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Prevalence of celiac autoimmunity in children and adolescents with type 1 diabetes mellitus in a high complexity hospital in Colombia

Abstract

Background: The prevalence of celiac disease in patients with type 1 diabetes mellitus is 5 to 10 times higher than in the general population. However, diagnosis is difficult given that patients are asymptomatic or with nonspecific symptoms and are confused with poor glycemic control or thyroid comorbidity.

Objective: To assess the prevalence of celiac autoimmunity in children and adolescents diagnosed with type 1 diabetes mellitus and to identify the clinical profile of patients with celiac autoimmunity.

Methods: One hundred patients with type 1 diabetes mellitus under 18 years, who consulted the department of pediatric endocrinology at Hospital Pablo Tobón Uribe – Medellin, between May and December 2015, were included. The concentration of antibodies, anti-tissue transglutaminase IgA, and total immunoglobulin A were measured in all patients; also a survey of signs and symptoms of celiac disease was applied.

Results: Patients were aged between 3 and 17 years. Four had celiac autoimmunity evidenced by positive anti-tissue transglutaminase IgA. The clinical profile of patients with celiac autoimmunity was patient <12 years with frequent hypoglycemia and abdominal pain; 20 out of 100 patients presented this profile, of which 1 in 5 patients had positive anti-tissue transglutaminase IgA.

Conclusion: Celiac autoimmunity is a diagnosis that is not considered frequently in the Colombian population, and we find a prevalence of 4% in children with type 1 diabetes mellitus and increases to 20% if they are under 12 years old with hypoglycemia and frequent abdominal pain. This group has a RR 6 (95% CI 3.83-9.38) of having celiac autoimmunity constituting the group with the strongest indication for serologic screening.

Keywords: celiac disease, type 1 diabetes, tissue transglutaminase autoantibody, autoimmunity, and prevalence

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Carolina Jaramillo-Arango,[1] Yúrika López-Alarcón,[2] Alejandro Marín-Agudelo,[2] Carlos Yepes-Delgado,[3] Verónica Abad-Londoño[1]

[1]Pediatrician Specialist in Pediatric Endocrinology, Diabetes Group Hospital Pablo Tobón Uribe, Colombia
[2]Pediatrician Specialist in Pediatric Intensive Care, Hospital General de Medellín, Colombia
[3]Epidemiologist Medical Research Unit Hospital Pablo Tobón Uribe, Professor Faculty of Medicine Universidad de Antioquia, Colombia

Correspondence: Carolina Jaramillo-Arango, Diabetes Group Hospital Pablo Tobón Uribe, Medellín, Calle 78B # 69–240, Colombia, Tel 57 (4) 4459000 ,
Email cjaramilloarango@gmail.com

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Abbreviations: Anti-TPO, anti peroxidase; BMI, body mass index; ELISA, enzime linked immunosorbent assay; HbA1c, glycated hemoglobin; HLA, human leukocyte antigen; IC, confidence interval; IgA, Immunoglobulin A; IgG, immunoglobulin G; ISPAD, International Society for Pediatric and Adolescent Diabetes; RR, relative risk; T1DM, type 1 diabetes mellitus; tTG, anti-tissue transglutaminase antibodies; UI, international units

Introduction

The association between T1DM and celiac disease has been described for 40 years.[1,2] Different studies show that while the global prevalence of celiac disease is about 1% of the population; in patients with type 1 diabetes the reported prevalence is 5 to 10 times higher.[3–6]. In South America most of the studies on celiac disease have been made in Brazil and Argentina, countries with a high prevalence of this disease, 1.26 to 1.5% in the general population.[7–9] In Colombia the prevalence of celiac disease is unknown not only in the general population, but also in patients with type 1 diabetes, only one study made in Cali[10] of children with compatible symptomatology or risk conditions that included T1DM, reports a prevalence of 4.51% in the entire study population, 27% of these patients were diabetic type 1 and prevalence in this population is unknown. In Medellin there are no studies on the prevalence of celiac disease and only one case report was found of two pediatric patients with celiac disease, none of them with T1DM.[11]

Despite the advent of highly sensitive and specific serological tests to guide the diagnosis[4] and that screening for celiac disease in high-risk patients such as diabetics, is recommended by medical literature[12] and by various scientific societies such as the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition,[13] the European Society for Pediatric Gastroenterology, Hepatology and Nutrition[14] and the International Diabetes Federation/International Society for Pediatric and Adolescent Diabetes[16] routine screening of patients with T1DM is not a universal practice.[16,17] However, this screening is very important to start early treatment, reducing the risk of complications associated with celiac disease mainly that long term as osteoporosis or cancer.[18–21]

In most patients, celiac disease occurs in a silent or subclinical way. Symptoms such as abdominal pain and bloating, hypoglycemia, failure to thrive or even seizures fail to discriminate patients with celiac autoimmunity from a healthy population.[22–24] In diabetic patients these symptoms are often attributed to poorly controlled diabetes or thyroid comorbidity and that is why its diagnosis requires a high degree of clinical suspicion.[4]

The primary objective of this study was to describe the prevalence

of celiac autoimmunity (antibodies associated with celiac disease) in children and adolescents diagnosed with type 1 diabetes in Medellin, Colombia. The secondary objective was to make an approximation of the association between the presence of celiac autoimmunity and the clinical manifestations of celiac disease to assess the utility of symptoms in the diagnostic suspicion of the disease.

Methods

Type of study

Descriptive, cross-sectional

Study population

Consecutively, all children and adolescents diagnosed with type 1 diabetes mellitus according to the criteria of ISPAD[25] that consulted the pediatric endocrinology service at the Hospital Pablo Tobón Uribe or were hospitalized at the same institution during the period from May to December 2015 were included.

Sampling: a sample was calculated for a ratio taking into account an expected prevalence of celiac disease in patients with type 1 diabetes of 7%, a confidence of 95%, and an error of 5%. The resulting sample size was 100 cases. All patients agreed to participate in the study and signed an informed consent, previously approved by the ethics committee of the IRB/IEC institution in accordance with the declaration of Helsinki 2008.

Sampling and data collection

Blood sampling was performed intravenously in the antecubital region of the arm, collecting the blood in a 10 ml sterile tube without anticoagulant. After the collection the sample was centrifuged at 4000 rpm for 10 minutes, subsequently the serum was separated in aliquots which were stored at -10°C for later analysis. At the time of sampling the patient's medical history was reviewed and a survey to collect the variables included in the study was conducted.

Measurement of anti-tissue transglutaminase antibodies by anti-linked immunosorbent assay (ELISA)

The concentration of anti-tissue transglutaminase antibodies type immunoglobulin A (tTGIgA) and IgG (tTGIgG) in the patient's serum was established by a commercial ELISA (QUANTA Lite h-tTG IgA or h-tTG IgG, INOVA Diagnostics, Inc. San Diego, CA) following manufacturer's instructions, processing the samples in duplicate. Readings were performed in an ELISA reader (Stat Fax 303, Awareness Technology, Inc. Palm City, FL) at 450 nm. Samples were considered positive above 20 U/ml according to manufacturer's instructions.

Measurement of Immunoglobulin A by immunoturbidimetry

Immunoglobulin A concentration in the serum of patients was established by using a commercial kit of immunoturbidimetry (BioSystems SA. Costabrava, Barcelona) following manufacturer's instructions, processing the samples in duplicate. Readings were performed in an automatic analyzer (A15 Random Access Analyzer, BioSystems SA. Costabrava, Barcelona) at 340nm.

Statistical analysis

The variables studied were: age, gender, weight, height, insulin scheme, insulin dose, glycosylated hemoglobin (HbA1c), presence of anti-thyroid antibodies anti-TPO type and/or anti-thyroglobulin, levels of tTGIgA antibodies, levels of immunoglobulin A (IgA), symptoms of celiac disease (low height, abdominal pain, diarrhea, frequent hypoglycemia, seizures), and other associated autoimmune diseases.

Absolute and relative frequencies were used to describe the qualitative variables, and the medians and interquartile ranges for quantitative variables. Normality of the distribution was assessed using the Shapiro-Wilks test. The concentration of IgA, tTGIgA, and tTGIgG was calculated by interpolation to standard non-linear regression curves.

The association between symptoms of celiac autoimmunity and the presence of anti-transglutaminase antibodies as markers of celiac autoimmunity was assessed using the Person coefficient of correlation, which allowed us to make an approximation to the question if the screening only of symptomatic patients is useful to detect patients with celiac autoimmunity. Likewise, we sought to establish a clinical profile of patients with celiac autoimmunity, through the analysis of associations of symptoms and the grouping of patients according to their pubertal status, according to the prevalence of celiac disease in children described in the literature.[4]

Results

A total of 100 patients with T1DM were collected between May and December 2015 with a male female ratio of 1:1. Patients were between 3 and 17 years old with a median of 12 years, most had acceptable control of diabetes demonstrated by a HbA1c between 4.7% (28 mmol/mol)–14 % (130 mmol/mol) with a median of 8.5 % (69 mmol/mol). Patients used an intermediate insulin dose of 0.21-2.4 Units/Kg with a median of 0.82 Units/kg. The clinical characteristics of the patients are described in table 1 and 2.

Table 1 Clinical characteristics of celiac disease of the patients include in the study

Characteristics of patients	
Age	3 – 17 years old (median 12)
Gender M:F	50:50
Celiac autoimmunity	4
Hypothyroidism	16
HbA1c (%)	4,7% (28 mmol/mol) – 14% (130 mmol/mol) (median 8,5% or 69 mmol/mol))
Insulin dose UI/Kg	0,21 – 2,4 (median 0.82)
Body mass index	13 – 28 (median 18)

Of the 100 patients with T1DM, we find 4 patients positive for tTGIgA, in 12 patients, selective deficiency of immunoglobulin A was identified, having total IgA concentrations below 2 standard deviations of the population mean according to age match.[26] Although none of the patients had an absolute immunoglobulin A deficiency, the concentration of tTGIgG was measure to all patients with selective

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deficiency, however no false negatives were detected of the screening test with IgA. We describe a prevalence of celiac autoimmunity for our population was 4%. The clinical characteristics of the patients are listed in table 3 according to the presence of celiac autoimmunity.

Table 2 Signs and symptoms of celiac disease of the patients include in the study

Signs and symptoms of celiac disease	
Frequent hypoglycemia	55%
Abdominal pain	46%
Diarrhea	13%
Low height	5%
Seizures	5%
Weight loss	4%

Table 3 Signs and symptoms of celiac disease of patients with and without antibodies markers of celiac autoimmunity

	Celiac autoimmunity +	Celiac autoimmunity -
Frequent hypoglycemia	4 (100%)	51 (53.1%)
Abdominal pain	4 (100%)	42 (43.7%)
Diarrhea	1 (25%)	12 (12.5%)
Low height	0 (0%)	5 (5.2%)
Seizures	0 (0%)	4 (4.1%)
Weight loss	0 (0%)	4 (4.1%)

All patients with celiac autoimmunity were under 12 years old with chronic abdominal pain and frequent hypoglycemia despite adequate doses of insulin, having an RR of 6 (95% CI 3.83-9.38) p=0.001. Conversely in none of the 80 patients who did not meet the profile, celiac autoimmunity was documented. The prevalence of celiac autoimmunity in patients who met the described profile was 20%. Taking only the 20 patients who met this profile, we found that 5 patients need to be screened in order to find a positive case.

Discussion

Celiac disease occurs in patients with T1DM more frequently than in the general population.[3–6] The possible explanation for this association is that these diseases have a common genetic background, the genotypes of the major histocompatibility complex (HLA) DR3-DQ2 are present both in a proportion of patients with type 1 diabetes and in patients with celiac disease.[27–29] This study reports the prevalence of anti-tissue transglutaminase antibodies in celiac autoimmunity markers in a population of Colombian children and adolescents with T1DM, emphasizing a possible clinical profile of patients that would help select patients whose screening is more important. This is the first study conducted in Colombia where the presence of celiac autoimmunity in patients with type 1 diabetes was characterized, this population was chosen because it is one of the most prevalent coexistence of the disease; and in whom the presence of celiac disease makes glycemic control more difficult, potentiating the complications of both diseases.

The measurement of serum levels of anti-tissue transglutaminase antibodies IgA (tTGIgA) is the most widely used diagnostic tool for screening of celiac autoimmunity, this being a minimally invasive tool that has very good sensitivity 98% (74–100) and specificity 97% (78–100).[4,30] In our study population, the prevalence of celiac autoimmunity evidenced by antibodies was 4%, which is consistent with previously published studies in different populations of patients with T1DM.[5,31,32]

The benefit of screening diabetic patients for celiac autoimmunity has been controversial for many years.[33] There is no consensus among the various scientific societies on the utility of screening patients with T1DM, and although some societies recommend screening all patients whether symptomatic or not[13–15], there are also consensuses such as the National Institute of Health (NIH), that do not justify screening in high-risk patients such as diabetics, who are asymptomatic.[34] Likewise a large proportion of patients with celiac autoimmunity have mild symptoms that are mistaken for poor control of the disease, thus it is difficult to discern which patients are truly asymptomatic and which are not.

Although we do not know the prevalence of celiac disease in the Colombian population, 4% of the patients with T1DM evaluated had positive anti-transglutaminase antibodies, which leads us to sift 25 children to find a positive case. However, we deem that screening of patients is very important because the appropriate dietary control could reduce the hypoglycemic events and improve the nutritional status maximizing the growth. Moreover, it has been documented that patients with concomitant T1DM and celiac disease have higher bone turnover[35] and future risk of developing osteopenia/osteoporosis, risk that increases if a gluten free diet is not started.[16,–18] The risk of eath is also higher in patients with hidden celiac autoimmunity as documented in a retrospective study in adults.[18]

Of the 100 patients that were evaluated, at least 70 had one symptom compatible with celiac disease; the main symptoms reported by patients were hypoglycemia and gastrointestinal symptoms (diarrhea, abdominal pain). Less than 5% of the patients reported other symptoms such as seizures, or weight loss or low height could be objectify and, by making the distinction between tTGIgA positive and non-positive patients, none of the patients with celiac autoimmunity had these symptoms, unlike other cohorts where low height and weight loss are one of the main manifestations of celiac disease in patients with T1DM.[36]

The clinical profile of celiac autoimmunity found in our diabetic patients is similar to others found in the literature, a study in Greece also found increased risk of celiac autoimmunity in prepubertal patients with T1DM and noticeably the main symptoms of these patients were gastrointestinal and had a poor glycemic control evidenced by frequent hypoglycemia, like our patients.[5] This clinical profile groups the patients who are the most likely to be a positive case, so we believe this is a plausible approach to detect patients with celiac autoimmunity in a developing country like ours.

In our group of patients, 3 of the 4 seropositive patients for celiac autoimmunity were diagnosed with T1DM over 2 years ago, unlike previous reports in literature which showed that most patients with T1DM at onset of the disease already had celiac autoimmunity[37] and that the subsequent higher risk of developing celiac disease in these children is in the first 2 years of the diabetes diagnosis.[38] However, since this study was designed as a cross-sectional study, we do not have different measurement times that enable us to evaluate how tTGIgA concentration changes in patients and at what moment after diagnosis the risk of developing celiac autoimmunity are higher.

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One of the difficulties with the screening of patients for celiac autoimmunity is that tests with higher sensitivity, specificity, and availability in the field are those based on type IgA antibodies. The selective deficit of IgA is the most common primary immunodeficiency in the Western Hemisphere with an approximate frequency of 1:600 in the general population, but that is increased to 1:100 in patients with celiac disease, and to 1:200 in patients with type 1 diabetes, apparently because of sharing with these other two diseases the genotype HLA DR3-DQ2.[39]

That is the reason why in patients with high clinical suspicion of celiac disease, it is recommended that the total IgA is quantified, in those where the tTGIgA are negative, to assess the possibility of having an associated selective deficit of IgA.[40] In those where IgA deficiency is documented, it is recommended to screen for celiac autoimmunity with IgG[41] antibodies, which have a sensitivity of 75-95% and a specificity of 94-100%.[42] In patients with T1DM, which constitute a high- risk population frequently asymptomatic and that in case of selective deficit of IgA may have frequent respiratory and gastrointestinal infections, symptoms that are common to all 3 diseases[39], it is suggested to measure the total IgA concomitant with screening for celiac autoimmunity with tTGIgA to eliminate the possibility of false negatives, although some authors question this behavior.[43] In 12 patients of our cohort partial selective deficiency of IgA was documented, in all of them type IgG anti-tissue transglutaminase antibodies were measured; however, in none of them celiac autoimmunity was documented, dismissing this way false negative results in the test based on type IgA antibodies. It should be noted that none of our patients had absolute IgA deficiency (<7 mg/dl), therefore we consider that only if absolute deficiency is documented, type IgG testing should be performed to rule out celiac autoimmunity.

One of the limitations of our study is that only the population with diabetes was evaluated, so we still do not know what is the prevalence of celiac disease in the Colombian general population, being considered the celiac disease a rare disease in our population having found a presence of celiac autoimmunity in diabetic children opens the possibility to expand the studies of this disease in the Colombian population. The other limitation is that we do not have histopathological confirmation of celiac disease to assess the correlation of serological findings. Only one of our patients with positive antibodies had compatible clinical symptoms for celiac disease consisting of chronic diarrhea for 1 year but diagnosis for celiac disease was not considered because this is an unknown disease in our environment, she was diagnosed with exocrine pancreatic insufficiency. Literature reports have shown the exocrine pancreatic insufficiency as a manifestation of celiac disease.[44,45]. All other patients had mild symptoms that had been considered secondary to a poor disease control; all patients with positive tTGIgA were referred to pediatric gastroenterology for conducting endoscopy/biopsy and to assess the need to start a gluten free diet.

Conclusion

Until a few years ago it was considered that in Colombia there was no celiac disease. This study carried out in a population with type 1 diabetes shows that 4% of this population has presence of celiac markers, and was more commonly found in prepubertal patients with hypoglycemia and frequent abdominal pain. Considering the findings of this study, we recommend an initial screening to all patients at diagnosis of diabetes. Subsequently in the case of hypoglycemia and frequent abdominal pain, a new screening is recommended to enable an early diagnosis and to prevent long-term complications. The necessary screening interval is unknown to diagnose celiac disease.

Declaration of funding interests

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Disclosure statement

The authors have nothing to disclose.

Declaration of personal interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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