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# Serum Pepsinogen I: An Early Marker of Pernicious Anemia in Patients with Type 1 Diabetes

Núria Alonso, M. Luisa Granada, Isabel Salinas, Ana M. Lucas, Jordi L. Reverter, Jordi Juncà, Albert Oriol, and Ana Sanmartí

*Departments of Endocrinology and Nutrition (N.A., I.S., A.M.L., J.L.R., A.S.), Clinical Biochemistry (M.L.G.), and Hematology (J.J., A.O.), Hospital Universitari Germans Trias i Pujol, Badalona, 08916 Catalonia, Spain*

**Context:** Pernicious anemia (PA) is an autoimmune organ disease much more common in type 1 diabetic patients (DM1) than in nondiabetic subjects, but it is clinically silent until its end stage.

**Objective:** This study aimed to determine biochemical markers of latent PA in a population of DM1 patients attending the endocrinology outpatient clinic of a university hospital.

**Study Subjects:** The population studied consisted of 186 unselected patients (32.4 ± 8.7 yr) and 118 healthy controls (30.9 ± 9.4 yr).

**Measurements and Interventions:** Plasma gastrin and pepsinogen I were determined in patients and controls, whereas hemoglobin $A_{1c}$, serum cobalamin, hemoglobin, and organ-specific antibodies were determined only in patients. Latent PA was defined as serum pepsinogen I less than 30 $\mu$g/liter. In patients with low pepsinogen I concentrations and hypergastrinemia, esophagogastroduodenoscopy (EGD) was performed.

**Results:** DM1 patients showed significantly lower pepsinogen I concentrations ($P < 0.001$) and higher gastrinemia than controls. Latent PA was present in 12.4% of patients *vs.* 0.9% of controls. Among patients, more women than men showed low plasma pepsinogen I concentrations ($P = 0.002$) and thyroperoxidase antibody positivity ($P < 0.001$). Only the highest parietal cell antibody titers (≥1:640) identified patients with significantly higher levels of plasma gastrin ($P < 0.001$) and lower levels of pepsinogen I ($P < 0.001$). The histopathological EGD findings confirmed different degrees of gastric body mucosa atrophy in all cases.

**Conclusion:** The high prevalence of latent PA found in our DM1 patients leads us to recommend its screening using serum pepsinogen I concentrations. In patients with hypergastrinemia and high parietal cell antibody titers, EGD should be considered to confirm gastric mucosa atrophy. **(*J Clin Endocrinol Metab* 90: 5254–5258, 2005)**

TYPE 1 DIABETES MELLITUS (DM1) is the consequence of the autoimmune destruction of β-cells of the islets of Langerhans (1). DM1 patients show an increased prevalence of associated organ-specific autoimmune aggression against other endocrine (thyroid and adrenal glands) and nonendocrine tissues (gastric and enteral mucosa) (2–6). Pernicious anemia (PA) is an autoimmune organ disease that leads to loss of parietal cells in the fundus and body of the stomach (7). It is reported to occur in DM1 patients with a frequency of 0.5–4% (4, 8) compared with 0.12% in the general (nondiabetic) population. Although PA remains clinically silent until its end stage, the underlying gastric lesion can be predicted many years before anemia develops and is not easily detected by classic methods. In this respect, serum pepsinogen I, a peptide secreted by zymogenic cells in the body and fundus of the stomach, which reflects the secretory state of this area, is considered to be one of the most sensitive markers of body gastric atrophy and, consequently, of PA (9, 10). Because PA is an autoimmune disease, it may be associated with other autoimmune disorders (11). The prevalence of parietal cell antibodies (PCA) found in juvenile patients with autoimmune thyroid disorders ranges from 14–30% (12, 13). Our group previously reported that patients with idiopathic thrombocytopenic purpura, another autoimmune disease, show very low serum pepsinogen I concentrations, confirming that latent PA and idiopathic thrombocytopenic purpura coexist (14).

The aims of the present study were to determine biochemical markers of latent PA and the autoimmune milieu in a population of type 1 diabetic patients, considering low serum pepsinogen I concentrations as the main selective parameter for the diagnosis of clinically latent PA.

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Abbreviations: ANA, Nuclear antibody; DM1, type 1 diabetes mellitus; EGD, esophagogastroduodenoscopy; $HbA_{1c}$, glycosylated hemoglobin; PA, pernicious anemia; PCA, parietal cell antibody; TGa, thyroglobulin antibody; TPOa, thyroperoxidase antibody.

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## Subjects and Methods

One hundred eighty-six unselected DM1 patients regularly attending the outpatient clinic of the Endocrinology-Diabetology Department of our hospital were studied. All fulfilled criteria for the diagnosis of type 1 diabetes established by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (15). The DM1 group consisted of 93 men and 93 women, with a mean age of 32.4 ± 8.7 yr and a median diabetes duration of 13 yr (range, 9–20 yr). Glycemic control measured by glycosylated hemoglobin ($HbA_{1c}$) averaged 7.4 ± 1.26%. A mean of three annual determinations of $HbA_{1c}$ were used to determine the degree of overall metabolic control.

No patient was using drugs that could affect acid gastric secretion, had Crohn's or celiac disease, or had undergone gastrointestinal surgery. All had normal renal function (assessed by plasma creatinine concentrations within normal range).

The control group consisted of 118 healthy subjects (67 men and 55 women) recruited from the hospital staff (mean age, 30.9 ± 9.4 yr).

In DM1 patients and control subjects, fasting blood samples were

obtained to determine plasma gastrin and pepsinogen I concentrations, whereas $HbA_{1c}$, serum cobalamin, hemoglobin, and organ-specific autoantibodies [PCA, thyroperoxidase antibodies (TPOa), thyroglobulin antibodies (TGa), and nuclear antibodies (ANA)] were only determined in DM1 patients.

The study was approved by the local ethics committee. Each subject gave informed consent in accordance with the Declaration of Helsinki.

### *Methods*

Blood samples were obtained after an overnight fast. Serum samples were stored at −20 C until assayed. $HbA_{1c}$ was measured in blood samples with EDTA by HPLC using a fully automated Menarini HI-AUTO A1c 8140 analyzer manufactured by Arkray (Kyoto, Japan) with interassay coefficients of variation of 3.0% and 1.8% at $HbA_{1c}$ levels of 4.8% and 9.0%, respectively (reference range, 3.7–5.1%). Serum pepsinogen I was measured in duplicate by a double-antibody RIA (Pepsik, Sorin Biomedica Diagnostics, Saluggia, Italy); intraassay coefficients of variation were 7.6% at 19.4 μg/liter, 7.0% at 66.4 μg/liter, and 6.9% at 316 μg/liter, and interassay coefficients of variation were 9.9% at 51 μg/liter and 9.4% at 202 μg/liter. The sensitivity of the assay was 1 μg/liter (reference range, 30–117 μg/liter). Gastrin was measured in duplicate by a double-antibody RIA (Diagnostic Products Corporation, Los Angeles, CA); intraassay coefficients of variation were 6.0% and 4.0% at 50 and 600 ng/liter mean concentrations, respectively, and interassay coefficients of variation were 6.8% and 5.0%, respectively, at the same concentrations. The detection limit of the assay was 4.5 ng/liter (reference range, undetectable to 100 ng/liter). Cobalamin concentrations were measured by RIA (Chiron Corp., Emeryville, CA); intraassay coefficients of variation were 8.5% at 144.6 pg/ml and 7.3% at 604.9 pg/ml, and interassay coefficients of variation were 4.3% and 4.5%, respectively, at the same concentrations. The detection limit of the assay was 60 pg/ml. To convert metric units (picograms per milliliter) to Systeme International units (picomoles per liter), multiply by 0.7378. Complete blood counts were obtained with a STKR or Coulter counter (Coulter, Hialeah, FL).

ANA were detected by indirect immunofluorescence on Hep-2 (human epithelioma type 2) cells using a Kallestad HEp-2 slide (Bio-Rad SA, Marnes-la Coquette, France). PCA were determined by indirect immunofluorescence on rat gastric mucosa as substrate following standard procedures (Menarini Diagnostics, Barcelona, Spain). A titer higher than 1:40 was regarded as positive for both antibodies. TPOa and TGa were assayed with an enzyme immunoassay (Orgentec Diagnostica, Mainz, Germany). Values greater than 100 and 150 U/ml, respectively, were considered positive.

Esophagogastroduodenoscopy (EGD; GIF-Q145 endoscope, Olympus Optical Co., Tokyo, Japan) was performed in all those patients with low serum pepsinogen I levels and hypergastrinemia. Each patient underwent three biopsies taken from the gastric antrum and three biopsies from the midbody along the greater curve using Paul Drach Jumbo biopsy forceps (Olympus Optical Co.) for conventional histopathological examination and for the evaluation of endocrine cells. The biopsies were examined by experienced histopathologists. The degree of gastritis was assessed according to the Updated Sydney System (16). Atrophy of the gastric body mucosa was defined as focal or complete oxyntic gland loss and/or replacement by metaplastic pyloric or intestinal glands. *Helicobacter pylori* status was considered positive when bacteria were detected at histology.

Latent PA was defined as serum pepsinogen I below the lower limit of normality in our laboratory (<30 μg/liter) in the absence of gastric surgery or infiltrative disease of the stomach (17).

### *Statistical analysis*

Descriptive results are expressed as the mean ± SD or median (interquartile range). Differences between groups were examined by Student's *t* test or Mann-Whitney *U* test when normality of the variable could not be assumed. Differences in proportions were analyzed by the $\chi^2$ test or Fisher's exact test. Departure from normality was assessed by the Kolmogorov-Smirnov distribution test. $P < 0.05$ was considered statistically significant. Statistical analyses were carried out with SPSS 11.0 software package (SPSS, Inc., Chicago, IL).

## Results

### *Comparisons between DM1 patients and controls*

No differences were found in age and sex distribution between diabetic patients and controls. Serum pepsinogen I concentrations were significantly lower in DM1 patients than in healthy controls ($P < 0.001$), whereas differences in plasma gastrin concentrations were of borderline significance ($P = 0.052$). The proportion of subjects with plasma gastrin above the upper limit (>100 ng/liter) or low plasma pepsinogen I (<30 μg/liter) was significantly higher in the group of DM1 patients ($P = 0.002$ and $P < 0.001$, respectively; Table 1).

### *Sex differences*

In the control group, no differences between sexes were found in plasma gastrin [median (percentile 25–percentile 75), 29.8 ng/liter (24.6–36) in men *vs.* 27.0 ng/liter (22.1–32.2) in women] or in plasma pepsinogen I concentrations [median (percentile 25–percentile 75), 64.3 μg/liter (53.5–95.3) in men *vs.* 61.7 μg/liter (49.7–79) in women].

Within the DM1 group, no differences between sexes were found in age, body mass index, metabolic control of diabetes, plasma gastrin concentrations, or plasma cobalamin concentrations, whereas hemoglobin concentrations were significantly higher in men ($P < 0.001$). Plasma pepsinogen I concentrations were significantly lower in women ($P = 0.02$). However, no differences were found in the proportion of patients with hypergastrinemia or low pepsinogen I concentrations. PCA were measured in 168 patients (90.3% of the cohort) and were positive in 26%. TPOa and TGa were measured in 172 (92.4%) and were positive in 18% and 5.8%, respectively. Finally, ANA were measured in 164 (88%) and were positive in 36% of the DM1 patients. Significantly more women (14.5%) than men (3.5%) were TPOa positive ($P = 0.001$) and ANA positive (21.3% women *vs.* 14.6% men; $P = 0.001$; Table 2). However, this female predominance was not observed in PCA prevalence.

### *Differences according to PCA status in DM1 patients*

Patients with lower PCA titers (1:40 to 1:320) did not differ from those who were PCA negative in plasma gastrin or pepsinogen I concentrations. However, higher PCA titers (≥1:640) identified patients with significantly higher levels of

**TABLE 1.** Differences between DM1 patients and controls

| | DM1 patients (n = 186) | Control group (n = 118) | *P* |
|---|---|---|---|
| Male/female | 93/93 | 53/65 | N.S. |
| Age (yr)[a] | 32.4 ± 8.7 | 30.9 ± 9.4 | N.S. |
| Plasma gastrin (ng/liter)[b] | 26 (19–35.5) | 28 (23–34) | N.S. |
| Plasma pepsinogen (μg/liter)[b] | 56 (40–74.5) | 63 (52–85) | <0.001 |
| Gastrin > 100 ng/liter[c] | 14 (7.5%) | 0 (0%) | 0.002 |
| Pepsinogen < 30 μg/liter[c] | 23 (12.4%) | 1 (0.9%) | <0.001 |
| Gastrin > 100 ng/liter and pepsinogen I < 30 μg/liter[c] | 9 (4.8%) | 0 (0%) | 0.016 |

[a] Expressed as mean ± SD. Student's *t* test.

[b] Expressed as median (interquartile range). Mann-Whitney *U* test.

[c] Expressed as percentage. Fisher's exact test.

**TABLE 2.** Clinical characteristics, diabetes profile, and percentage of associated organ-specific autoantibodies in 186 DM1 men and women

| | All DM-1 patients | Women | Men | *P* |
|---|---|---|---|---|
| N | 186 | 93 | 93 | |
| Age (yr)[a] | 30.9 ± 9.4 | 31.8 ± 10 | 29.9 ± 8.7 | N.S. |
| BMI (kg/m$^2$)[a] | 24.8 ± 3.3 | 24.5 ± 3.6 | 25.0 ± 2.8 | N.S. |
| $HbA_{1c}$ (%)[a] | 7.4 ± 1.3 | 7.6 ± 1.3 | 7.3 ± 1.2 | N.S. |
| Hemoglobin (g/dl)[a] | 13.8 ± 1.4 | 13.0 ± 1.2 | 14.7 ± 1.0 | <0.001 |
| Gastrin (ng/liter)[b] | 26 (19–35.5) | 26 (18.5–39) | 26 (18.5–34) | N.S. |
| Pepsinogen I (μg/liter)[b] | 56 (40–74.5) | 48 (37–71.5) | 60 (46.5–81) | 0.02 |
| Cobalamin (pg/ml)[b] | 547 (418–718) | 574 (418–792) | 521 (416–652) | N.S. |
| PCA(+) (n = 168)[c] | 44 (26) | 23 (52.3) | 21 (47.7) | N.S. |
| TPOa(+) (n = 172)[c] | 31 (18) | 25 (80.6) | 6 (19.4) | 0.001 |
| TGa(+) (n = 172)[c] | 10 (5.8) | 7 (70) | 3 (30) | N.S. |
| ANA(+) (n = 164)[c] | 59 (36) | 35 (59.3) | 24 (40.7) | 0.001 |
| Gastrin > 100 ng/liter)[d] | 14 (7.5) | 10 (71.4) | 4 (28.6) | N.S. |
| Pepsinogen < 30 μg/liter[c] | 23 (12.4) | 14 (60.9) | 9 (39.1) | N.S. |
| Gastrin > 100 ng/liter and pepsinogen 1 < 30 μg/liter[d] | 9 (4.8) | 7 (77.8) | 2 (22.2) | N.S. |
| PCA ≥ 1/640[d] | 14 (8.3) | 9 (64.3) | 5 (35.7) | N.S. |

N.S., Nonsignificant.
[a] Expressed as mean ± SD. Student's *t* test.
[b] Expressed as median (interquartile range). Mann-Whitney *U* test.
[c] Expressed as number (percentage). $\chi^2$ test.
[d] Expressed as number (percentage). Fisher's exact test.

plasma gastrin ($P < 0.001$) and lower levels of plasma pepsinogen I ($P < 0.001$; Table 3 and Fig. 1). No significant differences were observed between sexes in these patients.

*Prevalence of latent PA in the diabetic cohort*

Latent PA, defined as serum pepsinogen I concentrations below the lower limit of normality in our laboratory (<30 μg/liter), was observed in 12.4% (23 of 186) of DM1 patients, and 47.8% (11 of 23) also had positive PCA. Nine patients had low serum pepsinogen I concentrations and hypergastrinemia. All of them had positive PCA at high titers (1:640 in four patients, 1:1280 in one patient, and 1:2560 in four patients) and hemoglobin concentrations within the reference range for sex. Only three patients, corresponding to 1.6% of the diabetic cohort, had additionally, cobalamin concentrations less than 250 pg/ml (166, 109, and 207 pg/ml, respectively).

*Endoscopic and histological findings*

The nine patients with low serum pepsinogen I concentrations and hypergastrinemia underwent gastrointestinal endoscopy at latent PA diagnosis. All nine had focal mucosa atrophy in the gastric body (two severe, five moderate, and two mild). Metaplastic intestinal glands were reported in five cases. No carcinoid tumor was detected. In all five patients, *H. pylori* infection status was negative.

## Discussion

PA is the most common cause of vitamin B12 deficiency (7). Atrophy of gastric body mucosa constitutes the underlying cause in the majority of cases in northern Europe and the United States. Definitive diagnostic tests are the Schilling test and gastric analysis of intrinsic factor content. However, these tests may be difficult to obtain or interpret in some patients. Not all patients can reliably provide the complete 24-h urine collections necessary for the Schilling test, and the diagnostic second stage part of the test, in which oral intrinsic factor is given, may be unreliable due to the transient intestinal malabsorption of cobalamin that accompanies PA or technical problems (18). Consequently, the identification of patients who require replacement often demands supplementary tests (10). In PA, chronic atrophic gastritis is present, which involves the fundus and body of the stomach, both of which contain pepsinogen I-secreting zymogenic cells. Serum pepsinogen I as well as gastrin concentrations have been shown to correlate well with the morphology and function of gastric body mucosa (12, 19). Carmel (9) showed that low serum pepsinogen I concentrations could be a suitable screening tool for this disease. These results were later confirmed by Lindgren *et al.* (10). In their study, 110 patients with cobalamin deficiency were evaluated by endoscopy and gastric body and duodenum biopsies. When biopsy reports and serum pepsinogen I and gastrin concentration results were analyzed, they concluded that the first step in evaluating

**TABLE 3.** Profile of PCA-negative and PCA-positive DM1 patients with low titers (1/40–1/320) and PCA-positive at higher titers (≥ 1/640)

| | PCA < 1/640 (n = 154) | PCA ≥ 1/640 (n = 14) | *P* |
|---|---|---|---|
| Age (yr)[a] | 30.5 ± 8.8 | 35.6 ± 15 | N.S. |
| Plasma gastrin (ng/liter)[b] | 26 (19–33) | 381 (84–841) | <0.001 |
| Plasma pepsinogen (μg/liter)[b] | 58 (44–77.5) | 12.7 (9.4–42.2) | <0.001 |
| % Gastrin > 100 ng/liter[c] | 4 (2.6%) | 10 (71.4%) | <0.001 |
| % Pepsinogen < 30 μg/liter[c] | 10 (6.5%) | 10 (71.4%) | <0.001 |
| TPOa+[d] | 25 (16.2%) | 4 (28.6%) | N.S. |

N.S., Nonsignificant.
[a] Expressed as mean ± SD. Student's *t* test.
[b] Expressed as median (interquartile range). Mann-Whitney *U* test.
[c] Expressed as percentage. $\chi^2$ test.
[d] Expressed as number (percentage). Fisher's exact test.

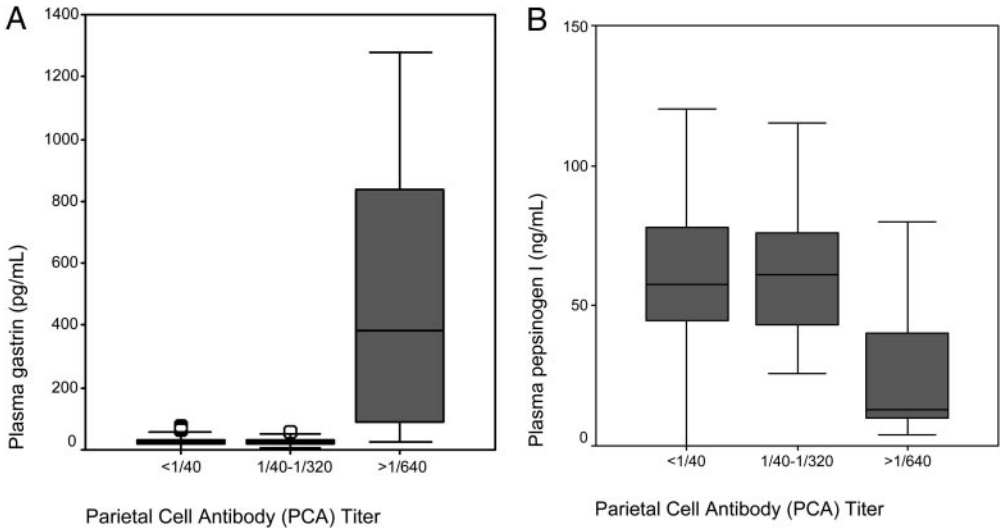


FIG. 1. Plasma gastrin (A) and pepsinogen I (B) concentrations in DM1 patients according to their PCA titers. *Blocks* represent the median and interquartile range.

patients with suspected cobalamin deficiency should be to apply a combined serum pepsinogen I and gastrin level assay, which identified 95–96% of patients with severe gastric body atrophy, a higher proportion than that obtained with serum pepsinogen I or gastrin as a single test. Taking these results into account, and because there is no established consensus about the adequate moment to perform EGD in patients with low serum pepsinogen I concentrations, we agreed to perform this examination in cases also with hypergastrinemia, because the highest diagnostic accuracy has been described with both abnormal tests.

In our cohort of 186 DM1 patients, plasma pepsinogen I concentrations were low in 12.4%, but in only 0.9% of the control group. Because none of our patients had undergone gastrointestinal surgery, and the decrease in serum pepsinogen I concentrations is attributable to the loss of gastric chief cells, we assumed it to be caused by the atrophic chronic gastritis present in PA. In fact, this was histologically confirmed in our patients.

Three of 186 DM1 patients with an advanced form of latent PA with low serum pepsinogen I concentrations also had low plasma cobalamin concentrations, hypergastrinemia, and positive high PCA titers, although none of them had megaloblastic anemia yet. This could occur because the onset and progression of PA are slow, and PA is usually diagnosed at a more advanced age than our cohort's age (7).

Positive PCA were found in 26% of DM1 patients. Previous studies reported that PCA-positive diabetic patients were older than those who were PCA negative (5, 20). In our study, PCA-positive patients did not differ from those PCA negative in age or sex distribution. PCA-positive patients with high titers (≥1:640) showed a higher proportion of hypergastrinemia (>100 ng/liter) and/or low serum pepsinogen I concentrations (<30 $\mu$g/liter) than patients with low titers or negative PCA, which indicated a more damaged gastric mucosa. As De Block's study showed (6), when autoimmune atrophic gastritis is evaluated with gastric biopsies in DM1 patients, the percentage of parietal cells in glands correlates inversely with PCA titers, showing a correlation between PCA titer and gastric body atrophy severity. The prevalence of positive PCA observed in DM1 patients in our study was higher than reported prevalences, ranging from 5–28% (21). A possible explanation could be the different genetic background of the patients, which may influence antibody status, or the methodological differences in PCA determinations. Some studies have shown that PCA are more common in patients with glutamic acid decarboxylase 65 antibodies and HLA-DQA1 or 501-B1*0301 haplotype (20), but these were not evaluated in the present study. Overall, the described percentages of sensitivity and specificity of positive PCA for the diagnosis of PA are not high. Positive titers of PCA are described in a wide range of other autoimmune disorders (22) and, as has been reported in some studies, only half of the patients with PA have positive PCA (23). Moreover, not every patient with autoimmune gastritis has positive PCA (6). Explanations for the PCA seronegative results in a percentage of patients with PA include faulty diagnosis, complete binding of antibody to antigen so that none is circulating at the time of measurement, disappearance of antibody due to disappearance of the antigen, or failure of production of the antibody (1). Thus, we consider that PCA should be used as a screening tool to confirm the autoimmune nature of the process; however, what really demonstrates the organ lesion is the low serum pepsinogen I levels. Unlike previous studies carried out in DM1 patients, we found no association between gastric and thyroid autoimmunities, possibly due also to the younger age of our cohort and/or the different genetic background of the patients that may influence antibody status.

The benefits of PA screening in the general population are unclear. Screening a diabetic population may be much more productive given their relatively high prevalence of PA. Moreover, population-based studies have revealed an excessive risk of gastric carcinoma and gastric carcinoid tumors in patients with PA (24). Because Schilling's test and gastric biopsies were not routinely performed in the entire cohort, we cannot define the proportion of patients with latent PA

who will ultimately develop clinical PA and within what period of time.

In conclusion, we found a high prevalence of latent PA among our DM1 patients, assessed by low plasma pepsinogen I concentrations, compared with a healthy, age-matched control group. Taking into account the present and previous studies, we recommend screening for latent PA using, in addition to PCA, serum pepsinogen I and, in cases with low pepsinogen I concentrations, testing serum gastrin at least at yearly intervals. In patients with low pepsinogen I, hypergastrinemia, and PCA positivity at high titers, endoscopy should be considered to confirm gastric atrophy and rule out (pre)malignant gastric lesions.

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Address all correspondence and requests for reprints to: Dr. Isabel Salinas, Department of Endocrinology and Nutrition, Hospital Universitari Germans Trias i Pujol, Ctra Canyet s/n, Badalona, 08916 Catalonia, Spain. E-mail: isalinas@ns.hugtip.scs.es.

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