Prevalence and clinical significance of organ-specific autoantibodies in type 1 diabetes mellitus

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ABSTRACT

As diabetes mellitus type 1 (DM1) is associated with other autoimmune diseases, clinical tools are needed to diagnose and predict the occurrence of other autoimmune diseases in DM1. We performed a systematic search of the literature on the prevalence, and the diagnostic and prognostic significance of organ-specific autoantibodies in DM1, focusing on the most prevalent autoimmune diseases in DM1: Hashimoto’s disease, autoimmune gastric disease, Addison’s disease and coeliac disease.

We found 163 articles that fulfilled our selection criteria. We analysed and compared the prevalence of autoantibodies in DM1 and control populations, studied the relation between antibody prevalence and age, gender, race and DM1 duration and studied the relation between the presence of autoantibodies and organ dysfunction. Because of the large variation in population characteristics and study design, a uniform conclusion on the relation of these autoantibody prevalences with age, gender, race, DM1 duration and target organ failure cannot be drawn easily. In addition, most studies reviewed used a cross-sectional design. Therefore, few data on the predictive value of the organ-specific antibodies in DM1 populations are present in these studies. Obviously, prospective studies are needed to fill this gap in knowledge.

Despite these restrictions, the general picture from the present review is that the prevalence of the organ-specific autoantibodies is significantly higher in DM1 than in control populations. Given the relevant risk for organ failure in DM1 patients with autoantibodies against thyroid, gastric, adrenal and intestinal antigens, we recommend checking these autoantibodies in these patients at least once, for instance at the diagnosis of DM1. For detailed advice on assessing the different organ autoantibodies and function we refer to the summaries in the results section.

KEYWORDS

Autoimmune antibodies, organ-specific dysfunction, type 1 diabetes mellitus

INTRODUCTION

Type 1 diabetes mellitus (DM1) is a clinical syndrome in which the destruction of the pancreatic islet β-cells leads to progressive insulin deficiency and hyperglycaemia, which in turn gives rise to microvascular complications such as retinopathy, nephropathy, and neuropathy as well as macrovascular complications. The presence of autoantibodies targeted against β-cell antigens represents the autoimmune character of DM1. Although the genetic risk for DM1 is considerably lower than for type 2 diabetes mellitus, certain human leucocyte antigen haplotypes are associated with an increased risk for DM1. The significance of environmental factors is still unclear, despite recent indications for an infectious origin and nutritional factors. DM1 is associated with other immune-mediated disorders such as autoimmune thyroiditis, Addison’s disease, pernicious anaemia, and coeliac disease. Autoimmune disorders can be subdivided in organ-specific and non-organ-specific diseases. In organ-specific autoimmune diseases, a single organ or organ system is affected, whereas in non-organ-specific autoimmune diseases, several organs or tissues are involved. As DM1 is associated with other autoimmune diseases, clinical tools are needed to diagnose and predict the occurrence of other autoimmune diseases in DM1.

Organ-specific autoimmune diseases can be part of autoimmune polyglandular syndromes (APS), of which three types can be distinguished. Type 1 (APS-1, also called APECED) is characterised by the triad of mucocutaneous candidiasis, autoimmune...
hypoparathyroidism and primary adrenal insufficiency (Addison's disease). Other phenomena, such as DM1, primary hypogonadism, alopecia and vitiligo, may also be present. APS-II is the most common form and consists of Addison's disease, autoimmune thyroid disease, DM1, primary hypogonadism, myasthenia gravis and coeliac disease. Vitiligo, alopecia, serositis and pernicious anaemia also occur with increased frequency in individuals with this syndrome. APS-III involves autoimmune thyroid disease, DM1 and vitiligo. Various other diseases including hypoparathyroidism, myasthenia gravis, stiff man syndrome, premature ovarian failure and hypergonadotropotrophic hypogonadism may also be present. Several theories exist to explain (the combinations of) these autoimmune endocrinological diseases, but despite extensive research, their exact aetiology is still unresolved. As DM1 is associated with other autoimmune diseases, clinical tools are needed to diagnose and predict the occurrence of other autoimmune diseases in DM1. We performed a search of the literature on the prevalence, and the diagnostic and prognostic significance of organ-specific autoantibodies in DM1, focusing on the most prevalent autoimmune diseases in DM1: Hashimoto's disease, autoimmune gastric disease, Addison's disease and coeliac disease.

**METHODS**

We studied antimicrosomal or antithyroid peroxidase antibodies (TPO-AB) and antithyroglobulin antibodies (Tg-AB), antiparietal cell antibodies (PCA), antithyroid microsomal antibodies (ACA) and antithyroid peroxidase antibodies (EMA). We performed a search in MEDLINE up to and including December 2005, using the query 'Search diabetes mellitus, type I [MeSH] AND (antibodies [MeSH] OR autoantibodies [MeSH] OR autoimmunity [MeSH] OR antibody OR polyendocrinopathies, autoimmune [MeSH]) NOT Case Reports [Publication Type] NOT (diabetes mellitus, type I [MeSH] AND (antibodies [MeSH] OR autoantibodies [MeSH] OR autoimmunity [MeSH] OR antibody) NOT (thyroid diseases [MeSH] OR thyroiditis [MeSH] OR thyroiditis, autoimmune [MeSH] OR hashimoto's OR TPO OR thyroglob OR Tg-AB OR Tg AB OR thyroid microsomal antibodies OR antithyperoxidase OR Gastric Mucosa [MeSH] OR Parietal Cells, Gastric [MeSH] OR Gastritis [MeSH] OR Gastritis, Atrophic [MeSH] OR Vitamin B12 Deficiency [MeSH] OR Anaemia, Pernicious [MeSH] OR gastritis OR parietal cell) OR (Addison's Disease. [MeSH] OR Adrenal Gland Diseases [MeSH] OR Adrenal Cortex [MeSH] OR adrenocortical OR addison's) OR (Coeliac Disease [MeSH] OR coeliac OR endomys OR anti-endomys OR villous atrophy) OR polyendocrinopathies, autoimmune [MeSH]) NOT Case Reports [Publication Type] Limits: only items with abstracts, English, Humans'. This search produced 387 articles. From the 387 hits originally found, an abstract-based selection was made of 220 articles that appeared to investigate organ-specific antibodies in an insulin-dependent diabetes mellitus (IDDM) population. Of them, 163 were available in the libraries of Leiden University Medical Centre or the Erasmus Medical Centre in Rotterdam. The other 57 articles could not be obtained and were therefore excluded from the review. Of the 163 articles we screened, 114 investigated organ-specific antibodies in an IDDM population and provided detailed data on at least two items of age, gender, origin or racial background and DM1 duration of the original research populations. From these 114 articles, only those 40 that reported on AB prevalence in both DM1 and controls were selected for comparison of AB prevalences between DM1 and control populations. General information about the various autoantibodies and about their relation with age, gender, race, duration of DM1 and organ dysfunction were gathered from the 163 articles mentioned above.

**RESULTS**

**Thyroid antibodies (Th-AB)**

Thyroid autoantibodies (Th-AB) are directed against thyroglobulin (Tg) and thyroid peroxidase (TPO). Tg is the thyroid prohormone and contains tyrosyl residues, which serve as targets for iodination, a process that is mediated by TPO. TPO-AB can activate complement and are directly or indirectly involved in the inflammatory process as observed in autoimmune thyroiditis. Tg-AB appear to play no pathogenic role in thyroid disease, probably because of their inability to fix complement, and they are merely regarded as markers of autoimmune thyroid disease.

**Thyroid peroxidase antibodies (TPO-AB)**

**Methods**

To detect TPO-AB, some authors used (haem)agglutination, while others used indirect immunofluorescence, ELISA, RIA or (indirect-)agglutination. In the article by Maclaren et al., the antibody detection method was not mentioned. When comparing the TPO-AB prevalences obtained by (haem)agglutination, indirect immunofluorescence, ELISA and RIA, the prevalences found by (haem-)agglutination were generally lower than the prevalences found by other methods. However, this difference did not reach statistical significance.

**Prevalences**

In general, TPO-AB prevalences in DM1 populations varied between 5.5 and 46.2% (interquartile range (IQR) 11.3-21.2, P5-P95 5.8-34.5) and in control populations, TPO-AB were present in 0 to 27.0% (IQR 2.0-6.8, P5-P95 0.1-20).

**De Graaff, et al. Prevalence and clinical significance of organ-specific autoantibodies in DM1.**
Relations
Kokkonen et al.\(^{39}\) investigated TPO-AB prevalence and found a significant relation with age in children with DM1; the highest prevalence of 15.0% was found in 40 patients aged 10 to 14 years, vs 5.9% of 17 patients younger than 10, and 11.1% of 26 patients older than 15 years. The results of Trimarchi et al.\(^{39}\) are similar to those of Kokkonen et al. Chang et al.\(^{64}\) found a significantly higher TPO-AB frequency in older than in younger age groups: 43.8% in the group older than 25 years, 27.2% in the group of 10 to 25 years and 15.6% in the group younger than 10 years (p<0.01). De Block et al.\(^{10}\) to 25 years and 15.6% in the group younger than 10 years, vs 5.9% of 17 patients younger than 10, and 11.1% of 26 patients older than 15 years. The results of Trimarchi et al.\(^{39}\) are similar to those of Kokkonen et al. Chang et al.\(^{64}\) found a significantly higher TPO-AB frequency in older than in younger age groups: 43.8% in the group older than 25 years, 27.2% in the group of 10 to 25 years and 15.6% in the group younger than 10 years (p<0.01). De Block et al.\(^{65}\) reported that TPO-AB positive DM1 patients were older than TPO-AB negative patients (30±16 years vs 25±16 years, p=0.012). Cardoso et al.\(^{74}\) also reported a significant correlation between age and TPO-AB (r=0.23, p<0.05). Verge et al.\(^{73}\) found that TPO-AB prevalence rose with age of DM1 diagnosis: 65% in the 0 to 4 years group, 66% in the 5 to 9 years group and 73% in the 10 to 14 years groups (p<0.05). In control populations, the prevalence of TPO-AB rises with age as well.\(^{527}\) Kokkonen et al.\(^{39}\) reported TPO-AB in none of 24 children younger than 10, in 4.1% of 73 children aged 10 to 14 and in 6.3% of 63 children older than 15 years. A female predominance was found in TPO-AB positive DM1 patients.\(^{38,43,51,55-56,61,64,69,71,74-76}\) Some authors compared the percentage of female patients in the TPO-AB positive group with that in the TPO-AB negative group, whereas others compared the TPO-AB prevalences between the two gender groups. Percentages of female patients ranged from 63 to 91% in TPO-AB positive DM1 patients and from 26 to 52% in TPO-AB negative DM1 patients.\(^{17,44,45,51,55-56,61,64,69,71,74-76}\) TPO-AB were present in 7 to 32% of female vs 3 to 18% of male DM1 patients.\(^{50,51,55-57,71,74}\) Other authors, however, did not find such a relation between gender and TPO-AB prevalence.\(^{18,38,41,59,64,77,78}\) A particular subgroup of DM1 patients are pregnant women or women post-partum. In this group of patients, not reviewed in this study, a prevalence of TPO-AB of up to 33.8% was reported.\(^{63,79}\) In the 15 to 20 year age group (12.8%), whereas Kokkonen et al.\(^{39}\) who also found the highest Tg-AB prevalence of 40.5% in controls. The authors suggested that the sensitivity of the detection method was probably responsible for their results. The Tg-AB prevalences found in control populations varied between 0 and 20% (IQR 1.5-8.4, P 5-P95 0.6-27.2),\(^{18,38,41-43,59,61,63,65,67,77,78}\) TPO-AB were present in 7 to 32% of female vs 3 to 18% of male DM1 patients.\(^{50,51,55-57,71,74}\) Other authors, however, did not find such a relation between gender and TPO-AB prevalence.\(^{18,38,41,59,64,77,78}\) A particular subgroup of DM1 patients are pregnant women or women post-partum. In this group of patients, not reviewed in this study, a prevalence of TPO-AB of up to 33.8% was reported.\(^{63,79}\) Although some authors reported higher TPO prevalences in their white than in their black DM1 patients,\(^{55,56,80}\) no clear relation between race and TPO-AB prevalence either. To detect Tg-AB, some authors used (haem)agglutination\(^{59,60-65,68-89}\) while others used ELISA\(^{39,60}\) or RIA.\(^{70-72}\) Hagglof et al.\(^{91}\) used a ‘tanned red cell assay’ and Kaino et al.\(^{90}\) an immune complex transfer enzyme immunoassay. When comparing the Tg-AB prevalences obtained by (haem)agglutination, indirect immunofluorescence, ELISA and RIA, the prevalences found by (haem)agglutination were generally lower than the prevalences found by the other methods. However, this difference did not reach statistical significance.

Prevalences
Tg-AB prevalences in DM1 populations varied between 2.1 and 40% (IQR 5.4-22.7, P 5-P95 2.6-57.3) with one exceptionally high score of 78%, reported by Kaino et al.\(^{90}\) who also found the highest Tg-AB prevalence of 40.5% in controls. The authors suggested that the sensitivity of the detection method was probably responsible for their results. The Tg-AB prevalences found in control populations varied between 0 and 20% (IQR 1.5-8.4, P 5-P95 0.6-27.2),\(^{18,38,41-43,59,61,63,65,67,77,78}\) with one exceptionally high score of 40.5%.\(^{90}\)

Relations
In the same way as TPO-AB, Tg-AB prevalence in DM1 patients increases with age.\(^{65,79}\) Kordonouri et al.\(^{77}\) reported the highest Tg-AB prevalence in DM1 children within the 15 to 20 year age group (12.8%), whereas Kokkonen et al.\(^{39}\) reported Tg-AB in none of 17 DM1 patients younger than 10, in 5% of 40 patients aged 10 to 14 and in 1.7% of 27 patients older than 15 years. In their control population Kokkonen et al.\(^{39}\) reported Tg-AB in none of 24 children younger than 10, in 2.7% of 73 children aged 10 to 14 and in 4.8% of 63 children older than 15 years, which is exceptionally higher than the 3.7% they reported in their DM1 patients of the same age. A female predominance was found in Tg-AB positive DM1 patients by some authors including Odugbesan et al.\(^{49}\) who reported 100% of their Tg-AB positive patients to be female and Landin-Olsson et al.\(^{61}\) who found 84% of their Tg-AB positive patients to be of the female gender. Others, however, did not report such an association between gender and Tg-AB prevalence.\(^{38,39,64,67}\) We did not find any articles about the relation between race and Tg-AB prevalence in DM1 patients. Cardoso et al.\(^{74}\) found a significant correlation...
between the presence of Tg-AB and DM1 duration (r=0.545, p<0.001). In controls, we did not find any articles about the relation between gender or race and Tg-AB prevalence.

**Thyroid antibodies (TPO-AB and/or Tg-AB)**

**Prevalences**

Some authors assessed the overall Th-AB prevalence and found that 17.6% of DM1 patients had either thyroid-stimulating antibodies (TSH, associated with Graves’ disease), TPO-AB or Tg-AB. Others found that 11 to 46% of DM1 patients had either TPO-AB or Tg-AB, vs 1.4 to 11.5% of control subjects, and that 9.3 to 11% of DM1 patients had TPO-AB and Tg-AB, vs 1.9 to 3.8% of control subjects.

**Relations**

Kordonouri et al. reported that DM1 children with Th-AB were significantly older (15 to 20 years) than those without Th-AB (<15 years). Shiao et al. found a Th-AB prevalence of 18.4% in patients older than 18 years (with a mean age of DM1 onset of 18.5 years and mean DM1 duration of 6.9 years) vs 12.8% in those younger than 18 years (with a mean age of DM1 onset of 3.6 years and a mean DM1 duration of 4.5 years). Many other authors also found that the Th-AB prevalence rises with age.41,49,71,72,75,92,93 Th-AB are associated with female gender: 58 to 78% of Th-AB positive patients were females. In Th-AB negative DM1 patients, only 27 to 45% were females. Several authors reported higher Th-AB prevalences in their white than in their black DM1 patients; Burek et al. reported TPO-AB and/or Tg-AB in 50% of 82 white and in 16% of 72 black DM1 patients and Bright et al. found Th-AB in 32% of 164 white and in 6% of 18 black DM1 patients. Kordonouri et al. reported the DM1 duration of patients with either TPO-AB and/or Tg-AB to be longer than the DM1 duration of patients without Th-AB (5.2±3.9 vs 4.4±3.9 years, p<0.05). Park et al. also reported a longer DM1 duration in patients with Th-AB, compared with patients without Th-AB (5.9±3.8 vs 4.2±3.3 years, p<0.05).

**Relation between thyroid antibodies and thyroid function**

Various authors have investigated the relation between TPO-AB and Tg-AB, and thyroid function.4,14,17,19,38,44,45,47,49,52,56,59,64,66,69,71,72,75,83,88,95,97 The authors of the articles we reviewed reported different types of thyroid dysfunction. We distinguish between subclinical hypothyroidism (defined as elevated serum thyrotropin (TSH) concentrations with serum free thyroxine (T4) levels within the reference range), clinical hypothyroidism (defined as both a raised TSH and a low free T4 level) and hyperthyroidism (defined as a raised free T4 with a low TSH level). The prevalences of organ failure in DM1 and in control populations depend on the type of organ dysfunction reported.

**Subclinical hypothyroidism**

Subclinical hypothyroidism was found in 6.3 to 18.9% of DM1 patients with Th-AB. Rattarasarn et al. reported subclinical hypothyroidism in 6.3% (and hyperthyroidism in 25%) of 16 patients who were either TPO-AB or Tg-AB positive. Roldán et al. found subclinical hypothyroidism in 11% of 36 patients who were either TSI, TPO-AB or Tg-AB positive. Court et al. reported subclinical hypothyroidism in 17.6% of Th-AB positive patients. Betterle et al. investigated 37 DM1 patients with TPO-AB and/or Tg-AB and found that seven (18.9%) had subclinical hypothyroidism. Of 19 first-degree relatives of DM1 patients with TPO-AB and/or Tg-AB, four (21.1%) had subclinical hypothyroidism and three Graves’ disease. In another article Betterle et al. investigated 49 Th-AB positive DM1 patients, 24 Th-AB positive first-degree relatives of DM1 patients and 15 Th-AB positive healthy controls. Of the 49 Th-AB positive DM1 patients, nine (18.4%) had subclinical hypothyroidism. Of the 24 Th-AB positive first-degree relatives of DM1 patients, two (8.3%) had subclinical hypothyroidism. The 15 Th-AB positive healthy controls all had normal thyroid function. Presotto et al. found subclinical hypothyroidism in 18% of 60 DM1 patients with Th-AB without clinical symptoms of thyroid disease. In their total group of 26 TPO-AB positive DM1 patients, Fernandez et al. found five (19.2%) patients with subclinical hypothyroidism.

**Change of subclinical to clinical hypothyroidism**

Rattarasarn et al. reported that two out of eight DM1 patients with Th-AB developed clinical hypothyroidism during a follow-up of 19±8 months; in the Th-AB negative DM1 group nobody developed thyroid dysfunction during 16.4±6.3 months follow-up.

**Clinical hypothyroidism**

In two groups of DM1 patients who were either TPO-AB or Tg-AB positive, clinical hypothyroidism was reported in 6.3 and 24% of the cases. In 26% of 53 patients with Th-AB and/or TPO-AB, Burek et al. found hypothyroidism; those with hypothyroidism all had both TPO- and Tg-AB. Betterle et al. investigated 37 DM1 patients with TPO-AB and/or Tg-AB and found seven patients who had clinical disease: Graves’ disease (4), Hashimoto’s thyroiditis (2) and idiopathic hypothyroidism (1). They did not detect clinical hypothyroidism in any of their Th-AB positive controls. Of isolated TPO-AB positive DM1 patients 11.5 to 72% were reported to have clinical hypothyroidism. In their total group of 26 TPO-AB positive DM1 patients, Fernandez et al. found four (15.4%) with clinical hypothyroidism. In 2.8% of 36 DM1 patients who were either TSI, TPO-AB or Tg-AB positive, Roldán et al. reported clinical hypothyroidism.
Otherwise specified thyroid dysfunction

Some authors either used other definitions for thyroid dysfunction than ours, or did not report their criteria for thyroid dysfunction, or did not distinguish between subclinical and clinical hypothyroidism. We summarise their results as being ‘(sub)clinical hypothyroidism’, which is found in a range of 0 to 33% of DM1 patients with Th-AB, 4,49,59,75,80,95,98,101 and in 7–1.1% of patients with isolated Tg-AB. 66 Lorini et al. 48 found that none of five Th-AB positive DM1 patients had (sub)clinical hypothyroidism. Falorni et al. 97 reported (sub)clinical hypothyroidism in 44% of TPO-Ab-positive patients with latent autoimmune diabetes in adults. Trimarchi et al. 19 did not find any relation between circulating TPO-Ab and (sub)clinical hypothyroidism in DM1 patients. Some authors combined hyperthyroidism and hypothyroidism under the heading ‘autoimmune thyroid disease’. 65 Barker et al. 59 found that autoimmune thyroid disease in 37% of 201 DM1 patients who had TPO-Ab (with or without Tg-Ab), compared with 10% in 20 DM1 patients with Tg-Ab alone. Glastras et al. 48 found that 46.2% of 13 children who were TPO-Ab positive at diagnosis of DM1 developed thyroid disease within 13 years, compared with 3.6% of 139 children who were TPO-Ab negative at diagnosis. They recommend annual screening for thyroid disease only in DM1 patients who are TPO-Ab positive at diagnosis, and TPO-Ab screening at two yearly intervals in patients who are TPO-Ab negative at diagnosis. Hanukoglu et al. 59 did not find (sub)clinical hypothyroidism in any of four non-DM1 TPO-Ab positive controls. De Block et al. 55 reported that none of 18 TPO-Ab positive first-degree relatives of DM1 patients had (sub)clinical hypothyroidism. Frasier et al. 60 found goitre in 26% of 31 DM1 patients with isolated TPO-Ab; seven were euthyroid and one hyperthyroid. Euthyroid goitre is not considered to be a form of thyroid dysfunction, but Frasier et al. suggested that euthyroid goitre could indicate compensated hypothyroidism. Cardoso et al. 74 found goitre in 53.8% of TPO-Ab and Tg-Ab positive DM1 patients. Gómez et al. 103 reported that otherwise healthy DM1 patients had larger thyroid volumes than healthy controls. The differences in thyroid volume were not related to thyroid dysfunction or autoimmunity, since patients and controls with previously diagnosed thyroid dysfunction, TPO-Ab, or abnormal TSH had been excluded. The authors suggested that differences in body composition could be related to the differences in thyroid volumes.

Relations

In his review, Blecher 105 found autoimmune thyroiditis to be four times more common in females than in males. De Block et al. 55 reported that 78% of their DM1 patients with subclinical hypothyroidism and 82% of their DM1 patients with overt hypothyroidism were females. Also Chang et al. 64 and Fernandez et al. 64 reported a higher percentage of females among patients with thyroid autoimmunity: 69% hypothyroidism and 67.7% hyperthyroidism in patients with thyroid autoimmunity vs 52 and 33.7% in patients without thyroid autoimmunity. Hanukoglu, 59 however, found hypothyroidism to be equally divided among both sexes: of seven patients with hypothyroidism, four were male and three were female. In his review, Blecher 105 reported autoimmune thyroid disease to be four times more common in white than in black patients.

In summary, both antithyroid peroxidase (TPO-Ab) and antithyroglobulin antibodies (Tg-Ab) are more frequently present in patients with type 1 diabetes mellitus (DM1) than in control populations (figure 1). TPO-Ab in 5.5 to 46% (IQR 11.3–21.2, P5–P95 5.8–34.5) of DM1 patients vs 0 to 27% (IQR 2.0–6.8, P5–P95 0.1–20) in controls, and Tg-Ab in 2.1 to 40% (IQR 5.4–22.7, P5–P95 2.6–57.3) of DM1 patients vs 0 to 20% (IQR 1.5–8.4, P5–P95 0.6–27.2) in controls. Prevalences seem to be highest among females and seem to increase with age and DM1 duration. Some authors reported higher thyroid antibody (Th-Ab) prevalences in their white than in their black DM1 patients, but no clear overall conclusion can be drawn with regard to race and Th-Ab prevalence, when results of populations of different racial background are compared. The prevalence of subclinical and clinical hypothyroidism varied from 6 to 72% of Th-Ab positive DM1 patients vs 0 to 25% in controls (figure 2), depending on other criteria as mentioned in the methods section.

Figure 1. Autoantibody prevalences (%) in type 1 diabetes mellitus patients and controls in 50 articles that were selected according to criteria as mentioned in the methods section.

DM1 = type 1 diabetes mellitus; Co = controls; ACA = antiadrenocortical antibodies; EMA = antientomysial antibodies; PCA = antiparietal cell antibodies; Tg-Ab = antithyroglobulin antibodies; TPO-Ab = antithyroid peroxidase antibodies. Bars represent interquartile range, lines represent P5 and P95.
on whether they had TPO-AB or Tg-AB or both. Given the estimated upper level of IQR of the prevalence of thyroid failure of 27% in TH-AB positive DM1 patients, we recommend checking thyroid function biennially in these patients. Given the upper level of IQR of the prevalence of TH-AB of 21 to 23% in DM1 patients and the possible relation to age, female gender and DM1 duration, we recommend checking TH-AB in these patients at regular intervals. Although the optimal time interval should be determined by prospective studies, a practical approach could be to check TH-AB every five years.

Parietal cell antibodies (PCA)

PCA are directed against the parietal cells in the stomach, chronically targeting H+/K+ ATPase, which leads to atrophic gastritis, hypochlorhydria or achlorhydria, and a decline in intrinsic factor production, causing hypergastrinaemia, vitamin B12 malabsorption and ultimately pernicious anaemia. Hypochlorhydria may also impair iron absorption and cause iron deficiency anaemia. De Block et al. confirmed the relation between PCA titre and the severity of corpus atrophy, earlier found by Sipponen et al. suggesting that humoral mechanisms involving cytotoxic AB play a role in mediating mucosal damage in autoimmune gastritis. The pathogenicity of PCA, however, remains unclear, because circulating AB do not have direct access to gastric H+/K+ ATPase. PCA in gastric secretions on the other hand might have direct access to this target. The fact that PCA is not found in every patient with autoimmune gastritis could be explained by the possible mediation of autoimmune gastritis by CD4+ T cells recognising H+/K+ ATPase. Other explanations for the existence of autoimmune gastritis without PCA could be exhaustion of the autoimmune response as parietal cells are depleted or failure to recognise autoantibodies.

Methods

To detect PCA, most authors used indirect immunofluorescence, whereas others used the ELISA method.

Prevalences

The PCA prevalences in DM1 populations ranged from 3 to 34% (IQR 6.3-9.5, P5-P95 4.2-24.4) and in control populations from 0 to 13% (IQR 1.5-4.8, P5-P95 0-9.8). In the literature, different observations about the relation between age and PCA prevalence in DM1 patients were made. Bright et al. found a PCA prevalence of 14.6% in 48 DM1 children younger than 13 years vs 30% in 40 patients older than 13 years. Kokkonen et al. reported PCA in 5.9% of 17 DM1 children younger than 10 years, in 12.5% of 40 patients aged 10 to 14 and in 7.4% of 27 patients aged 15 years or older. De Block et al. found that PCA-positive DM1 patients were older than EMA-negative patients (31±17 vs 25±16 years, p=0.002). They also reported that according to logistic regression, PCA status was determined by age (β=0.03, p=0.002). Other authors, however, did not find a significant relation between PCA positivity and age in DM1 populations. Maclaren et al. reported a relation between PCA positivity and age in DM1 patients, close relatives of DM1 patients and controls. In healthy children, Kokkonen et al. also related PCA prevalence to age: none of 24 children younger than ten years were PCA positive, but 6.8% of 73 children aged 10 to 14 and 4.8% of 63 children older than 15 years were PCA positive. De Block et al. reported PCA in 11% of 397 first-degree relatives of DM1 patients, who were older than the EMA-negative first-degree relatives (26±9 vs 22±9 years, p=0.023). Riley et al. found a predominance of 63% females vs 57% males in their PCA-positive patients. Other authors, however, did not find such a relation between gender and PCA prevalence. Overall, PCA prevalences in European populations are reported in 3 to 15%, whereas others used the ELISA method.

Relations

In the literature, different observations about the relation between age and PCA prevalence in DM1 patients were made. Bright et al. found a PCA prevalence of 14.6% in 48 DM1 children younger than 13 years vs 30% in 40 patients older than 13 years. Kokkonen et al. reported PCA in 5.9% of 17 DM1 children younger than 10 years, in 12.5% of 40 patients aged 10 to 14 and in 7.4% of 27 patients aged 15 years or older. De Block et al. found that PCA-positive DM1 patients were older than EMA-negative patients (31±17 vs 25±16 years, p=0.002). They also reported that according to logistic regression, PCA status was determined by age (β=0.03, p=0.002). Other authors, however, did not find a significant relation between PCA positivity and age in DM1 populations. Maclaren et al. reported a relation between PCA positivity and age in DM1 patients, close relatives of DM1 patients and controls. In healthy children, Kokkonen et al. also related PCA prevalence to age: none of 24 children younger than ten years were PCA positive, but 6.8% of 73 children aged 10 to 14 and 4.8% of 63 children older than 15 years were PCA positive. De Block et al. reported PCA in 11% of 397 first-degree relatives of DM1 patients, who were older than the EMA-negative first-degree relatives (26±9 vs 22±9 years, p=0.023). Riley et al. found a predominance of 63% females vs 57% males in their PCA-positive patients. Other authors, however, did not find such a relation between gender and PCA prevalence. Overall, PCA prevalences in European populations are reported in 3 to 15%, whereas others used the ELISA method.
found PCA-positive DM1 patients to have a significantly longer DM1 duration than EMA-negative DM1 patients (11±10 vs 9±8 years, p=0.011). Bright et al.,15 however, did not find any relation between DM1 duration and PCA prevalence.

Relation between parietal cell antibodies and parietal cell function
For a good interpretation of research articles about the clinical significance of PCA, clearly described criteria are necessary to define organ failure. Frequently used criteria are the presence of atrophic gastritis, achlorhydria, hypergastrinaemia and pernicious anaemia.

Atrophic gastritis
Of PCA-positive DM1 patients, 43 to 50% had atrophic gastritis.14,22,49 Presotto et al.14 performed gastroscopy in 20 PCA-positive DM1 patients and found macroscopic atrophic gastritis in ten, of which four were mild, three moderate and three severe. Of the remaining ten patients, eight had superficial gastritis and two had a normal mucosa. De Block et al.16 performed gastroscopy in 14 PCA-positive DM1 patients with symptoms of dyspepsia and found atrophic gastritis in 92.8 vs 56.3% in 16 symptomatic EMA-negative DM1 patients. In another study14 they compared 47 PCA-positive and 41 EMA-negative DM1 patients and found a significant difference in prevalence of autoimmune atrophic gastritis of 57 vs 10%. Betterle et al.51 reported that four out of six PCA-positive, non-DM1 relatives of DM1 patients had atrophic gastritis.

Hypochlorhydria or achlorhydria
Of PCA-positive DM1 patients, 25 to 73% had achlorhydria.57,112 When de Block et al.22 compared 47 PCA-positive and 41 PCA-negative DM1 patients, they found a significant difference in prevalence of hypochlorhydria of 73 vs 19%.

Hypergastrinaemia
De Block et al.22 reported hypergastrinaemia in 27% of their PCA-positive DM1 patients. When they compared 47 PCA-positive and 41 EMA-negative DM1 patients,19 they found a significant difference in prevalence of hypergastrinaemia of 47 vs 22%, which confirmed the results of Kokkonen et al.,53 who reported significantly higher gastrin levels in PCA-positive than in EMA-negative DM1 patients. De Block et al.53 found significantly elevated gastrin levels in 10.8% of 397 PCA-positive first-degree relatives of DM1 patients. They also reported that gastrin levels correlated inversely with the percentage of parietal cells.19 Others109,114 noted that gastrin levels correlated with corpus atrophy and (inversely) with peak acid output. The gastrin level therefore seems to be good indicator of atrophic gastritis and, especially in PCA-positive patients, could serve as a screening tool, although sensitivity and specificity vary between studies.109,117

Pernicious anaemia
For pernicious anaemia, which is seen as the end-stage of autoimmune gastritis,14,49 lower prevalences of 1 to 23% were reported in DM1 patients14,22,49,51 than for gastritis, hypergastrinaemia or hypergastrinaemia. When de Block et al.16 compared 47 PCA-positive and 41 PCA-negative DM1 patients, they found a significant difference in prevalence of pernicious anaemia of 21 vs 2%. In another study50 of 397 PCA-positive first-degree relatives of DM1 patients, they detected pernicious anaemia in only two relatives.

In summary, antiparietal cell antibodies (PCA) are more prevalent in patients with type 1 diabetes mellitus (DM1) (3-34%, IQR 6.3-9.5, P25-P75 4.2-24.4) than in control populations (0-13%, IQR 1.5-4.8, P25-P75 0-9.8) (figure 1). In DM1 populations, non-DM1 controls and healthy relatives of DM1 patients, PCA prevalence is correlated with age. PCA prevalence also seems to be higher in patients with longer DM1 duration. Due to lack of data no conclusions can be drawn with respect to the relation of gender or race with PCA prevalence in DM1 patients or controls. The relation between PCA positivity and organ dysfunction (figure 2) depends on the criteria used to define organ dysfunction. Given the clinical significance of the insidious development of pernicious anaemia with a prevalence to 23% in PCA-positive DM1 patients, we recommend monitoring parietal cell function biennially in patients with PCA by measuring fasting gastrin and vitamin B12 levels. Although there are no follow-up data for the development of PCA in EMA-negative DM1 patients, the likelihood of developing PCA with increasing age and DM1 duration makes it worthwhile to monitor PCA at regular intervals in these patients. Although the optimal time interval should be determined by prospective studies, a practical approach could be to check PCA every five years.

Adrenocortical antibodies (ACA)
Adrenocortical autoimmune disease, also called primary adrenal insufficiency or Addison’s disease, is the result of humoral and cell-mediated inflammation of the adrenal cortex.48 Adrenocortical antibodies (ACA) are directed against 21-hydroxylase, a microsomal cytochrome P450-enzyme that converts 17α-progesterone and progesterone into 11-deoxycortisol and 11-deoxycorticosterone.104,107 These antibodies can fix complement and mediate cytotoxicity, thus destroying the adrenal cortex.

Methods
Most authors used indirect immunofluorescence to detect ACA.16,43,45,49,54,55,57,60,61 Others used a radio-binding assay.119,121 No significant differences were observed when the prevalences, obtained by different assays, were compared.
Prevalences
The ACA prevalences in DM1 populations ranged from 0 to 4% (IQR 0.9-1.8, P<0.05 to 0.3) and in control populations from 0 to 0.7% (IQR 0.0-3.0, P<0.05 to 0.7). 3,4,34,54,55,57,58,80,120-123

Relations
Some authors found a female predominance of ACA prevalence in DM1 patients (1.9-6% of females vs 1.2-3% of males) 49,54,57, but de Block et al. 69 did not report any differences in frequency between the sexes, neither did Betterle, 49 nor Barker. 93 De Block et al. 69 found a positive relation between DM1 duration and ACA prevalence. They reported an ACA prevalence of 1% in ICA-positive patients with a DM1 duration of more than five years vs 1% in ICA-positive patients with a DM1 duration of less than five years. In ICA-negative patients, they found no relation between ACA prevalence and DM1 duration. Barker et al. 93 reported that patients with ACA had a longer DM1 duration than ACA-negative patients (8.9 vs 3.2 years, p=0.03). No articles were found in which the relation between race and ACA in DM1 patients, nor between age, gender or race, and ACA in control populations was described.

Relation between adrenocortical antibodies and adrenal function
Most authors use an abnormal response to ACTH during a test, or the clinical syndrome of Addison’s disease, as their criterion for adrenal dysfunction. 14,49,122,123 A strong relation has been found between the presence of ACA and the subsequent development of overt adrenal impairment. Among ACA-positive DM1 patients, 3.3 to 40% had Addison’s disease, 49,54,91,122 although Peterson et al. 19 did not find Addison’s disease in any of five DM1 patients with ACA. Yu et al. 124 reported that nine of 966 DM1 patients had known Addison’s disease; seven of them had ACA, two were not tested; of the 957 DM1 patients without known Addison’s disease, 15 were ACA positive, of which three had newly diagnosed Addison’s disease. Betterle et al. 126 performed a longitudinal analysis of 15 DM1 patients with organ-specific autoimmune disease who were positive for ACA. 40% developed Addison’s disease during a mean observation period of 2.3 years. In another study, Betterle et al. 69 found that none of two ACA positive, non-DM1 relatives of DM1 patients, had adrenal dysfunction.

In summary, antiadrenocortical antibody (ACA) prevalence, like other autoantibody prevalences, is higher in patients with type 1 diabetes mellitus (DM1) (0-4%, IQR 0.9-1.8, P<0.05 to 0.3) than in control populations (0-0.7%, IQR 0.0-0.6, P<0.05 to 0.7) (figure 1). The relation of ACA prevalence with age, DM1 duration and gender is not clear. Of ACA-positive DM1 patients, 3 to 40% develop Addison’s disease (figure 2). Because of the high risk of developing overt Addison disease (to 40%), patients with ACA should undergo annual ACTH testing. Although the prevalence of ACA in DM1 patients is low, the development of ACA in ACA-negative DM1 patients is associated with a high risk of developing overt Addison disease. It may therefore be advisable to monitor ACA in these patients at regular intervals. Although the optimal time interval should be determined by prospective studies, a practical approach could be to monitor ACA every five years.

Endomysial antibodies (EMA)
Coeliac disease (CD) is a malabsorption disease, which is due to an immune-mediated destruction of the villous structure in the small intestine. The clinical manifestations depend on the extent and severity of the lesion and vary from isolated anaemia to severe malabsorption. The most common symptoms in patients with extensive disease include diarrhoea, weight loss and a malabsorption syndrome, reflected by extraintestinal symptoms such as anaemia, osteopenia, muscular atrophy, and peripheral neuropathy. 105,106 However, many patients do not have any symptoms, and are therefore said to have silent CD.127 T cells are probably the key mechanism of villous atrophy in coeliac disease, but autoantibodies also appear to be involved in inducing villous atrophy by acting against cellular proteins in response to the presence of gliadin.106,128 The endomysial antibodies (EMA) discussed here are IgA antibodies,129 directed against the endomysium, the smooth muscle inter-myofibrillary substance in the gut.130 The exact role of autoantibodies in the pathogenesis of coeliac disease remains unknown.131

Methods
Indirect immunofluorescence was usually used to detect EMA. 24,87,126,132-135

Prevalences
EMA prevalences between 1.5 and 10% (IQR 0.1-8.7, P<0.05 to 3.4-9.8) have been documented in DM1 patients and in controls between 0 and 2% (IQR 0.0-3.0, P<0.05 to 0.1-5). 34,87,126,132-135

Relations
Little research has been published in DM1 patients about the relation between age, gender, race or DM1 duration on the one hand, and EMA prevalence on the other. Shabazkhani et al. 136 reported that DM1 patients with EMA were older than DM1 patients without EMA (29.5 vs 18.4 years, p<0.001), but neither de Block et al. 69 Aygun et al. 137 nor Talal et al. 138 found any relation between EMA prevalence and age or DM1 duration. Schober et al. 138 reported that EMA-positive DM1 patients had a lower age of onset of DM1 (median 5.6, range 1-12 years) than EMA-negative patients (median 8.4, range 1-15 years).139 Barera et al. 139,140 found that
EMA seroconversion took place within three to five years after the onset of DM1. Cron et al.\textsuperscript{146} however, reported seroconversion to occur throughout the course of DM1, and not just in the first years. Schober et al.\textsuperscript{19} found a female predominance in EMA positivity: 10 out of 12 EMA-positive DM1 patients were females. No information was found about the relation between race and EMA prevalence in DM1 patients, nor about the relation between age, gender or race, and the EMA prevalence in controls.

Relation between endomysial antibodies and intestinal villous function

In EMA-positive DM1 patients, 44 to 100\% have CD,\textsuperscript{24,26,77,78,87} compared with 0 to 0.6\% in control populations.\textsuperscript{59,85,116,139,161} Cerutti et al.\textsuperscript{146} assessed the prevalence of CD in DM1 patients with and without siblings with DM1 and reported CD in 37.5\% of the first group vs 6.1\% in the second. Hanukoglu et al.\textsuperscript{59} detected biopsy-proven CD in 6\% of first-degree relatives of DM1 patients. Glastras et al.\textsuperscript{28} reported that all four patients who had EMA at diagnosis of DM1 developed CD within the first year after diagnosis and that EMA seroconversion took place 2.8 to 10.2 years after diagnosis of DM1 in patients with negative EMA titres at diagnosis. Coeliac disease did not develop for some years after diagnosis of diabetes in patients who were EMA negative at diagnosis. They therefore recommend screening for coeliac disease only at two-yearly intervals, not annually.

Relations

Information about the relation between age, gender, race or DM1 duration, and CD prevalence was less scarce than the information about the relation between these parameters and EMA prevalence. Cerutti et al.\textsuperscript{146,160} found that female gender was associated with the presence of the combination of DM1 and CD (odds ratio (OR) 1.75, 95\% CI 1.35-2.29, p<0.0001). Roldan et al.\textsuperscript{149} Shabazkhani et al.\textsuperscript{116} and Mahmud et al.\textsuperscript{19} also found a clear female predominance among their DM1 patients with CD (female:male ratio: 6:1, 6:0 and 9:2, respectively). Verge et al.\textsuperscript{77} and Buyssecaert\textsuperscript{135} found no such female predominance. Roldan et al.\textsuperscript{149} and Hansen et al.\textsuperscript{87} reported that DM1 patients with CD generally had a younger age of onset of DM1 than DM1 patients without CD: 4.243.6 vs 8.444.0 years (p<0.005) and 3.2 (0.7-9.3) vs 7.4 (1.3-16.6) years (median (range)) (p=0.005) respectively. Cerutti et al.\textsuperscript{149} reported that in comparison with age of onset being older than nine years, age of onset younger than four years conferred an OR of 3.27 (95\% CI 2.20-4.85, p<0.001). They\textsuperscript{160} also found that CD prevalence decreased from 3.5\% in patients with a DM1 duration of less than one year to 0.6\% in patients with DM1 duration of more than ten years. This confirmed the results of Barera et al.\textsuperscript{140} who reported that all new cases of CD developed before the fourth year after onset of DM1. In contrast, Buysschaert\textsuperscript{160} found that duration of DM1 was comparable between DM1 patients with and without CD. Ashabani et al.\textsuperscript{146} reported that age, gender and DM1 duration did not help identify DM1 patients with CD.

In summary, antiendomysial antibody (EMA) prevalence is higher in patients with type 1 diabetes mellitus (DM1) (1.5-10\%, IQR 5.1-8.7, P<5.97) than in control populations (0-2\%, IQR 0.0-3.9, P<1.97) (\textsuperscript{149}figure 1). There seems to be little consensus about the relation of age, gender, race or diabetes duration with EMA prevalence. Of EMA-positive DM1 patients 44 to 100\% have biopsy proven coeliac disease (\textsuperscript{146}figure 2). Therefore in these EMA-positive patients an intestinal biopsy should be performed annually. Although the prevalence of EMA in DM1 patients is rather low, the high predictive value of EMA for the development of CD makes it worthwhile to monitor EMA at regular intervals. Although the optimal time interval should be determined by prospective studies, a practical approach could be to monitor EMA every five years.

REFERENCES


