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Utility of the Plasma Pancreatic Polypeptide Response to Modified Sham Feeding in Diabetic Gastroenteropathy and Non-Ulcer Dyspepsia

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Abstract

Background.—The relationship between cardiovascular and gastrointestinal (ie, plasma pancreatic polypeptide [PP] response to modified sham feeding [MSF]) indices of vagal function is unclear. Hyperglycemia inhibits PP secretion via vagally-mediated mechanisms. Our aims were to (i) compare the PP response, (ii) its relationship with glycemia and (iii) the relationship between PP response to MSF, gastric emptying (GE) of solids, and symptoms during GE study in healthy controls, patients with diabetic gastroenteropathy (DM), and non-ulcer dyspepsia (NUD).

Methods.—In 24 healthy controls, 40 DM, and 40 NUD patients, we measured plasma PP concentrations during MSF, cardiovascular functions, GE, and symptoms during a GE study.

Key Results.—Baseline PP concentrations were higher in DM than in controls and NUD ($P=0.01$), and in type 2 than in type 1 DM patients ($P<0.01$). The PP increment during MSF was normal (> 20 pg/mL) in 70% of controls, 54% of DM and 47% of NUD patients. Overall, the PP response and cardiovascular tests were concordant ($p=0.01$). Among patients with a reduced PP increment with MSF, 7/10 of T1DM and 1/7 of T2DM patients had moderate or severe cardiovascular dysfunctions ($P<0.05$). The PP response to MSF was not associated with GE.

Conclusions & Inferences.—Up to 30% of healthy controls have a reduced PP increment during MSF, limiting the utility of this test to detect vagal injury. The PP response is more useful when it is normal than abnormal. A reduced PP response is more likely to be associated with cardiovascular dysfunctions in T1DM than in T2DM.

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DISCLOSURES

Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH.

Keywords

Diabetic gastroparesis; diabetes mellitus; vagus; autonomic; autonomic neuropathy

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Introduction

In addition to conveying afferent information (e.g., in response to distention or chemical stimuli), the vagus nerve exerts both excitatory and inhibitory control over gastric and intestinal tone and motility.(1, 2) Autonomic neuropathy and surgical injury (e.g., after fundoplication) are arguably the commonest causes of vagal nerve injury among patients with upper gastrointestinal symptoms. Vagal nerve function can be assessed with cardiovascular tests (i.e., heart rate responses to deep breathing and Valsalva maneuver) or by measuring the plasma concentrations of pancreatic polypeptide (PP) in response to insulin-induced hypoglycemia, sham feeding, or modified sham feeding.(3, 4) Insulin-induced hypoglycemia and sham feeding, which entails swallowing food but preventing it from reaching the stomach, are cumbersome procedures. Hence, the cardiovascular indices of vagal nerve function and modified sham feeding (MSF), in which food is chewed and spat out but not swallowed are used in clinical practice.

During MSF, anticipation of a meal, then visual, olfactory, gustatory, and oropharyngeal stimuli, initiate the cephalic phase of digestion, which increases the plasma concentration of pancreatic polypeptide (PP).(5) This reflex entails afferent signals that are relayed to, and integrated in, the central nervous system followed by activation of neurons in vagal motor nuclei that project to the pancreatic D cells, inducing release of PP among other effects. After the cephalic phase, swallowing of food evokes the gastric and intestinal phases that are accompanied by a more pronounced rise in PP. Hence, while it has been used to assess vagal function in patients with suspected diabetic neuropathy,(6, 7) the PP response to a meal is flawed for evaluating vagal function since meal ingestion also activates local gastric and intestinal reflexes to increase PP secretion separate from central vagal mechanisms.

Five studies with a total of 83 patients evaluated the PP response to MSF in patients with diabetes mellitus (DM) and gastrointestinal symptoms.(8–12) Identifying vagal nerve injury with the PP response to MSF or cardiovascular vagal tests is limited by several factors. First, the normal PP response to MSF is variable.(8, 11–15) Several studies considered an increment of 20 pg/ml or greater, or 25 pg/ml or greater, as normal.(11, 16) In the largest study with 24 healthy controls, the average (range) for the PP increment was 219 pg/ml (20–460 pg/ml).(11) However, MSF does not increase PP in some healthy controls.(13) Since the PP response is variable in healthy people, studies evaluating the PP response in disease should ideally include healthy controls. However, most studies are uncontrolled. Second, the relationship between the plasma PP response and cardiovascular vagal tests, which are widely used for evaluating vagal functions in clinical practice, is variable.(11, 17, 18) Hence, the utility of cardiovascular vagal tests for assessing vagal innervation of the gastrointestinal tract is unclear. Third, the consequences of an impaired PP response on gastric emptying and sensation are unclear because the relationship between the PP response and gastric emptying has only been evaluated in patients with fundoplication, which can affect gastric emptying

independent of vagal nerve injury.(19) Conceivably afferent vagal dysfunction explains why a majority of patients with DM and delayed gastric emptying have no or mild symptoms. (20) Indeed, in one study, abnormal cortical evoked potential responses to esophageal stimulation, suggestive of afferent vagal nerve dysfunction, were associated with reduced gastrointestinal symptoms in DM.(21) Fourth, in healthy people, hyperglycemia inhibits PP secretion via vagally-mediated mechanisms.(22, 23) However, the effect of ambient blood glucose concentrations on the PP response to MSF in patients has not been evaluated.

Hence, the aims of this study were to compare the plasma PP response to MSF (i) in healthy controls, patients with diabetic gastroenteropathy, and non-ulcer dyspepsia and separately in patients with type 1 (T1DM) and type 2 (T2DM) diabetes mellitus, (ii) with cardiovascular indices of vagal function (iii) with gastric emptying and (iv) symptoms during the gastric emptying study

Methods

Study participants

Participants between the ages of 18 and 70 years were recruited through public advertisement (controls, n=24) and from the clinical practice (patients, n=80). The main exclusion criteria for all participants were age <18 or >70 years; another condition or gastrointestinal structural disorder that may cause gastrointestinal symptoms; DM (controls only); clinically significant systemic (e.g., cardiovascular, respiratory, renal) disease that may interfere with study objectives or pose safety concerns; GI surgery other than appendectomy, cholecystectomy, hysterectomy, tubal ligation, or inguinal hernia repair; or medications likely to affect GI motility. The results of the gastric emptying studies in this cohort have been published previously.(24, 25) The study was approved by the Mayo Clinic Institutional Review Board and conducted between June 2014 and May 2017 at the Mayo Clinic, Rochester, Minnesota. All participants signed informed consent.

Questionnaires

Patients recorded their daily gastrointestinal symptoms in the Gastroparesis Cardinal Symptom Index-Daily Diary (GCSI-DD) for 2 weeks.(26, 27) Anxiety and depression were recorded with the Hospital Anxiety and Depression Scale (HADS) questionnaire; scores of 11 or greater were considered abnormal.(28)

Assessment of pancreatic polypeptide response to modified sham feeding

Before the test, participants fasted for 8 hours, abstained from coffee for 12 hours, and stopped all cholinergic agents for 48 hours. During MSF, they were asked to chew and spit out but not swallow fried bacon.(29) After placement of an IV in the hand or forearm vein for blood draws, this hand was placed in a hotbox heated to 55°C. Blood was drawn at 5 minutes before baseline, at baseline, and at 5, 10, 15, 20, 25, and 30 minutes after participants started chewing bacon. HPP concentrations were analyzed by radioimmunoassay using rabbit anti-human pancreatic polypeptide (PP) antiserum, a standard or patient plasma specimen, and radiolabeled human PP that has been iodinated by a modified Hunter-Greenwood technique.(30) During MSF, an increment of 25 pg/ml or

greater above the baseline or 5 minutes before baseline value, whichever was lower, was considered to be normal.(16)

Gastric emptying

Gastric emptying of solids and liquids was assessed with scintigraphy.(31, 32) The test meal (296 kcal; 32% protein, 35% fat, and 33% carbohydrate) consisted of 2 eggs labeled with technetium Tc 99m sulfur colloid (1 mCi) served on 1 slice of bread with milk (240 ml) labeled with indium In 111 diethylenetriaminepentaacetate (0.1 mCi). During the four hour GE study, participants recorded the severity of six symptoms – nausea, fullness, bloating, abdominal pain, belching, and burning - at 15-minute intervals on a Likert scale marked absent(0), light(1), moderate(2), severe(3) and intolerable(4).(24, 33) Participants who had symptoms with a VAS score ≥ 3 for any sub-score were considered to have severe symptoms.

Cardiovagal function

Using extensively validated techniques, the heart rate responses to deep breathing and the Valsalva maneuver were studied under standardized conditions.(34) Using a semi-quantitative composite autonomic severity score (CASS), the responses were characterized as 0 (none), 1 (mild dysfunction), 2 (moderate dysfunction), and 3 (severe dysfunction), adjusted for age and sex.(34)

Statistical Analysis

Plasma PP concentrations at baseline and the greatest difference during MSF were compared among the groups using an analysis of variance. Spearman's correlation coefficients were used to compare the relationship between the PP response and BMI, fasting blood glucose, gastric emptying $t_{1/2}$, symptoms during the gastric emptying study and during lipid infusion and the CASS scores. The association between the PP response and cardiovagal tests and other variables was evaluated using Fisher's exact test. All statistical analyses were performed using JMP® Pro (Version 13.0).

Results

Demographic and Clinical Characteristics

The distribution of age, sex, and BMI was not significantly different among healthy controls, DM, and NUD (Table 1). However, among DM patients, the BMI was greater ($P=0.004$) in T2DM ($n=18$) than T1DM ($n=21$) (Table 2). The complications of DM included neuropathy ($n=30$), nephropathy ($n=16$), and retinopathy ($n=16$). The GCSI daily diary scores suggested none (score=0; 11 controls, 1 DM), very mild (score $>0-1.0$; 11 controls, 14 DM, 10 NUD), mild (score $>1.0-2.0$; 12 DM, 11 NUD), moderate (score $>2.0-3.0$; 9 DM, 14 NUD), severe (score $>3.0-4.0$; 1 DM, 1 NUD) or very severe (score $>4-5.0$; 1 NUD) upper gastrointestinal symptoms. The DM patients were being treated with insulin (32 patients), metformin (11 patients), sulfonylureas (2 patients), and dipeptidyl peptidase-4 (DPP-4) inhibitors (2 patients). One patient each was being treated with a SGLT2 inhibitor, a thiazolidinedione, and a GLP-1 agonist. Among patients with DM, 5 had definite anxiety, one had definite

depression, and one had both. Eight NUD patients had definite anxiety while 3 patients had definite depression and anxiety.

Baseline plasma pancreatic polypeptide concentrations

In one control and one patient each with DM and NUD, the plasma PP increased progressively over 30 minutes by 889 pg/ml, 204 pg/ml and 476 pg/ml, which suggests gastric and/or intestinal stimulation probably resulting from swallowed food. Another NUD patient did not complete the test. Hence, the PP data were analyzed in 23 of 24 controls, 39 of 40 DM, and 39 of 40 NUD patients.

The average of two plasma PP values (i.e., 5 minutes before and immediately before the sham feeding study was started) was used as the baseline. The baseline PP concentration differed among the three groups ($P=0.01$) (Table 1). Compared to controls (113 ± 8 pg/mL, Mean $\pm$ SEM), values were greater (151 ± 19 pg/mL) in DM and lower (94 ± 9 pg/mL) in NUD. The baseline plasma PP concentrations were correlated ($r=0.26$, $P=0.01$) with BMI in all participants. Among DM patients, fasting PP concentrations were greater ($P=0.02$) in T2DM than in T1DM, even after adjusting for BMI (Table 2). Of 40 DM patients, only two had increased serum creatinine (i.e., 4.3 and 1.7 mg/dl).

PP response to modified sham feeding

In 16 of 23 controls (70%), 21 of 39 DM patients (54%), and 18 of 38 NUD patients (47%), the PP increased by 20 pg/ml or greater above the baseline (Figure 1). Among DM patients, the PP response was not significantly different between T1DM and T2DM. The baseline PP response and PP response were not correlated with fasting glucose concentrations, serum creatinine or the HbA_{1c} (data not shown).

CASS vagal scores and comparison with plasma PP response to modified sham feeding

Of 23 controls, 1 patient each had mild and moderate cardiovagal dysfunctions (Table 1). Among 39 patients with DM, 11 (28%) had mild and 15 (38%) had moderate or severe cardiovagal dysfunctions ($P<0.0001$ vs controls). Among 38 NUD patients, 8 (21%) had mild, and 1 (3%) had moderate cardiovagal dysfunctions ($P=0.15$).

In the *entire* cohort, the results from cardiovagal tests and the PP response were associated ($p=0.01$); thus, among 40 participants both tests were normal and in 23 participants, both tests were abnormal (Figures 2 and 3). The results of these 2 tests were discordant in the remaining 36 participants. The results of these two tests were associated ($p=0.02$) in NUD but not in the overall DM group ($p=0.31$). However, the association between an impaired PP response and moderate or severe cardiovagal functions differed ($P<0.05$) between T1DM and T2DM. Among patients with a PP increment less than 20 pg/ml, 7/10 (70%) of T1DM and 1/7 (14%) of T2DM had moderate or severe cardiovagal dysfunctions. Conversely, among patients with a plasma PP increment ≥ 20 pg/ml, 4 of 11 (36%) T1DM and 3 of 11 (27%) T2DM had moderate or severe cardiovagal dysfunction.

Relationship between plasma PP response to modified sham feeding and gastric emptying

The gastric emptying was normal and rapid in respectively 18 (75%) and 4 (17%) controls, 22 (55%) and 5 (12%) DM patients, and 30 (75%) and 5 (12.5%) NUD patients. Sixteen of 22 (72%) DM patients with a normal PP response and 9 of 17 (53%) DM patients with a reduced PP response had normal or rapid gastric emptying. These proportions were comparable in patients with T1DM and T2DM (data not shown). Thirteen DM patients (33%) and 5 NUD patients (12.5%) had delayed gastric emptying. Of these 13 DM patients, 9 had cardiovagal dysfunctions and 8 had an impaired PP response. Of these 5 NUD patients, 4 had cardiovagal dysfunctions and 3 had an impaired PP response. Compared to controls, the PP response to MSF was not significantly different in NUD or DM patients with delayed gastric emptying.

Relationship between plasma PP response to modified sham feeding and symptoms during gastric emptying study

In DM patients, 13 of 21 (62%) with a preserved and 10 of 18 (56%) with an impaired PP response to MSF had severe symptoms ($P=0.7$) during the gastric emptying study. The PP response to MSF was not correlated with the mean symptom scores during the gastric emptying study in controls, DM or NUD patients (data not shown).

Discussion

The PP response to MSF is used to assess gastrointestinal vagal function. In this study, MSF increased the plasma PP by 20 pg/ml or greater in 16 of 23 (70%) healthy controls. Six of the 7 controls with an impaired PP response had no risk factors or clinical features of an autonomic neuropathy and normal cardiovagal functions. Likewise, in the original report, the PP increment was greater than 20 pg/ml in 10 of 13 healthy participants (77%).⁽¹³⁾ Perhaps some healthy people lack a PP response to MSF because this is a relatively mild stimulus for PP release. The PP response to MSF is much smaller than the response to sham feeding, a meal, or insulin-induced hypoglycemia.⁽¹³⁾ Since the secretion of gastrointestinal hormones (e.g., GLP1) is correlated with number of chews per bite, insufficient chewing may explain an inadequate PP increment.⁽³⁵⁾ In addition to encouraging patients to chew vigorously and for a longer duration, perhaps a lengthier discussion of food, which augments gastric acid secretion in response to MSF, may be useful.⁽³⁶⁾ From a clinical perspective, these findings demonstrate that a PP increment less than 20 pg/ml does not imply vagal nerve dysfunction (e.g., after fundoplication).

The results of the PP and cardiovagal tests were associated with each other in the entire cohort and in patients with NUD but not in DM. Indeed, in 16 DM patients, the results of the PP response and cardiovagal tests were discrepant i.e., the PP response was normal and cardiovagal functions were abnormal or vice versa. In patients with normal cardiovascular vagal tests, an impaired PP response may reflect a length-dependent axonal neuropathy with early involvement of distal fibers.^(37, 38) By contrast, a normal PP response in patients with abnormal cardiovagal tests is inconsistent with a length-dependent neuropathy. Buysschaert et al also observed that the PP response to MSF was preserved in 4 of 9 patients with abnormal cardiovagal parameters.⁽⁸⁾ Of interest, the gastric acid response to MSF was

reduced in 8 of these 9 patients, suggesting that the gastric acid response to MSF is more strongly associated with abnormal cardiovagal indices than the PP response to MSF. Perhaps the PP response to MSF is only impaired in patients who have complete vagal injury (e.g., vagotomy).(39)

Intriguingly, the association between an impaired PP response and moderate or severe cardiovagal abnormalities differed between T1DM and T2DM. Most T1DM patients with an impaired PP response had cardiovagal abnormalities. By contrast, only a minority of T2DM patients and an impaired PP response had cardiovagal dysfunctions. Hyperglycemia inhibits PP secretion via an *intact* vagus.(22, 23) Among patients with T2DM, hyperglycemia rather than vagal dysfunction may explain the attenuated the PP response to MSF. Hence, hyperglycemia should be treated if feasible before starting the MSF test.

An impaired PP response to MSF, which reflects efferent vagal dysfunction, was not associated with delayed gastric emptying. The symptoms during the gastric emptying study were also not associated with an impaired PP response, possibly because the latter evaluates efferent not afferent vagal dysfunction. A small study of 10 healthy controls and 10 patients with DM and gastrointestinal symptoms suggested that afferent vagal dysfunction might explain the lack of symptoms in patients with delayed gastric emptying.(21) However, of 4 patients with normal cortical evoked potentials in response to esophageal electrical stimulation in that study, 2 patients each had minor and severe symptoms. Hence, further studies are necessary to evaluate the relationship between afferent vagal function and gastrointestinal symptoms in patients with DM.

Twenty patients (53%) with NUD had an impaired PP response to MSF. Of these 20 patients, 12 had normal cardiovascular vagal parameters and normal gastric emptying. Perhaps the PP response was impaired because the stimulus (e.g., the amount of chewing) during MSF was insufficient. Alternatively, it is conceivable that since dorsal motor vagal (DMV) neurons regulate gastric and pancreatic functions, at least in rodents,(40) that these patients had isolated dysfunction of the vagus nerve that mediates PP release but normal gastric emptying. Another possible explanation is that the gastric and pancreatic vagal fibers were initially affected by a neuropathy. Later, neuroplasticity in the brainstem or enteric nervous system restored gastric emptying but not pancreatic D cell innervation.(41)

This large study comprehensively evaluated the PP response to MSF, cardiovascular vagal functions, and gastric emptying in healthy controls and patients with NUD and DM. However, there were a few limitations. In the absence of patients with a surgical vagotomy, the diagnostic utility of the PP response to MSF could not be completely evaluated. Two patients were on DPP-4 inhibitors, which inhibit the breakdown of PP.(42) One patient was taking a GLP-1 agonist, which should not affect the PP response because GLP-1 depolarizes pancreas-projecting neurons in the dorsal motor nucleus of rats that regulate pancreatic endocrine secretion but not PP.(43)

In summary, there are 3 important implications of these findings. First, because the PP response to MSF in healthy people is variable, the test is perhaps more useful when the PP response is normal than when it is abnormal; an abnormal response may not always reflect

vagal dysfunction. Second, the PP response and cardiovagal responses are generally concordant. Third, a reduced PP response is more likely to be associated with cardiovagal dysfunctions and reflect a vagal neuropathy, in T1DM than in T2DM. Taken together, these findings underscore the need to develop different techniques to assess gastrointestinal vagal functions. One option, which deserves further study, is to measure plasma ghrelin concentrations, which also increase during MSF.(5, 44, 45)

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Abbreviations.

PP	Pancreatic polypeptide
GE	gastric emptying
DM	Diabetes Mellitus
NUD	Non-ulcer dyspepsia
t1/2	time taken for 50% emptying
DM	diabetes mellitus
CI	confidence interval
IV	intravenous
pg/mL	picogram/mililitre
CASS	composite autonomic severity score

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Figure 1. PP response to modified sham feeding in controls, diabetes mellitus and non-ulcer dyspepsia.

Error bars indicate SEM.

Figure 2. Comparison of PP responses to modified sham feeding and cardiovagal functions characterized as normal and abnormal in controls, diabetes mellitus and non-ulcer dyspepsia.

* Cardiovagal functions were not evaluated in one patient with NUD.

Figure 3. Distribution of PP response to modified sham feeding versus cardiovascular functions in controls, diabetes mellitus and non-ulcer dyspepsia.

CASS scores of 0, 1, 2, and 3 respectively represent no, mild, moderate, and severe cardiovascular dysfunctions. Cardiovascular functions were not evaluated in one patient with NUD.

Table 1.

Demographic Features, Blood Glucose, Plasma Pancreatic Polypeptide, and Cardiovascular Functions

Characteristic	Controls (N=23)	DM (N=39)	NUD (N=39)
Age, years	41.0 (2.7)	44.3 (2.2)	41.3 (2.1)
Women, n (%)	13 (57)	30 (77)	30 (77)
BMI, kg/m ²	26 (1)	28 (1)	27 (1)
HbA _{1C} , %	5.2 (0.07)	8.8 (0.3)	5.2 (0.06)
Fasting blood glucose (mg/dl)	93 (2)	159 (10)	90 (1)
Baseline PP value, pg/ml	113 (8)	151 (19) *	94 (9) *
PP increment during MSF, pg/ml	41 (11)	27 (8)	32 (6)
Cardiovascular functions			
Normal, n (%)	21 (92%)	13 (33%)	30 (77%)
Mild dysfunction, n (%)	1 (4%)	11 (28%) *	8 (20%)
Moderate dysfunction, n (%)	1 (4%)	5 (13%) *	1 (3%)
Severe dysfunction, n (%)	0 (0%)	10 (26%) *	0 (0%)

PP – pancreatic polypeptide, MSF – modified sham feeding

All figures are expressed as Mean (SEM) unless specified otherwise.

* $P < 0.05$ versus controls

Table 2.

Comparison of Patients with Type 1 and Type 2 Diabetes Mellitus

	T1DM (N=21)	T2DM (N=18)
BMI (kg/m ²)	25 (1)	31 (1) [#]
Patients on insulin, n	21	10
Fasting glucose, mg/dl	216 (71)	165 (68)
HbA1c (%)	9.2 (0.5)	8.1 (0.4)
Baseline PP level, pg/ml	99 (8)	210 (36) [*]
PP response, pg/ml	26 (9)	29 (13)

Mean (SEM)

[#]P=0.004^{*}P=0.02 vs T1DM adjusted for BMI