Neuroendocrine Tumor Markers and Enterochromaffin-Like Cell Hyper/Dysplasia in Type 1 Diabetes

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OBJECTIVE — Parietal cell antibodies (PCAs) are found in 20% of type 1 diabetic patients, denoting autoimmune gastritis and pernicious anemia, which may predispose to enterochromaffin-like (ECL) cell hyper/dysplasia and gastric carcinoid tumors. We evaluated whether chromogranin A (CgA), 5-hydroxyindole acetic acid (5-HIAA), and neuron-specific enolase (NSE) contribute to screening for ECL cell hyper/dysplasia.

RESEARCH DESIGN AND METHODS — Sera from 93 type 1 diabetic patients (53 men and 40 women, 31 PCA+ and 62 PCA−, aged 45 ± 13 years) were analyzed for PCAs by indirect immunofluorescence and for CgA, NSE, and gastrin by radioimmunoassay. Urinary 5-HIAA was tested by high-performance liquid chromatography. Corpus atrophy and ECL cell proliferation were assessed in gastric biopsies.

RESULTS — PCA+ patients had higher gastrin (P < 0.0001) and CgA levels (P = 0.003) and were more prone to autoimmune gastritis (odds ratio [OR] 17, P < 0.0001) and ECL cell hyper/dysplasia (OR = 23, P = 0.005) than PCA− subjects. ECL cell hyper/dysplasia was present in seven PCA+ patients who showed higher CgA levels (P < 0.0001) than subjects without ECL cell hyper/dysplasia, but NSE and 5-HIAA levels were similar. CgA levels correlated with gastrinemia (r = 0.50, P < 0.0001), PCA titer (r = 0.42, P = 0.001), and 5-HIAA levels (r = 0.38, P = 0.012). Logistic regression identified the CgA level (B = 0.01, P = 0.027) as an independent risk factor for ECL cell hyper/dysplasia when PCA, CgA, 5-HIAA, NSE, gastrin, sex, and age were tested. Multivariate linear regression demonstrated that CgA level was determined by ECL cell density (r = 0.59, P < 0.0001) and gastrin level (r = 0.67, P = 0.02). One PCA+ patient with elevated gastrin, CgA, and 5-HIAA levels had a gastric carcinoid tumor.

CONCLUSIONS — PCA+ patients, particularly those with high gastrin and CgA levels, risk developing ECL cell hyper/dysplasia. The determination of CgA, but not NSE and 5-HIAA, may complement histology in evaluating ECL cell mass.

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Abbreviations: CgA, chromogranin A; ECL, enterochromaffin-like; 5-HIAA, 5-hydroxyindole acetic acid; NSE, neuron-specific enolase; PCA, parietal cell antibody; RIA, radioimmunoassay; ROC, receiver operating characteristic.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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RESEARCH DESIGN AND METHODS — A total of 93 type 1 diabetic patients aged 45 ± 13 years (53 men and 40 women), comprising 31 PCA+ and 62 PCA− subjects matched for age, sex, duration of diabetes, and metabolic control were studied. They were consecutively recruited according to PCA status, irrespective of symptoms, from 185 patients (75 PCA+ and 110 PCA−) attending the outpatient Antwerp University diabetes clinic (9). Every patient fulfilled the criteria of type 1 diabetes (23), and 31 PCA+ and 41 matched PCA− subjects agreed to undergo gastroscopy.

No patient had renal impairment, liver failure, inflammatory bowel disease, or used proton pump inhibitors — conditions which are associated with elevated CgA levels (20,22). Subjects were instructed not to eat bananas, pineapples, avocados, kiwis, or nuts and not to drink tea or coffee at least 3 days before the start of the urine collection because they can elevate the level of urinary 5-HIAA (21). No patient used methyldopa, sympathomimetic amines, antibiotics, anti-inflammatory drugs, or prokinetics or had celiac disease (tested by biopsy and endoscopy IgA antibodies) or systemic lupus erythematosus. The study was approved by the local ethics committee. Each subject gave informed consent, in accordance with the Helsinki Declaration.

Methods
PCAs were detected using indirect immunofluorescence on rat gastric mucosa (NI [normal level] <1/20 dilution; Medical Diagnostics California, Carlsbad, CA) (1). This assay correlated well with the enzyme immunoassay for H+/K+ ATPase antibodies (NI <10 units/ml Varelisa; Pharmacia & Upjohn, Sweden) (r = 0.85; P < 0.0001) (9). Antibodies to intrinsic factor were measured by radiobinding assay (NI <1.1; Diagnostic Products, Los Angeles). Iron deficiency anemia was defined as microcytic hypochromic anemia with a transferrin saturation ≤20% or a decreased iron level (<50 and <40 μg/dl for men and women, respectively) or ferritin level (<20 and <12 μg/l, respectively) (7). Pernicious anemia was defined as macrocytic anemia and low vitamin B12 levels with positive antibodies to intrinsic factor and PCAs (9). Serum gastrin was measured by radioimmunoassay (RIA) technique (NI <110 ng/l; Euro-Diagnostics, Malmo, Sweden), vitamin B12 (NI 190–970 pg/ml), and erythrocyte folate levels (NI 120–860 ng/ml) using a Simultrace-SNB RIA kit (ICN, Orangeburg, NY). HLA-DQ typing was performed as described before (9).

CgA was measured by polyclonal RIA, using human CgA isolated from pheochromocytomas as tracer and standard (within-assay coefficients of variation [CVs] 6.5 and 8.6% at levels of 95 and 1,160 ng/ml, detection sensitivity 1.6 ng/ml). The reference value in 568 normal subjects of both sexes, aged 6–50 years, is 90 ± 24 ng/ml (24). The upper cutoff value in this study was 120 ng/ml. NSE was determined using a double-antibody RIA kit (NSE RIA kit; Pharmacia & Upjohn, Sweden) targeted against the γ-subunit (NSE γγ-dimer + αγ-hybrid form), with a sensitivity 0.5 μg/ml CV 3.8% at a level of 17.9 μg/l (cutoff 12.5 μg/l). Urinary 5-HIAA was tested by high-performance liquid chromatography (Bio-Rad, Nazareth-Eke, Belgium), with a CV of 1.82% at a level of 3.3 mg/24 h (reference range 0.7–8.2 mg/24 h), on a Millennium instrument (Waters, Brussels, Belgium).

Serum was assayed for H. pylori IgG antibodies by enzyme-linked immunosorbent assay (Roche Diagnostics, Brussels). 13C-urea breath tests were performed as described before (25). Antrum, corpus, and fundus biopsies were examined for H. pylori colonization using modified Giemsa and/or immunostaining (25). H. pylori infection was diagnosed if any test was positive. The period between urea breath test and gastroscopy was maximally 14 days.

Gastric acid secretion studies were performed in 42 patients (15 PCA+ and 27 PCA−) after a 12-h overnight fast using pentagastrin-stimulated acid output (6 μg/kg s.c. Pentagastrin Injection BP; Cambridge Laboratories, Newmarket, UK) (25). Hypochlorhydria was defined as a maximal acid output <15 mmol H+/h.

Gastroscopy and histology
At upper gastrointestinal endoscopy (GIF/Q140 videoscope; Olympus, Melville, NY), at least two biopsies from fundus, corpus, antrum, and descending duodenum were taken and evaluated by two investigators who were unaware of the patient’s clinical and laboratory data to minimize interobserver variation.

The visual analog scale of the updated Sydney system was used to evaluate inflammation (chronic infiltrate), activity (acute infiltrate), atrophy (glandular loss), intestinal metaplasia, and H. pylori colonization (26). Autoimmune gastritis was diagnosed as described before (5,9,26). Furthermore, ECL cell status was evaluated according to the Solcia classification (12). Immuno staining was performed for H. pylori (B0471 polyclonal rabbit H. pylori IgG antibodies, dilution 1:200; Dako, Glostrup, Denmark) (25), CgA (DAK-A3, M0869, dilution 1:200; Dako), and H+/K+ ATPase (clone 2611, MA3-923, dilution 1:4,000; Affinity Bioreagents, Golden, CO), as described before (9).

Statistical analysis
Results were analyzed using SPSS (SPSS, Chicago). Distributions of continuous data were tested for normality by the Kolmogorov-Smirnov test. Unpaired Student’s t tests, Mann-Whitney U tests, or ANOVA was used to determine differences between groups. Bonferroni adjustments for multiple comparisons were made. A Spearman rank correlation test was used. Differences in distributions of categorical data were evaluated by χ2 or Fisher’s exact test. Stepwise forward logistic regression and multivariate linear regression were used to assess the strength and independence of associations. A two-tailed P < 0.05 was considered significant.

RESULTS

PCA and H. pylori status
Basal, maximal, and peak acid output were lower, and hypochlorhydria (odds ratio [OR] 7.0, 95% CI 1.3–37.2, P = 0.02) was more frequent in PCA+ than PCA− patients (Table 1). PCA+ subjects were more prone to iron deficiency anemia (5.0, 1.4–18.4, P = 0.018) and pernicious anemia (21.2, 2.5–179.2, P = 0.0005) and exhibited lower vitamin B12 levels (P = 0.028). PCA− patients had higher gastrin (P < 0.0001) (Fig. 1A) and CgA levels (P = 0.003) but similar concentrations of NSE and urinary 5-HIAA. No differences in the levels of these four markers were observed between sexes. Autoimmune gastritis was more common in PCA+ than PCA− patients (11.2, 3.2–39.2, P < 0.0001). ECL cell proliferative changes were present in seven PCA+ patients with autoimmune gastritis, but they
were not present in any PCA− patients (25.4, 1.4–464.9, P = 0.0018). Pernicious anemia (P = 0.1) and ECL cell hyper/dysplasia (3 of 14 vs. 4 of 79 patients, P = 0.067) tended to be more prevalent in patients with a history of autoimmune dysthryoidism (n = 14).

H. pylori infection was diagnosed in 26 patients with a similar prevalence in PCA+ and PCA− patients. Two-way ANOVA with PCA and H. pylori as fixed factors showed that H. pylori infection did not influence gastrin, CgA, NSE, and urinary 5-HIAA levels. Moreover, no link was observed between H. pylori status and pernicious anemia, autoimmune gastritis, or ECL cell hyper/dysplasia.

**Histological findings and endocrine tumor markers**

A subgroup of 9 PCA+ H. pylori+, 22 PCA+ H. pylori−, 17 PCA− H. pylori+, and 24 PCA− H. pylori− patients agreed to undergo gastroscopy. Intra- and interobserver variations in evaluating histological sections were minimal (2.4 and 5.1%, respectively) (9). Autoimmune gastritis was equally common in men and women. No differences in age, duration of diabetes, or HLA-DQ haplo/genotypes were observed between patients with or without autoimmune gastritis. Hypochlorhydria (OR 12.5, 95% CI 2.2–70.2, P = 0.0021), iron deficiency anemia (9.8, 2.3–42.5, P = 0.0015), and pernicious anemia (30.8, 3.5–268.7, P = 0.0001) were more frequent in patients with autoimmune gastritis (Table 2). Gastrin (P < 0.0001) (Fig. 1B) and CgA levels (P = 0.038) were higher, but those of NSE and urinary 5-HIAA were similar in subjects with or without autoimmune gastritis. ECL cell hyper/dysplasia was only found in seven patients with autoimmune gastritis (53.3, 2.9–989.9, P < 0.0001). Of these seven PCA+ subjects (three men and four women), one subject, who also had elevated gastrin, CgA, and 5-HIAA levels, was diagnosed with a gastric carcinoid tumor (16). Subjects with ECL cell hyper/dysplasia showed higher CgA (293 ± 196 vs. 117 ± 60 ng/ml, P < 0.0001) and gastrin levels (520 ± 355 vs. 163 ± 121 ng/l, P = 0.005) than those without ECL cell hyperplasia, but NSE and 5-HIAA levels were similar.

To detect ECL cell proliferative changes, CgA had 100% sensitivity, 59% specificity, 27% positive predictive value, and 100% and negative predictive value. The respective values for gastrin (>110 ng/l) were 83, 23, 14, and 90%. Using both elevated CgA and gastrin levels, these values were 100, 72, 35, and 100%. Using both elevated CgA levels and PCA+, they were 100, 80, 43, and 100%.

**Table 1—Clinical, laboratory, and histological features in PCA+ versus PCA− type 1 diabetic patients**

<table>
<thead>
<tr>
<th></th>
<th>PCA+</th>
<th>PCA−</th>
<th>P</th>
<th>NS</th>
<th>Y</th>
<th>FL</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (M/F)</td>
<td>31 (17/14)</td>
<td>62 (36/26)</td>
<td></td>
<td>NS</td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46 ± 13</td>
<td>45 ± 14</td>
<td></td>
<td>NS</td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>24 ± 12</td>
<td>22 ± 10</td>
<td></td>
<td>NS</td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.9 ± 1.1</td>
<td>7.8 ± 1.1</td>
<td></td>
<td>NS</td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>H. pylori+ (n)</td>
<td>9 (29)</td>
<td>17 (27)</td>
<td></td>
<td>NS</td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>H+K+ ATPase (units/ml)</td>
<td>207 ± 325</td>
<td>5.6 ± 8.8</td>
<td>&lt;0.0001</td>
<td></td>
<td>Y</td>
<td>FL</td>
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<tr>
<td>Gastrin (ng/l)</td>
<td>313 ± 215</td>
<td>100 ± 55</td>
<td>&lt;0.0001</td>
<td></td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>Iron deficiency anemia (n)</td>
<td>8 (26)</td>
<td>6 (2)</td>
<td></td>
<td>NS</td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>Pernicious anemia (n)</td>
<td>8 (26)</td>
<td>1 (2)</td>
<td></td>
<td>NS</td>
<td>Y</td>
<td>FL</td>
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<tr>
<td>BAO (mmol/l/h)</td>
<td>0.79 ± 0.80</td>
<td>1.76 ± 1.70</td>
<td>0.05</td>
<td></td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>MAO (mmol/l/h)</td>
<td>7.1 ± 6.7</td>
<td>16.1 ± 10.2</td>
<td>0.009</td>
<td></td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>PAO (mmol/l/h)</td>
<td>10.8 ± 10.6</td>
<td>22.4 ± 12.2</td>
<td>0.008</td>
<td></td>
<td>Y</td>
<td>FL</td>
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<tr>
<td>Hypochlorhydria (n)</td>
<td>13/15</td>
<td>13/27</td>
<td></td>
<td>NS</td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>Vitamin B12 (pg/ml)</td>
<td>368 ± 163</td>
<td>485 ± 246</td>
<td>0.028</td>
<td></td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>Red blood cell folic acid (ng/ml)</td>
<td>461 ± 203</td>
<td>501 ± 225</td>
<td>NS</td>
<td></td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>Autoimmune gastritis (n)</td>
<td>17/31</td>
<td>4/41</td>
<td>&lt;0.0001</td>
<td></td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>ECL hyperplasia (n)</td>
<td>7/31</td>
<td>0/41</td>
<td>0.0018</td>
<td></td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>CgA (ng/ml)</td>
<td>161 ± 121</td>
<td>110 ± 36</td>
<td>0.003</td>
<td></td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>5-HIAA (mg/24 h)</td>
<td>3.34 ± 1.80</td>
<td>4.35 ± 1.64</td>
<td>NS</td>
<td></td>
<td>Y</td>
<td>FL</td>
</tr>
<tr>
<td>NSE (μg/l)</td>
<td>10.09 ± 1.90</td>
<td>10.67 ± 2.64</td>
<td>NS</td>
<td></td>
<td>Y</td>
<td>FL</td>
</tr>
</tbody>
</table>

Data are means ± SE or n (%), unless otherwise indicated. BAO, basal acid output, MAO, maximal acid output, PAO, peak acid output.

CONCLUSIONS—Because of the increased risk of gastric carcinoids in hypergastrinemic states, periodic surveillance by gastroscopy with biopsy is recommended. Reliable serum/urine markers would be a valuable contribution to complement histology for the diagnosis of ECL cell hyper/dysplasia and gastric carcinoids.

**Neuroendocrine tumor markers**

PCAs target gastric H+K+ATPase (4). Acid output was lower in PCA+ patients. Achlorhydria interrupts the negative feedback of somatostatin on antral G-cells, thus inducing hypergastrinemia, a trophic stimulus for ECL cell proliferation. We and others demonstrated a positive correlation between gastrin and ECL cell density (21,27). Also, CgA levels were increased in all patients with ECL cell hyper/dysplasia. ECL cells may indicate the risk of carcinoid tumor. CgA may indicate,
the presence of an increased gastric ECL cell mass more accurately than histology. This is supported by the correlations we found between CgA and gastrin and ECL cell proliferative changes. The assessment of gastric ECL cell proliferation is hampered by the fact that such lesions are usually not endoscopically detectable and may be overlooked. Moreover, part of an increased ECL cell density in atrophic mucosa may not be true hyperplasia but rather an expression of a selective glandular atrophy sparing the ECL cells (21). Therefore, morphology is subject to sampling error and may over- or underestimate ECL cell mass. Efficient and noninvasive methods to monitor gastric endocrine lesions are warranted.

Among general neuroendocrine tumor markers, CgA has been shown to be the most sensitive because of its ubiquitous presence in neuroendocrine tissues and its cosecretion with amines and peptide hormones from neurosecretory granules (19,29). CgA has a specificity of 85–90% and a sensitivity of 65–75% to detect carcinoids, whereas NSE and urinary 5-HIAA have a very high specificity of 100% but a low sensitivity of 30–35% (19,20,28). We and others observed no correlation between ECL cell density and concentrations of NSE or 5-HIAA (28). CgA levels may reflect tumor load, and they may be an independent prognostic marker in patients with carcinoid tumors (19,20,30). However, not only carcinoids but also ECL cells in autoimmune gastritis stain positively with CgA (21,31). We show a sensitivity of 100% and specificity of 59% for CgA to detect ECL cell hyper/dysplasia, and by using both gastrin and CgA, the sensitivity and specificity increase further (32). Serum CgA is a useful screening test for gastric ECL cell proliferative changes during acid-suppressive therapy (22).

The function of CgA is not well known. The main CgA-derived peptide, pancreastatin, inhibits insulin and glucagon secretion (33) and gastric parietal cell function (34) and thus may further upregulate gastrin secretion in a self-perpetuating process.

Some studies suggest that in patients with acid suppression, H. pylori infection is a risk factor for the development of ECL cell hyper/dysplasia (35,36). However, the present and previous studies showed no link between H. pylori and autoimmune gastritis or ECL hyper/dysplasia (9,25).

Histology
At least eight biopsies per patient were studied to document autoimmune gastritis, thereby reducing sampling error. From the total group of 185 patients, 41% of all PCA+ and 37% of all eligible matched PCA− subjects agreed to undergo gastroscopy. However, because not all eligible patients agreed to undergo gastroscopy, this might have introduced some bias. ECL cell proliferative changes were present in seven PCA+ patients with
autoimmune gastritis (33%), including one subject with a gastric carcinoid tumor. In the total PCA+ population, we estimate this at 9% (7 of 75). The prevalence of gastric carcinoids ranges from 4 to 7% in patients with autoimmune gastritis/pernicious anemia and is 13 times higher than in control subjects (12–15). Gastric carcinoids may constitute as much as 10–30% of carcinoid tumors (37). Up to 85% of gastric carcinoids are associated with autoimmune gastritis/pernicious anemia (38).

Management proposal, treatment, and prognosis
Awaiting a consensus statement, we suggest to test type 1 diabetic patients for PCAs, particularly those with positive islet cell antibodies ≥3 years after onset of diabetes, GAD-65 antibodies, and thyroid peroxidase antibodies (1,3). It seems prudent to test PCA status at onset of diabetes, then yearly for 3 years, and then every 5 years thereafter, or at any other time if there are clinical indications because the test may later (with advancing age) become positive (1,3).

At yearly intervals, gastrin, iron, vitamin B12 levels, and a complete blood count should be performed. Iron or vitamin B12 supplements should be given to patients with iron deficiency or pernicious anemia. The need for endoscopy with biopsy is not fully known, but we suggest to perform it at least once in patients with PCA+ or anemia. We propose endoscopic surveillance at 5-year intervals for patients with high gastrin (>300 ng/l) and CgA (>120 ng/ml) levels and for those with ECL cell hyperplasia (14). For carcinoid tumors associated with autoimmune gastritis/pernicious anemia that are <1 cm and/or fewer than three to five in number, expectant therapy or endoscopic removal of accessible tumors has been proposed (15,37). For lesions >1 cm and/or more than five in number, antrectomy has been advocated because it removes the bulk of antral G-cells, the source of gastrin, which is the proposed principal promoter of tumor growth (39). Either antrectomy or endoscopic polypectomy should be followed by endoscopic surveillance at 6 months intervals, and any recurrence should be treated with surgery.

An alternative pharmacological option is represented by octreotide, a somatostatin analogue (40,41). Ferraro et al. showed in a limited group of eight patients with hypergastrinemic atrophic gastritis that once a day administration of octreotide is safe and effective in reducing hypergastrinemia and associated ECL changes (41). This is probably due to the reduced trophic stimulus of lowered gastrin levels on ECL cells. A direct effect of octreotide on these cells may also be involved because ECL cells possess a specific somatostatin receptor, belonging to subtype 2 that is the specific subtype for octreotide binding (42).

Autoimmune gastritis–associated car-

### Table 2—Clinical, laboratory, and histological features in type 1 diabetic patients with and without histologically proven autoimmune gastritis

<table>
<thead>
<tr>
<th></th>
<th>Autoimmune gastritis+</th>
<th>Autoimmune gastritis−</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>n (M/F)</td>
<td>21 (11/10)</td>
<td>51 (30/21)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47 ± 13</td>
<td>43 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>24 ± 13</td>
<td>23 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>H. pylori+ (n)</td>
<td>6 (29)</td>
<td>20 (39)</td>
<td>NS</td>
</tr>
<tr>
<td>PCA+ (n)</td>
<td>17 (81)</td>
<td>14 (27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gastrin (ng/l)</td>
<td>451 ± 369</td>
<td>134 ± 84</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Iron deficiency anemia (n)</td>
<td>8 (38)</td>
<td>3 (6)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Pernicious anemia (n)</td>
<td>8 (38)</td>
<td>1 (2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>BAO (mmolH+/h)</td>
<td>0.75 ± 1.02</td>
<td>1.28 ± 0.84</td>
<td>NS</td>
</tr>
<tr>
<td>MAO (mmolH+/h)</td>
<td>3.1 ± 4.4</td>
<td>13.5 ± 10.5</td>
<td>0.048</td>
</tr>
<tr>
<td>PAO (mmolH+/h)</td>
<td>4.3 ± 6.1</td>
<td>19.7 ± 14.1</td>
<td>0.042</td>
</tr>
<tr>
<td>Hypochlorhydria (n)</td>
<td>10/12</td>
<td>8/27</td>
<td>0.0021</td>
</tr>
<tr>
<td>Vitamin B12 (pg/ml)</td>
<td>350 ± 216</td>
<td>469 ± 237</td>
<td>0.037</td>
</tr>
<tr>
<td>Red blood cell folic acid (ng/ml)</td>
<td>486 ± 234</td>
<td>465 ± 198</td>
<td>NS</td>
</tr>
<tr>
<td>ECL hyper/dysplasia (n)</td>
<td>7 (33)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CgA (ng/ml)</td>
<td>178 ± 144</td>
<td>113 ± 59</td>
<td>0.038</td>
</tr>
<tr>
<td>5-HIAA (mg/24 h)</td>
<td>5.25 ± 2.36</td>
<td>4.57 ± 1.80</td>
<td>NS</td>
</tr>
<tr>
<td>NSE (µg/l)</td>
<td>9.92 ± 1.34</td>
<td>10.22 ± 2.27</td>
<td>NS</td>
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</tbody>
</table>

Data are means ± SE or n (%), unless otherwise indicated. BAO, basal acid output; MAO, maximal acid output; PAO, peak acid output.
cinoids are usually indolent, metastasizing in <10% of cases (13,38). They rarely provoke a carcinoid syndrome and rarely result in death (43).

Conclusions
One-fifth of type 1 diabetic patients studied exhibit PCAs. Nearly 10% of PCA+ subjects, particularly those with high gastrin and CgA levels, may develop ECL cell hyper/dysplasia and possibly carcinoid tumors. This provides a strong rationale for screening, early diagnosis, and treatment. The use of PCAs, gastrin, and CgA complements histology and might in the future reduce the age at diagnosis and improve the likelihood of cure and survival in patients with gastric carcinoid tumors.

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