

Soluble Transferrin Receptor Level

A new marker of iron deficiency anemia, a common manifestation of gastric autoimmunity in type 1 diabetes

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OBJECTIVE — A total of 15–20% of type 1 diabetic patients have parietal cell antibodies (PCAs). PCA⁺ subjects are at increased risk for iron deficiency anemia and atrophic gastritis. Recently, soluble transferrin receptor (sTfR) levels have proven to be a sensitive indicator for iron deficiency. They are, in contrast with ferritin levels, independent of inflammation, liver and hormonal status, and sex. We are the first to evaluate sTfR levels in type 1 diabetes and tested the hypothesis of higher sTfR levels in patients with PCAs and/or autoimmune gastritis.

RESEARCH DESIGN AND METHODS — We examined 148 type 1 diabetic patients (85 men and 63 women; 50 were PCA⁺) and 59 sex- and age-matched control subjects (30 men and 29 women). The main outcome measures were sTfR levels, iron deficiency anemia, and atrophic gastritis. Logistical regression analysis tested risk factors for iron deficiency.

RESULTS — Iron deficiency was present in 38 subjects. Iron ($P < 0.0001$) and ferritin ($P < 0.0001$) levels but not sTfR levels were lower in women. sTfR levels were similar in diabetic and control subjects but were higher in PCA⁺ subjects ($P = 0.015$). In diabetic subjects, iron deficiency anemia was more prevalent in PCA⁺ than in PCA⁻ patients (odds ratio 3.07, $P = 0.013$) and was associated with sex ($P = 0.0001$), age ($P = 0.046$), and sTfR ($P = 0.0008$) levels. Atrophic gastritis was present in 15 of 28 PCA⁺ and in 1 of 11 PCA⁻ diabetic subjects ($P = 0.014$). sTfR levels tended to be higher in patients with atrophic gastritis ($P = 0.062$).

CONCLUSIONS — In type 1 diabetes, sTfR levels can be used to diagnose iron deficiency anemia, which is more prevalent in PCA⁺ subjects. sTfR levels are higher in PCA⁺ individuals who are at risk for developing atrophic gastritis.

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Type 1 diabetes results from autoimmune destruction of pancreatic β -cells (1). In addition, we and others (2–4) have found that 15–20% of these patients have parietal cell antibodies (PCAs), which are cytotoxic to the gastric mucosa. This chronic autoimmune aggres-

sion can lead to atrophic gastritis (5,6). Moreover, PCAs target the gastric proton pump (7), which results in decreased gastric acid secretion and decreased iron absorption. This may cause iron deficiency anemia, which is a common (although frequently overlooked) manifestation of

autoimmune gastritis (8–12). On the other hand, iron deficiency anemia can also arise by malignant or inflammatory diseases, especially from the gastrointestinal tract (13,14), and atrophic gastritis predisposes patients to gastric carcinoma and carcinoid tumors (15,16).

Iron plays an essential role in hemoglobin synthesis, electron transport for cellular respiration, DNA synthesis, and other vital enzymatic reactions (13). Early detection and treatment of iron deficiency and the conditions that are at its origin could significantly reduce morbidity. Recently, soluble transferrin receptor (sTfR) levels have been shown to be a sensitive and highly quantitative indicator of early iron deficiency (17–19). Moreover, sTfR levels discriminate between iron deficiency anemia and anemia of chronic disease (20,21). However, the use of sTfR levels to detect iron deficiency in type 1 diabetic patients has never been studied. To our knowledge, this is the first study to evaluate whether sTfR levels are higher in PCA⁺ subjects or in type 1 diabetic patients with atrophic gastritis.

RESEARCH DESIGN AND METHODS

Patients

Of a group of 497 type 1 diabetic patients attending the outpatient diabetes clinic of the University Hospital Antwerp, 148 patients (85 men and 63 women) were selected on the basis of their PCA status. A total of 50 PCA⁺ and 98 PCA⁻ patients with a mean age of 40 ± 12 years, a mean duration of disease of 17 ± 10 years, and a mean HbA_{1c} level of $7.9 \pm 1.1\%$ were studied. The diabetic patients were matched for sex and all aforementioned parameters. The nondiabetic control group consisted of 59 sex- and age-matched healthy individuals (30 men and 29 women), of whom 7 subjects were PCA⁺ (Table 1).

Individuals with decreased serum vitamin B₁₂ concentrations, positive anti-intrinsic factor, and/or pernicious anemia were excluded because, in inefficient erythropoiesis, sTfR levels may be elevated in the absence of functional iron depletion (22).

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Abbreviations: ANOVA, analysis of variance; AUC^{ROC}, area under the curve for receiver operating characteristics; CV, coefficient of variation; NI, normal range; PCA, parietal cell antibody; sTfR, soluble transferrin receptor.

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

Table 1—Comparison of iron status between diabetic and control subjects

	Total	Diabetic men	Diabetic women	Control men	Control women	P (ANOVA)
n	207	85	63	30	29	—
Age (years)	40 ± 12	41 ± 14	37 ± 10	41 ± 10	44 ± 13	NS (P = 0.06)
Iron (µg/dl)	84 ± 41	98 ± 38	71 ± 39	92 ± 40	60 ± 26	<0.0001*
Transferrin saturation (%)	33 ± 15	37 ± 15	28 ± 15	37 ± 13	29 ± 11	0.0001*
Ferritin (µg/l)	78 ± 76	95 ± 81	46 ± 54	124 ± 84	48 ± 52	<0.0001*
Transferrin (mg/dl)	247 ± 43	227 ± 35	254 ± 44	256 ± 31	281 ± 45	<0.0001*†
sTfR (mg/l)	1.19 ± 0.32	1.17 ± 0.30	1.24 ± 0.37	1.11 ± 0.21	1.24 ± 0.36	NS (P = 0.24)
sTfR/ferritin ratio	47.6 ± 90.7	21.1 ± 19.2	79.2 ± 115.3	17.1 ± 25.5	88.1 ± 148.9	<0.0001*
PCA ⁺ (≥1/20)	57 (27.35)	23 (27.6)	27 (42.9)	4 (13.3)	3 (10.3)	NS
Iron deficiency‡	38 (18.4)	8 (9.4)	19 (30.2)	5 (16.7)	6 (20.7)	0.004*

Data are means ± SD or n (%). Two-way ANOVA was performed between the groups with sex and health status as fixed factors. *Statistical significance reached according to sex; †statistical significance reached according to health status; ‡iron deficiency as defined in RESEARCH DESIGN AND METHODS.

Subjects with other causes of iron malabsorption such as anti-endomysium antibodies and/or celiac disease were excluded (12). Other exclusion criteria were reticulocytosis, abnormal differential blood count, increased erythrocyte sedimentation rate or C-reactive protein, increased serum creatinine levels, abnormal urine sediment, abnormal liver function tests, and chronic gynecological blood loss. Most women, if not already postmenopausal, were taking contraceptive drugs. In all patients, fecal occult blood testing was repeatedly negative. None of the subjects was vegetarian, and none used anti-inflammatory drugs, acid suppression therapy, or folic acid, vitamin B₁₂, or vitamin C supplements. All patients were euthyroid.

Study design

HbA_{1c} levels were determined by high-performance liquid chromatography (Variant Hemoglobin A_{1c} Reorder Pack; Bio-Rad, Richmond, CA, normal range [NI] 4.8–6.0%). PCAs were assayed with indirect immunofluorescence using rat gastric mucosa as a substrate (MeDiCa Kit; Medical Diagnostics California, Carlsbad, CA, NI <1/20 dilution) as described previously (4). Fecal occult blood testing was performed by means of Hemocult II Sensa (SmithKline Diagnostics, San José, CA). Serum gastrin was measured using a radioimmunoassay technique (Euro-Diagnostics, Malmö, Sweden). Serum iron was determined colorimetrically (Hitachi 912; Roche Diagnostics, Brussels, Belgium). Levels of sTfR, transferrin, and ferritin were assayed with a commercially available kit based on (latex-enhanced) nephelometry (BN II; Dade Behring, Leiderbach, Germany).

Iron deficiency anemia was defined as a decreased hemoglobin concentration (men

<13 and women <12 g/dl) and microcytic (mean corpuscular volume <76 fl) and hypochromic indexes (mean corpuscular hemoglobin <27 pg) accompanied by at least 1 of the following laboratory values for iron deficiency: a decreased serum iron level (men <50 and women <40 µg/dl), a transferrin saturation ≤20% (NI 20–60%), or a decreased serum ferritin concentration (men <20 µg/dl and women <12 µg/l).

Normal ranges, coefficients of variation (CVs), and sensitivities were as follows: serum iron (men 50–200 and women 40–180 µg/dl, CV <3%, sensitivity 1 µg/dl), transferrin (men 210–340 and women 200–310 mg/dl, CV 2.8%, sensitivity 8.4 mg/dl), ferritin (men 20–450 and women 12–250 µg/l, CV 1.5%, sensitivity 0.48 µg/l), hemoglobin (men 13–17 and women 12–16 g/dl, CV 1.2%, sensitivity 0.5 g/dl), and gastrin (men and women <110 pg/ml, CV 9.3%, sensitivity 1.1 pg/ml). The normal range provided by the kit manufacturer for sTfR levels is 0.83–1.76 mg/l (CV <3.3%, sensitivity 0.035 mg/l). The commercial cutoff value (1.76 mg/l) or the 95th percentile (1.84 mg/l) found in our study population (n = 207) identified the same iron-deficient individuals.

A gastroscopic and histological examination was performed in a subgroup of 39 diabetic patients (28 PCA⁺ vs. 11 PCA⁻) with gastric symptoms or who were suspected to have atrophic gastritis or ulcers. With an upper gastrointestinal endoscopy using a fiber-optic endoscope (Olympus Videoscope, GIF/Q140, Melville, NY), 2 tissue fragments from the corpus, 2 from the fundus, 2 from the antrum, and 2 from the postbulbar duodenum were obtained and assessed for evidence of gastric atrophy and *Helicobacter pylori* colonization as defined by the updated Sydney system (23).

The study was approved by the Ethical Committee of the University Hospital Antwerp. Informed consent was obtained from each person in accordance with the Helsinki Declaration.

Statistical analysis

All data for this cross-sectional study were analyzed using the statistical package SPSS Version 8.0 (SPSS, Chicago). The unpaired *t* test or analysis of variance (ANOVA) with Tukey's test as post hoc analysis was used for comparison of means. The χ^2 test or Fisher's exact test was performed to test frequency distributions. Pearson's correlation was used where indicated. Stepwise forward multiple logistical regression analysis was used to assess the strength and independence of associations and to describe a predictive model. All tests were 2-tailed. A *P* value ≤0.05 was considered significant.

RESULTS — Table 1 shows that, in both the diabetic and nondiabetic populations, nearly 1 of 5 subjects (18.4%) presented with iron deficiency with a female preponderance (odds ratio 2.93 [95% CI 1.40–6.12], *P* = 0.004). Women (n = 92) had lower levels of serum iron (*P* < 0.0001) and ferritin (*P* < 0.0001) and higher levels of transferrin (*P* < 0.0001) than men (n = 115). sTfR levels did not differ significantly between sexes. The sTfR/ferritin ratio, however, was higher for women (*P* < 0.0001).

Diabetic subjects had lower transferrin levels than control subjects (*P* < 0.0001), but sTfR levels were similar. Moreover, sTfR concentrations did not correlate with HbA_{1c} levels, C-peptide levels, or dose of insulin. The number of subjects in the study subgroups is shown in Fig. 1.

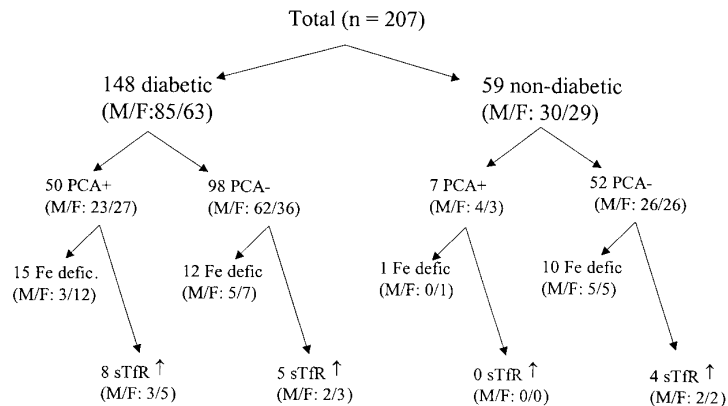


Figure 1—Subjects in the study groups. *defic*, deficiency.

Individuals with iron deficiency had higher transferrin levels (264 ± 56 vs. 244 ± 39 mg/dl, respectively, $P = 0.008$), higher sTfR levels (1.33 ± 0.43 vs. 1.16 ± 0.29 mg/l, respectively, $P = 0.002$), and a higher sTfR/ferritin ratio (117 ± 166 vs. 32 ± 52 , respectively, $P < 0.0001$) than those without iron deficiency, but ferritin levels were similar (62 ± 93 vs. 81 ± 71 μ g/l, respectively). The area under the curve for receiver operating characteristics (AUC^{ROC}) provided by transferrin saturation to identify iron-deficient patients was 0.85 ± 0.04 , and that for sTfR/ferritin ratio was 0.71 ± 0.06 (Fig. 2). The positive predictive value of sTfR was 76%, the negative predictive value was 87%, the specificity was 98%, and the sensitivity was 34%. The level of serum iron correlated with the sTfR concentration ($r = -0.13$, $P = 0.05$) and with the transferrin level ($r = -0.28$, $P < 0.0001$) and was strongest with the sTfR/ferritin ratio ($r = -0.34$, $P < 0.0001$). In addition, PCAs were more prevalent in subjects with than without iron deficiency (16 of 38 vs. 41 of 169; 2.27 [1.09 – 4.73], $P = 0.043$). To determine independent risk factors for iron deficiency, logistical regression analysis was used. In both the diabetic and control populations, sex ($\beta = -0.98$, $P = 0.011$) and sTfR levels ($\beta = 1.31$, $P = 0.012$) were predictive of iron deficiency when age, sex, transferrin, ferritin, sTfR levels, and PCA status were tested. We also observed an association between PCA status and sTfR levels ($\beta = 1.10$, $P = 0.0185$) when all iron parameters and sTfR levels were evaluated.

Because iron deficiency was highly prevalent in subjects with PCAs and because the diabetic group was selected according to PCA status, we compared the iron status in patients ($n = 148$) with and

without these antibodies. Table 2 shows that PCA⁺ diabetic subjects had lower levels of serum iron ($P = 0.041$), higher sTfR concentrations ($P = 0.016$), and a higher sTfR/ferritin ratio ($P = 0.02$) than PCA⁻ patients. In addition, mean levels of serum gastrin were higher ($P = 0.007$) in PCA⁺ subjects. Sex did not influence the gastrin levels. In the PCA⁺ cohort, we observed a strong correlation between gastrin and sTfR concentrations ($r = 0.52$, $P < 0.0001$).

Diabetic patients with iron deficiency anemia had high sTfR levels (sTfR > 1.76 mg/l) in 33.3% of cases compared with 3.3% of nonanemic subjects (14.63 [4.07 – 52.52], $P < 0.0001$). Iron deficiency anemia was associated with sex ($\beta = -2.36$, $P = 0.0001$), age ($\beta = 0.04$, $P = 0.047$), and sTfR levels ($\beta = 2.11$, $P = 0.0004$) when age, sex, duration of diabetes, transferrin, ferritin, sTfR levels, and PCA status were tested.

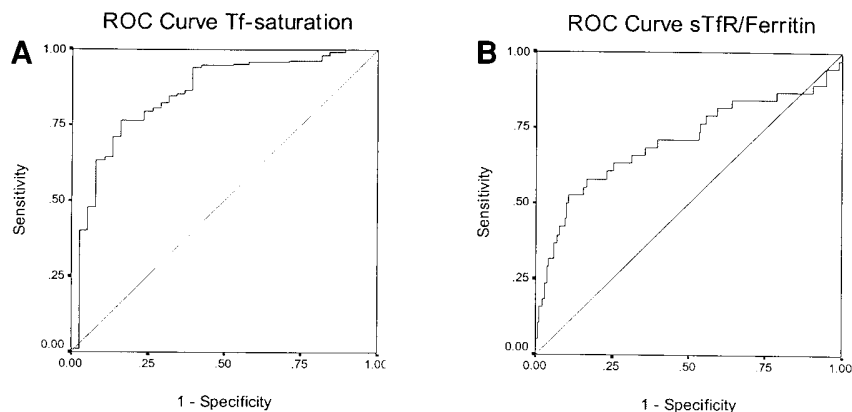


Figure 2—Receiver operating characteristic (ROC) plots generated from data of 207 subjects for transferrin (Tf) saturation (A) and for sTfR/ferritin ratio (B) to identify iron-deficient subjects. The area under the curve (AUC), which quantifies the diagnostic accuracy of a laboratory test, is 0.85 ± 0.04 for transferrin saturation and 0.71 ± 0.06 for sTfR/ferritin ratio.

A gastroscopy with multiple biopsies was performed in a subgroup of 39 diabetic subjects (18 men and 21 women), which demonstrated gastric symptoms or subjects suspected to have atrophic gastritis, which could explain the iron deficiency anemia. *H. pylori* colonization was not found in any biopsy specimen using modified Giemsa staining and/or immunohistochemistry. In the PCA⁺ group, 15 of 28 patients showed atrophic body gastritis compared with 1 of 11 PCA⁻ subjects (11.5 [1.3 – 102.7], $P = 0.0136$). The prevalence of atrophic gastritis was not associated with sex. Patients with atrophic gastritis were more prone to have iron deficiency anemia than subjects without atrophic gastritis (8 of 12 vs. 8 of 27; 4.75 [1.11 – 20.40], $P = 0.041$). Moreover, we observed a tendency toward an association between high sTfR levels and atrophic gastritis ($P = 0.062$).

CONCLUSIONS—Iron deficiency was present in nearly 20% of the population studied, with a female preponderance. Despite the fact that most premenopausal women were taking contraceptives, menstrual blood loss in some women can explain this observation. Iron is an essential element in diverse aspects of physiology (13). Besides the known consequences of anemia, various nonhematological effects of iron deficiency (e.g., reduced work performance, defects in immunity, and impaired intestinal function) have been observed (24,25).

Serum iron, transferrin, transferrin saturation, and ferritin are widely used parameters to detect iron deficiency. However, they are considerably influenced by acute-phase responses and acute liver injury or

Table 2—Comparison of iron status between PCA⁺ and PCA⁻ type 1 diabetic patients

	Type 1 diabetic patients		P	Odds ratio (95% CI)
	PCA ⁺	PCA ⁻		
n (M/F)	50 (23/27)	98 (62/36)	NS	—
Age (years)	40 ± 12	40 ± 13	NS	—
Duration of diabetes (years)	18 ± 10	17 ± 10	NS	—
Age at onset (years)	21 ± 11	22 ± 13	NS	—
HbA _{1c} (%)	7.9 ± 1.0	8.0 ± 1.0	NS	—
Iron (μg/dl)	78 ± 45	93 ± 40	0.041	—
Ferritin (μg/l)	66 ± 76	78 ± 73	NS	—
Transferrin (mg/dl)	243 ± 41	237 ± 42	NS	—
sTfR (mg/l)	1.29 ± 0.37	1.15 ± 0.30	0.016	—
sTfR/ferritin ratio	71.3 ± 117.5	38.6 ± 76.7	0.02	—
Gastrin (pg/ml)	230 ± 265	87 ± 31	0.007	—
Iron deficiency anemia	15 (30)	12 (12.2)	0.0125	3.07 (1.31–7.21)
sTfR >1.76 mg/l	8 (16)	5 (5.1)	0.0345	3.54 (1.09–11.5)
Atrophic gastritis (n = 39)	15/28 (53.6)	1/11 (9.1)	0.0136	11.5 (1.3–102.7)

Data are means ± SD or n (%). All parameters were analyzed in every subject unless otherwise indicated.

malnutrition, which complicates the interpretation of test results (26). Moreover, serum iron and transferrin saturation levels show large day-to-day variations (27). Serum ferritin is the only readily available measurement to assess the iron storage status, but it is not sufficient to detect marginal iron deficiency (28). The fact that ferritin levels did not differ between subjects with and without iron deficiency in our study confirms this observation. The absence of stainable iron in bone marrow examination is regarded as the definitive marker of iron deficiency. However, a bone marrow biopsy is invasive, and therefore, an evident clinical need exists for noninvasive and sensitive means to detect iron deficiency.

Recently, sTfR has been proposed as the best marker of functional iron status because of its superior ability to distinguish iron deficiency anemia from the anemia of chronic disorders (17–21) and because of its small day-to-day variation (29). Moreover, the concentration of sTfR is not influenced by inflammatory diseases and is independent of liver parenchymal status and hormonal status (estrogens and thyroid function) (21). Circulating sTfR levels are derived by proteolytic cleavage from transferrin receptors expressed on the cell surface (30) and primarily circulate attached to transferrin (31). They are present in direct quantitative proportion to their total tissue content and vary according to body iron content and to the intensity of erythropoiesis (32,33). Measuring sTfR levels, for which only a few microliters of serum are needed, would be especially useful at outpatient clinics. How-

ever, the sTfR level is a relatively new parameter, and, as suggested by a recent report evaluating the practicality, comparability, and ability to discriminate between presence or absence of iron deficiency of 3 commercially available sTfR kits, a need exists for internationally accepted reference material and comparable units (34). We studied a larger group well characterized regarding iron status, thereby minimizing uncertainties. Moreover, the upper normal level provided by the manufacturer identified the same subjects as the 95th percentile in our study group. Our results confirm the importance of the choice of an adequate cutoff value and expand the applicability of sTfR levels to diabetic patients.

In a previous study of 497 type 1 diabetic patients, we observed that ~20% were PCA⁺ and that PCA⁺ subjects were at increased risk for iron deficiency anemia (4). Therefore, we tested the use of sTfR in type 1 diabetic patients with or without PCA and compared their iron status with a matched group of healthy control subjects. We and others found that circulating sTfR concentrations did not differ between men and women (20). Apart from lower transferrin levels in diabetic patients, all parameters of iron status were similar in the diabetic and control groups. Diabetes-related parameters such as HbA_{1c}, C-peptide levels, and insulin dose did not influence the sTfR concentration, which implies that sTfR can be used in diabetic patients. Although the subjects were only moderately iron deficient, sTfR levels (besides sex and age) were shown to predict iron deficiency anemia. Moreover, the level of

serum iron correlated with the sTfR concentration and was strongest correlated with the sTfR/ferritin ratio. This suggests that sTfR levels provide physicians with a more sensitive marker of iron deficiency than other parameters of iron status. The AUC^{ROC} for sTfR/ferritin also suggests this. Because of the reciprocal relationship between sTfR levels and ferritin measurements, the ratio of sTfR/ferritin allows accurate definition of the entire range of iron status (35).

Iron deficiency anemia can be caused by dietary deprivation of iron, but in this study, none of the subjects was a vegetarian or followed a low-iron diet. Although no absorption of iron occurs in the stomach, the gastric acid produced by the H⁺/K⁺ ATPase plays a significant role. Hydrochloric acid helps to remove protein-bound iron, to solubilize iron, and to reduce it from the ferric to the ferrous state (25). Reduction of iron is necessary because most dietary iron is found in the ferric form and is poorly absorbed. Decreased gastric acidity resulting from overconsumption of antacids or achlorhydria in atrophic gastritis may lead to impaired iron absorption (8–12). Type 1 diabetic patients show a high prevalence of PCAs (2–4) that target the H⁺/K⁺ ATPase (7) and thus result in a compromised gastric acid production (8–12). The present study clearly demonstrates that PCA⁺ subjects show an increased prevalence of iron deficiency anemia compared with PCA⁻ individuals, regardless of sex. The strongest predictor of iron status was the sTfR level that, on its own, was associated with PCA status. In addition, high gastrin levels, which are frequently seen in PCA⁺ subjects, indicate a lower gastric acid output. The strong correlation we observed between gastrin and sTfR levels in the PCA⁺ group supports the idea of a causal relationship between PCA positivity and impaired gastric acid secretion, which leads to iron malabsorption and iron deficiency anemia.

Moreover, PCAs are recognized as a marker of atrophic gastritis, which predisposes patients to gastric carcinoma and gastric carcinoid tumors (15,16). Given the relatively high probability that ulcers or malignant tumors may be the cause of blood loss, this anemic condition warrants extensive investigation of the gastrointestinal tract (12–14). Fecal occult blood testing was repeatedly negative, as were the history and clinical examination, and none of the patients undergoing gastroscopy showed these lesions. Even in the presence of atrophic gastritis, full gastrointestinal investigation must be considered because dual

pathology causing iron deficiency may exist, although this is rather unlikely (14,36). Clinicians may choose not to undertake a colonoscopy if a lesion has been detected in the upper gastrointestinal tract. However, particularly in older patients, this may be warranted, and clinical judgment and follow-up (e.g., response to iron treatment) are essential. In the present study, atrophic gastritis was associated with PCA positivity, and iron deficiency anemia was more prevalent in patients with autoimmune gastritis. High sTfR levels showed a strong tendency toward association with the presence of atrophic gastritis that was not statistically significant, probably because of the small number of patients who underwent a gastroscopy.

In conclusion, the present data support the contention that sTfR concentrations are a sensitive marker of iron status in patients with type 1 diabetes. sTfR levels are higher, and iron deficiency anemia and atrophic gastritis are more prevalent in PCA⁺ subjects. Therefore, screening for these conditions, certainly in PCA⁺ patients (who are at increased risk for autoimmune gastropathy), is warranted because it may significantly reduce the morbidity from anemia, iron deficiency, or the conditions that cause them.

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