

Autoimmune Associated Diseases in Pediatric Patients with Type 1 Diabetes Mellitus According to HLA-DQ Genetic Polymorphism

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1. Introduction

Diabetes mellitus type 1 is the most common endocrine metabolic disorder in childhood and adolescence. In this condition there is an absolute insulin deficiency secondary to progressive destruction of pancreatic beta cells, causing severe alterations in the metabolism of all essential elements (carbohydrates, lipids and proteins).

The most obvious alteration is chronic hyperglycemia, which is essential to diagnose the disease, and moreover, is the main responsible of many vascular and neurological complications that diabetic patients may develop long-term.

In the development of diabetes mellitus type 1 involving both genetic and environmental factors. The traditional concept is that environmental factors may act as triggers of the immune response against β of Langerhans cell phenotype in a genetically predisposed to the development of diabetes mellitus type 1.

Autoimmune diseases are syndromes caused by activation of T cells or B or both, without evidence of other causes such as infection or cancer. When dendritic cells expressing self-antigens in the context of HLA molecules stimulate peripheral T cells, they do so that they remain alive but anergic, no response until they contact a dendritic cell with multiple moleculescostimulatory expressing microbial antigens.

Although many autoimmune diseases characterized by abnormal production of pathogenic autoantibodies, most of it is caused by an overreaction, combined T and B cells. In animal models of type 1 diabetes mellitus have demonstrated the high expression of MAdCAM-1 and GlyCAM-1 on HEV (high endothelial venules) of the inflamed pancreatic islets and the treatment of animals with inhibitors of the L-function selectin and $\alpha 4$ integrin, blockeddevelopment of type 1 diabetes mellitus.

The American Diabetes Association divides the type 1 diabetes mellitus in two subgroups: 1A is the result of autoimmune destruction of beta cells and the 1B subtype, which do not immunomarkers indicating a destructive autoimmune process of beta cellspancreas. However develop insulin deficiency by unidentified mechanisms and are prone to ketosis. It has been a predominance of African Americans and Asians in the 1B subtype.

Genetic studies have shown that it is an inherited disease with polygenic trait. Genome wide studies have indicated the presence of at least 20 chromosomal regions that may contribute to genetic predisposition to type 1 diabetes mellitus. The most important genes that

influence susceptibility to type 1 diabetes are located in the HLA complex located on the short arm of chromosome 6 (6p21.3).

The HLA-DQ is the locus that confers the major genetic susceptibility to develop type 1 diabetes in humans. DQ molecules have two chains, alpha and beta, encoded by the DQA and DQB genes. Susceptibility to type 1 diabetes mellitus has been described by combining alpha-beta chains with no amino acid aspartic acid at position 57 of beta chain (DQB1*0302 linked to DR4 and DQB1*0201 linked to DR3) and the presence of the amino acid arginine at position 52 of the alpha chain (DQA1*0301 linked to DR4 and DQA1*0501 linked to DR3).

Based on these findings have been described both genotypes DQA/DQB disease associated with DQA1*0501/DQB1*0201 and DQA1*0301/DQB1*0302, which is more specific than DR3/DR4 genotype.

Although other types of islet cells and α cells (glucagon producing), delta cells (somatostatin producing) cells or PP (pancreatic polypeptide-producing) are functionally and embryologically similar to beta cells and express the most same. These proteins, inexplicably are free of autoimmune process.

From the pathological standpoint, the cells of the pancreatic islets are infiltrated by lymphocytes (a process called insulitis). After the destruction of beta cells, the inflammatory process forwards, the islets are atrophic and disappear immunomarkers.

Insulitis studies in humans and in animal models of type 1 diabetes mellitus (NOD mouse and BB rat) have identified the following abnormalities in both humoral branch as in the immune system cells:

1. Autoantibodies against cell islet.
2. Activated lymphocytes in islets, peripancreatic lymph nodes and widespread circulation.
3. T lymphocytes that proliferate when stimulated with islet proteins.
4. Release of cytokines within the insulitis.

The beta cells appear to be particularly vulnerable to the toxic effect of some cytokines (tumor necrosis factor), interferon gamma and interleukin 1. Precise mechanisms are unknown the death of beta cells, but may involve formation of nitric oxide metabolites, apoptosis and direct cytotoxic effects of CD8+ T cells. It is believed that the destruction process does not involve autoantibodies against islet cells, since these antibodies do not react in general to the surface of islet cells and are capable of transferring diabetes mellitus in animals.

Among islet molecules that are targets of the autoimmune process are insulin, glutamic acid decarboxylase (glutamic acid decarboxylase, GAD), the biosynthetic enzyme of the neurotransmitter gamma aminobutyric acid (gamma-aminobutyric acid, GABA), ICA-512/IA-2 (with homology to tyrosine phosphatases, and fogrina (protein in secretory granules of insulin). Other less precisely defined autoantigens are islet ganglioside and carboxypeptidase H. Except none of the insulin-specific autoantigens are beta cells, which makes us wonder how these are destroyed selectively.

Current theories favor the onset of an autoimmune process directed against beta cell molecule, which then spreads to other islet molecules as the autoimmune process destroys the beta cells and creates a series of secondary autoantigens. Beta cells of individuals with type 1 diabetes mellitus do not differ from the beta cells of normal people, because the transplanted islets are destroyed by the recurrence of autoimmune process of type 1 diabetes mellitus.

Autoantibodies against islet cells (ICA) is a combination of several different antibodies directed against islet molecules such as GAD, insulin, IA-2/ICA-512 and islet ganglioside and serve as a marker of the autoimmune process of type 1 diabetes mellitus. The determination of the ICA may be useful to classify as type 1 diabetes mellitus and nondiabetic individuals identify risk. The ICA is present in most (> 75%) of individuals newly diagnosed with type 1 diabetes mellitus in a significant minority of diabetics newly diagnosed type 2 (5-10%) and sometimes, in pregnant women with gestational diabetes (<5%).

In 3-4% of first-degree relatives of individuals with type 1 diabetes mellitus ICA exist. Along with the presence of a disorder of insulin secretion in the proof of intravenous glucose tolerance predict a 50% higher risk of developing type 1 diabetes mellitus in the next 5 years. Without this disorder of insulin secretion, the presence of ICA predicts a five-year risk <25%. After this it follows that the risk of a first degree relative of type 1 diabetes mellitus is low. Today no approved treatment to prevent development of type 1 diabetes mellitus, so the detection of ICA in non-diabetic population has not been established as screening.

There is another theory that talks about environmental factors as triggers of the autoimmune process in genetically vulnerable patients, but it is difficult to find an environmental trigger, since the event may precede by several years the development of the disease. Among the hypothetical environmental triggers include viruses (coxsackie and rubella), proteins early exposure to cow's milk and nitrosoureas.

A major advance would get delay or prevent diabetes, there have been some intervention in animal models, whose main objective has been the immune system (immunosuppression, selective deletion of T cell subsets, immune tolerance induction to protein island), while others avoid the death of islet cells by blocking the cytotoxic cytokines or increasing islet resistance to the destruction process.

Type 1 diabetes mellitus is often associated with autoimmune diseases. Thus, there has been an increased prevalence of autoantibodies related to celiac disease and many other autoantibodies against endocrine and nonendocrine organs. Not infrequently, these diseases manifest themselves associated paucisymptomatic and are diagnosed late. Despite this apparent relationship between type 1 diabetes mellitus and these autoimmune diseases has not been shown that the degree of glycemic control influence the likelihood of developing or subsequent developments. We must not forget that many of these clinical situations produce per se a decrease in the expectancy and quality of life of patients, another reason to actively pursue and establish treatment as soon as detected.

Autoantibodies can be found in up to 25% of children and adolescents with diabetes, but only 3-5% have hypothyroidism. Hyperthyroidism is less common, but more often than children without diabetes.

Autoimmune hypothyroidism may be associated with goitre (Hashimoto's thyroiditis or goiter), or in later stages of the disease, minimal residual thyroid tissue (atrophic thyroiditis). Because the autoimmune process gradually reduces thyroid function, there is a compensatory phase during which thyroid hormone levels are maintained by an elevated TSH.

Although some patients may have mild symptoms, this phase is called subclinical or mild hypothyroidism. Later, T4 levels fall and TSH levels increase even more, the symptoms become more obvious at this stage (usually $TSH > 10 \text{ mU/L}$) is called clinical hypothyroidism.

In Hashimoto's thyroiditis, there is a marked lymphocytic infiltration of the thyroid with germinal center formation, atrophy of thyroid follicles accompanied by oxyphil metaplasia, absence of colloid and mild or moderate fibrosis. As with most autoimmune disorders, susceptibility to this type of hypothyroidism depends on a combination of genetic and environmental factors and is increased sibling risk of autoimmune hypothyroidism or Graves disease.

Genetic risk factors for this type of hypothyroidism in subjects caucasians are HLA-DR polymorphisms, specifically the HLA-DR3, HLA-DR4 and HLA-DR5. There is also a weak relationship between polymorphism of CTLA-4, a gene regulating T cells and autoimmune hypothyroidism. HLA-DR polymorphisms and CTLA-4 constitute about half of cases hipotiroïdsimo autoimmune susceptibility. It is still necessary to identify other contributing loci. A gene located on chromosome 21 could be the cause of the relationship between autoimmune hypothyroidism and Down syndrome.

The lymphocytic infiltrate thyroid autoimmune hypothyroidism is composed of CD4+ T cells and activated CD8+ and B cells. It is believed that the destruction of thyroid cells is mediated in a primary CD8+ T cells cytotoxic, which destroy their targets by perforin that cause cellular necrosis or through granzyme B, which induces apoptosis.

Addition, cytokine production by local T cells, such as tumor necrosis factor, IL-1 and interferon gamma, can return to thyroid cells more susceptible to apoptosis mediated by death receptors such as Fas, which activate their ligands respective T cellIn addition, these cytokines directly disrupt the function of thyroid cells, and induce the expression of other proinflammatory molecules by thyroid cells themselves, such as cytokines, molecules of HLA class I and II, adhesion molecules, CD40 and nitric oxide.

The administration of high concentrations for therapeutic cytokines (notably IFN alpha) is associated with enhancement of autoimmune thyroid disease, possibly by mechanisms similar to those involved in sporadic disease.

The Tg and TPO antibodies are markers of thyroid autoimmunity with clinical utility, but their pathogenic effect is limited to a secondary role in the amplification of a developing immune response. TPO antibodies fix complement and are complex to the complement membrane attack the thyroid gland in case of autoimmune hypothyroidism. However, the transplacental passage of anti-Tg antibodies or anti-TPO has no effect on fetal thyroid gland, indicating that it takes an injury mediated by T cells to initiate autoimmune injury of the gland.

Although it has been associated with the presence of subclinical hypothyroidism with an increased risk of symptomatic hypoglycemia and hipocrecimiento, it is quite common for thyroid dysfunction clinically pass unnoticed, so you must determine the levels of thyrotropic hormone (TSH) annually in those without autoantibodies or more often if there are or the patient has any symptoms.

Celiac disease is 10 times more common in diabetics than in the general population and may affect up to 1-10% of diabetic patients. Also known as celiac sprue or gluten sensitive enteropathy is an autoimmune disorder triggered by ingestion of gliadin fractions present in the gluten and similar proteins of rye and barley in genetically predisposed individuals.

Gluten is the main protein component of wheat, rye and barley. In celiac disease is triggered by an immune reaction that leads to inflammation of the small intestine mediated by T lymphocytes, with the development of hyperplastic crypts, intraepithelial lymphocytes and

villous atrophy, causing a chronic enteropathy with a broad range of manifestations, which make a systemic disease of varying severity.

Adherence to a gluten-free diet is followed by clinical and histological improvement in these patients, with normalization of long-term intestinal architecture, and the property of the recurrence of symptoms when gluten is reintroduced in the diet .

The presence of an immune component in the etiology of the disease was suspected for three reasons. First, no serum IgA antigliadin antibodies and endomysial, although it is unclear whether primary or secondary to tissue injury. Endomysial antibody has a sensitivity of 90 and specificity 95%, and its antigen is tissue transglutaminase. Secondly, treatment with prednisolone for four weeks in a celiac patient who continues to eat gluten induces remission and duodenal epithelium gives a more normal level. Finally, the gliadin peptides interact with gliadin-specific T cells, which in turn can act as mediators of tissue injury or cause the release of one or more cytokines that are responsible for tissue injury.

In celiac disease are also implicated genetic factors, its incidence varies widely among different population groups (high in Caucasians and low in color and eastern race) and is 10% in first degree relatives of patients with celiac disease. In addition, about 95% of celiac patients express the allele of the human leukocyte antigen DQ2, whereas only a minority of all people who express DQ2 have celiac disease.

Not forget that the diagnosis of celiac disease is made by biopsy of the small intestine. Is performed on patients with symptoms and laboratory findings suggestive of malabsorption or lack of nutrients.

Is often asymptomatic, but can cause gastrointestinal symptoms, short stature and anemia. This condition is also associated with an increased number of hypoglycemic episodes and a progressive decrease in insulin requirements in the year prior to diagnosis. It is also recommended measuring endomysial or tissue transglutaminase after diagnosis and every 2-3 years in post, in asymptomatic patients or whenever there is clinical suspicion, given the possibility of seroconversion over time in some patients in which antibodies were initially detected.

Addison's disease, another autoimmune disease is present up to 2% of type 1 diabetes presenting autoantibodies against the enzyme 21-hydroxylase and the enzyme cleavage of the side chain, but it ignores the importance of these antíneurófagos in the pathogenesis of adrenal insufficiency. Some antibodies cause adrenal insufficiency by blocking the binding of ACTH to its receptors.

The appearance of two or more of these autoimmune endocrine same person characterized in a polyglandular autoimmune syndrome type II (thyroid, parathyroid and gonadal tissue), this syndrome has yet mutated gene on chromosome 6 and is associated with alleles B8 and HLA DR3.

The presence of adrenal insufficiency is rare, so it is recommended not look systematically. In addition to the classic symptoms for adrenal insufficiency are at risk of frequent hypoglycemia and reduced daily insulin requirements.

The 15-20% of adults have diabetes autoimmune gastropathy presenting autoantibodies to gastric parietal cells, and 50% have clinical or pathological signs of atrophic gastritis. Yet there are no recommendations regarding the detection of these antibodies, given the lower prevalence in childhood.

With respect to autoimmune diseases of the skin, vitiligo has been found up to 7% of children and adolescents with type 1 diabetes mellitus.

The objectives of this study are the following: make an epidemiological study of type 1 diabetes mellitus in childhood and adolescence, to study the HLA-DQ genetic group and general parameters in the onset of the disease, and the pursuit of development of autoimmune diseases.

Today diabetes education is fundamental and essential, in consultation diabetes control emphasizes good glycemic control in order to reduce microvascular complications, rare in children because their development is in adulthood. It also reports on the association with microvascular problems such as diabetic retinopathy, microalbuminuria leading to nephropathy, and diabetic neuropathy, as well as on macrovascular problems such as atherosclerosis.

Are known to coexist in these patients, with chronic hyperglycemia in cardiovascular risk factors. Diabetes education programs and health promotion should report on the harmful effects of some of them, such as smoking, overweight or sedentary. We should not forget the high prevalence of these diseases justifies the systematic implementation of its screening in the units of pediatric endocrinology. The early diagnosis of these can improve the control of type 1 diabetes mellitus.

2. Patient and methods

This study was carried out at the Department of Pediatrics, General Hospital of Ciudad Real. This work is a descriptive epidemiological study on 129 children and adolescents under age 16 with type 1 diabetes mellitus, studied in this hospital since 1990. With regard to epidemiological studies by our group in the province of Ciudad Real, with an estimated total of 423 patients with DM1, of which 204 are under 16 years, the size of the sample makes it representative of the distribution of type 1 diabetes mellitus population.

The analysis began in January 2003 starting with a retrospective study of patients and performing a 3-year prospective follow-up on these patients and patients who were going to the Department of Pediatrics at the start of his diabetes. The analysis and recruitment was completed in December 2007. This study was approved by the Research and Ethics Committee of the General Hospital of Ciudad Real. Reported and informed consent was obtained from parents or guardians.

In our study we asked whether there is a relationship between the occurrence of autoimmune diseases in pediatric patients with type 1 diabetes mellitus, with the HLA-DQ genetic group. Main objective genetic group analyzed HLA-DQ by molecular biology of our patients. According to these HLA-DQ haplotypes have organized groups I, II and III, considered by the usual bibliography and diabetogenic risk.

- **Group I:** HLA-DQA1*0501/DQB1*0201
- **Group II:** HLA-DQA1*0301/DQB1*0302
- **Group III:** HLA-DQA1*0501,*0301/HLA-DQB1*0201,*0302
- **Group IV:** No genetic group associated with DM1

As secondary objectives we analyzed the disease onset general parameters such as sex and age. We collected data on whether patients had autoimmune disease associated with type 1 diabetes mellitus, if the onset of the disease has been before or after the debut of type 1 diabetes mellitus and the median time to onset of the disease. These parameters are studied during a follow-up period of 3 years with updates every 6 months. All of these secondary objectives relate them to the diabetogenic risk group assigned to each of our patients.

The degree of innovation under our study was that the determination of HLA-DQ alleles was performed by molecular biology techniques, to avoid large differences, about 50% errors (58% according to the results of our group), which are generated if only the serological determinations. HLA-DQ alleles were determined by reaction polymerase chain, with allele specific amplification (PCR-SSP). We used specific primers for DQA1 and DQB1 genes (Protrans, Ger.) Amplified products were separated by agarose gel electrophoresis in 2% and were assigned allele specific amplification.

Determinations of antithyroid antibodies, and antithyroglobulin antimicrosomal performed by chemiluminescence, IMMULITE 2000 (Dipesa ®). Thyroid hormones: T4 and TSH by chemiluminescent immunoassay technology microparticles, ARCHITECT (Abbott ®).

As serologic marker in detecting celiac disease transglutaminase antibodies were analyzed by enzyme immunoassay with recombinant human tissue transglutaminase (Eurospital ®) with a sensitivity around 95% and a specificity above 95% for populations pediatric. Patients with positive markers underwent a biopsy of the duodenum and subsequent intestinal pathology.

For the analysis of the data is first created a database with Microsoft Access and have subsequently be exported for statistical analysis by SPSS for Windows, version 12.0. We conducted a 6x4 design. Each patient was studied in 6 different moments of its evolution, with 4 viable possibilities, different genetic risk groups.

Study possible changes in the variables under study during the monitoring period, if the changes are influenced by risk group HLA-DQ, and if it influenced other control variables such as sex, age, etc. All statistical tests were performed with a significance level of 95% and an alpha of 0.05%.

2.1 Results

According to the HLA-DQ haplotypes obtained, the distribution of diabetogenic risk groups was as follows: group I (HLA-DQA1*0501/DQB1*0201): 45 patients, accounting for 34.9%, group II (HLA-DQA1*0301/DQB1*0302): 38 patients, representing 29.5%, group III (HLA-DQA1*0501,*0301/HLA-DQB1*0201,*0302): 38 patients, representing 29.5%, and group IV (no gene associated with DM1 group): 8 patients, representing 6, 2% (Figure 1).

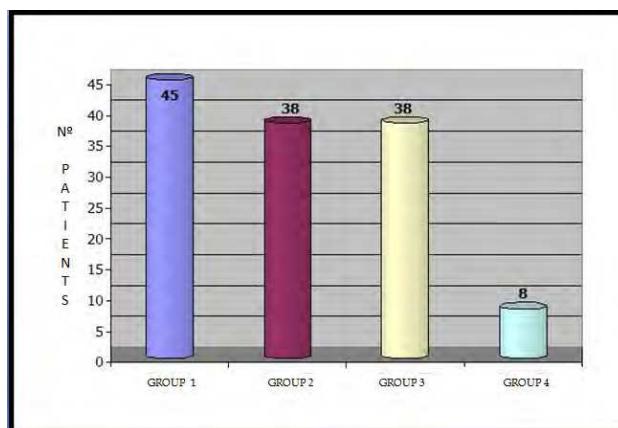


Fig. 1. HLA-DQ Diabetogenic risk groups

The gender distribution of our study population of 129 patients was as follows: males 67 patients representing 51.9% and women 62 patients representing 48.1%, with a ratio child of 1.08.

The distribution of patients by age at onset was as follows: 0 to 4 years 32 patients representing 24.8%, between 5 and 9 years 67 patients, representing 51.9%, between 10 and 14 years 29 patients who account for 22.4% and between 15 and 16 years 1 patient represents 0.8%. The mean age of patients, whose mean values ($\text{mean} \pm \text{SD}$), expressed in years, diabetogenic risk groups were as follows: Group I (8.6 ± 3.4), Group II (7 ± 3), Group III (6.1 ± 2.7) and Group IV (6.8 ± 2.6). In our study found significant differences in age at debut by diabetogenic risk groups, age at onset being significantly lower in group III with group I (Figure 2).

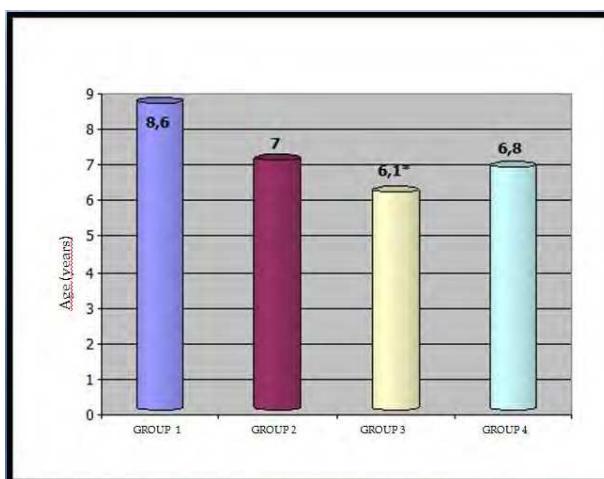


Fig. 2. Distribution of patients by age at onset

The incidence of patients with autoimmune thyroiditis in our series is 15.5%, representing a total of 20 patients. At the time of diagnosis of thyroiditis, 85% were euthyroid autoimmune thyroiditis and 15% had undergone an underactive thyroid. In the euthyroid, 17.6% ($n = 3$) associated with thyroid hypofunction later.

The sex distribution is as follows: 55% ($n = 11$) were women and 45% ($n = 9$) were male. No significant differences were observed in the distribution of autoimmune thyroiditis by sex.

Distribution diabetogenic risk groups was as follows: Group I: 6 patients, Group II: 5 patients, Group III: 8 patients, and Group IV: 1 patient. No significant differences were found in the diagnosis of autoimmune thyroiditis diabetogenic risk groups (Figure 3).

When analyzing patients with autoimmune thyroiditis, it was observed that 76.4% started after the debut of type 1 diabetes mellitus, whereas 23.6% were diagnosed simultaneously with the debut of it. By contrast patients with underactive thyroiditis, 28.6% presented prior to the commencement of type 1 diabetes mellitus, 42.8% thereafter, and 28.6% to debut simultaneously do the same.

In our series we found a case of hyperthyroidism in a 11-year-old was diagnosed with type 1 diabetes three years ago. The frequency of patients with celiac disease associated with type 1 diabetes mellitus in our series is 6.2%, which corresponds to 8 patients. The sex

distribution is as follows: 75% ($n = 6$) are women and 25% ($n = 2$) are male. We found significant differences in favor of women ($p < 0.001$).

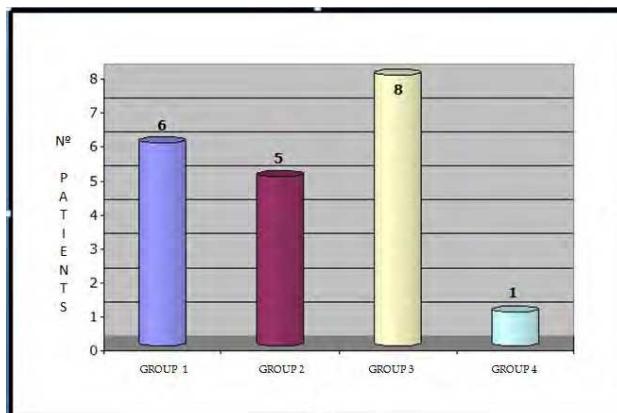


Fig. 3. Autoimmune thyroiditis by diabetogenic risk groups

Distribution diabetogenic risk groups was as follows: Group I: 2 patients, Group II: 2 patients, Group III: 3 patients, and Group IV: 1 patient. No significant differences were found in the diagnosis of celiac disease by diabetogenic risk groups (Figure 4).

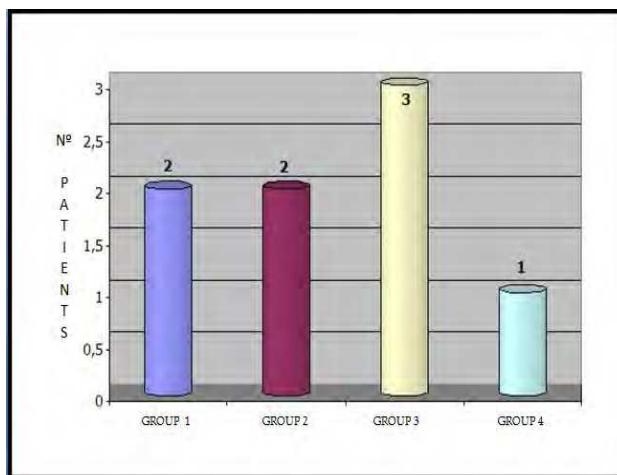


Fig. 4. Celiac disease by diabetogenic risk groups

As for the timing of the debut has been observed that in 75% ($n = 6$), the debut of celiac disease after debut of type 1 diabetes mellitus, and 25% ($n = 2$) the onset is earlier. In most cases of celiac disease were asymptomatic at diagnosis and only observed the existence of signs of malabsorption in 1 patient, abdominal distention and diarrhea. The average time between debut and diagnosis was 22 months with a minimum of 6 months and a maximum of 34 months.

In our series, 2 patients are associated with type 1 diabetes mellitus, celiac disease and autoimmune thyroiditis (1 patient 1 patient euthyroid and hypothyroid).

In 13 patients (10.1%) were type allergic processes associated allergic rhinitis and conjunctivitis, 8 patients (6.2%) had asthma, 8 patients (6.2%) were diagnosed with atopic dermatitis and 1 patient (0.7%) of vitiligo.

2.1.1 Discussion

In type 1 diabetes mellitus there is a polygenic susceptibility. The most important genes that influence human susceptibility to type 1 diabetes mellitus are located in the complex HLA class II. In our series, these data are corroborated, and that these associations are most common. 93.8% of our patients with type 1 diabetes mellitus corresponds to the genetic risk groups as has been described elsewhere, so a 6.2% suffer from type 1 diabetes mellitus without belonging to a group of HLA-DQ risk.

Our results agree with others, as published by the EURODIAB indicating that in most mediterranean countries the male/female ratio is around 1, with a slight male predominance, but with no significant differences between them.

The period of highest incidence in the study is between 5 and 9 years. These findings are consistent with studies in other countries, which show a tendency for the disease much earlier debut. In our study found significant differences in age at debut by diabetogenic risk groups, age at onset being significantly lower in group III with group I. These results indicate that the combination of different molecules in susceptibility, heterozygous in group III, accelerating the destruction of beta cells by promoting an early onset of type 1 diabetes mellitus.

Autoimmune disease most often associated to type 1 diabetes mellitus is an autoimmune thyroid disease. Our results, 15.5% compared to the percentage of subjects who agree thyroiditis associated with many studies, such as in Spain by Roland and cols (1999) or made in Italy by Lorini and cols (1996). However, some international studies show higher prevalence, such as that conducted by Lindberg et al (1997), with a prevalence of 38%.

As in other studies in our series of cases in which thyroiditis manifested clinically, it is in the form of an underactive thyroid. Although thyroid status of the majority of subjects with positive markers is euthyroid.

In our series we found a case of hyperthyroidism in a 11-year-old was diagnosed with type 1 diabetes three years ago. Hyperthyroidism is associated with type 1 diabetes mellitus present in 1% of cases, most often in adults. Other studies indicate that hyperthyroidism is usually diagnosed before or while type 1 diabetes mellitus.

Studies show that thyroiditis is more prevalent in diabetic girls than in boys. However, our results do not indicate such a difference, matching other studies.

The prevalence of celiac disease associated with children with type 1 diabetes mellitus varies between 1-16%. In our series, we found a total of 8 patients under 6.2% of all patients. These results are consistent with those of Vitoria et al. However, some studies show minor incidents, such as by Barera and colleagues (2002) with a prevalence of 3.9%. In some other series have reported higher frequencies, between 8 and 12.3%.

As for the timing of the debut our results coincide with those published by Barera et al, and Holmes et al (2002), in which the majority of patients the diagnosis of celiac disease is posterior to that of type 1 diabetes mellitus. The time elapsed since the debut of the type 1 diabetes mellitus and identification of antibodies in our series are consistent with the results

of Saukkonen et al (1996), which are located around the 2 years following the onset of type 1 diabetes mellitus. Other studies such as Maki and colleagues (1995), who observed a lower average interval around 13 months. Our results on the significant association in women are endorsed by other studies in this regard, as published in Spain by Roldan et al (1998).

Most patients were asymptomatic at the time of his presentation and noted that there were no signs of frank malnutrition. Were diagnosed by serological screening and subsequent confirmation with intestinal biopsy. Our results are consistent with those of Barrera et al.

Not found in our series more partnerships with other autoimmune diseases such as pernicious anemia, Addison's disease, Sjögren syndrome, alopecia areata, and rheumatoid arthritis.

Among the background approximately 10% of the patients had atopy and bronchial asthma. These data are consistent with those reported by Lopez Medina et al in their series. The presence of vitiligo in our series (0.7%) is lower than that observed in other studies like the one made in Italy by Romano et al (1998), showing a prevalence of 9%.

3. Conclusion

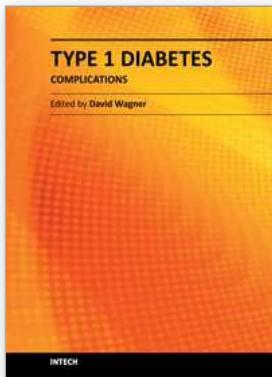
The major autoimmune diseases, autoimmune thyroiditis and celiac disease are more prevalent in our diabetic patients than in the nondiabetic population. Although we found more patients in risk group III, no significant differences with other groups.

In conclusion, these data support the recommendation that from the moment of diagnosis of type 1 diabetes mellitus regular determination of thyroid antibodies and celiac disease related. Current recommendations are vague as to what should be the most appropriate timing for this in pediatric patients. We must try to detect such diseases early, but that does not justify excessive and unnecessary repetition of diagnostic tests. The use of standardized monitoring protocols is becoming increasingly necessary to ensure better health care for children and adolescents with type 1 diabetes mellitus.

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This book is a compilation of reviews about the complication of Type 1 Diabetes. T1D is a classic autoimmune disease. Genetic factors are clearly determinant but cannot explain the rapid, even overwhelming expanse of this disease. Understanding etiology and pathogenesis of this disease is essential. The complications associated with T1D cover a range of clinical obstacles. A number of experts in the field have covered a range of topics for consideration that are applicable to researcher and clinician alike. This book provides apt descriptions of cutting edge technologies and applications in the ever going search for treatments and cure for diabetes.

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