REVIEW

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

L.C.G. de Graaff, J.W.A. Smit*, J.K. Radder

Department of Endocrinology, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, the Netherlands, *corresponding author: tel.: +31 (0)71-526 30 82, fax: +31 (0)71-524 81 36, e-mail: J.W.A.Smit@lumc.nl

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.[1-4] The presence of autoantibodies targeted against β-cell antigens represents the autoimmune character of DM1.[5] 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.[6-10] The significance of environmental factors is still unclear, despite recent indications for an infectious origin[2,11,12] and nutritional factors.[13] DM1 is associated with other immune-mediated disorders[14,15] such as autoimmune thyroiditis,[16-19] Addison's disease,[20,21] pernicious anaemia,[22,23] and coeliac disease.[24-26] 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.[27,28] Type 1 (APS-I, 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.[2,27,29] Various other diseases including hypoparathyroidism, myasthenia gravis, stiff man syndrome, premature ovarian failure and hypergonadotrope hypogonadism may also be present.[2] Several theories exist to explain (the combinations of) these autoimmune endocrinological diseases,[30,31] but despite extensive research, their exact aetiology is still unresolved.[2,32] 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), antiadrenocortical antibodies (ACA) and antiendomysial 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 antibod* 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 antibod*)) 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 antithyr*) OR (Gastric Mucosa [MeSH] OR Parietal Cells, Gastric [MeSH] OR Gastritis [MeSH] OR Gastritis, Atrophic [MeSH] OR Vitamin B 12 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 adrenocortic* 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.[33] TPO-AB can activate complement and are directly or indirectly involved in the inflammatory process as observed in autoimmune thyroiditis.[34,35] Tg-AB appear to play no pathogenic role in thyroid disease, probably because of their inability to fix complement,[33] 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,[19,36-48] while others used indirect immunofluorescence,[23,49-58] ELISA,[59-63] or RIA[17,18,64-69] and Kobayashi *et al.*[70] used the microsome test. In the article by Maclaren *et al.*,[71] 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, P_5-P_{95} 5.8-34.5) and in control populations, TPO-AB were present in 0 to 27.0% (IQR 2.0-6.8, P_5-P_{95} 0.1-20).[18,23,38-41,43,47,50,53-57,59,61-66,68,70,71]

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.*[19] 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.*[69] reported that TPO-AB positive DM1 patients were older than TPO-AB negative patients (30±16 *vs* 25±16 years, p=0.012). Cardoso *et al.*[72] also reported a significant correlation between age and TPO-AB (r=0.23, p<0.05). Verge *et al.*[73] found that TPO 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.[23,71] 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.[17,44,50,51,55-57,61,64,69,71,74-76] 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.[17,44,55,61,64,69,72,74,75] 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.[18,38,43,59,62,67,77,78] 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 prevalence in DM1 was found when articles studying different races were compared.[18,31,38,39-44,47,53,55,56,59,62-68,71,74,75,77,80-86] We did not find any articles about the relation between gender or race and TPO-AB prevalence in control populations. When we compared articles that studied TPO-AB prevalence in control populations of different races, we did not find a clear relation between race and TPO-AB prevalence either. When duration of DM1 was considered, some authors reported significantly higher TPO-AB prevalences in populations with longer DM1 duration.[36,38,41,69,72] Magzoub *et al.*[41] for example found a higher TPO-AB prevalence in patients with a DM1 duration of more than ten years than in those with a DM1 duration of less than ten years (21.4 *vs* 4.9%). De Block *et al.*[69] reported that TPO-AB positive DM1 patients had a longer DM1 duration than TPO-AB negative patients (11±9 *vs* 9±8 years, p=0.048). Cardoso[72] also found a significant correlation between the presence of TPO-AB and DM1 duration (r=0.553, p<0.001). Riley *et al.*, however, did not find such a relation.[23]

Thyroglobulin antibodies (Tg-AB)
Methods
To detect Tg-AB, some authors used (haem) agglutination[19,6-49,6] while others used ELISA[59-63] or RIA.[17,18,66,67,87-89] Hagglof *et al.*[53] 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-P_{95} 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-P_{95} 0.6-27.2),[18,38-41,43,53,59,61,63,66,90] 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.[46,72] Kordonouri *et al.*[17] 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 3.7% 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.*[43] 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.[18,38,59,62,67] We did not find any articles about the relation between race and Tg-AB prevalence in DM1 patients. Cardoso *et al.*[72] 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 (TSI, associated with Graves' disease), TPO-AB or Tg-AB.[45] 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,[36,37,46,49,59,66,72,88,91] and that 9.5 to 11% of DM1 patients had TPO-AB *and* Tg-AB, *vs* 1.9 to 3.8% of control subjects.[59,66]

Relations

Kordonouri *et al.*[17] reported that DM1 children with Th-AB were significantly older (15 to 20 years) than those without Th-AB (<15 years). Shiau *et al.*[46] found a Th-AB prevalence of 18.4% in patients older than 18 years (with a mean age of DM1 onset of 18.0 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.[17,44,46,88,93] In Th-AB negative DM1 patients, only 27 to 45% were females.[17,44] Several authors reported higher Th-AB prevalences in their white than in their black DM1 patients; Burek *et al.*[80] reported TPO-AB and/or Tg-AB in 50% of 82 white and in 16% of 72 black DM1 patients and Bright *et al.*[36] found Th-AB in 32% of 164 white and in 6% of 18 black DM1 patients. Kordonouri *et al.*[17] 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<0.001) as did Barker (5.35 *vs* 2.62 years, p<0.0001).[93] Park *et al.*[94] 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.[14,17,19,38,40,44,45,49,52,56,59,64,66,69,71,72,75,80,83-85,95-100] 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 (T_4) levels within the reference range), clinical hypothyroidism (defined as both a raised TSH and a low free T_4 level) and hyperthyroidism (defined as a raised free T_4 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.*[44] 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.*[45] found subclinical hypothyroidism in 11% of 36 patients who were either TSI, TPO-AB or Tg-AB positive. Court *et al.*[96] reported subclinical hypothyroidism in 17.6% of Th-AB positive patients. Betterle *et al.*[49] 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.*[95] 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.*[14] 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.*[84] found five (19.2%) patients with subclinical hypothyroidism.

Change of subclinical to clinical hypothyroidism

Rattarasarn *et al.*[44] 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.[44,59] In 26% of 53 patients with Tg-AB and/or TPO-AB, Burek *et al.*[80] found hypothyroidism; those with hypothyroidism all had both TPO- and Tg-AB. Betterle *et al.*[49] 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.[52,69,71,83,100] In their total group of 26 TPO-AB positive DM1 patients, Fernandez *et al.*[84] 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.*[45] reported clinical hypothyroidism.

Otherwise specified thyroid dysfunction

Some authors either used other definitions for thyroid dysfunction than ours,[56,66,95] did not report their criteria for thyroid dysfunction,[38,59] or did not distinguish between subclinical and clinical hypothyroidism.[49,80,97,98,101] We summarise their results as being '(sub)clinical hypothyroidism', which is found in 0 to 33% of DM1 patients with Th-AB.[42,49,59,75,80,95,98,101] Kordonouri *et al.*[17] reported (sub)clinical hypothyroidism in 16% of patients with Th-AB *vs* 8% without Th-AB ($p<0.001$). (Sub)clinical hypothyroidism was reported in 20% of patients with both Th-AB,[66] in 45% of patients with isolated TPO-AB,[56] and in 7.1% of patients with isolated Tg-AB.[66] Lorini *et al.*[40] 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-positive patients with latent autoimmune diabetes in adults. Trimarchi *et al.*[19] did not find any relation between circulating Th-AB and (sub)clinical hypothyroidism in DM1 patients. Some authors combined hyperthyroidism and hypothyroidism under the header 'autoimmune thyroid disease'.[78,93] Barker *et al.*[93] found 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.*[78] 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.*[65] reported that none of 18 TPO-AB positive first-degree relatives of DM1 patients had (sub)clinical hypothyroidism.

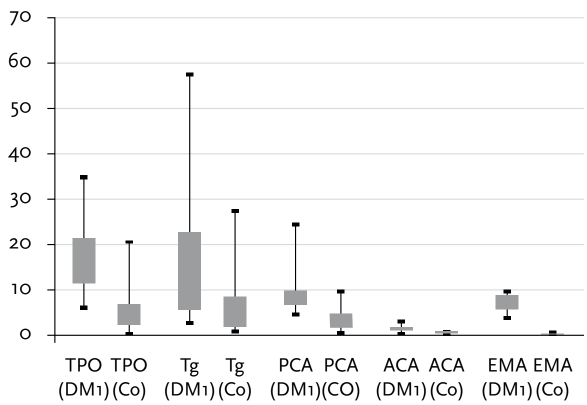
Frasier *et al.*[38] found goitre in 26% of 31 DM1 patients with isolated TPO-AB; seven were euthyroid and one hyperthyroid. Euthyroid goitre is not considered to be a form of thyroid dysfunction, but Frasier *et al.* suggested that euthyroid goitre could indicate compensated hypothyroidism. Cardoso *et al.*[72] found goitre in 53.8% of TPO-AB *and* Tg-AB positive DM1 patients. Gómez *et al.*[102] 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[103] found autoimmune thyroiditis to be four times more common in females than in males. De Block *et al.*[65] 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.*[84] 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[103] reported autoimmune thyroid disease to be four times more common in white than in black patients.

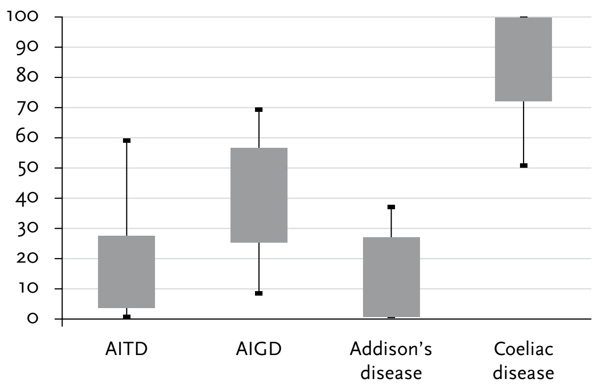
In summary, both antithyroid peroxidase (TPO-AB) and antithyroglobulin antibodies (Tg-AB) are more frequently present in patients with type 1 diabetes mellitus (DM1) than in control populations (*figure 1*): TPO-AB in 5.5 to 46% (IQR 11.3-21.2, P_5-P_{95} 5.8-34.5) of DM1 patients *vs* 0 to 27% (IQR 2.0-6.8, P_5-P_{95} 0.1-20) in controls, and Tg-AB in 2.1 to 40% (IQR 5.4-22.7, P_5-P_{95} 2.6-57.3) of DM1 patients *vs* 0 to 20% (IQR 1.5-8.4, P_5-P_{95} 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

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 = antiendomysial antibodies; PCA = antiparietal cell antibodies; Tg-AB = antithyroglobulin antibodies; TPO-AB = antithyroid peroxidase antibodies. Bars represent interquartile ranges, lines represent P_5 and P_{95}.

Figure 2. *Prevalence (%) of organ dysfunction in autoantibody positive type 1 diabetes mellitus patients*



AITD = autoimmune thyroid disease; AIGD = autoimmune gastric disease. Bars represent interquartile ranges, lines represent P_5 and P_{95}.

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,[104-106] 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.[106-107] Hypochlorhydria may also impair iron absorption and cause iron deficiency anaemia.[108] De Block *et al.*[22] confirmed the relation between PCA titre and the severity of corpus atrophy, earlier found by Sipponen *et al.*[109] 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.[110] 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.[111] 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,[23,36,39,40,41,43,49,53-55,57,60,65] whereas others used the ELISA method.[61]

Prevalences

The PCA prevalences in DM1 populations ranged from 3 to 34% (IQR 6.3-9.5, P_5-P_{95} 4.2-24.4) and in control populations from 0 to 13% (IQR 1.5-4.8, P_5-P_{95} 0-9.8).[23,36,39,40,41,43,49,53-55,57,60,61,65]

Relations

In the literature, different observations about the relation between age and PCA prevalence in DM1 patients were made. Bright *et al.*[36] 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.*[39] reported PCA in 5.9% of 17 DM1 children younger than 10 years, in 12.5% of 40 patients aged 10 to 14 years and in 7.4% of 27 patients aged 15 years or older. De Block *et al.*[69] 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.[41,61,112] Maclaren *et al.*[71] reported a relation between PCA positivity and age in DM1 patients, close relatives of DM1 patients and controls. In healthy children, Kokkonen *et al.*[39] 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.*[65] 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=0.025). Riley *et al.*[57] found a predominance of 63% females *vs* 37% males in their PCA-positive patients. Other authors, however, did not find such a relation between gender and PCA prevalence.[36,41,49,51,61,69,76,92,113] Overall, PCA prevalences in European populations are reported in 3 to 15%,[23,36,39,49,53,54,57,60,61,65] except for Lorini[40] who found PCA in 34% of their Italian DM1 patients. As far as non-European patients are concerned, 8% of Indian-Asian DM1[43] and 6.3% of Sudanese patients had PCA.[41] Neufeld *et al.*[55] found PCA in 10% of black *vs* 8.5% of Caucasian DM1 patients. Riley *et al.*[57] reported a PCA prevalence of 9.4% in black *vs* 7.8% in Caucasian DM1 patients. We found no articles about the relation between gender or race, and PCA prevalence in control populations. Neufeld *et al.*[55] reported a PCA prevalence of 17% in islet cell antibody (ICA) positive patients with a DM1 duration of more than five years *vs* 7% in ICA-positive patients with a DM1 duration of less than five years. In ICA-negative patients, they found no relation between PCA prevalence and DM1 duration. De Block *et al.*[69]

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.*,[36] 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.[14,57,111] 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.*[51] 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 study[22] 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.*[49] 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.*[51] reported hypergastrinaemia in 27% of their PCA-positive DM1 patients. When they compared 47 PCA-positive and 41 EMA-negative DM1 patients,[22] they found a significant difference in prevalence of hypergastrinaemia of 47 *vs* 22%, which confirmed the results of Kokkonen *et al.*,[39] who reported significantly higher gastrin levels in PCA-positive than in EMA-negative DM1 patients. De Block *et al.*[65] 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.[22] Others[109,114] 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.[115-117]

Pernicious anaemia

For pernicious anaemia, which is seen as the end-stage of autoimmune gastritis,[104] lower prevalences of 1 to 23% were reported in DM1 patients[14,22,49,51] than for gastritis, achlorhydria or hypergastrinaemia. When de Block *et al.*[22] compared 47 PCA-positive and 41 PCA-negative DM1 patients, they found a significant difference in prevalence of pernicious anaemia of 23 *vs* 2%. In another study[65] 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, P_5-P_{95} 4.2-24.4) than in control populations (0-13%, IQR 1.5-4.8, P_5-P_{95} 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 B 12 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.[28] Adrenocortical antibodies (ACA) are directed against 21-hydroxylase, a microsomal cytochrome P450-enzyme that converts 17-α-progesterone and progesterone into 11-deoxycortisol and 11-deoxycorticosterone.[104,117] These antibodies can fix complement and mediate cytotoxicity, thus destructing the adrenal cortex.

Methods

Most authors used indirect immunofluorescence to detect ACA.[36,43,49,54,55,57,58,60,11] 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_5-P_{95} 0-3.3) and in control populations from 0 to 0.7% (IQR 0-0.6, P_5-P_{95} 0-0.7).[36,43,49,54,55,57,58,60,120-123]

Relations

Some authors found a female predominance of ACA prevalence in DM1 patients (1.9-6% of females *vs* 1.2-3% of males) [49,55,57], 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 no relation of ACA with age or DM1 duration. Neufeld *et al.*[55] found a positive relation between DM1 duration and ACA prevalence. They reported an ACA prevalence of 11% 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 (8.92 *vs* 3.29 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,[49,54,93,122] although Peterson *et al.*[119] did not find Addison's disease in any of five DM1 patients with ACA. Yu *et al.*[122] 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.*[124] 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 3.2 years. In another study, Betterle *et al.*[49] 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_5-P_{95} 0-3.3) than in control populations (0-0.7%, IQR 0-0.6, P_5-P_{95} 0-0.7) (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.[125,126] 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 5.1-8.7, P_5-P_{95} 3.4-9.8) have been documented in DM1 patients and in controls between 0 and 2% (IQR 0-0.3, P_5-P_{95} 0-1.5).[24,87,126,132-135]

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.*[26] 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).[137] Barera *et al.*[139,140] found that

EMA seroconversion took place within three to five years after the onset of DM1. Crone *et al.*[141] however, reported seroconversion to occur throughout the course of DM1, and not just in the first years. Schober *et al.*[138] 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,[24,26,77,78,87,126,132-134,137-158] compared with 0 to 0.6% in control populations.[59,87,126,133,159-161]

Cerutti *et al.*[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.*[59] detected biopsy-proven CD in 6% of first-degree relatives of DM1 patients. Glastras *et al.*[78] 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.*[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.*[149] Shabazkhani *et al.*[136] and Mahmud *et al.*[156] 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.*[77] and Buysschaert[155] found no such female predominance. Roldan *et al.*[149] and Hansen *et al.*[87] reported that DM1 patients with CD generally had a younger age of onset of DM1 than DM1 patients without CD: 4.2±3.6 *vs* 8.4±4.0 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.*[146] 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[160] also found that CD prevalence decreased from 3.3% in patients with a DM1 duration of less then one year to 0.6% in patients with DM1 duration of more than ten years. This confirmed the results of Barera *et al.*[140] who reported that all new cases of CD developed before the fourth year after onset of DM1. In contrast, Buysschaert[156] found that duration of DM1 was comparable between DM1 patients with and without CD. Ashabani *et al.*[162] 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-P_{95} 3.4-9.8) than in control populations (0-2%, IQR 0-0.3, P_5-P_{95} 0-1.5) (*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 (*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

1. Greenspan FS. Basic and Clinical Endocrinology. New York, Appleton and Lange, 1993.
2. Baker JR Jr. Autoimmune endocrine disease. JAMA 1997;278:1931-7.
3. Brink SJ. Complications of pediatric and adolescent type 1 diabetes mellitus. Curr Diab Rep 2001;1:47-55.
4. Loomans CJ, de Koning EJ, Staal FJ, et al. Endothelial progenitor cell dysfunction: a novel concept in the pathogenesis of vascular complications of type 1 diabetes. Diabetes 2004;53:195-9.
5. Bingley PJ. Prediction of IDDM in the general population: strategies based on combinations of autoantibody markers. Diabetes 1997;46:1701-10.
6. Todd JA, Bell JI, McDevitt HO. HLA-DQ beta gene contributes to susceptibility and resistance to insulin-dependent diabetes mellitus. Nature 1987;6140:599-604.
7. Bilbao JR, Martin-Pagola A, Perez De Nanclares, G et al. HLA-DRB1 and MICA in autoimmunity: common associated alleles in autoimmune disorders. Ann N Y Acad Sci 2003;1005:314-8.
8. Heimberg H, Nagy ZP, Somers G, et al. Complementation of HLA-DQA and -DQB genes confers susceptibility and protection to insulin-dependent diabetes mellitus. Hum Immunol 1992;33:10-7.
9. Johansson S, Lie BA, Todd JA, et al. Evidence of at least two type 1 diabetes susceptibility genes in the HLA complex distinct from HLA-DQB1, -DQA1 and -DRB1. Genes Immun 2003;4:46-53.
10. Kanga U, Vaidyanathan B, Jaini R, et al. HLA haplotypes associated with type 1 diabetes mellitus in North Indian children. Hum Immunol 2004;65:47-53.
11. De Vries RR, Roep BO. Clinical and preclinical immunology of type 1 diabetes. Neth J Med 1998;53:127-9.
12. Hiemstra HS, Schloot NC, van Veelen PA, et al. Cytomegalovirus in autoimmunity: T cell crossreactivity to viral antigen and autoantigen glutamic acid decarboxylase. Proc Natl Acad Sci USA 2001;98:3988-91.
13. Ziegler AG, Schmid S, Huber D, Hummel M, Bonifacio E. Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. JAMA 2003;290:1721-8.
14. Presotto F, Betterle C. Insulin-dependent diabetes mellitus: a constellation of autoimmune diseases. J Ped End Metab 1997;10:455-69.

15. Roitt I. Immunology. 5th ed. London: Mosby, 1998.

16. Bilimoria KY, Pescovitz OH, DiMeglio. LA Autoimmune thyroid dysfunction in children with type 1 diabetes mellitus: screening guidelines based on a retrospective analysis. J Ped End Metab 2003;16:1111-7.

17. Kordonouri O, Klinghammer A, Lang EB, Gruters-Kieslich A, Grabert M, Holl RW. Thyroid autoimmunity in children and adolescents with type 1 diabetes: a multicenter survey. Diabetes Care 2002;25:1346-50.

18. Lindberg B, Ericsson UB, Ljung R, Ivarsson SA. High prevalence of thyroid autoantibodies at diagnosis of insulin-dependent diabetes mellitus in Swedish children. J Lab Clin Med 1997;130:585-9.

19. Trimarchi F, de Luca F, Vanelli M, et al. Circulating thyroid antibodies and thyroid function studies in children and adolescents with insulin-dependent diabetes mellitus. Eur J Pediatr 1984;142:253-6.

20. Boscaro M, Betterle C, Sonino N, Volpato M, Paoletta A, Fallo F. Early adrenal hypofunction in patients with organ-specific autoantibodies and no clinical adrenal insufficiency. J Clin Endocrinol Metab 1994;79:452-5.

21. Robles DT, Fain PR, Gottlieb PA, Eisenbarth GS. The genetics of autoimmune polyendocrine syndrome type II. Endocrinol Metab Clin North Am 2002;31:353-68.

22. De Block CE, de Leeuw IH, Bogers JJ, et al. Autoimmune gastropathy in type 1 diabetic patients with parietal cell antibodies: histological and clinical findings. Diabetes Care 2003;26:82-8.

23. Riley WJ, Winer A, Goldstein D. Coincident presence of thyro-gastric autoimmunity at onset of type 1 (insulin-dependent) diabetes. Diabetologia 1983;24:418-21.

24. Aktay AN, Lee PC, Kumar V, Parton E, Wyatt DT, Werlin SL. The prevalence and clinical characteristics of coeliac disease in juvenile diabetes in Wisconsin. J Pediatr Gastroenterol Nutr 2001;33:462-5.

25. Holmes GK. Screening for coeliac disease in type 1 diabetes. Arch Dis Child 2002;87:495-8.

26. Talal AH, Murray JA, Goeken JA, Sivitz WI. Coeliac disease in an adult population with insulin-dependent diabetes mellitus: use of endomysial antibody testing. Am J Gastroenterol 1997;92:1280-4.

27. Betterle C, Zanchetta R. Update on autoimmune polyendocrine syndromes (APS) Acta Biomed Ateneo Parmense 2003;74:9-33.

28. Wilson JD. Williams textbook of endocrinology. 9th ed. Philadelphia: WB Saunders, 1998.

29. Papadopoulos KI, Hallengren B. Polyglandular autoimmune syndrome type III associated with coeliac disease and sarcoidosis. Postgrad Med J 1993;69:72-5.

30. Collin P, Kaukinen K, Valimaki M Salmi J. Endocrinological disorders and coeliac disease. Endocr Rev 2002;23:464-83.

31. Dittmar M, Kahaly GJ. Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up. J Clin Endocrinol Metab 2003;88:2983-92.

32. Roep BO. The role of T-cells in the pathogenesis of Type 1 diabetes: from cause to cure. Diabetologia 2003;46:305-21.

33. Brunt LM. Immunologic disorders of the thyroid gland and autoimmune polyendocrinopathies. In: Samter M (ed). Immunologic diseases. 5th ed. Boston: Little, Brown and Company, 1998, pp 975-93.

34. Bernet V. Autoimmune thyroid disease. In: Rich RR (ed) Clinical Immunology, London: Mosby, 1998.

35. Blanchin S, Estienne V, Durand-Gorde JM, Carayon P, Ruf J. Complement activation by direct C4 binding to thyroperoxidase in Hashimoto's thyroiditis. Endocrinology 2003;144:5422-9.

36. Bright GM, Blizzard RM, Kaiser DL, Clarke WL. Organ-specific autoantibodies in children with common endocrine diseases. J Pediatr 1982;100:8-14.

37. Chang YH, Hwang J, Shang HF, Tsai ST. Characterization of human DNA topoisomerase II as an autoantigen recognized by patients with IDDM. Diabetes 1996;45:408-14.

38. Frasier SD, Penny R, Snyder R, Goldstein I, Graves D. Antithyroid antibodies in Hispanic patients with type I diabetes mellitus. Prevalence and significance. Am J Dis Child 1986;140:1278-80.

39. Kokkonen J, Kiuttu J, Mustonen A, Rasanen O. Organ-specific antibodies in healthy and diabetic children and young adults. Acta Paediatr Scand 1982;71:223-6.

40. Lorini R, Larizza D, Livieri C, et al. Auto-immunity in children with diabetes mellitus and in their relatives. Eur J Pediatr 1986;145:182-4.

41. Magzoub MM, Abdel-Hameed AA, Bottazzo GF. Prevalence of islet cell and thyrogastric autoantibodies in Sudanese patients with type 1 diabetes. Diabet Med 1994;11:188-92.

42. McKenna MJ, Herskowitz R, Wolfsdorf JI. Screening for thyroid disease in children with IDDM. Diabetes Care 1990;13:801-3.

43. Odugbesan O, Fletcher JA, Sanders A, Bradwell AR, Botazzo GF, Barnett AH. Autoantibodies in Indian-Asians with insulin-dependent diabetes in the UK. Postgrad Med J 1988;64:357-60.

44. Rattarasarn C, Diosdado MA, Ortego J, et al. Thyroid autoantibodies in Thai type 1 diabetic patients: clinical significance and their relationship with glutamic acid decarboxylase antibodies. Diabetes Res Clin Pract 2000;49:107-11.

45. Roldan MB, Alonso M, Barrio R. Thyroid autoimmunity in children and adolescents with Type 1 diabetes mellitus. Diabetes Nutr Metab 1999;12:27-31.

46. Shiau MY, Tsai ST, Hwang J, Wu CY, Chang YH. Relationship between autoantibodies against glutamic acid decarboxylase, thyroglobulin/thyroid microsome and DNA topoisomerase II in the clinical manifestation of patients with type 1 diabetes mellitus in Taiwan. Eur J Endocrinol. 2000;142:577-85.

47. Vakeva A, Kontiainen S, Miettinen A, Schlenzka A, Maenpaa J. Thyroid peroxidase antibodies in children with autoimmune thyroiditis. J Clin Pathol 1992;45:106-9.

48. Walikonis JE, Lennon VA. Radioimmunoassay for glutamic acid decarboxylase (GAD65) autoantibodies as a diagnostic aid for stiff-man syndrome and a correlate of susceptibility to type 1 diabetes mellitus. Mayo Clin Proc 1998;73:1161-6.

49. Betterle C, Zanette F, Pedini B, et al. Clinical and subclinical organ-specific autoimmune manifestations in type 1 (insulin-dependent) diabetic patients and their first-degree relatives. Diabetologia 1984;26:431-6.

50. Riley WJ, Maclaren NK, Lezotte DC, Spillar RP, Rosenbloom AL. Thyroid autoimmunity in insulin-dependent diabetes mellitus: the case for routine screening. J Pediatr 1981;99:350-4.

51. De Block CE, de Leeuw IH, van Gaal LF. High prevalence of manifestations of gastric autoimmunity in parietal cell antibody-positive type 1 (insulin-dependent) diabetic patients. The Belgian Diabetes Registry. J Clin Endocrinol Metab 1999;84:4062-7.

52. Gilani BB, MacGillivray MH, Voorhess ML, Mills BJ, Riley WJ, Maclaren NK. Thyroid hormone abnormalities at diagnosis of insulin-dependent diabetes mellitus in children. J Pediatr 1984;105:218-22.

53. Hagglof B, Rabinovitch A, Mackay P, et al. Islet cell and other organ-specific autoantibodies in healthy first-degree relatives to insulin-dependent. Acta Paediatr Scand 1986;75:611-8.

54. Ketchum CH, Riley WJ, Maclaren NK. Adrenal dysfunction in asymptomatic patients with adrenocortical autoantibodies. J Clin Endocrinol Metab 1984;58:1166-70.

55. Neufeld M, Maclaren NK, Riley WJ, et al. Islet cell and other organ-specific antibodies in U.S. Caucasians and Blacks with insulin-dependent diabetes mellitus. Diabetes 1980;29:589-92.

56. Riley WJ, Maclaren NK, Lezotte DC, Spillar RP, Rosenbloom AL. Thyroid autoimmunity in insulin-dependent diabetes mellitus: the case for routine screening. J Pediatr 1981;99:350-4.

57. Riley WJ, Toskes PP, Maclaren NK, Silverstein JH. Predictive value of gastric parietal cell autoantibodies as a marker for gastric and hematologic abnormalities associated with insulin-dependent diabetes. Diabetes 1982;31:1051-5.

58. Winter WE, Maclaren NK, Riley WJ, Unger RH, Neufeld M, Ozand PT. Pancreatic alpha cell autoantibodies and glucagon response to arginine. Diabetes 1984;33:435-7.

59. Hanukoglu A, Mizrachi A, Dalal I, et al. Extrapancreatic autoimmune manifestations in type 1 diabetes patients and their first-degree relatives: a multicenter study. Diabetes Care 2003;26:1235-40.

60. Jaeger C, Hatziagelaki E, Petzoldt R, Bretzel RG. Comparative analysis of organ-specific autoantibodies and coeliac disease-associated antibodies in type 1 diabetic patients, their first-degree relatives, and healthy control subjects. Diabetes Care 2001;24:27-32.
61. Landin-Olsson M, Karlsson A, Dahlquist G, Blom L, Lernmark A, Sundkvist G. Islet cell and other organ-specific autoantibodies in all children developing type 1 (insulin-dependent) diabetes mellitus in Sweden during one year and in matched control children. Diabetologia 1989;32:387-95.
62. Roman SH, Davies TF, Witt ME, Ginsberg-Fellner F, Rubinstein P. Thyroid autoantibodies in HLA-genotyped type 1 diabetic families: sex-limited DR5 association with thyroid microsomal antibody. Clin Endocrinol (Oxf) 1986;25:23-33.
63. Triggiani V, Ciampolillo A, Guastamacchia E, et al. Prospective study of post-partum thyroid immune dysfunctions in type 1 diabetic women and in a healthy control group living in a mild iodine deficient area. Immunopharmacol Immunotoxicol 2004;26:215-24.
64. Chang CC, Huang CN, Chuang LM. Autoantibodies to thyroid peroxidase in patients with type 1 diabetes in Taiwan. Eur J Endocrinol 1998;139:44-8.
65. De Block CE, de Leeuw IH, Decochez K, et al. The presence of thyrogastric antibodies in first degree relatives of type 1 diabetic patients is associated with age and proband antibody status. J Clin Endocrinol Metab 2001;86:4358-63.
66. Hansen D, Bennedbaek FN, Hansen LK, Hoier-Madsen M, Jacobsen BB, Hegedus L. Thyroid function, morphology and autoimmunity in young patients with insulin-dependent diabetes mellitus. Eur J Endocrinol 1999;140:512-8.
67. Hansen D, Bennedbaek FN, Hoier-Madsen M, Hegedus L, Jacobsen BB. A prospective study of thyroid function, morphology and autoimmunity in young patients with type 1 diabetes. Eur J Endocrinol 2003;148:245-51.
68. Mochizuki M, Amemiya S, Kobayashi K, et al. Association of the CTLA-4 gene 49 A/G polymorphism with type 1 diabetes and autoimmune thyroid disease in Japanese children. Diabetes Care 2003;26:843-7.
69. De Block CE, de Leeuw IH, Vertommen JJ, et al. Beta-cell, thyroid, gastric, adrenal and coeliac autoimmunity and HLA-DQ types in type 1 diabetes. Clin Exp Immunol 2001;126:236-41.
70. Kobayashi T, Sawano S, Sugimoto T, et al. Islet-cell antibodies in IDDM and NIDDM in a Japanese population. Tohoku J Exp Med 1983;141(Suppl):271-4.
71. Maclaren NK, Riley WJ. Thyroid, gastric, and adrenal autoimmunities associated with insulin-dependent diabetes mellitus. Diabetes Care 1985;8(Suppl 1):34-8.
72. Cardoso C, Ohwovoriole AE, KuKu SF. A study of thyroid function and prevalence of thyroid autoantibodies in an African diabetic population. J Diabetes Complications 1995;9:37-41.
73. Verge CF, Howard NJ, Rowley MJ, et al. Anti-glutamate decarboxylase and other antibodies at the onset of childhood IDDM: a population-based study. Diabetologia 1994;37:1113-20.
74. Abrams P, de Leeuw I, Vertommen J. In new-onset insulin-dependent diabetic patients the presence of anti-thyroid peroxidase antibodies is associated with islet cell autoimmunity and the high risk haplotype HLA DQA1*0301-DQB1*0302. Belgian Diabetes Registry. Diabet Med 1996;13:415-9.
75. Holl RW, Bohm B, Loos U, Grabert M, Heinze E, Homoki J. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. Effect of age, gender and HLA type. Horm Res 1999;52:113-8.
76. Alonso N, Granada ML, Salinas I, et al. Serum pepsinogen I: an early marker of pernicious anemia in patients with type 1 diabetes. J Clin Endocrinol Metab 2005;90:5254-8.
77. Verge CF, Howard NJ, Rowley MJ, et al. Anti-glutamate decarboxylase and other antibodies at the onset of childhood IDDM: a population-based study. Diabetologia 1994;37:1113-20.
78. Glastras SJ, Craig ME, Verge CF, Chan AK, Cusumano JM, Donaghue KC. The role of autoimmunity at diagnosis of type 1 diabetes in the development of thyroid and coeliac disease and microvascular complications. Diabetes Care 2005;28:2170-5.
79. Gallas PR, Stolk RP, Bakker K, Endert E, Wiersinga WM. Thyroid dysfunction during pregnancy and in the first postpartum year in women with diabetes mellitus type 1. Eur J Endocrinol 2002;147:443-51.
80. Burek CL, Rose NR, Guire KE, Hoffman WH. Thyroid autoantibodies in black and in white children and adolescents with type 1 diabetes mellitus and their first degree relatives. Autoimmunity 1990;7:157-67.
81. Bergamaschini L, Gardinali M, Poli M, Lorini R, Bosi E, Agostoni A. Complement activation in diabetes mellitus. J Clin Lab Immunol 1991;35:121-7.
82. Chen BH, Chung SB, Chiang W, Chao MC. GAD65 antibody prevalence and association with thyroid antibodies, HLA-DR in Chinese children with type 1 diabetes mellitus. Diabetes Res Clin Pract 2001;54:27-32.
83. Davis RE, McCann VJ, Stanton KG. Type 1 diabetes and latent pernicious anaemia. Med J Aust 1992;156:160-2.
84. Fernandez-Castaner M, Molina A, Lopez-Jimenez L, Gomez JM, Soler J. Clinical presentation and early course of type 1 diabetes in patients with and without thyroid autoimmunity. Diabetes Care 1999;22:377-81.
85. Snajderova M, Martinek J, Horejsi J, Novakova D, Lebl J, Kolouskova S. Premenarchal and postmenarchal girls with insulin-dependent diabetes mellitus: ovarian and other organ-specific autoantibodies, menstrual cycle. J Pediatr Adolesc Gynecol 1999;12:209-14.
86. Yokota I, Matsuda J, Naito E, Ito M, Shima K, Kuroda Y. Comparison of GAD and ICA512/IA-2 antibodies at and after the onset of IDDM. Diabetes Care 1998;21:49-52.
87. Hansen D, Bennedbaek FN, Hansen LK, et al. High prevalence of coeliac disease in Danish children with type I diabetes mellitus. Acta Paediatr 2001;90:1238-43.
88. Kim EY, Shin CH, Yang SW. Polymorphisms of HLA class II predispose children and adolescents with type 1 diabetes mellitus to autoimmune thyroid disease. Autoimmunity 2003;36:177-81.
89. Park YS, Kim TW, Kim WB, Cho BY. Increased prevalence of autoimmune thyroid disease in patients with type 1 diabetes. Korean J Intern Med 2000;15:202-10.
90. Kaino Y, Kida K, Goto Y, et al. Thyroglobulin antibodies in type 1 diabetic patients and their relatives: measurement with highly sensitive assay. Diabetes Res Clin Pract 1994;22:147-54.
91. Hansen D, Bennedbaek FN, Hansen LK, Hoier-Madsen M, Jacobsen BB, Hegedus L. Thyroid function, morphology and autoimmunity in young patients with insulin-dependent diabetes mellitus. Eur J Endocrinol 1999;140:512-8.
92. Landin-Olsson M and Karlsson FA, Lernmark A Sundkvist G. Islet cell and thyrogastric antibodies in 633 consecutive 15- to 34-yr-old patients in the diabetes incidence study in Sweden. Diabetes 1992;41:1022-7.
93. Barker JM, Yu J, Yu L, et al. Autoantibody "subspecificity" in type 1 diabetes: risk for organ-specific autoimmunity clusters in distinct groups. Diabetes Care 2005;28:850-5.
94. Park Y, Kim S, Park S, et al. Differential expression of nonislet autoimmunity: comparison of Korean and U.S. patients with type 1 diabetes. Ann N Y Acad Sci 2004;1037:69-73.
95. Betterle C, Callegari G, Presotto F, et al. Thyroid autoantibodies: a good marker for the study of symptomless autoimmune thyroiditis. Acta Endocrinol (Copenh) 1987;114:321-7.
96. Court S, Parkin JM. Hypothyroidism and growth failure in diabetes mellitus. Arch Dis Child 1982;57:622-4.
97. Falorni A, Calcinaro F. Autoantibody profile and epitope mapping in latent autoimmune diabetes in adults. Ann N Y Acad Sci 2002;958:99-106.
98. Hathout EH, Hartwick N, Fagoaga OR, et al. Clinical, autoimmune, and HLA characteristics of children diagnosed with type 1 diabetes before 5 years of age. Pediatrics 2003;111:860-3.
99. Kordonouri O, Deiss D, Danne T, Dorow A, Bassir C, Gruters-Kieslich. A. Predictivity of thyroid autoantibodies for the development of thyroid disorders in children and adolescents with Type 1 diabetes. Diabet Med 2002;19:518-21.
100. Umpierrez GE, Latif KA, Murphy MB, et al. Thyroid dysfunction in patients with type 1 diabetes: a longitudinal study. Diabetes Care 2003;26:1181-5.
101. McCanlies E, O'Leary LA, Foley TP, et al. Hashimoto's thyroiditis and insulin-dependent diabetes mellitus: differences among individuals with and without abnormal thyroid function. J Clin Endocrinol Metab 1998;83:1548-51.
102. Gomez JM, Maravall FJ, Guma A, Abos R, Soler J, Fernandez-Castaner M. Thyroid volume as measured by ultrasonography in patients with type 1 diabetes mellitus without thyroid dysfunction. Horm Metab Res 2003;35:486-91.

103. Blecher M. Receptors, antibodies, and disease. Clin Chem 1984;30:1137-56.

104. Karlsson FA, Kampe O, Winqvist O, Burman P. Autoimmune disease of the adrenal cortex, pituitary, parathyroid glands and gastric mucosa. J Intern Med 1993;234:379-86.

105. Alonso N, Granada ML, Salinas I, et al. Serum pepsinogen I: an early marker of pernicious anemia in patients with type 1 diabetes. J Clin Endocrinol Metab 2005;90:5254-8.

106. Strober W, Neurath MF. Immunologic diseases of the gastrointestinal tract. In: Rich RR (ed). Clinical Immunology. London: Mosby, 1998. pp 1408-23

107. Brown WR. Immunologic diseases of the gastrointestinal tract. In: Samter M (ed) Immunologic diseases. 5th ed. Boston: Little, Brown and Company, 1998. pp 1158-65

108. Schade SG, Cohen RJ Conrad ME. Effect of hydrochloric acid on iron absorption. N Engl J Med 1968;279:672-4.

109. Sipponen P, Valle J, Varis K, Kekki M, Ihamaki T, Siurala M. Fasting levels of serum gastrin in different functional and morphologic states of the antrofundal mucosa. An analysis of 860 subjects. Scand J Gastroenterol 1990;25:513-9.

110. Toh BH, Sentry JW, Alderuccio F. The causative H+/K+ ATPase antigen in the pathogenesis of autoimmune gastritis. Immunol Today 2000;21:348-54.

111. Karlsson FA, Burman P, Loof L, Olsson M, Scheynius A, Mardh S. Enzyme-linked immunosorbent assay of H+,K+-ATPase, the parietal cell antigen. Clin Exp Immunol. 1987;70:604-10.

112. Kokkonen J. Parietal cell antibodies and gastric secretion in children with diabetes mellitus. Acta Paediatr Scand 1980;69:485-9.

113. Ramachandran A, Rosenbloom AL, Mohan V, et al. Autoimmunity in South Indian patients with IDDM. Diabetes Care 1986;9:435-6.

114. Trudeau WL, McGuigan JE. Relations between serum gastrin levels and rates of gastric hydrochloric acid secretion. N Engl J Med 1971;284:408-12.

115. Sipponen P, Harkonen M, Alanko A, Suovaniemi O. Diagnosis of atrophic gastritis from a serum sample. Minerva Gastroenterol Dietol 2003;49:11-21.

116. Vaananen H, Vauhkonen M, Helske T, et al. Non-endoscopic diagnosis of atrophic gastritis with a blood test. Correlation between gastric histology and serum levels of gastrin-17 and pepsinogen I: a multicentre study. Eur J Gastroenterol Hepatol 2003;15:885-91.

117. Kuipers EJ. In through the out door: serology for atrophic gastritis. Eur J Gastroenterol Hepatol 2003;15:877-9.

118. Botazzo GF. Adrenalitis, oophoritis and autoimmune polyglandular disease. In: Rich (ed). Clinical immunology. London: Mosby, 1998. pp. 1523-35.

119. Peterson P, Salmi H, Hyoty H, et al. Steroid 21-hydroxylase autoantibodies in insulin-dependent diabetes mellitus. Childhood Diabetes in Finland (DiMe) Study Group. Clin Immunol Immunopathol 1997;82:37-42.

120. Falorni A, Laureti S, Nikoshkov A, et al. 21-hydroxylase autoantibodies in adult patients with endocrine autoimmune diseases are highly specific for Addison's disease. Belgian Diabetes Registry. Clin Exp Immunol 1997;107:341-6.

121. Tandon N, Shtauvere-Brameus A, Hagopian WA, Sanjeevi CB. Prevalence of ICA-12 and other autoantibodies in north Indian patients with early-onset diabetes. Ann N Y Acad Sci 2002;958:214-7.

122. Yu L, Brewer KW, Gates S, et al. DRB1*04 and DQ alleles: expression of 21-hydroxylase autoantibodies and risk of progression to Addison's disease. J Clin Endocrinol Metab 1999;84:328-35.

123. Riley WJ, Maclaren NK, Neufeld M. Adrenal autoantibodies and Addison disease in insulin-dependent diabetes mellitus. J Pediatr 1980;97:191-5.

124. Betterle C, Scalici C, Presotto F, et al. The natural history of adrenal function in autoimmune patients with adrenal autoantibodies. J Endocrinol 1988;117:467-75.

125. Del Rosario MA, Fitzgerald JF, Chong SK, Croffie JM, Gupta SK. Further studies of anti-endomysium and anti-gliadin antibodies in patients with suspected coeliac disease. J Pediatr Gastroenterol Nutr 1998;27:191-5.

126. Cronin CC, Feighery A, Ferriss JB, Liddy C, Shanahan F, Feighery C. High prevalence of coeliac disease among patients with insulin-dependent (type I) diabetes mellitus. Am J Gastroenterol 1997;92:2210-2.

127. Shamir R. Advances in coeliac disease. Gastroenterol Clin North Am 2003;32:931-47.

128. Korponay-Szabo IR, Halttunen T, Szalai Z, et al. In vivo targeting of intestinal and extraintestinal transglutaminase 2 by coeliac autoantibodies. Gut 2004;53:641-8.

129. Weile B, Grodzinsky E, Skogh T, Jordal R, Cavell B, Krasilnikoff PA. Screening Danish blood donors for antigliadin and antiendomysium antibodies. Acta Paediatr 1996;412:46.

130. Volta U, Molinaro N, Fusconi M, Cassani F, Bianchi FB. IgA antiendomysial antibody test. A step forward in coeliac disease screening. Dig Dis Sci 1991;36:752-6.

131. Brown WR. Immunologic diseases of the gastrointestinal tract. In: Samter M (ed) Immunologic diseases. 5th ed. Boston: Little, Brown and Company, 1998. pp 1158-65.

132. Sategna-Guidetti C, Grosso S, Pulitano R, Benaduce E, Dani F, Carta Q. Coeliac disease and insulin-dependent diabetes mellitus. Screening in an adult population. Dig Dis Sci 1994;39:1633-7.

133. Carlsson AK, Axelsson IE, Borulf SK, et al. Prevalence of IgA-antiendomysium and IgA-antigliadin autoantibodies at diagnosis of insulin-dependent diabetes mellitus in Swedish children and adolescents. Pediatrics 1999; 103:1248-52.

134. Doolan A, Donaghue K, Fairchild J, Wong M, Williams AJ. Use of HLA typing in diagnosing coeliac disease in patients with type 1 diabetes. Diabetes Care 2005;28:806-9.

135. Prazny M, Skrha J, Limanova Z, et al. Screening for associated autoimmunity in type 1 diabetes mellitus with respect to diabetes control. Physiol Res 2005;54:41-8.

136. Shahbazkhani B, Faezi T, Akbari MR, et al. Coeliac disease in Iranian type I diabetic patients. Dig Liver Dis 2004;36:191-4.

137. Aygun C, Uraz S, Damci T, et al. Coeliac disease in an adult Turkish population with type 1 diabetes mellitus. Dig Dis Sci 2005;50:1462-6.

138. Schober E, Bittmann B, Granditsch G, et al. Screening by anti-endomysium antibody for coeliac disease in diabetic children and adolescents in Austria. Pediatr Gastroenterol Nutr 2000;30:391-6.

139. Barera G, Bianchi C, Calisti L, et al. Screening of diabetic children for coeliac disease with antigliadin antibodies and HLA typing. Arch Dis Child 1991;66:491-4.

140. Barera G, Bonfanti R, Viscardi M, et al. Occurrence of coeliac disease after onset of type 1 diabetes: a 6-year prospective longitudinal study. Pediatrics 2002;109:833-8.

141. Crone J, Rami B, Huber WD, Granditsch G, Schober E. Prevalence of coeliac disease and follow-up of EMA in children and adolescents with type 1 diabetes mellitus. J Pediatr Gastroenterol Nutr 2003;37:67-71.

142. Sumnik Z, Kolouskova S, Cinek O, Kotalova R, Vavrinec J, Snajderova M. HLA-DQA1*05-DQB1*0201 positivity predisposes to coeliac disease in Czech diabetic children. Acta Paediatr 2000;89:1426-30.

143. Sjoberg K, Eriksson KF, Bredberg A, Wassmuth R, Eriksson S. Screening for coeliac disease in adult insulin-dependent diabetes mellitus. J Intern Med 1998;243:133-40.

144. Rensch MJ, Merenich JA, Lieberman M, Long BD, Davis DR, McNally PR. Gluten-sensitive enteropathy in patients with insulin-dependent diabetes mellitus. Ann Intern Med 1996;124:564-7.

145. Acerini CL, Ahmed ML, Ross KM, Sullivan PB, Bird G, Dunger DB. Coeliac disease in children and adolescents with IDDM: clinical characteristics and response to gluten-free diet. Diabet Med 1998;15:38-44.

146. Cerutti F, Bruno G, Sacchetti C, Rabbone I, Cavallo F, Ansaldi N. Risk for silent coeliac disease is higher in diabetic children with a diabetic sibling than in sporadic cases. Diabetes Care 2000;23:1027-8.

147. Arato A, Korner A, Veres G, Dezsofi A, Ujpal I, Madacsy L. Frequency of coeliac disease in Hungarian children with type 1 diabetes mellitus. Eur J Pediatr 2003;162:1-5.

148. Kordonouri O, Dieterich W, Schuppan D, et al. Autoantibodies to tissue transglutaminase are sensitive serological parameters for detecting silent coeliac disease in patients with Type 1 diabetes mellitus. Diabet Med 2000;17:441-4.

149. Roldan MB, Barrio R, Roy G, et al. Diagnostic value of serological markers for coeliac disease in diabetic children and adolescents. J Pediatr Endocrinol Metab 1998;11:751-6.

150. Fraser-Reynolds KA, Butzner JD, Stephure DK, Trussell RA, Scott RB. Use of immunoglobulin A-antiendomysial antibody to screen for coeliac disease in North American children with type 1 diabetes. Diabetes Care 1998;21:1985-9.

151. Li Voon Chong JS, Leong KS, Wallymahmed M, Sturgess R, MacFarlane IA. Is coeliac disease more prevalent in young adults with coexisting Type 1 diabetes mellitus and autoimmune thyroid disease compared with those with Type 1 diabetes mellitus alone? Diabet Med 2002;19:334-7.

152. Martin-Villa JM, Lopez-Suarez JC, Perez-Blas M, et al. Coeliac- and enteropathy-associated autoantibodies in Spanish insulin-dependent diabetes mellitus patients and their relation to HLA antigens. J Diabetes Complications 2001;15:38-43.

153. Peretti N, Bienvenu F, Bouvet C, et al. The temporal relationship between the onset of type 1 diabetes and coeliac disease: a study based on immunoglobulin a antitransglutaminase screening. Pediatrics 2004;113:e418-22.

154. Vitoria JC, Castano L, Rica I, Bilbao JR, Arrieta A, Garcia-Masdevall MD. Association of insulin-dependent diabetes mellitus and coeliac disease: a study based on serologic markers. J Pediatr Gastroenterol Nutr 1998;27:47-52.

155. Buysschaert M, Tomasi JP, Hermans MP. Prospective screening for biopsy proven coeliac disease, autoimmunity and malabsorption markers in Belgian subjects with Type 1 diabetes. Diabet Med 2005;22:889-92.

156. Mahmud FH, Murray JA Kudva YC, et al. Coeliac disease in type 1 diabetes mellitus in a North American community: prevalence, serologic screening, and clinical features. Mayo Clin Proc 2005;80:1429-34.

157. Picarelli A, Sabbatella L, Di Tola M, Vetrano S, Casale C, Anania MC. Anti-endomysial antibody of IgG1 isotype detection strongly increases the prevalence of coeliac disease in patients affected by type I diabetes mellitus. Clin Exp Immunol 2005;142:111-5.

158. Sakly W, Bienvenu F, Peretti N, et al. IgA anti-transglutaminase antibodies as a tool for screening atypical forms of coeliac disease in a French at-risk paediatric population. Eur J Gastroenterol Hepatol 2005;17:235-9.

159. Sategna-Guidetti C, Grosso S, Pulitano R, Benaduce E, Dani F, Carta Q. Coeliac disease and insulin-dependent diabetes mellitus. Screening in an adult population. Dig Dis Sci 1994;39:1633-7.

160. Cerutti F, Bruno G, Chiarelli F, Lorini R, Meschi F, Sacchetti C. Younger age at onset and sex predict coeliac disease in children and adolescents with type 1 diabetes: an Italian multicenter study. Diabetes Care 2004;27:1294-8.

161. Schober E, Rami B, Granditsch G, Crone J. Coeliac disease in children and adolescents with type 1 diabetes mellitus: to screen or not, to treat or not? Horm Res 2002; 57 Suppl 1:97-100.

162. Ashabani A, Abushofa U, Abusrewill S, Abdelazez M, Tuckova L, Tlaskalova-Hogenova H. The prevalence of coeliac disease in Libyan children with type 1 diabetes mellitus. Diabetes Metab Res Rev 2003;19:69-75.