Autoimmune Disorders Associated to Type 1 Diabetes Mellitus in Children and Adolescents

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1. Introduction

Autoimmune diseases occur when an individual develops an immune response targeted against specific organ or number of organs. Genetic susceptibility and environmental factors are the main responsible of the development of the autoimmune process leading to a clinically evident disease. The majority of organ-specific autoimmune diseases are characterized by an initial infiltration by lymphocytes and macrophages, of the organ, with impaired activity of the organ followed by atrophy. This progressive autoimmune process takes time, and is T cell mediated. Antibodies against specific antigens of the involved gland are detectable in the blood before the clinical onset of the specific disease, so they represent a risk marker and their screening and follow-up allow precocious diagnosis and treatment of autoimmune-related disease in genetically susceptible individuals (Allen et al., 2008).

Genetic factors and autoimmunity are closely related since the developmental maturation of T cells occurs through an interaction between HLA antigen and T cell receptor. In genetically susceptible individuals, disease-prone HLA molecules are ineffective at binding and presenting peptides from tissue-specific antigens, therefore auto-reactive T cells can survive and trigger a poorly regulated immune response thereafter (Van den Driessche, 2009).

Patients affected by type 1 diabetes mellitus are at increased risk of developing other autoimmune conditions like celiac disease, autoimmune thyroid disease, adrenal insufficiency, atrophic gastritis, autoimmune hepatitis, primary ovarian failure. The frequency of organ specific autoimmunity in patients with type 1 diabetes might be due to multiple immunologic abnormalities, i.e an imbalance in B and T lymphocytes, or a tendency to react against specific antigens, or poor ability to develop immune tolerance.

2. Type 1 diabetes mellitus

2.1 Background

Type 1 diabetes mellitus is the most common endocrinopathy to have clinical onset in childhood or adolescence, with varied pathogenesis, clinical appearance and outcome, and seriously affects patients’ and families’ life. A combination of genetic, environmental and immunological factors exerts to a T-cell mediated autoimmune process targeted against insulin-producing β-cells in the pancreatic islet of Langerhans (Daneman, 2006).


title

2.2 Epidemiology

The incidence of Type 1 diabetes is increasing worldwide and may double the burden of the disease in youngest children by 2020. Large collaborative studies like DiaMond and EURODIAB Registries demonstrated that one century ago childhood diabetes was rare and fatal, while at the end of the century a steady increase in several parts of the world has been observed. In particular, DiaMond Project reported the trend in incidence of Type 1 diabetes from 1990 to 1999; over this period the average annual increase in incidence was 2.8%, with a slight higher rate in the last 5 year-period as compared to the first 5-year period. Similarly, EURODIAB Study reported a 3.9% annual increase from 1989-2003 (Vehil & Dabelea, 2011). The rising incidence of Type 1 diabetes over the past decades is too quick to be attributed to an increased genetic susceptibility, since the proportion of newly-diagnosed patients carrying the highest-risk HLA genotype (HLA DR3/DR4) seems unchanged.

2.3 Pathogenesis

Genetic susceptibility plays an important pathogenetic role in type 1 diabetes mellitus, with the HLA -DR and –DQ genes explaining about 50% of the risk. The different penetrance of these genes can partially explain the role of environmental factors. Whereas differences in incidence between populations may be due to genetic susceptibility or protection genes, the increasing incidence is to be ascribed to environmental factors. Studies aimed to analyze the temporal changes in the frequency of genotypes associated with type 1 diabetes susceptibility reported a decreasing frequency of those higher-risk HLA genotypes (DRB1 03-DQA1*0501-DQB1*0201/DRB104-DQA1*0301-DQB1*0302) between recently diagnosed patients as compared to those diagnosed 50 years before (Hermann et al., 2003). Therefore the increasing incidence of type 1 diabetes could be explained by a more permissive environment, exerting in increased penetrance of low/moderate risk genotypes or in interplay between environmental factors and other non-HLA genes (Nejentsev et al., 2007, Todd et al., 2007). On the other hand, several environmental factors such as dietary habits, sedentary lifestyle, climate changes, pollution, viral (also maternal) and other infectious disease frequency and type, have changed over the past years and deserve attention (Oikarinen et al., 2011).

The immune-mediated β-cell destruction occurs over several years and exerts in progressive insulin deficiency, leading to various degrees of hyperglycemia up to severe metabolic derangement, i.e. diabetic ketoacidosis (Devendra et al., 2004).

Studies in both humans and animal models are trying to clarify the specific antigenic targets involved in the islet cell autoimmunity. Islet cell antibodies (ICA) detected by immunofluorescence, were firstly isolated in patients with diabetes mellitus and autoimmune polyendocrine syndrome (Bottazzo et al., 1974). These autoantibodies are transient, being observed in 70-80% of newly-diagnosed cases and tend to disappear thereafter. Their positivity in subjects at risk of diabetes (i.e. first-degree relatives) represents a useful means to predict the future development of the disease.

Anti-insulin autoantibodies (IAA) can be detected both by radioimmunoassay (RIA) or by ELISA, but the first method is recommended. IAA positivity is inversely related to age at diabetes diagnosis (81% in patients younger than 10 and 61% in older ones), and is higher and adolescent males (Williams et al., 2003). IAA are the first autoantibodies to become positive, and they can later decline. Interestingly, substitutive insulin therapy can be followed by an immune response against itself, and this subtype of insulin antibodies can be distinguished from anti-insulin autoantibodies.
In 1990 Baekkeskov and co-workers reported that the 64,000 M(R) molecule previously defined as an antigenic target of Type 1 diabetes was the GABA-synthesizing enzyme glutamic acid decarboxylase (GAD) (Baekkeskov et al., 1990). GAD is not expressed exclusively on $\beta$-cells, but also in other islet cells. Anti-GAD autoantibodies (GADA) can be detected both by RIA or by ELISA. The prevalence of anti-GAD autoantibodies positivity is 84%, and is positively related to age and female sex. Their peak level can be reached after diabetes diagnosis and persist longer than anti-islet cell antibodies, making them a useful marker especially for adult patients.

In 1994 a cDNA coding a 548 aminoacid protein named ICA-512 was described as a major target of humoral immunity by screening an islet c-DNA expression library with patients’ sera (Rabin et al., 1994). Moreover it has been reported that IA-2, a 979 aminoacid transmembrane protein of the tyrosine phosphatase family, is a major autoantigen in type 1 diabetes. IA-2 is a intrinsic membrane protein of secretory granules neuroendocrine cells, like pancreatic islets. IA-2 autoantibodies (IA-2A) can be detected by RIA as well as by ELISA. Recently a not radio-isotopic method (time-resolved immunofluorometric assay (TR-IFMA) showed comparable results with RIA. The prevalence of IA-2A has been reported about 73%, and no correlation with age was found (Tsirogianni et al., 2009).

Recently the cation efflux transporter 8 (ZnT8) has been identified as a novel target autoantigen in patients with type 1 diabetes. Autoantibodies to ZnT8 (ZnT8 A) are detectable in about 70% of newly diagnosed patients, independent of age (Achenbach et al., 2009). Patients presenting with a single islet cell autoantibody were also positive for ZnT8 A, suggesting that they could be a marker for type 1 diabetes risk stratification. Three variants of ZnT8 A have been recognized: 1) ZnT8RA (arginine 325 zinc transporter 8 autoantibody), 2) ZnT8WA (tryptophan 325 zinc transporter 8 autoantibody), 3) ZnT8QA (glutamine 325 zinc transporter 8 autoantibody). These 3 ZnT8 variants precede T1DM clinical onset and are all detectable by radio-binding assay (Andersson et al., 2011).

### 2.4 Diagnosis and treatment

Diagnosis of type 1 diabetes is based on symptoms of hyperglycemia: polyuria, polydipsia, with mild symptoms up to severe ketoacidosis. After intravenous fluid, insulin and salt replacement for metabolic imbalance recovery, treatment of type 1 diabetes consists of lifelong substitutive subcutaneous insulin therapy, together with correct dietary habits, self-management of the disease and regular physical activity, as result of a prolonged educational intervention starting at the time of clinical diagnosis (Maffeis & Pinelli, 2008, Bangstad et al., 2007). Recognition, management and prevention of hypoglycemic episodes as well as hyperglycemic spikes is mandatory. Continuous education implementation starting at the time of clinical diagnosis, designed for children, adolescents and their parents, is necessary thereafter (Weinzimer et al., 2005).

### 2.5 Follow-up

The most serious problem related to pediatric type 1 diabetes is the risk, even in young adulthood, of microvascular and macrovascular complications, i.e. retinopathy, nephropathy, neuropathy, cardiovascular and cerebrovascular diseases (Donaghue et al., 2007). The key role of good glycaemic control to prevent diabetes-related complications has been firmly established by the Diabetes Control and Complications Trial Study, which demonstrated the protective role of intensive insulin treatment (DCCT, 1993). Sustained
chronic hyperglycaemia and acute blood glucose fluctuations have a deleterious effect on the metabolic mechanisms involved in the development of microangiopathy, such as protein glycation and oxidative stress. In particular, glucose variability from peaks to nadirs, with upward as in the postprandial periods, and nadirs, as in the interprandial periods activates the oxidative stress (Monnier & Colette, 2008). As regards pediatric diabetes, despite better insulin preparations and strict self-management of the disease few children and adolescents maintain mean glycated hemoglobin A1c (HbA1c) levels within the normal ranges, with serious impact on metabolic control and subjects’ caregiver quality of life (Rewers et al, 2009).

3. Celiac disease

3.1 Background and epidemiology
Celiac disease is an immune-mediated disorder, the only one with a well-established causal agent, resulting from a permanent gluten intolerance triggered by the ingestion of the gliadin fraction of wheat gluten and similar alcohol-soluble proteins named prolamins of barley and rye (Di Sabatino & Corazza, 2009). Gluten intolerance exerts a chronic inflammatory lesion characterized by flattened villi of the small bowel mucosa and sub-mucosa, with a diverse clinical heterogeneity ranging from asymptomatic disease to severe malabsorption syndrome in genetically susceptible individuals (Branski et al., 2006). Once considered a rare childhood disorder, celiac disease is now known to be a very common condition, even if it remains widely unrecognized and underdiagnosed worldwide both in children and in adults. Availability of new very sensitive and specific serological markers (initially anti-gliadin and anti-reticulin antibodies, and thereafter anti-endomysial and anti-transglutaminase antibodies) allowed more efficient screening, independently from classical clinical picture. Thanks to these serological markers, celiac disease has been identified in a high proportion of children adolescents and adults who did not previously received a correct clinical diagnosis. The prevalence of celiac disease was dramatically increased, and defined as 1 case in 99 schoolchildren in Finland (Mäki et al., 2003), and 1 in 106 in Italy (Tommasini et al., 2004).

3.2 Pathogenesis
Celiac disease develops from the interplay between a well-defined environmental factor and genetic susceptibility, with the participation of other causative cofactors (drugs like interferon-α, infectious agents like intestinal rotavirus, modifications in infant-feeding timing) (Di Sabatino & Corazza, 2009). The causal agent, for CD are specific immunogenic peptides present exclusively in the dietary gluten proteins, from wheat and other cereals like rye and barley. Gluten proteins can be divided into 2 fractions, gliadins and glutenins, both characterized by immunogenicity and by toxicity. Among gluten immunostimulatory peptides, some are more active than others. In particular, a 33 aminoacid immuno-dominant peptide identified from an α-gliadin fraction has functional properties attributable to many proline and glutamine residues. Proline increases the peptide resistance to gastrointestinal proteolysis, with more strength binding with HLA-DQ2 and HLA-DQ8 molecules on antigen presenting cells. Glutamine residues are a preferred substrate for transglutaminase-mediated deamination, with subsequent increased immunogenicity (Shan et al., 2002).
Genetic factors play an important pathogenetic role, as demonstrated by a concordance rate of 85% in monozygotic twins and by familiar aggregation. HLA-DQ genes, in particular DQ2 variant (alleles DQA1*05/DQB1*02) and DQ8 variant (alleles DQA1*03/DQB1*0302) are strongly associated to CD. Beside the HLA genes (i.e. COELIAC 1, on chromosome p21), other non-HLA genes are recognized to confer additional susceptibility: COELIAC 2, on chromosome 5q31-33, which contains cytokine gene clusters; COELIAC 3, on chromosome 2q33, which codes the negative co-stimulatory molecule CTLA4; COELIAC 4, on chromosome 19p13.1, which contains the myosin IXB gene variant encoding a myosin that alters actin remodeling (Di Sabatino & Corazza, 2009).

As regards pathophysiology of CD, it has been demonstrated that gluten peptides, which are resistant to digestion by gastric and pancreatic enzymes, after crossing intestinal epithelium, are deaminated by tissue transglutaminase and then presented by DQ2+ or DQ8+ antigen-presenting cells to gluten-specific CD4+ T cells. These cells once activated drive a Th1 response, characterized by production of pro-inflammatory cytokines, and responsible for the development of celiac lesions, i.e. lamina propria infiltration of inflammatory cells, crypt hyperplasia and villous atrophy (Di Sabatino & Corazza, 2009).

3.3 Clinical presentation and diagnosis

The clinical range of celiac disease has a wide spectrum, from asymptomatic to severe malnutrition, with gastrointestinal and extra-intestinal manifestations. The most common feature of celiac disease includes gastrointestinal symptoms (i.e. abdominal pain, increased frequency of bowel movements), weight loss, bone disease, various degree of anemia and weakness.

Different subtypes of celiac disease have been described. Symptomatic or classic celiac disease means typical gastrointestinal symptoms with severe malabsorption syndrome. The term atypical celiac disease is applied to cases with mild or absent gastrointestinal symptoms (colitis or irritable bowel), and characterized by extra-intestinal manifestations, including iron deficient anemia, osteoporosis, failure to thrive. In both cases villous atrophy is observed during endoscopy or intestinal biopsies (Alaedini & Green, 2005). More recently it has been suggested to define celiac disease as silent, minor or major. Silent celiac disease is referred to asymptomatic subjects, sometimes relatives of patients with known celiac disease, or subjects eventually found to be positive at screening procedures. Minor celiac disease is referred to subjects with transient symptoms (dyspepsia, irritable bowel syndrome without malabsorption), anemia, cryptic hypertransaminasemia, infertility, peripheral and central neurological disorders, osteoporosis, dental enamel defects, failure to thrive, dermatitis herpetiformis. Major celiac disease is referred to patients with major gastrointestinal symptoms (Di Sabatino & Corazza, 2009).

The mechanism underlying the severity of clinical presentation at present remains unknown. Researchers have shown that neither the degree of duodenal villous atrophy nor the extent of visible enteropathy assessed by capsule endoscopy correlates with presentation (Di Sabatino & Corazza, 2009).

The recognition of a pre-celiac disease state is usually retrospective and this condition has been termed latent celiac disease. Potential celiac disease is characterized by positive antibodies but normal mucosa; there is no evidence to support managing these patients with a gluten-free diet. A higher prevalence of potential CD was found in patients with type 1 diabetes, and this observation may be
ascribed to the routine screening preformed in these patients, although the influence of genetic factors cannot be excluded. (Franzese et al., 2011).

Refractory celiac disease is relatively rare complication occurring approximately from 2% to 5% of patients. It is classified as persistent or recurrent symptoms of malabsorption and enteropathy. Refractory celiac disease is divided into two key categories, type I and type II. As regards celiac disease diagnosis, it has been demonstrated that case-finding by serological markers detection followed by histological confirmation on duodenal biopsy is an accurate, cost-effective and valid approach for diagnosis, in particular for high-risk subjects, like those affected by other autoimmune conditions, like type 1 diabetes mellitus. Celiac disease is associated with circulating antibodies against gliadin and endomysial tissue. Anti-endoMysial antibodies showed higher specificity and sensitivity than anti-gliadin antibodies, and represent a useful means for screening procedures. Anti-reticulin antibodies screening showed less sensibility and it has been replaced by anti-endomysial antibodies. In 1997 the transglutaminase 2 enzyme was found to be the autoantigen for anti-endomysial antibodies. Both anti-endomysial and anti-transglutaminase antibodies belong to the IgA class. The first are detected by immunofluorescence staining antibodies and results are qualitative or semiquantitative, while anti-transglutaminase antibodies are detected by an enzyme linked immunosorbent assay (ELISA) or radioimmunoprecipitation, and the results are quantitative. Testing for IgG anti-transglutaminase and antibodies and, more recently for IgG anti-deaminated gliadin peptides are a useful alternative for patients with IgA deficiency (Di Sabatino & Corazza, 2009).

In subjects with serological markers of celiac disease, a small intestinal biopsy is the “gold standard” for diagnosis. The finding of histological picture of villous atrophy with increased number of intraepithelial lymphocytes makes sure diagnosis of celiac disease, irrespective of serological markers result. The Marsh criteria (Marsh et al., 2005) are commonly used for histological staging.

3.4 Treatment

The only proven treatment for celiac disease is lifelong gluten-free diet. Foods containing gluten from wheat, rye, barley and their derivatives must be avoided since also small amounts of gluten are harmful. It has been reported that no more than 10 mg of gluten ingested can be tolerated.

Compliance to gluten-free diet is sometimes difficult, particularly during adolescence and for patients with silent celiac disease diagnosed by means of screening procedures. Dietary compliance can be evaluated through anti-endomysial and anti-deaminated gliadin antibodies detection. Complications of celiac disease are frequently observed in patients with delayed diagnosis and with poor compliance and include non-Hodgkin lymphoma, probably due to accumulation in the intestinal epithelium of aberrant and clonal intraepithelial lymphocytes (Al-Toma et al., 2007). Other complications include refractory celiac disease and ulcerative jejunoileitis (Rubio-Tapia et al., 2009).

3.5 Celiac disease and type 1 diabetes mellitus

That celiac disease prevalence is higher in patients with type 1 diabetes mellitus as compared to general population is universally accepted. After autoimmune thyroiditis, the second most commonly reported autoimmune disease in type 1 diabetes is celiac disease (Van den Driessche, 2009).
Gluten consumption could be a common causative factor, as confirmed by the possible diagnosis of both diseases at the same time (Frisk et al. 2008). Moreover the duration of gluten exposure seems to increase the risk of other autoimmune diseases (Ventura et al., 1999). Dietary gluten could act as a modifier rather than a determinant causative factor, facilitating the progression of other dietary antigens to the small bowel lamina propria, where they can activate the immune response against β-cells. Based on this hypothesis, the removal of gluten from diet has been proposed in subjects at risk as prevention trial to reduce the progression to type 1 diabetes mellitus (Pastore et al., 2003). A six-month of gluten-free diet in subjects at risk of type 1 diabetes did not influence β-cells autoantibody titer, but only improved endogenous insulin secretion (Pastore et al., 2003).

Recently, in samples from the small bowel mucosa from patients with celiac disease and type 1 diabetes a low expression of tight junction protein 1 (TJP1) mRNA has been observed, indicating an increase in intestinal permeability that might represent a causative factor. Furthermore, the highest expression of Forkhead box P3 (FoxP3) mRNA, a marker of regulatory T cells was observed, suggesting an increased immunoregulatory mechanisms (Uibo et al., 2011).

The mean prevalence of celiac disease in type 1 diabetes is about 8%, with an extremely variable range (from 1% up to 11%) (Kakleas et al., 2010), almost 10-20 fold higher than observed in general pediatric population (Maki et al., 2003). The different prevalence data could be due to different screening procedures and diagnostic tests used. The prevalence of celiac disease in type 1 diabetes increased over recent decade as compared to the past (Salardi et al., 2008), and seems to be related to changes in environmental factors like dietary habits or infectious diseases. Another possible explanation of this high association could be the same genotypes involved in both diseases. Three celiac disease loci, i.e. RGS1 on chromosome 1q31, IL18RAP on chromosome 2q12 and TAGAP on chromosome 6q25 were associated with type 1 diabetes mellitus. Moreover, the 32-bp insertion-deletion variant on chromosome 3p21, the PTPN2 on chromosome 18p11 and CTLA4 on chromosome 2q33 and SH2B3 on chromosome 12q24 are shared by both diseases (Smyth et al., 2008). Younger age at diabetes clinical onset, female gender, and coexistence of another autoimmune disease are predictive factors for celiac disease development (Cerutti et al., 2004).

In the majority of patients with type 1 diabetes clinical presentation of celiac disease is usually silent, and thanks to screening procedure is diagnosed (Holmes, 2001, Barera et al., 2002). On the other hand, a detailed medical history allows to identify several signs or symptoms attributable to celiac disease. Extra-intestinal manifestations such as failure to thrive, delayed puberty, iron-deficiency anemia, increased levels of liver enzyme tests, bleeding tendency, precocious osteoporosis, and unexplained hypoglycemic episodes are frequently reported. Gastrointestinal symptoms, i.e. diarrhea and abdominal pain, are reported in 28% and 14% of patients, respectively (Bhadada et al., 2011). Symptoms attributable to celiac disease are more common in children than in adolescents or adults (Larsson et al., 2008).

Type 1 diabetes precedes celiac disease diagnosis (Holmes, 2001); in a small proportion (up to 25%) of cases type 1 diabetes develops in already diagnosed celiac patients (Valerio et al., 2002).

In the majority of cases type 1 diabetes precedes celiac disease diagnosis (Holmes, 2001); in a small proportion of cases (up to 25%) type 1 diabetes develops in patients with already diagnosed celiac disease (Valerio et al., 2002).
Positivity for disease-related antibodies allows identification of patients with suspected celiac disease who must undergo intestinal biopsy. IgA-transglutaminase antibodies show the highest sensitivity and allow to identify around 98% of patients with celiac disease, while their specificity is lower, especially at a low titer (Salardi et al., 2008). IgA-anti-endomysial antibodies show lower sensitivity (98%) but higher specificity. Fluctuating positivity for anti-endomysial antibodies at a low titer can be detected at time of diabetes clinical onset, and in absence of signs or symptoms related to celiac disease only periodical screening is recommended.

Total IgA screening is mandatory before celiac disease-related antibodies detection. Patients with IgA deficiency benefit from IgG anti-transglutaminase antibody detection (Lenhardt et al., 2004) and, as recently reported, by IgG anti-deamimated gliadin peptides (Volta et al., 2010). IgA deficiency deserves attention, since this condition is more frequent in patients with celiac disease (1.7%) as compared to control population (0.25%) (Cataldo et al., 1997).

As regards timing of screening, it has been reported that the serological screening of celiac disease allows diagnosing 1% of patients with celiac disease. The frequency of diagnoses increases to 5% when screening is performed in the next 5 years after diabetes diagnosis (Larsson et al., 2008). It has been reported that up to 85% of cases of celiac disease is diagnosed 2-5 years after type 1 diabetes clinical onset (Saukkonen et al., 1996). Markers of celiac disease can appear within 10 years, so it is recommended to perform screening yearly for the first 4 years after diabetes diagnosis, and every 2 years in the following 6 years (Kordonouri et al., 2009).

Fig. 1. Linear growth in a girl with type 1 diabetes and concomitant celiac disease, who developed autoimmune thyroiditis

Diagnosis of celiac disease by intestinal biopsy requires a lifelong gluten-free diet. Major problems related to gluten-free diet include quality of life, impairment of social life, poor compliance especially in adolescents and in patients with silent celiac disease diagnosed...
through screening procedures. Moreover, gluten-free diet can exert an increased insulin requirement since persistent hyperglycemia can occur. Gluten-free diet exerts in increased weight and height (Goh et al., 2010), as well as serum ferritin and hemoglobin (Hansen et al., 2006). Moreover improvement of bone status in patients with type 1 diabetes and adherence to gluten-free diet has been reported (Valerio et al., 2008).

4. Autoimmune thyroid disease

4.1 Hashimoto’s thyroiditis

4.1.1 Background and genetic susceptibility

Autoimmune thyroid diseases include many thyroid gland disorders, with different histological and clinical pictures ranging from the hypothyroidism of chronic lymphocytic thyroiditis to the hyperthyroidism of Graves’ disease. As other autoimmune diseases, chronic lymphocytic thyroiditis (also defined Hashimoto’s thyroiditis from the physician who firstly described this condition) derives from a combination of genetic susceptibility and some environmental trigger factors (Pearce et al., 2003). Hashimoto’s thyroiditis is more frequent in females than in males (3.5 cases/1000 people/year versus 0.8 cases/1000 people/year, respectively), and global prevalence is increasing with age. Hashimoto thyroiditis is the most common cause of acquired hypothyroidism in children and adolescents (formerly called “adolescent” or “simple” goiter), and usually presents itself during early adolescence or among schoolchildren, with or without goit, with a prevalence of 1% among schoolchildren (Lorini et al, 2003).

Susceptibility to Hashimoto’s thyroiditis is determined by individual genetic background, including both major histocompatibility complex (MHC) and non-MHC genes. Associations have been reported between Hashimoto’s thyroiditis and HLA-DR3, HLA-DR4, or HLA-DR5. Furthermore, in children and adolescents paternal alleles and antibodies status have been shown to influence susceptibility to autoimmune thyroid disease. The expression of HLA-DR antigens on thyroid cells have a potential role in perpetuating the immune response, related to certain HLA-DR subtypes. As regards non-HLA susceptibility genes, several studies demonstrated the association between a polymorphism of the CTLA-4 gene and autoimmune thyroid disease (Barker, 2006). In literature are reported linkage with loci on the X chromosome and on chromosome 20 or 14. Observations in twins are correlated with a genetic predisposition to thyroid autoimmunity. There are several cases of identical twins where one twin showed Graves’ disease and the others Hashimoto’s thyroiditis. It is common to find family clusters with HT and the incidence in parents or siblings of patient with HT can reach about 25% (Lorini et al., 2003).

4.1.2 Pathogenesis

There is no evidence that a clear infectious agent is responsible for autoimmune thyroiditis. However, long-term follow-up of patients with subacute thyroiditis showed a possible reaction to viral infection with signs of persistence thyroid autoimmune disease. To this purpose, hepatitis C can act as a trigger for the development of autoimmune thyroiditis through thyroid follicular cell apoptosis. Potential mechanisms of infectious triggers include cell damage with the release of auto-antigens, expression of new antigens and molecular mimicry mechanisms.
Drugs containing iodine or supplementary dietary iodine can trigger an autoimmune thyroiditis in subjects at risk, although the mechanism is still unknown. Accumulation of iodine in animal models leads to iodination of thyroglobulin which triggers an immune reaction because T-cell-reactive peptides can be more antigenic when iodinated. Moreover dietary supplementation of iodine in the population of iodine-deficient regions such as the use of drugs rich in iodine (i.e. amiodarone) induce cases of thyroiditis, and a significant increase in lymphocytic infiltration by thyroid-specific auto-antibodies. Furthermore, patients treated with cytokines such as IL-1 or α-interferon can trigger an autoimmune thyroiditis, which is more frequent in patients with pre-existing positivity for anti-thyroid auto-antibodies.

Hashimoto's thyroiditis is an organ-specific autoimmune disease, characterized histologically by a lymphocytic infiltration of the thyroid gland, initially characterized by hyperplasia and subsequently by infiltration of lymphocytes and plasma cells between follicles, then resulting in a follicle atrophy. Lymphocytic infiltration is composed of B lymphocytes, about 30%, and T-lymphocytes, about 60%, including CD4+ helper and CD 8+ suppressor. Autoimmune thyroiditis is characterized by thyroid cell apoptosis leading to follicular destruction, rather than thyroid stimulation and cellular hyperplasia. Thyroid gland is infiltrated by B- and T-lymphocytes, the later are capable of destroying thyroid cells, which express Fas, via apoptosis and release several cytokines that increase the damage. The process is exacerbated by the action of auto-antibodies directed against several thyroid antigens, like thyroid peroxidase antibodies (TPO-Abs), detectable in 90% of patients with Hashimoto’s thyroiditis, previously considered non-pathogenic, but now their role has been shown. They inhibit enzyme activity and stimulate cytotoxicity by natural killer. Anti-thyroglobulin antibodies (TgA) are detectable in a small percentage of patients, while high levels of thyrotopin receptor-blocking antibodies are often present, particularly in patients who develop autoimmune hypothyroidism.

4.1.3 Clinical picture
Hashimoto’s thyroiditis is the most common cause of acquired hypothyroidism in the pediatric population, occurring in about 1% of children and adolescents. Goiter is the hallmark of this autoimmune disease, and often may appear either insidiously or variable in size, however is usually enlarged with accentuation of the normal lobular architecture. Occasionally goiter gives the sensation of local pressure or causes difficulty in swallowing. Hashimoto’s thyroiditis is more frequent in girls than in boys (four to seven times), with onset at 3 years but often sharply to 6 years with a peak incidence during adolescence.

The most common clinical symptoms are related to hypothyroidism, and include deceleration in the rate of growth, although some children are apparently asymptomatic, and show abnormal values in laboratory tests only. A few children complain clinical signs and symptoms of thyroid hyperfunction, such as nervousness, irritability, agitation, hot intolerance, weight loss. Eventually patient with Hashimoto’s thyroiditis can show ophthalmopathy in absence of Graves’ disease. The most frequent symptom in Hashimoto’s thyroiditis is goiter, followed by menstrual disorders, short stature, and nervousness in girls, while constipation and exophthalmos are more frequently reported in boys. Other signs are hot and cold intolerance, weight loss or weight gain and sweating. The clinical course of Hashimoto’s thyroiditis is quite variable. In fact, the goiter may reduce or disappear, or persist unchanged for years, while the patient remains euthyroid or
progressively develops hypothyroidism. Spontaneous remission is frequent in adolescents (Lorini et al, 2003).

4.1.4 Laboratory findings
In patients with autoimmune thyroiditis high serum levels of thyroid antibodies are present, therefore their detection is mandatory. Anti-thyroglobulin antibodies have been reported in 60% of patients with diffuse goiter or hypothyroidism or both while anti-thyroid peroxidase antibodies are detectable in 95% of cases so they represent a more sensitive marker. In 20% of cases there are significant antibody titers in the absence of thyroiditis, while lower titer are related to other thyroid diseases and in normal population. Subclinical hypothyroidism means altered values of thyroid hormones in presence of a slightly or moderately elevated TSH. Many children with HT have normal level of TSH because the goiter is caused by lymphocytic infiltrations or growth-stimulating immunoglobulin.

4.1.5 Imaging
On imaging studies, the thyroid gland shows enlargement without specific characteristics. High resolution ultrasound may show hypoechogenic micronodules (Fig. 2). Scintigraphic findings are variable; in some patients with Hashimoto’s thyroiditis have thyroid gland enlarged with dysomogeneous distribution of tracer, in other cases the thyroid scan is normal but in most patients the uptake of radioiodine is decreased or increased. The perchlorate washout is positive in 60% of patients. Often children and adolescents, evaluated at diagnosis, show a thyroid ultrasound picture altered. The definitive diagnosis of HT is confirmed by a biopsy of the thyroid, that confirmed the elevated titers of thyroid autoantibodies in the serum. High serum TSH concentration can be found in 30-40% of cases, associated with low serum T4, with normal or near-normal serum T3 concentration. Thyroid scan exclude thyroid dysgenesis. Elevated level of TSH clarifies if hypothyroidism is originated from pituitary or thyroid disease.

Fig. 2. Hashimoto’s thyroiditis: thyroid ultrasound showing hypoechogenicity
4.1.6 Treatment
The treatment of autoimmune thyroid follows the guidelines of congenital hypothyroidism. If the TSH level is greater than 10 μU/ml, L-thyroxin is the drug of choice. The initial dose is related on patient’s age and on patient’s clinical status from 25 μg/day to 100-150 μg/day. The therapy required periodic reevaluation, in particular when prominent nodules persist despite suppressive therapy, because there is a greater risk of cancer in patients with lymphocytic thyroiditis.

4.2 Graves’ disease
Graves’ disease is the most important cause of thyrotoxicosis in pediatrics and affects about 0.02% in children and adolescents. Its frequency increases with age: it is rare before the four years, gradually rises, reaching a peak during adolescence, with a preponderance for female gender (Kaguelidou et al, 2009). The aim of therapy is to reduce the excessive hormone production. First, this can be done with anti-thyroid drugs, as thionamides, with side effects especially after long-term therapy. Secondly, can be used thyroidectomy; however this surgical procedure may be complicated by several problems, such as hypoparathyroidism or recurrent nerve injury. Third method, is based on the use of radioiodine, that has not been yet universally accepted in children. Initial treatment, is medication and in the second instance, surgery or radioiodine. The goal of treatment is to maintain euthyroidism for a period at least 24 month and then discontinue the medical therapy. The positive results, with pharmacological treatment alone reaches 25% of cases. In adults the disease control is accomplished through the use of radioactive iodine or with drug for short periods. In children, however, use the medication for long periods, and then radioiodine, is just as an alternative option. The average age of onset is at 11 years (from 2.5 to 19 years), with preponderance in girls and with more cases of exophthalmos, low BMI, and higher height SDS. The goal of treatment is to limit the biosynthesis of thyroid hormones and maintain euthyroidism by maintaining a check on lab tests. Adverse effects are recorded in 5-32% of cases with skin rashes, transient neutropenia and agranulocytosis. Children have more adverse effects but less severe, often reversible spontaneously or with therapy change. Alternatively, using radioiodine in patients with hyperthyroidism resistant to drug treatment of 4.5 years, there was more remission (about 25% between 2-4 years of follow up). Most side-effect of the therapy is a permanent hypothyroidism, which can be treated with replacement therapy. The problem of this method is a potential carcinogenic risk (thyroid cancer and leukaemia), that declines with age, genetic damage, and a possible damage to reproduction. Radioiodine for safety, low cost and morbidity, could be the definitive treatment of Graves’ disease in older children and young adolescents, but no in children younger than 5 years old (Gruneiro-Papendich et al, 2003).

4.3 Autoimmune thyroid disease and type 1 diabetes
Autoimmune thyroid disease is frequently reported in patients with type 1 diabetes mellitus, sometimes associated with celiac disease (Ergur et al, 2010). Serological screening studies aimed to evaluate the prevalence of thyroid involvement have gained momentum in recent years (Kadiyala et al. 2010). The prevalence of thyroid autoimmunity in patients with type 1 diabetes has been reported to be two to four times more frequent than in control population.
In control population the prevalence of thyroid autoimmunity ranges from 2.9% to 3.2%, while in young patients with type 1 diabetes the prevalence is higher, ranging from 19% to 23.4% (Kakleas et al., 2009). In children and adolescents with type 1 diabetes, risk factors for developing thyroid autoimmunity are quite similar to those reported in adult population, and include mainly female gender and increasing age. The role of anti-glutamic acid decarboxylase antibody persistence, age at diabetes diagnosis and duration of diabetes remains unclear. At-risk haplotypes for autoimmune thyroiditis include HLA-DQA1*0301 (linked to DR4), DQB1*0301 (linked to DR5) and DQB1*0201 (linked to DR3), which is associated with autoimmune hyperthyroidism, while the HLA-DQA1*0501 is associated with autoimmune hypothyroidism. The HLA haplotype DR3-DQB1*0201 confers the genetic susceptibility to type 1 diabetes mellitus, autoimmune thyroiditis and autoimmune polyendocrine syndrome type II. Finally, the HLA-haplotype DQB1*05 seems to be protective for autoimmune thyroid disease development (Kakleas et al., 2009). Other loci, i.e. VNTR and CTLA-4 may influence disease phenotype and severity (Van Driessche et al., 2009).

A symmetric, painless goitre is usually the first presentation of autoimmune thyroid disease, while atrophic thyroid gland is observed in 10% of patients. A subclinical hypothyroidism has been reported up to 58% of patients with thyroid autoantibodies. Early recognition and treatment of hypothyroidism is important, since the decrease in basal metabolism may exert weight gain, dyslipidemia, atherosclerotic heart disease, sometimes goiter, and may negatively affect metabolic control. Hypothyroidism is confirmed by low free thyroxin and high TSH levels. Compensated hypothyroidism mean normal thyroxine levels with increased TSH. Substitutive L-thyroxin treatment exerts normalization of TSH levels and goitre regression when present. Treatment with L-thyroxin in patients with type 1 diabetes, thyroid autoantibodies and thyroid enlargement is safe and effective to reduce thyromegaly, with no effect on thyroid autoantibodies titer (Brown, 2007, Kordonouri et al, 2007, Karges et al. 2007).

Autoimmune thyroid disease and type 1 diabetes mellitus are sometimes associated with chronic urticaria, also in young patients, as a possible consequence of thyroid chronic inflammations. However the mechanisms underlying this association have not yet been defined, but this association emphasizes the need for a routine screening (Hyman et al., 2008). In young patients with type 1 diabetes mellitus overt hyperthyroidism is rarely encountered. It may be expression of Graves’ disease or the transient hyperthyroid phase of Hashimoto’s thyroiditis. Unstable metabolic control despite strict compliance, weight loss despite regular food intake, agitation, tremors, tachycardia, insomnia, heat intolerance, thyroid enlargement and characteristic eye signs are the main clinical features. Treatment is based on anti-thyroid drugs like propylthiouracil and metimazole. During acute thyrotoxicosis beta-adrenergic blockers agents are indicated. Persistent hyperthyroidism requires surgery or radioiodine (Kordonouri et al, 2009).

5. Atrophic gastritis

5.1 Background

While the association between type 1 diabetes and celiac disease and/or thyroid autoimmunity is clearly documented, particularly in young patients, few data are available about the frequency of other autoimmune diseases, like autoimmune gastritis and pernicious anemia.
Autoimmune gastritis, firstly described by Thomas Addison in 1849, is characterized by autoantibodies directed against gastric parietal cells, atrophy of gastric corpus and fundus, hypochlorhydria/achlorhydria, hypergastrinemia, iron deficiency anemia and pernicious anemia. In adult general population the frequency of autoimmune gastritis is about 1-2%, and is 3-5 fold increased in patients with type 1 diabetes (De Block et al, 2008). As regards children, adolescents and young adults with type 1 diabetes, the frequency of parietal cells antibodies is 15.8%, with a close association with older age and duration of disease (De Block et al, 2008, Warncke et al, 2010). Female gender association is controversial.

5.2 Pathogenesis
Antibodies against parietal cells (PCA) and their secretory product Intrinsic Factor (AIF) are serological markers for autoimmune gastritis and are targeted towards H+, K+-ATPase of gastric parietal cells and denote autoimmune gastritis, characterized by atrophy of corpus and fundus. The chronic auto-aggression to the proton pump exerts in hypochlorhydria/achlorhydria and hypergastrinemia and iron-deficiency anemia as a consequence of impaired gastric secretion and iron absorption. Moreover PCA are responsible for the reduced intrinsic factor secretion with subsequent pernicious anemia due to vitamin 12 deficiency. PCA and AIF are detectable not only in serum, but also in gastric juice. PCA titer is positively related to severity of gastric atrophy and negatively related to concentration of parietal cells. Low serum levels of pepsinogen I, as a consequence of chief cell destruction, represent another early marker of autoimmune gastritis and pernicious anemia. Both pernicious anemia and autoimmune gastritis may predispose to gastric cancer. Gastric adenocarcinomas are reported on 1-10% of adult patients with autoimmune gastritis through intestinal meta/dysplasia. (De Block et al., 2003) Helicobacter Pylori infection has been reported as a risk factor for autoimmune gastritis, by stimulating granulocytes to produce oxygen radicals, which are mutagenic and lead to corpus atrophy (D’Elios et al., 2004). Molecular mimicry and/or T-helper l-induced expression of HLA-class II and co-stimulatory molecules on gastric epithelial cells are considered as pathogenic mechanisms for Helicobacter Pylori induced autoimmunity (Lahner et al., 2011). The evidence of a link between pernicious anemia and particular HLA haplo/genotypes is not strong. As regards type 1 diabetes, a weak association between PCA positivity and the HLA-DQA1*0501-B1*0301 haplotype, linked to HLA-DR5, has been observed. In mouse models, four distinct genetic regions that confer susceptibility to autoimmune gastritis have been identified: two loci, located on distal chromosome 4, are called Gasa1 and Gasa2; two other loci, located on chromosome 6, are called Gasa3 and Gasa4, respectively. Interestingly, three out of these four susceptibility loci are non-major histocompatibility complex genes which co-localize with those of type 1 diabetes. This is the strongest concordance identified between any two autoimmune disease so far (De Block et al., 2008).

5.3 Diagnosis
Parietal cell antibodies are measured using immunoblotting or enzyme linked immunoassay (ELISA), which are more sensitive than indirect immunofluorescence technique. Iron deficiency anemia is defined as microcytic hypochromic anemia with a transferrine saturation of less than 20% and low iron and ferritin levels. Pernicious anemia is defined as macrocytic anemia with subnormal vitamin B12 levels and positive levels of PCAs
Diagnosis of AG requires gastroscopy with at least two biopsies from gastric antrum and gastric body. Atrophy of the gastric body mucosa is defined as focal or complete oxyntic gland loss and/or replacement by metaplastic pylori or intestinal glands. To each graded variable, the scores usually employed are: 0 = absence; 1 = mild; 2 = moderate; 3 = severe (Bordi et al., 1997).

5.4 Treatment
Therapy of autoimmune gastritis includes supplementation of iron or vitamin B12 or removal of pre-malignant gastric lesions. Patients with PCA antibodies and high gastrin levels should undergo endoscopy with biopsies. Determining risk factors for and early diagnosis of autoimmune gastritis is mandatory to prevent and treat iron-deficiency anemia, pernicious anemia and pre-malignant gastric lesions. In all PCA positive patients gastroscopy with multiple biopsies should be performed and subsequent clinical and endoscopic close follow-up are mandatory.

5.5 Autoimmune gastritis and type 1 diabetes
Autoimmune gastritis is rarely encountered in children and adolescents with type 1 diabetes, since the prevalence of parietal cell antibodies increases with age and with longer duration of disease. It is noteworthy that even young patients with type 1 diabetes are positive for parietal cell antibodies, with a frequency about 4%, which is higher than in controls (1.9%) (De Block et al., 2008). On the other hand, autoimmune gastritis is more frequent in children and adolescents with autoimmune thyroid disorder (Fig. 3).

Fig. 3. Atrophic gastritis and sessile antral polyp with signs of esophageal candidiasis (personal data)
6. Addison’s disease

6.1 Background
In 1849 Thomas Addison firstly described a group of patients characterized by anemia and disease of adrenal glands. Addison's disease is an insidious, chronic disorder of the adrenal cortex resulting in decreased production of glucocorticoids, mineralocorticoids, and androgens. There is a concomitant increased secretion of ACTH from the pituitary gland aimed to stimulate the adrenal gland. In developed countries an autoimmune process is recognized as the most common etiological factor of adrenal gland insufficiency (70-90%); the second cause is tuberculosis of the adrenal gland (10 to 20%). Three clinical forms of adrenal insufficiency are recognized: Addison disease within syndromes characterized by autoimmune involvement of several organs and named Autoimmune Polyendocrine Syndromes (APS-1 and APS-2), and Addison disease as an isolated condition.

6.2 Pathogenesis
Genetically predisposed individuals develop autoantibodies toward the 21-hydroxylase enzyme and eventually lose the ability to produce cortisol. Autoantibodies against 21-hydroxylase are present in the majority of recently diagnosed patients. Susceptibility is conferred through the genes encoding the class II Major Histocompatibility Complex. Similarly as for type 1 diabetes mellitus, there is a strong association with the DR3 haplotype. The highest risk genotype, occurring in 30% of patients with Addison's disease, is represented by DR3/4, DQ2/DQ8 and the DRB1*0404/DQ8-DRB1*0301/DQ2 genotype occurs at an increased frequency in individuals with isolated AD and in those with AD and type 1 diabetes mellitus (El Fassi et al., 2007).

6.3 Diagnosis
Addison’s disease is preceded by a long prodromic, asymptomatic period, followed by subtle clinical manifestations up to adrenal insufficiency. Main symptoms are persistent vomiting, anorexia, hypoglycemia, unexplained weight loss, malaise, ill-defined fatigue, muscular weakness, hypotension, and craving for salt. The most specific sign of primary adrenal insufficiency is generalized hyperpigmentation of the skin and mucosal surfaces, as a consequence of high plasma concentrations of melanocyte stimulating activity of β-lipotropin, which origins from the same precursor as ACTH. Laboratory tests can aid in the diagnosis: hypoglycemia, hyponatriemia, hyperkaliemia, acidosis, high levels of ACTH and a deficiency of cortisol. Furthermore, adrenal antibodies represent a useful marker, with a higher predictive value in younger than in adult patient, being present in more than 90% of patients with autoimmune Addison disease. Antibodies are directed against steroidogenic enzymes (CYP21A2 and 21 hydroxylase) or adrenal cortex (Adrenal cortex autoantibodies, ACA). In addition, hypocorticism may cause frequent hypoglycemic events (Van den Driessche et al 2009). We recommend screening patients with type 1A diabetes, hypoparathyroidism, and polyendocrine autoimmunity for 21-hydroxylase autoantibodies. If present, yearly monitoring with an ACTH stimulation test is performed to allow early diagnosis and prevent an adrenal crisis (Aaron et al., 2008).

6.4 Treatment
Addison’s disease treatment consists of urgent lifelong glucocorticoids replacement, with clear counseling about the need for stress dose steroids for illnesses and prior to surgical
procedures (Aaron et al., 2008). In some cases supplementation with mineralcorticoids is mandatory.

### 6.5 Addison’s disease and type 1 diabetes

In adolescents with type 1 diabetes Addison’s disease is rarely encountered, and symptoms are sometimes asymptomatic. Addison’s disease usually follows type 1 diabetes diagnosis, being more frequently observed within the Autoimmune Polyendocrine Syndrome type 1 and type 2 (Kordonouri et al., 2009). Correct diagnosis of Addison’s disease requires a high degree of clinical suspicion and since the disease is a life-threatening condition, several investigators recommend periodical screening of Addison’s disease in all young patients since type 1 diabetes diagnosis (Brewer et al., 1997). In an adolescent with type 1 diabetes, Addison’s disease should be suspected in case of recurrent hypoglycemic episodes, unexplained decrease of insulin requirement and improvement of metabolic control, fatigue, weight loss, hyponatremia and hyperkaliemia. Diagnosis confirmation requires low cortisol levels after ACTH stimulation test. Screening procedures allow to detect asymptomatic children and adolescents with positive adrenal antibodies; where raised ACTH levels suggest the presence of adrenal insufficiency. Risk factors for Addison’s disease in patients with type 1 diabetes include a history of other autoimmune conditions, in particular thyroid disease, and a positive family history for autoimmunity, as reported in a case series of 4 adolescents with pre-existing type 1 diabetes who developed Addison disease (Thomas et al., 2004). Three out of 4 patients showed unexplained hypoglycemia and the other one showed unexplained improvement in diabetes control. Two out of 4 patients reported skin hyperpigmentation. In all 4 patients a positive personal and family history of other autoimmune conditions has been reported, in particular celiac and/or thyroid autoimmune diseases and Autoimmune Polyendocrine Syndrome type 2. A more recent study in 491 newly diagnosed children with type 1 diabetes aimed to define the prevalence of additional autoimmune conditions reported 1% positivity of antibodies to 21-hydroxylase, while overt Addison’s disease was found only in 20% of the positive patients (Triolo et al., 2011). Noteworthy, all young patients with type 1 diabetes and adrenal autoantibodies develop Addison’s disease during the follow-up period, with a progression to overt adrenal failure much more rapid than in adults, indicating that different autoimmune responses may be evoked at different age periods (Betterle et al., 1997).

### 7. The Autoimmune Polyglandular Syndromes (APS)

From the time of Addison’s original description of his disease onwards, it has been apparent that multiple autoimmune endocrine disease can affect individual patients and their families in recognizable clinical clusters. Twenty years ago, the autoimmune polyglandular syndromes (APS) were classified into three basic types based on the patient’s age at onset, their clinical associations with specific endocrinopathies and HLA typing. **Type I APS**, called also APECED (Autoimmune PolyEndocrinopathy-Candidiasis-Ectodermal Dystrophy) is a rare autosomal recessive disorder originally identified through the typical association of mucocutaneous candidiasis with Addison’s disease and hypoparathyroidism. These symptoms usually constitute the first manifestation of the
disease in early childhood; other endocrine and non-endocrine disorders can be associated: thyroiditis, autoimmune hypogonadism, hypophysitis, chronic active hepatitis, atrophic gastritis, pernicious anemia, alopecia, vitiligo and ectodermal dystrophy (Mazza et al., 2011). The disease results from the inheritance of recessive genes (AIRE gene) mapping to 21q22.3 and it is not linked to genes within the HLA-DR/DQ genetic region of chromosome 6.

**Type II APS** is more common than type 1 APS, the prevalence is 1/20,000 with a female preponderance (male/female ratio = 1/3) and has a peak incidence between the ages of 20 and 60 years, mostly in the third or fourth decade (Van den Driessche et al., 2009). It is defined by the association of Addison’s disease with thyroid autoimmunity, type 1 diabetes and sometimes pernicious anemia, vitiligo and hypogonadism. Type II APS is HLA-associated (DQB1*0302/0201), while Hashimoto’s thyroiditis itself is associated with HLA-DQB1*0301. Multiple antigens have now been identified for the component disease of type II APS ie: thyroperoxydase and thyroglobulin in Hashimoto’s thyroiditis; TSH receptors I Graves’ disease; insulin, GAD and IA-2 and IA-2B in type 1 diabetes mellitus; 21 hydroxylase in Addison’s disease; 17 hydroxylase and SCC (all p450 enzymes) in hypogonadism; tyrosine in vitiligo; H+K+ATPase an intrinsic factor in pernicious anemia and the calcium sensing receptor (CaSR) in hypoparathyroidism. Indeed the autoantibody that reacts to CaSR does so through its external domain, suggesting that the respective autoimmunity (hypoparathyroidism) may be antibody dependent. In mice, such immune responses proceeded through a T cell helper-2 (Th2) pathway; whereas those that result in cell mediated pancreatic β-cell loss are though to occur through a Th1 pathway. It could be that APS I results from an inherited defective Th1 responsiveness resulting in uninhibited Th2 overactivity. On the other hand, APSII/III appears to results from Th1 autoimmunity, perhaps explaining why APS-I does not co-exist with APS-II or III.

CD4+ T helper (Th) cells play important roles in regulating immune responses including that of immunological tolerance to self. When these regulatory processes go away, one or more organ-specific autoimmune disease may develop. One prevailing theory developed in the mice is that immunoresponsiveness follows at least two polarized pathways. While one track (Th1) promotes cellular immune responses, the other (Th2) pathway favours antibody or allergic immunoresponsiveness. Such differentiated Th cells can be distinguished based upon their cytokine phenotypes.

**8. Conclusions**

It is now established that patients with type 1 diabetes are at increased risk of other autoimmune diseases as compared to general populations (Michels & Eisenbarth, 2010). Besides islet-cell autoantibodies, other antibodies against numerous non β-cell antigens have been frequently reported. Clinically-evident diseases are rarely observed in young patients with type 1 diabetes, and can be considered as the tip of the iceberg. Latent forms of these autoimmune-associated diseases, characterized by the presence of circulating autoantibodies with mild or no symptoms, are more frequent. Early detection of antibodies and latent organ-specific dysfunction are advocated to alert physicians to take appropriate actions aimed to prevent full-blown disease. Moreover patients and their relatives should be instructed to recognize subclinical signs and symptoms attributable to these autoimmune-associated diseases. Several risk factors have been identified for a group of autoimmune diseases like genetic background, gender, age, age at clinical onset and duration of diabetes.
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Autoimmune Disorders Associated to Type 1 Diabetes Mellitus in Children and Adolescents

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Autoimmune disorders are caused due to breakdown of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

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