI]	p	β [95% CI]	p
Cholecystokinin						
Model 1	10.328 [− 4.384, 25.039]	0.169	− 1.435 [− 8.624, 5.754]	0.691	58.989 [− 7.440, 125.417]	0.077
Model 2	10.069 [− 3.675, 23.814]	0.151	− 1.439 [− 7.220, 4.343]	0.626	43.271 [− 26.370, 112.913]	0.223
Model 3	11.481 [− 2.319, 25.281]	0.103	− 1.703 [− 8.435, 5.030]	0.620	74.708 [25.494, 123.922]	**0.003**
Model 4	11.138 [− 1.572, 23.848]	0.086	− 2.305 [− 7.956, 3.347]	0.424	262.767 [203.043, 322.491]	< **0.001**
GIP						
Model 1	0.145 [0.096, 0.195]	< **0.001**	0.051 [0.015, 0.086]	**0.006**	0.208 [0.074, 0.343]	**0.005**
Model 2	0.146 [0.099, 0.193]	< **0.001**	0.029 [− 0.003, 0.062]	0.075	0.219 [0.111, 0.326]	< **0.001**
Model 3	0.150 [0.100, 0.201]	< **0.001**	0.049 [0.016, 0.083]	**0.004**	0.336 [0.216, 0.457]	< **0.001**
Model 4	0.162 [0.116, 0.208]	< **0.001**	0.038 [0.006, 0.070]	**0.021**	0.333 [0.213, 0.452]	< **0.001**
Ghrelin						
Model 1	0.640 [0.167, 1.114]	**0.008**	0.379 [0.141, 0.617]	**0.002**	1.019 [− 0.865, 2.903]	0.270
Model 2	0.491 [0.026, 0.957]	**0.039**	0.262 [0.036, 0.489]	**0.023**	0.952 [− 0.504, 2.407]	0.200
Model 3	0.666 [0.187, 1.144]	**0.006**	0.385 [0.157, 0.612]	**0.001**	4.319 [1.460, 7.178]	**0.003**
Model 4	0.535 [0.079, 0.992]	**0.021**	0.244 [0.010, 0.478]	**0.041**	4.933 [0.905, 8.960]	**0.016**
Glicentin						
Model 1	0.180 [− 0.106, 0.467]	0.218	0.351 [0.132, 0.571]	**0.002**	0.040 [− 0.654, 0.734]	0.904
Model 2	0.120 [− 0.150, 0.391]	0.383	0.358 [0.180, 0.536]	< **0.001**	− 0.021 [− 0.543, 0.500]	0.937
Model 3	0.155 [− 0.132, 0.443]	0.289	0.360 [0.145, 0.575]	**0.001**	− 0.170 [− 0.918, 0.578]	0.655
Model 4	0.150 [− 0.120, 0.421]	0.276	0.404 [0.219, 0.589]	< **0.001**	− 0.453 [− 1.023, 0.117]	0.119
GLP-1						
Model 1	0.269 [− 0.019, 0.557]	0.067	0.263 [0.087, 0.438]	**0.004**	0.162 [− 0.670, 0.995]	0.686
Model 2	0.104 [− 0.183, 0.391]	0.476	0.024 [− 0.187, 0.236]	0.822	− 0.074 [− 0.793, 0.644]	0.839
Model 3	0.223 [− 0.094, 0.536]	0.165	0.253 [0.076, 0.429]	**0.005**	0.548 [− 0.392, 1.487]	0.253
Model 4	0.106 [− 0.213, 0.425]	0.514	0.054 [− 0.156, 0.265]	0.613	0.237 [− 1.067, 1.541]	0.721
Oxyntomodulin						
Model 1	0.105 [− 0.269, 0.478]	0.582	− 0.037 [− 0.215, 0.141]	0.678	3.158 [1.116, 5.199]	**0.005**
Model 2	0.212 [− 0.143, 0.567]	0.242	− 0.023 [− 0.166, 0.121]	0.757	2.446 [0.610, 4.281]	**0.009**
Model 3	0.133 [− 0.226, 0.492]	0.469	− 0.054 [− 0.218, 0.111]	0.521	3.892 [1.985, 5.800]	< **0.001**
Model 4	0.263 [− 0.081, 0.607]	0.134	− 0.033 [− 0.175, 0.109]	0.650	3.528 [1.639, 5.417]	< **0.001**
Peptide YY						
Model 1	0.082 [0.043, 0.121]	< **0.001**	0.031 [0.009, 0.054]	**0.007**	0.155 [0.019, 0.291]	**0.028**
Model 2	0.071 [0.032, 0.110]	< **0.001**	0.013 [− 0.007, 0.033]	0.194	0.123 [0.006, 0.240]	**0.039**
Model 3	0.073 [0.034, 0.111]	< **0.001**	0.029 [0.009, 0.050]	**0.006**	0.328 [0.201, 0.455]	< **0.001**
Model 4	0.070 [0.032, 0.107]	< **0.001**	0.013 [− 0.007, 0.032]	0.203	0.355 [0.232, 0.478]	< **0.001**
Secretin						
Model 1	38.446 [10.277, 66.614]	**0.007**	5.413 [− 6.303, 20.129]	0.465	151.361 [52.617, 250.104]	**0.005**
Model 2	29.452 [2.034, 56.870]	**0.035**	1.461 [− 10.571, 13.492]	0.812	161.394 [79.021, 243.767]	< **0.001**
Model 3	43.372 [14.053, 72.692]	**0.004**	1.973 [− 13.746, 17.693]	0.806	164.081 [48.308, 279.855]	**0.005**
Model 4	44.238 [16.388, 72.088]	**0.002**	0.191 [− 13.404, 13.786]	0.978	175.457 [86.625, 264.289]	< **0.001**
VIP						
Model 1	20.570 [− 1.887, 43.027]	0.073	9.613 [− 2.054, 21.279]	0.104	67.853 [− 15.065, 150.770]	0.102
Model 2	19.380 [− 2.553, 41.314]	0.083	3.657 [− 6.327, 13.640]	0.473	39.653 [− 26.320, 105.626]	0.239
Model 3	23.379 [1.253, 45.505]	**0.038**	5.948 [− 5.830, 17.725]	0.322	89.493 [27.038, 151.948]	**0.005**
Model 4	26.089 [4.372, 47.806]	**0.019**	0.562 [− 10.190, 11.315]	0.918	72.589 [21.259, 123.918]	**0.006**

All data are presented as β coefficients with corresponding 95% CI, and p value. p values < 0.05 are shown in bold. Model 1 was the unadjusted model. Model 2 was adjusted for age, sex, ethnicity, BMI, and smoking. Model 3 was adjusted for recurrence, time since acute pancreatitis, severity of acute pancreatitis, and aetiology. Model 4 was adjusted for all covariates in models 2 and 3

CI confidence intervals, *GIP* gastric inhibitory peptide, *GLP-1* glucagon-like peptide-1, *VIP* vasoactive intestinal peptide

Table 3 Contribution of gut hormones to the variance of interleukin-6

	Cholecystokinin	GIP	Ghrelin	Glicentin	GLP-1	Oxyntomodulin	Peptide YY	Secretin	VIP
Cholecystokinin	0.025								
GIP	0.367	0.290							
Ghrelin	0.379	0.303	0.080						
Glicentin	0.379	0.307	0.087	0.019					
GLP-1	0.380	0.307	0.088	0.054	0.040				
Oxyntomodulin	0.385	0.307	0.088	0.055	0.044	0.004			
Peptide YY	0.387	0.308	0.189	0.185	0.175	0.175	0.174		
Secretin	0.399	0.326	0.235	0.235	0.230	0.228	0.220	0.081	
VIP	0.413	0.333	0.252	0.251	0.244	0.240	0.223	0.081	0.039

Cells shown in yellow report an R^2 value of 0.000–0.200; cells shown in green report an R^2 value of 0.210–0.400; cells shown in red report an R^2 value of >0.400. For example, ghrelin independently contributes 8.0% to circulating IL-6 variance while oxyntomodulin, peptide YY, secretin, and VIP cumulatively contribute 24.0% to circulating IL-6 variance

IL-6 interleukin-6, *GIP* gastric inhibitory peptide, *GLP-1* glucagon-like peptide-1, *VIP* vasoactive intestinal peptide

Contribution of gut hormones

The contribution of each gut hormone (independently and in combination with each other) to the variance of MCP-1 is shown in Table 7. Of all the studied gut hormones, the three hormones independently contributing most to variance of circulating MCP-1 were GIP (36.5%), peptide YY (32.4%), and cholecystokinin (5.4%). All the studied gut hormones cumulatively contributed 50.4% to the circulating MCP-1 variance (Table 7).

Discussion

Metabolic derangements are common after acute pancreatitis and, at least in part, are driven by the immune system. This is the first clinical study to investigate the role of gut hormones in modulating the inflammatory response in post-pancreatitis state. The main finding of this study is that GIP and peptide YY independently contribute nearly 50% to variance of circulating levels of IL-6, TNFα, and MCP-1. Further, they are significantly associated with higher circulating levels of IL-6, TNFα, and MCP-1 consistently across all the four statistical models. Importantly, there was a clear evidence of interaction effect, with the associations between cytokines (IL-6 and MCP-1) and gut hormones (GIP and peptide YY) being significantly stronger in individuals with new-onset hyperglycaemia after acute pancreatitis as compared with normoglycaemic individuals. These findings provide evidence for the possible involvement of gut hormones (in particular, GIP and peptide YY) in mediating the immune response after an episode of acute pancreatitis, with translational and therapeutic implications.

Gastric inhibitory peptide, a 42 amino acid gut hormone secreted by the enteroendocrine K cells, has a well-established role in glucose homeostasis [27]. The structural similarities between GIP and other gut hormones, such as secretin and VIP (known insulin secretagogues), prompted speculation on the role of GIP as an "incretin" (insulin-releasing factor) in the 1970s [27]. It is now proven that GIP acts through GIP-specific G-protein-coupled receptors predominantly expressed on pancreatic β cells, in adipose tissue, and in the central nervous system [11]. Research to date has shown that in the state of chronic hyperglycaemia, sustained GIP receptor signalling results not only in glucose-dependent insulin exocytosis but also enhanced insulin biosynthesis, and stimulation of β-cell proliferation and resistance to apoptosis [11]. However, whether GIP mediates its glucoregulatory actions in a similar manner in post-pancreatitis setting, or uses alternative pathways, has never been investigated.

There are two hypotheses as to how GIP may be involved in glucose homeostasis in individuals after acute pancreatitis. The first hypothesis is that GIP mediates glucose regulation through the innate immune system. The importance of persistent low-grade inflammation in glucose dysregulation has increasingly been recognised, with recent studies showing that pro-inflammatory cytokine levels are elevated in individuals with post-pancreatitis (pre)diabetes mellitus [28, 29]. Evidence to date suggests that in individuals with chronic hyperglycaemia, the incretin effect of GIP is stunted and that it acts more as an inflammatory stimulator [9]. A study by Timper et al. [9], using isolated human pancreatic islets from cadaveric pancreata and rats, investigated GIP stimulated GLP-1 production by pancreatic islets via IL-6. Findings of the study showed that, in diabetic islets and murine models, GIP stimulated IL-6 secretion occurred exclusively in the α cells, followed by increased GLP-1 secretion, and that, in absence of IL-6, GIP-stimulated GLP-1 and insulin secretion was impaired. The authors concluded that in GIP stimulated GLP-1, insulin, and IL-6 secretion and improved glucose tolerance [9]. Findings from

Table 4 Associations between gut hormones and tumour necrosis factor α in hyperglycaemia versus normoglycaemia

Gut hormones	Overall		Normoglycaemia		Hyperglycaemia	
	β [95% CI]	*p*	*β* [95% CI]	*p*	*β* [95% CI]	*p*
Cholecystokinin						
Model 1	1.923 [− 0.824, 4.670]	0.170	− 0.075 [− 3.143, 2.993]	0.962	10.478 [6.597, 14.360]	**< 0.001**
Model 2	2.099 [− 0.526, 4.725]	0.117	0.160 [− 2.678, 2.997]	0.912	8.594 [4.099, 13.089]	**< 0.001**
Model 3	1.613 [− 1.074, 4.300]	0.239	− 0.201 [− 3.247, 2.845]	0.897	6.801 [3.885, 9.718]	**< 0.001**
Model 4	1.704 [− 0.871, 4.280]	0.195	− 0.296 [− 3.191, 2.599]	0.841	13.141 [10.706, 15.576]	**< 0.001**
GIP						
Model 1	0.031 [0.022, 0.040]	**< 0.001**	0.047 [0.035, 0.058]	**< 0.001**	0.018 [0.003, 0.032]	**0.016**
Model 2	0.029 [0.020, 0.039]	**< 0.001**	0.045 [0.033, 0.058]	**< 0.001**	0.009 [− 0.005, 0.023]	0.212
Model 3	0.032 [0.023, 0.041]	**< 0.001**	0.045 [0.034, 0.057]	**< 0.001**	0.012 [− 0.006, 0.030]	0.194
Model 4	0.031 [0.022, 0.040]	**< 0.001**	0.046 [0.034, 0.058]	**< 0.001**	0.001 [− 0.016, 0.019]	0.894
Ghrelin						
Model 1	0.135 [0.045, 0.226]	**0.003**	0.112 [0.004, 0.220]	**0.043**	0.199 [0.033, 0.365]	**0.019**
Model 2	0.121 [0.030, 0.212]	**0.009**	0.129 [0.015, 0.242]	**0.026**	0.165 [0.031, 0.300]	**0.016**
Model 3	0.125 [0.033, 0.217]	**0.008**	0.122 [0.015, 0.230]	**0.026**	0.179 [− 0.143, 0.502]	0.277
Model 4	0.117 [0.028, 0.206]	**0.010**	0.153 [0.035, 0.272]	**0.011**	− 0.104 [− 0.522, 0.314]	0.627
Glicentin						
Model 1	0.038 [− 0.018, 0.093]	0.184	− 0.062 [− 0.165, 0.040]	0.233	0.078 [0.021, 0.135]	**0.007**
Model 2	0.035 [− 0.018, 0.088]	0.200	− 0.048 [− 0.145, 0.049]	0.332	0.064 [0.020, 0.108]	**0.004**
Model 3	0.039 [− 0.015, 0.094]	0.156	− 0.071 [− 0.175, 0.032]	0.176	0.065 [− 0.001, 0.131]	0.054
Model 4	0.039 [− 0.013, 0.091]	0.142	− 0.059 [− 0.161, 0.043]	0.259	0.092 [0.055, 0.129]	**< 0.001**
GLP-1						
Model 1	0.045 [− 0.011, 0.101]	0.117	0.066 [− 0.014, 0.146]	0.107	0.023 [− 0.057, 0.103]	0.573
Model 2	0.036 [− 0.020, 0.092]	0.212	0.074 [− 0.030, 0.179]	0.163	0.024 [− 0.048, 0.096]	0.510
Model 3	0.021 [− 0.040, 0.082]	0.494	0.053 [− 0.031, 0.136]	0.216	− 0.038 [− 0.130, 0.054]	0.420
Model 4	0.028 [− 0.034, 0.090]	0.375	0.087 [− 0.016, 0.190]	0.099	− 0.091 [− 0.203, 0.022]	0.115
Oxyntomodulin						
Model 1	0.052 [− 0.019, 0.124]	0.151	0.044 [− 0.032, 0.120]	0.258	0.207 [− 0.026, 0.440]	0.082
Model 2	0.068 [0.000, 0.136]	0.052	0.052 [− 0.017, 0.121]	0.138	0.048 [− 0.167, 0.264]	0.660
Model 3	0.055 [− 0.014, 0.123]	0.120	0.043 [− 0.031, 0.118]	0.255	0.140 [− 0.101, 0.381]	0.255
Model 4	0.069 [0.002, 0.136]	**0.043**	0.051 [− 0.019, 0.122]	0.154	0.008 [− 0.218, 0.233]	0.946
Peptide YY						
Model 1	0.026 [0.021, 0.032]	**< 0.001**	0.029 [0.022, 0.036]	**< 0.001**	0.024 [0.013, 0.035]	**< 0.001**
Model 2	0.025 [0.019, 0.031]	**< 0.001**	0.026 [0.018, 0.034]	**< 0.001**	0.019 [0.009, 0.029]	**< 0.001**
Model 3	0.026 [0.020, 0.032]	**< 0.001**	0.028 [0.022, 0.035]	**< 0.001**	0.027 [0.013, 0.041]	**< 0.001**
Model 4	0.024 [0.018, 0.030]	**< 0.001**	0.027 [0.019, 0.035]	**< 0.001**	0.016 [− 0.001, 0.033]	0.061
Secretin						
Model 1	4.302 [− 1.294, 9.899]	0.132	1.317 [− 5.087, 7.721]	0.687	14.607 [4.434, 24.779]	**0.005**
Model 2	3.289 [− 2.202, 8.780]	0.240	1.271 [− 4.722, 7.263]	0.678	12.218 [2.561, 21.875]	**0.013**
Model 3	4.567 [− 1.343, 10.478]	0.130	2.304 [− 4.938, 9.546]	0.533	7.042 [− 5.776, 19.860]	0.282
Model 4	4.567 [− 1.130, 10.264]	0.116	2.826 [− 4.017, 9.670]	0.418	9.181 [− 0.875, 19.237]	0.074
VIP						
Model 1	0.398 [− 3.993, 4.790]	0.859	0.793 [− 4.339, 5.924]	0.762	− 0.366 [− 9.038, 8.306]	0.934
Model 2	− 0.363 [− 4.623, 3.898]	0.867	− 0.259 [− 5.078, 4.561]	0.916	− 5.748 [− 12.164, 0.667]	0.079
Model 3	0.064 [− 4.473, 4.601]	0.978	− 0.861 [− 6.475, 4.754]	0.764	− 1.637 [− 8.744, 5.471]	0.652
Model 4	− 0.506 [− 5.030, 4.017]	0.826	− 1.751 [− 7.429, 3.927]	0.546	− 5.177 [− 10.232, − 0.122]	**0.045**

All data are presented as *β* coefficients with corresponding 95% CI, and *p* value. *p* values < 0.05 are shown in bold. Model 1 was the unadjusted model. Model 2 was adjusted for age, sex, ethnicity, BMI, and smoking. Model 3 was adjusted for recurrence, time since acute pancreatitis, severity of acute pancreatitis, and aetiology. Model 4 was adjusted for all covariates in models 2 and 3

CI confidence intervals, *GIP* gastric inhibitory peptide, *GLP-1* glucagon-like peptide-1, *VIP* vasoactive intestinal peptide

Table 5 Contribution of gut hormones to the variance of tumour necrosis factor α

	Cholecystokinin	GIP	Ghrelin	Glicentin	GLP-1	Oxyntomodulin	Peptide YY	Secretin	VIP
Cholecystokinin	0.025								
GIP	0.340	0.354							
Ghrelin	0.351	0.369	0.096						
Glicentin	0.349	0.370	0.101	0.022					
GLP-1	0.352	0.374	0.101	0.046	0.030				
Oxyntomodulin	0.361	0.386	0.113	0.061	0.054	0.025			
Peptide YY	0.603	0.566	0.541	0.541	0.531	0.502	0.489		
Secretin	0.608	0.568	0.541	0.541	0.531	0.503	0.490	0.027	
VIP	0.610	0.574	0.543	0.542	0.535	0.513	0.489	0.022	0.000

Cells shown in yellow report an R^2 value of 0.000–0.200; cells shown in green report an R^2 value of 0.210–0.400; cells shown in red report an R^2 value of > 0.400. For example, GLP-1 independently contributes 3.0% to circulating TNFα variance while secretin and VIP cumulatively contribute 2.2% to circulating TNFα variance

GIP gastric inhibitory peptide, *GLP-1* glucagon-like peptide-1, *TNF*α tumour necrosis factor α, *VIP* vasoactive intestinal peptide

our study are in line with those reported by Timper et al. [9] in that, in individuals with hyperglycaemia, every 1 ng/mL change in GIP results in a 33.3% increase in IL-6 compared to a 3.8% increase in individuals with normoglycaemia. It is likely that this increase is triggered by the state of hyperglycaemia after acute pancreatitis. However, in contrast to the study by Timper et al. [9], we did not observe a significant association between GLP-1 and any of the studied cytokines. Evidence from a recent study shows that fasting GLP-1 concentrations are not changed in individuals after acute pancreatitis [30]. Given that GLP-1 is an insulin secretagogue and has glucose-lowering effect, it is possible that hyperglycaemia after acute pancreatitis could be attributed to the compromised GIP-cytokine-GLP-1 pathway. However, given that GLP-1 is considered to be secreted mainly postprandially, in order to determine whether or not this pathway is indeed compromised in individuals with hyperglycaemia after acute pancreatitis, future studies should investigate the interaction between GIP, pro-inflammatory cytokines, and GLP-1 using the gold standard hyperglycaemic-euglycaemic clamps or mixed-meal tolerance test [31, 32].

The second hypothesis as to how GIP may be involved in glucose homeostasis after acute pancreatitis is via the adipose tissue—a recognised endocrine organ that is involved in persistent low-grade inflammation. Pre-clinical and clinical studies show that adipose tissue plays a critical role in both glucose metabolism and acute pancreatitis [12, 33, 34]. Evidence to date suggests that macrophages infiltrate adipose tissue and release pro-inflammatory cytokines (such as IL-6, TNFα, and MCP-1), which act directly on adipocytes affecting their insulin sensitivity (among other biological actions) [12]. Several studies spanning over two decades have shown that adipose tissue, in addition to glucose, is a potent stimulant of GIP [35–38]. A randomised controlled trial by Gogebakan et al. [12], involving 17 obese males with normal glucose metabolism and no evidence of any other metabolic disease, found that GIP infusions, compared to saline infusions, resulted in significantly increased MCP-1 levels in both blood and adipose tissue [12]. The authors concluded that GIP induces a broad inflammatory response involving MCP-1 and IL-6 in human adipose tissue. Given that inflammatory signals originating from adipose tissue are well-known components in the development of insulin resistance and resulting disease states (such as type 2 diabetes), and have also been implicated in glucose derangements following pancreatitis [28, 29], we hypothesise that GIP may modulate glucose homeostasis via the GIP receptors present on adipose-tissue infiltrating macrophages. Although we did not conduct a detailed body-composition analysis, all analyses were adjusted for BMI (an accepted proxy for general obesity) [39, 40]. Nonetheless, in order to accurately determine the involvement of adipose tissue in GIP-modulated glucose homeostasis, the use of magnetic resonance imaging or dual-energy X-ray absorptiometry [41, 42] is warranted in future studies.

In addition to GIP, peptide YY is another gut hormone that plays an important role in subclinical inflammation [43, 44] in individuals after acute pancreatitis. Peptide YY is a 36 amino acid peptide that is, similarly to GIP, cleaved by dipeptidyl peptidase-4 [44]. It may mediate its actions through Y receptors with particular affinity to the Y2 receptor and is expressed by cell systems at distinct levels of the gut-brain axis, albeit the major source of peptide YY is the enteroendocrine L cells. The gut-brain axis is defined as a bi-directional communication between the gut and the brain with mediators (such as pro-inflammatory cytokines and gut hormones) transmitting information from the gut to the brain. Recent evidence shows that glucose dysregulation after acute pancreatitis may be attributed to a dysfunctional gut-brain axis [30]. Yet, the interaction between peptide YY and pro-inflammatory cytokines specifically in individuals with hyperglycaemia after acute pancreatitis has never been

Table 6 Associations between gut hormones and monocyte chemoattractant protein-1 in hyperglycaemia versus normoglycaemia

Gut hormones	Overall		Normoglycaemia		Hyperglycaemia	
	β [95% CI]	p	β [95% CI]	p	β [95% CI]	p
Cholecystokinin						
Model 1	44.550 [1.766, 87.334]	**0.041**	11.525 [− 32.865, 55.915]	0.611	208.380 [124.606, 292.154]	**< 0.001**
Model 2	41.454 [0.881, 82.028]	**0.045**	14.053 [− 27.954, 56.061]	0.512	171.302 [104.186, 238.418]	**< 0.001**
Model 3	38.033 [− 4.229, 80.296]	0.078	8.479 [− 36.292, 53.250]	0.710	178.421 [111.451, 245.392]	**< 0.001**
Model 4	34.360 [− 5.954, 74.673]	0.095	17.894 [− 29.159, 64.948]	0.448	237.369 [109.365, 365.374]	**0.010**
GIP						
Model 1	0.495 [0.351, 0.639]	**< 0.001**	0.742 [0.580, 0.903]	**< 0.001**	0.282 [− 0.013, 0.578]	0.061
Model 2	0.449 [0.303, 0.595]	**< 0.001**	0.709 [0.539, 0.879]	**< 0.001**	0.094 [− 0.166, 0.354]	0.480
Model 3	0.543 [0.402, 0.685]	**< 0.001**	0.752 [0.591, 0.913]	**< 0.001**	0.414 [0.106, 0.723]	**0.008**
Model 4	0.508 [0.372, 0.644]	**< 0.001**	0.709 [0.543, 0.876]	**< 0.001**	0.038 [− 0.342, 0.417]	0.846
Ghrelin						
Model 1	0.857 [− 0.648, 2.361]	0.265	0.505 [− 1.148, 2.158]	0.549	1.702 [− 1.934, 5.339]	0.359
Model 2	0.736 [− 0.752, 2.223]	0.332	1.145 [− 0.629, 2.918]	0.206	1.411 [− 1.639, 4.462]	0.365
Model 3	0.845 [− 0.684, 2.375]	0.279	0.666 [− 1.020, 2.352]	0.439	3.552 [− 2.927, 10.031]	0.283
Model 4	0.825 [− 0.629, 2.279]	0.266	1.456 [− 0.345, 3.256]	0.113	4.263 [− 1.901, 10.427]	0.175
Glicentin						
Model 1	0.468 [− 0.417, 1.353]	0.300	0.071 [− 1.476, 1.617]	0.929	0.600 [− 0.631, 1.832]	0.339
Model 2	0.336 [− 0.509, 1.181]	0.436	0.309 [− 1.200, 1.819]	0.688	0.197 [− 0.673, 1.067]	0.658
Model 3	0.448 [− 0.453, 1.349]	0.330	0.095 [− 1.523, 1.712]	0.909	0.166 [− 1.283, 1.616]	0.822
Model 4	0.383 [− 0.456, 1.223]	0.371	− 0.141 [− 1.733, 1.450]	0.862	0.727 [0.175, 1.279]	**0.010**
GLP-1						
Model 1	0.443 [− 0.448, 1.335]	0.330	0.765 [− 0.432, 1.961]	0.210	0.062 [− 1.460, 1.584]	0.936
Model 2	0.342 [− 0.554, 1.237]	0.455	1.296 [− 0.267, 2.859]	0.104	− 0.500 [− 1.809, 0.809]	0.454
Model 3	0.226 [− 0.758, 1.210]	0.652	0.803 [− 0.472, 2.079]	0.217	− 0.517 [− 2.339, 1.305]	0.578
Model 4	0.287 [− 0.711, 1.285]	0.573	1.159 [− 0.413, 2.731]	0.149	0.012 [− 1.635, 1.659]	0.989
Oxyntomodulin						
Model 1	0.842 [− 0.301, 1.984]	0.149	0.632 [− 0.504, 1.768]	0.276	4.364 [0.053, 9.214]	**0.047**
Model 2	1.077 [− 0.014, 2.168]	0.053	0.727 [− 0.332, 1.786]	0.178	0.582 [− 3.462, 4.625]	0.778
Model 3	0.861 [− 0.258, 1.981]	0.132	0.617 [− 0.512, 1.746]	0.284	5.141 [0.526, 9.756]	**0.029**
Model 4	0.955 [− 0.124, 2.034]	0.083	0.630 [− 0.444, 1.704]	0.250	0.894 [− 2.537, 4.325]	0.610
Peptide YY						
Model 1	0.338 [0.230, 0.446]	**< 0.001**	0.323 [0.194, 0.451]	**< 0.001**	0.426 [0.200, 0.652]	**< 0.001**
Model 2	0.329 [0.220, 0.438]	**< 0.001**	0.316 [0.186, 0.447]	**< 0.001**	0.346 [0.154, 0.538]	**< 0.001**
Model 3	0.336 [0.225, 0.446]	**< 0.001**	0.320 [0.190, 0.449]	**< 0.001**	0.641 [0.431, 0.850]	**< 0.001**
Model 4	0.321 [0.213, 0.429]	**< 0.001**	0.317 [0.186, 0.447]	**< 0.001**	0.360 [0.107, 0.614]	**0.005**
Secretin						
Model 1	79.094 [− 12.046, 170.234]	0.089	26.131 [− 68.915, 121.177]	0.590	342.174 [117.962, 566.387]	**0.003**
Model 2	62.816 [− 25.868, 151.501]	0.165	42.257 [− 47.404, 131.919]	0.356	219.700 [3.557, 435.843]	**0.046**
Model 3	97.077 [− 0.088, 194.243]	0.050	42.951 [− 65.937, 151.838]	0.439	260.018 [4.971, 515.066]	**0.046**
Model 4	79.971 [− 12.426, 172.367]	0.090	39.726 [− 62.727, 142.179]	0.447	201.028 [82.480, 319.576]	**0.001**
VIP						
Model 1	44.791 [− 23.898, 113.480]	0.201	49.540 [− 22.697, 121.777]	0.179	30.645 [− 148.418, 209.708]	0.737
Model 2	37.807 [− 28.362, 103.975]	0.263	46.567 [− 22.305, 115.439]	0.185	− 92.148 [− 216.521, 32.226]	0.146
Model 3	40.857 [− 31.906, 113.621]	0.271	39.443 [− 40.653, 119.538]	0.334	82.031 [− 72.322, 236.384]	0.298
Model 4	21.820 [− 50.133, 93.773]	0.552	32.954 [− 46.877, 112.785]	0.418	− 92.304 [− 163.607, − 21.002]	**0.011**

All data are presented as β coefficients with corresponding 95% CI, and p value. p values < 0.05 are shown in bold. Model 1 was the unadjusted model. Model 2 was adjusted for age, sex, ethnicity, BMI, and smoking. Model 3 was adjusted for recurrence, time since acute pancreatitis, severity of acute pancreatitis, and aetiology. Model 4 was adjusted for all covariates in models 2 and 3

CI confidence intervals, *GIP* gastric inhibitory peptide, *GLP-1* glucagon-like peptide-1, *VIP* vasoactive intestinal peptide

Table 7 Contribution of gut hormones to the variance of monocyte chemoattractant protein-1

	Cholecystokinin	GIP	Ghrelin	Glicentin	GLP-1	Oxyntomodulin	Peptide YY	Secretin	VIP
Cholecystokinin	0.054								
GIP	0.394	0.365							
Ghrelin	0.401	0.369	0.016						
Glicentin	0.405	0.376	0.024	0.014					
GLP-1	0.405	0.376	0.026	0.023	0.012				
Oxyntomodulin	0.414	0.398	0.043	0.041	0.038	0.026			
Peptide YY	0.502	0.491	0.408	0.379	0.371	0.342	0.324		
Secretin	0.503	0.493	0.421	0.384	0.376	0.343	0.332	0.035	
VIP	0.504	0.496	0.426	0.392	0.380	0.344	0.337	0.033	0.021

Cells shown in yellow report an R^2 value of 0.000–0.200; cells shown in green report an R^2 value of 0.210–0.400; cells shown in red report an R^2 value of >0.400. For example, cholecystokinin independently contributes 5.4% to circulating MCP-1 variance while peptide YY, secretin, and VIP cumulatively contribute 33.7% to circulating MCP-1 variance

GIP gastric inhibitory peptide, *GLP-1* glucagon-like peptide-1, *MCP-1* monocyte chemoattractant protein 1, *VIP* vasoactive intestinal peptide

investigated. Findings from our present study show, for the first time, that peptide YY independently contributes substantially to variance in circulating levels of pro-inflammatory cytokines in all individuals after acute pancreatitis (17.4, 48.9, and 32.4% to IL-6, TNFα, and MCP-1, respectively). Another novel finding of this study is that peptide YY contributes to higher IL-6 and MCP-1 levels in individuals with hyperglycaemia after acute pancreatitis compared to those with normoglycaemia. Specifically, every 1 ng/mL change in peptide YY in the former results in a 35.5% increase in IL-6 compared to a 1.3% increase in the latter. Similarly, every 1 ng/mL change in peptide YY results in a 64.1% increase in MCP-1 in individuals with hyperglycaemia after acute pancreatitis compared to a 32.0% increase in individuals with normoglycaemia. The lack of effect on TNFα levels may be attributed to short circulating half-life of the cytokine in blood [10].

Findings of this study may have translational implications [45–49]. Taking into account the important role GIP, peptide YY, and the pro-inflammatory cytokines play in development of hyperglycaemia after acute pancreatitis, the receptors of these mediators may be (in general) promising therapeutic targets. Given that GIP-dependent recruitment of macrophages in adipose tissue results in inflammation (particularly due to MCP-1 secretion) and subsequent hyperglycaemia [12], GIP receptor antagonist and MCP-1 receptor antagonist may prove beneficial in reducing adipose tissue inflammation [50] and, thereby, in prevention of hyperglycaemia. The Y receptors, to which peptide YY binds, could prove to be another therapeutic option in breakdown of the vicious metabolic cycle resulting in glucose dysregulation and subsequent prevention of diabetes of the exocrine pancreas. To date, peptide YY-binding Y receptors (with the exception of the extensively investigated Y1 receptor) have received minimal research attention. Gene knock-out and transgenic models may now need to be developed to isolately study the effect of each receptor and to determine the one that may be targeted to abrupt the inflammatory process and mitigate hyperglycaemia.

In conclusion, GIP and peptide YY appear to be key modulators of persistent low-grade inflammation in individuals after acute pancreatitis, and also appear to be involved in the interaction between the gut and the pancreas (via the immune system) specifically in individuals with deranged glucose homeostasis after acute pancreatitis. It is also worth noting that GIP and peptide YY independently contribute to nearly half of circulating levels of the studied pro-inflammatory cytokines. Investigations using hyperglycaemic-euglycaemic clamps or mixed-meal tolerance test, as well as magnetic resonance imaging or dual-energy X-ray absorptiometry, are now warranted to gain further insights into the cross-talk between GIP/peptide YY and pro-inflammatory cytokines (via adipose tissue) in individuals after acute pancreatitis.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

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