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Artigo Original

Immunoglobulin Deficiency and Respective Clinical Manifestations in Pediatric Patients with Type 1 Diabetes Mellitus

Teresa Ferreira [a,*], Cíntia Correia [b]

[a] Faculty of Medicine, University of Porto, Porto, Portugal
[b] Department of Pediatrics, São João Hospital and University Center, Porto, Portugal; Faculty of Medicine, University of Porto, Porto, Portugal. Faculty of Nutrition, University of Porto, Porto, Portugal

INFORMAÇÃO SOBRE O ARTIGO

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A B S T R A C T

Introduction: Our objective was to evaluate the prevalence of immunoglobulin deficiency among pediatric patients with type 1 diabetes followed in São João Hospital and University Center, and analyze the clinical characteristics of these patients, namely the occurrence of infections and the presence of comorbidities.
Methods: A retrospective cohort study was performed including patients aged 4 to 18, with an established diagnosis of type 1 diabetes. The measurement of immunoglobulin levels, glycated hemoglobin, IgA anti-tissue transglutaminase and antithyroid antibodies were obtained in routine appointments. The caregivers were asked to answer a questionnaire about the children's medical history, which was complemented with medical records. IgA, IgM and IgG deficiency were considered when the value of the respective immunoglobulin was below the normal age-adjusted reference range, and IgE deficiency when IgE <2 kU/L, regardless of the value of other classes of immunoglobulins. Selective IgA, IgE, IgM or IgG deficiency was defined when a single class of immunoglobulin deficiency was present.
Results: Of the 40 patients enrolled, 22 (55.0%) were males, the median age was 13.0 years old, with a median type 1 diabetes duration of 6.0 years. A total of six (15%) patients were found to have immunoglobulin deficiency, 7.5% for IgA (n=3), 5.0% for IgE (n=2), and 2.5% for IgM (n=1). No association between selective IgA, selective IgE, or any type of immunoglobulin deficiency was found with age, type 1 diabetes duration or age at type 1 diabetes onset, glycated hemoglobin, first-degree relative with immunodeficiency or type 1 diabetes, other comorbidities, number of infections per year, infection-related hospitalization, previous history of infection (either of the skin, central nervous system, respiratory, gastrointestinal or urinary), or abnormally elevated values of IgA anti-tissue transglutaminase or antithyroglobulin antibody. Antithyroid peroxidase antibody >5.6 UI/mL was associated with IgE deficiency (p=0.046).
Conclusion: Immunoglobulin deficiency is frequent among pediatric patients with type 1 diabetes, suggesting a common background. Immunoglobulin deficit did not seem to be related to a higher risk of infection or comorbidities. Selective IgE deficiency may be associated with the presence of antithyroid peroxidase antibodies.

Palavras-chave:
Criança;
Diabetes Mellitus Tipo 1;
Imunoglobulinas;
Síndromes de Imunodeficiência.

Deficiência de Imunoglobulinas e Respetivas Manifestações Clínicas em Pacientes Pediátricos com Diabetes *Mellitus* Tipo 1

R E S U M O

Introdução: O nosso objetivo foi avaliar a prevalência da deficiência de imunoglobulinas em doentes pediátricos com diabetes tipo 1 acompanhados no Centro Hospitalar Universitário de São João, e analisar as características clínicas destes doentes, nomeadamente a ocorrência de infeções e comorbilidades.

* Autor Correspondente / Corresponding Author.
E-Mail: teresaferreira8899@hotmail.com (Teresa Margarida Soares Ferreira)
Alameda Prof. Hernâni Monteiro, 4200-319, Porto, Portugal.

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Métodos: Foi realizado um estudo de coorte retrospetivo, incluindo pacientes entre os 4 e os 18 anos, com diagnóstico estabelecido de diabetes tipo 1. Os valores das imunoglobulinas, hemoglobina glicada, IgA anti-transglutaminase tecidual e anticorpos anti-tiroideus foram obtidos em consultas de rotina. Os representantes legais preencheram um questionário sobre a história médica prévia da criança ou jovem, que foi complementado com a análise dos registos clínicos. Foi considerada deficiência de IgA, IgM e IgG quando o valor da respetiva imunoglobulina estava abaixo do intervalo normal de referência ajustado para idade, e deficiência de IgE quando IgE <2 kU/L, independentemente do valor das outras classes de imunoglobulinas. A deficiência seletiva de IgA, IgE, IgM ou IgG foi definida quando estava presente a deficiência de uma única classe de imunoglobulina.
Resultados: Dos 40 pacientes incluídos, 22 (55,0%) eram do sexo masculino, a mediana de idade era de 13,0 anos, com uma duração mediana de diabetes tipo 1 de 6,0 anos. Um total de seis (15%) pacientes apresentavam deficiência de imunoglobulina, 7,5% para IgA (n=3), 5,0% para IgE (n=2) e 2,5% para IgM (n=1). Nenhuma associação entre deficiência seletiva de IgA, IgE ou qualquer tipo de deficiência de imunoglobulina foi encontrada com idade, duração ou idade de diagnóstico de diabetes, hemoglobina glicada, parente de primeiro grau com imunodeficiência ou diabetes tipo 1, outras comorbidades, número de infeções por ano, hospitalização relacionada com infeção, história prévia de infeção (da pele, sistema nervoso central, respiratória, gastrointestinal ou urinária) ou valores anormalmente elevados de IgA anti-transglutaminase tecidual ou anticorpo anti-tiroglobulina. A presença de anticorpo antiperoxidase >5,6 UI/mL associou-se à presença de deficiência IgE (p=0,046).
Conclusão: A deficiência de imunoglobulinas é frequente em pacientes pediátricos com diabetes tipo 1, sugerindo uma possível etiologia comum. O défice de imunoglobulinas não parece estar relacionado com maior risco de infeção ou comorbidades. A deficiência seletiva de IgE pode estar associada à presença de anticorpos antiperoxidase.

Introduction

Type 1 diabetes (T1D) is one of the most common autoimmune diseases and the most frequent type of diabetes in children. The number of pediatric patients with type 1 diabetes continues to increase worldwide.[1] It is caused by the autoimmune destruction of insulin-producing pancreatic beta cells, leading to low or absent insulin secretory capacity. Pathophysiology is complex and seems to be related to immunological factors, environmental triggers, and genetic susceptibility. Polymorphisms of the HLA region, involved in the immune response, are the most important contributors to genetic susceptibility to type 1 diabetes.[2] Many comorbid conditions may be present in children with type 1 diabetes, mostly autoimmune manifestations such as celiac disease, autoimmune thyroid disease, and Addison's disease.[3] Patients with diabetes have an increased risk of infections, suggesting an impaired immune response compared to healthy subjects.[4,5]

Inborn errors of immunity encompass a large group of disorders that disable normal immune function. The clinical presentation is wide. Some patients may be completely asymptomatic, while others present with severe and frequent infections, increased susceptibility to malignancies, autoimmunity, and autoinflammatory conditions.[6] Some patients may exhibit alarm signs such as growth retardation, the frequent need for intravenous antibiotic treatment, lymphopenia, and the presence of a positive family history of immunodeficiency.[7]

Many genetic variants have been related to inborn errors of immunity, some leading to rare diseases with manifestations of both immunodeficiency and autoimmunity, in which T1D may be an associated feature, such as POLE2 (polymerase subunit 2) deficiency, IPEX (immune dysregulation, polyendocrinopathy, enteropathy X-linked), APECED (autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy), IKAROS and STAT1 gain of function.[6,8]

Predominantly antibody deficiencies are the most frequent type of immunologic defect, with selective IgA deficiency being the most common.[9-11] Some reports suggest that the prevalence of IgA deficiency is increased in patients with type 1 diabetes.[10-12] Certain HLA polymorphisms seem to increase the risk of this association, suggesting a shared genetic background.[13] IgA, IgE, IgG, or IgM deficiency does not always lead to clinical manifestations, as in many patients are asymptomatic. When clinically significant, they are associated with recurrent infections of the respiratory or gastrointestinal tract, recurrent bacterial infections, allergic diseases, malignancies, autoimmune diseases, and chronic inflammatory diseases.[13-15] Although some reports highlight the association between T1D and IgA deficiency,[10-12] the relation between IgE, IgG and IgM levels and T1D has not been so deeply studied.

Therefore, the aim of this study was to evaluate the prevalence of immunoglobulin deficiencies among pediatric patients with type 1 diabetes from São João Hospital and University Center, and analyze some clinical characteristics of these patients compared to those without immunoglobulin deficiency, like the quality of glycemic control, number of infections per year, previous history of infection-related hospitalization or different types of infections that did not require hospitalization, and the presence of other autoimmune or non-autoimmune comorbidities.

Material and Methods

This study included patients aged 4 to 18 years old, with an established diagnosis of type 1 diabetes, regularly followed in the endocrinology pediatric consultation in São João Hospital and University Center, and under treatment with insulin pump therapy. Of the total of 180 pediatric patients regularly followed in this consultation, 43 were randomly assessed for eligibility. The inclusion criteria were an established diagnosis of type 1 diabetes, more than 12 months since diagnosis.

Exclusion criteria were the presence of conditions known to cause secondary antibody deficiency, such as use of drugs known to cause decreased immunoglobulin levels (for example corticosteroids, anticonvulsants, rituximab), the presence of hematologic malignancies, treatment with chemotherapeutic agents, conditions causing protein-losing states (such as protein-losing enteropathy or nephrotic syndrome), being under immunoglobulin substitution or presence of infection at the time of immunoglobulin measurement.[16,17]

The protocol of the study was approved by the Bioethics Committee of São João Hospital and University Center (approval

number 171/22). Procedures were followed according to the regulations established by the Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013. Written informed consent was obtained from all children's legal careers before their inclusion in the study. Confidentiality was ensured for all subjects.

Pediatric patients who went to routine appointments between October 2022 and February 2023 were assessed for inclusion in this study, the same period on which data collection was made. The measurement of immunoglobulin levels, glycated hemoglobin, IgA anti-tissue transglutaminase, and antithyroid antibodies were obtained in routine appointments. Also, the caregivers were asked to answer a questionnaire about the children's comorbidities (autoimmune and non-autoimmune), T1D duration, age at T1D onset, family history of T1D or immunodeficiencies (first-degree relative with T1D or with immunodeficiency), number of infections per year, previous history of infection-related hospitalization and previous history of skin infection, central nervous system infection, respiratory infection, gastroenteritis or urinary tract infection. The clinical information of each participant was complemented with medical records.

IgA anti-tissue transglutaminase and immunoglobulins (IgA, IgE, IgG and IgM) were quantified by nephelometry using BN™ II System by Siemens (Siemens Healthcare®, Porto, Portugal). Glycated hemoglobin was measured in the Abbott Afinion 2 Analyser (Abbott laboratories®, Amadora, Portugal), by boronate affinity assay. Antithyroid peroxidase and antithyroglobulin antibodies were determined by immunoassay testing, using the Architect i2000SR by Abbott (Abbott laboratories®, Amadora, Portugal).

Definitions

Immunoglobulin levels in pediatric patients vary with age, therefore we used age-adjusted reference ranges for IgA, IgE, IgM and IgG, defined in healthy children in previous studies.[18]

We identify IgA, IgM and IgG deficiency when the value of the respective immunoglobulin was below normal age-adjusted reference values, and IgE deficiency when it was <2 kU/L, regardless of the value of other classes of immunoglobulins. Then, we defined selective immunoglobulin deficiency (selective IgA, IgE, IgM or IgG deficiency), when a single class of immunoglobulin deficiency was present, with other immunoglobulins within normal range. Two degrees of severity of selective IgA deficiency were taken into account: severe, when serum IgA concentration was below 7 mg/dL, and partial, when serum IgA was higher than 7 mg/dL but below the normal range.[19] Unspecified hypogammaglobulinemia was defined for patients with two or more classes of immunoglobulin deficiency present.[20,21]

Elevated IgA anti-tissue transglutaminase was considered when superior to 7 U/mL, elevated antithyroid peroxidase antibody when superior to 5.6 UI/mL and elevated antithyroglobulin antibody when superior to 4.1 UI/mL, accordingly to reference values given by the laboratory of reference.

Statistical analysis

Statistical analyses were performed with software SPSS, version 27.0.22 For descriptive statistics of categorical variables, we used frequencies (n) and proportions (%). For descriptive statistics of continuous variables, we used medians (Mdn) and quartiles (Q1 – Q3) after checking for symmetry with symmetry coefficient and histograms. Associations between outcomes and IgA deficiency, IgE deficiency and any immunoglobulin deficiency were performed with Mann-whitney tests for continuous outcomes and Fisher exact tests for categorical outcomes. Fisher exact tests were used because Cochran rules for chi-square tests were not met. Statistical tests were implemented for immunoglobulin deficient groups with a minimum of two patients. Tests significance was considered for $p<0.05$.

Results

Of 43 pediatric patients with T1D followed in the endocrinology pediatric consultation in São João Hospital and University Center who were assessed for eligibility, 3 were excluded due to meeting exclusion criteria, as described in the flow diagram (Fig. 1). Therefore, forty individuals were included in the study. A questionnaire about the children clinical history and measurement of immunoglobulins levels, glycated hemoglobin, IgA anti-tissue transglutaminase, and antithyroid antibodies were obtained from all patients.

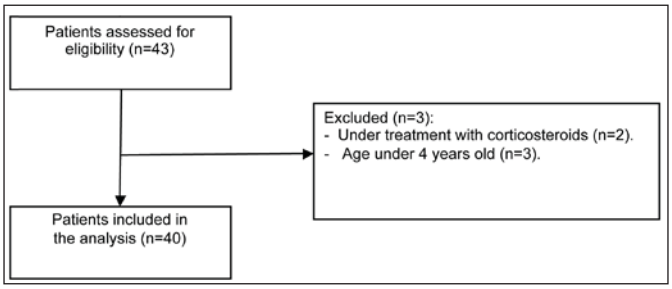

Figure 1. Flow diagram of included pediatric patients (n).

Of the 40 patients enrolled, 22 (55.0%) were males and 18 (45.0%) were females, aged from 6 to 17 years old, median of 13.0 years old (Q1=9.5, Q3=15.5), with T1D duration ranging from 1 to 16 years, median of 6.0 years (Q1=3.0, Q3=9.5). Median age at T1D onset was 5.0 years (Q1=3.0, Q3=7.0) with minimum of 1 and maximum of 14 years. Median glycatedhemoglobin (%) was 7.3 (Q1=6.8, Q3=8.1), ranging from 5.7 to 10.1. No associations were found with gender (Table 1).

Table 1. Comparisons of age, type 1 diabetes duration, age at type 1 diabetes onset and glycated hemoglobin by gender.

	Total	Female (n=18)	Male (n=22)	*p*-value (a)
Female	18 (45.0%)			
Male	22 (55.0%)			
Age (years)	13.0 (9.5 - 15.5) [6 - 17]	14.5 (12.0 - 16.0)	11.5 (9.0 - 15.0)	p=0.125
T1D duration (years)	6.0 (3.0 - 9.5) [1 - 16]	8.0 (4.0 - 9.0)	6.0 (3.0 - 10.0)	p=0.798
Age at T1D onset (years)	5.0 (3.0 - 7.0) [1 - 14]	6.0 (4.0 - 10.0)	4.5 (3.0 - 7.0)	p=0.286
Glycated hemoglobin (%)	7.3 (6.8 - 8.1) [5.7 – 10.1]	7.3 (6.9 - 8.3)	7.4 (6.6 - 8.1)	p=0.697

(a) Calculated with Mann-Whitney test; T1D: type 1 diabetes.

The prevalence of immunoglobulin deficiency was 7.5% for IgA (n=3), 2.5% for IgM (n=1), 5.0% for IgE (n=2) and a total of 15% for any of the previous (n=6) (Table 2). Therefore, we identified three patients with partial selective IgA deficiency, two patients with selective IgE deficiency, and one patient with selective IgM deficiency. None of the patients included had IgG deficiency or unspecified hypogammaglobulinemia.

Table 2. Prevalence of Immunoglobulin deficiency.

	n (%)
Immunoglobulin deficiency	
IgA	3 (7.5%)
IgM	1 (2.5%)
IgG	0 (0.0%)
IgE	2 (5.0%)
Any (IgA/ IgM/ IgG/ IgE)	6 (15.0%)

Further analysis considered selective IgA deficiency, selective IgE and any type of immunoglobulin deficiency, because a minimum of two patients are required to calculate comparison statistics.

Tables 3 and 4 present selective IgA deficiency, selective IgE deficiency and any type of immunoglobulin deficiency associations with continuous and categorical outcomes. No associations of selective IgA, selective IgE or any type of immunoglobulin deficiency were found with age, T1D duration, age at T1D onset, glycated hemoglobin, first-degree relative with immunodeficiency, first-degree relative with T1D, other autoimmune comorbidities, non-autoimmune comorbidities, number of infections per year, infection-related hospitalization, previous history of skin infection, central nervous system infection, respiratory infection, gastroenteritis, urinary tract infection, IgA anti-tissue transglutaminase >7 U/mL and antithyroglobulin antibody >4.1 UI/mL.

Table 3. Associations between continuous outcomes and selective IgA deficiency, selective IgE deficiency and any type of immunoglobulin deficiency.

Outcomes	Selective IgA deficiency (n=3)			Selective IgE deficiency (n=2)			Any type of Ig deficiency (n=6)		
	No	Yes		No	Yes		No	Yes	
	Mdn (Q_1 – Q_3)	Mdn (Q_1 – Q_3)	*p*-value	Mdn (Q_1 – Q_3)	Mdn (Q_1 – Q_3)	*p*-value	Mdn (Q_1 – Q_3)	Mdn (Q_1 – Q_3)	*p*-value
Age (years)	13.0 (10.0 - 15.0)	15.0 (7.0 - 17.0)	*p*=0.698	13.0 (9.0 - 16.0)	12.0 (12.0 - 12.0)	*p*=0.741	13.0 (9.0 - 16.0)	13.5 (12.0 - 15.0)	*p*=0.726
T1D duration (years)	7.0 (3.0 - 10.0)	5.0 (4.5 - 8.0)	*p*=0.77	6.0 (3.0 - 10.0)	8.0 (8.0 - 8.0)	*p*=0.656	6.0 (3.0 - 10.0)	8.0 (5.0 - 8.0)	*p*=0.470
Age at T1D onset (years)	5.0 (3.0 - 7.0)	6.0 (2.5 - 12.0)	*p*=0.698	5.8 (3.0 - 8.0)	4.0 (4.0 - 4.0)	*p*=0.656	5.8 (3.0 - 8.0)	4.0 (2.5 - 6.0)	*p*=0.493
Glycated hemoglobin (%)	7.4 (6.9 - 8.1)	6.8 (5.7 - 10.1)	*p*=0.626	7.4 (6.8 - 8.3)	7.3 (7.3 - 7.3)	*p*=0.877	7.4 (6.8 - 8.3)	7.3 (6.8 - 7.8)	*p*=0.754

Mdn: medians; Q_1 – Q_3: quartiles; Ig: immunoglobulin; T1D: type 1 diabetes.

Table 4. Associations between categorical outcomes and selective IgA deficiency, selective IgE deficiency and any type of immunoglobulin deficiency.

	Selective IgA deficiency (n=3)			Selective IgE deficiency (n=2)			Any type of Ig deficiency (n=6)		
	No	Yes	*p*-value	No	Yes	*p*-value	No	Yes	*p*-value
First-degree relative with immunodeficiency			*p*>0.990 (b)			*p*>0.990 (b)			*p*>0.990 (b)
No	35 (94.6%)	3 (100.0%)		36 (94.7%)	2 (100.0%)		32 (94.1%)	6 (100.0%)	
Yes	2 (5.4%)	0 (0.0%)		2 (5.3%)	0 (0.0%)		2 (5.9%)	0 (0.0%)	
First-degree relative with type 1 diabetes			*p*=0.560 (b)			*p*>0.990 (b)			*p*=0.307 (b)
No	27 (73.0%)	3 (100.0%)		28 (73.7%)	2 (100.0%)		24 (70.6%)	6 (100.0%)	
Yes	10 (27.0%)	0 (0.0%)		10 (26.3%)	0 (0.0%)		10 (29.4%)	0 (0.0%)	
Other autoimmune comorbidities			*p*=0.538 (b)			*p*=0.100 (b)			*p*>0.990 (b)
No	24 (64.9%)	3 (100.0%)		27 (71.1%)	0 (0.0%)		23 (67.6%)	4 (66.7%)	
Yes	13 (35.1%)	0 (0.0%)		11 (28.9%)	2 (100.0%)		11 (32.4%)	2 (33.3%)	
Non-autoimmune comorbidities			p>0.990 (b)			*p*=0.533 (b)			*p*>0.990 (b)
No	24 (64.9%)	2 (66.7%)		24 (63.2%)	2 (100.0%)		22 (64.7%)	4 (66.7%)	
Yes	13 (35.1%)	1 (33.3%)		14 (36.8%)	0 (0.0%)		12 (35.3%)	2 (33.3%)	
Number of infections per year			*p*=0.295 (b)			*p*=0.483 (b)			*p*=0.585 (b)
0	5 (13.5%)	0 (0.0%)		5 (13.2%)	0 (0.0%)		5 (14.7%)	0 (0.0%)	
1	13 (35.1%)	0 (0.0%)		11 (28.9%)	2 (100.0%)		10 (29.4%)	3 (50.0%)	
2	7 (18.9%)	2 (66.7%)		9 (23.7%)	0 (0.0%)		7 (20.6%)	2 (33.3%)	
3+	12 (32.4%)	1 (33.3%)		13 (34.2%)	0 (0.0%)		12 (35.3%)	1 (16.7%)	
Infection-related hospitalization			*p*=0.560 (b)			*p*>0.990 (b)			*p*=0.307 (b)
No	27 (73.0%)	3 (100.0%)		28 (73.7%)	2 (100.0%)		24 (70.6%)	6 (100.0%)	
Yes	10 (27.0%)	0 (0.0%)		10 (26.3%)	0 (0.0%)		10 (29.4%)	0 (0.0%)	
Previous history of skin infection			*p*>0.990 (b)			*p*>0.990 (b)			*p*>0.990 (b)
No	35 (94.6%)	3 (100.0%)		36 (94.7%)	2 (100.0%)		32 (94.1%)	6 (100.0%)	
Yes	2 (5.4%)	0 (0.0%)		2 (5.3%)	0 (0.0%)		2 (5.9%)	0 (0.0%)	
Previous history of central nervous system infection			-			-			-
No	37 (100.0%)	3 (100.0%)		38 (100.0%)	2 (100.0%)		34 (100.0%)	6 (100.0%)	
Yes	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Previous history of respiratory infection			*p*=0.579 (b)			*p*>0.990 (b)			*p*=0.381 (b)
No	16 (43.2%)	2 (66.7%)		17 (44.7%)	1 (50.0%)		14 (41.2%)	4 (66.7%)	
Yes	21 (56.8%)	1 (33.3%)		21 (55.3%)	1 (50.0%)		20 (58.8%)	2 (33.3%)	
Previous history of gastroenteritis			*p*>0.990 (b)			*p*=0.519 (b)			*p*=0.381 (b)
No	23 (62.2%)	2 (66.7%)		23 (60.5%)	2 (100.0%)		20 (58.8%)	5 (83.3%)	
Yes	14 (37.8%)	1 (33.3%)		15 (39.5%)	0 (0.0%)		14 (41.2%)	1 (16.7%)	
Previous history of urinary tract infection			*p*>0.990 (b)			*p*>0.990 (b)			*p*>0.990 (b)
No	31 (83.8%)	3 (100.0%)		32 (84.2%)	2 (100.0%)		29 (85.3%)	5 (83.3%)	
Yes	6 (16.2%)	0 (0.0%)		6 (15.8%)	0 (0.0%)		5 (14.7%)	1 (16.7%)	
IgA anti-tissue transglutaminase >7 (U/ml)			-			-			-
No	37 (100.0%)	3 (100.0%)		38 (100.0%)	2 (100.0%)		34 (100.0%)	6 (100.0%)	
Yes	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Antithyroid peroxidase antibody >5.6 (UI/ml)			*p*>0.990 (b)			***p*=0.046*(b)**			*p*=0.602 (b)
No	28 (75.7%)	3 (100.0%)		31 (81.6%)	0 (0.0%)		27 (79.4%)	4 (66.7%)	
Yes	9 (24.3%)	0 (0.0%)		7 (18.4%)	2 (100.0%)		7 (20.6%)	2 (33.3%)	
Antithyroglobulin antibody >4.1 (UI/ml)			*p*=0.262 (b)			*p*=0.154 (b)			*p*>0.990 (b)
No	21 (56.8%)	3 (100.0%)		24 (63.2%)	0 (0.0%)		20 (58.8%)	4 (66.7%)	
Yes	16 (43.2%)	0 (0.0%)		14 (36.8%)	2 (100.0%)		14 (41.2%)	2 (33.3%)	

Results presented as n (%); p-values calculated with (a) chi-square test or (b) Fisher exact test, when Cochran rules were not met. Ig: Immunoglobulin

Antithyroid peroxidase antibody >5.6 UI/mL was associated with selective IgE deficiency (p=0.046).

None of the patients with any type of immunoglobulin deficiency had reported history of infection-related hospitalization. All IgA deficient patients had IgA anti-tissue transglutaminase <7 U/mL, antithyroid peroxidase antibody <5.6 UI/mL, and antithyroglobulin antibody <4.1 UI/mL. All patients with any type of immunodeficiency had IgA anti-tissue transglutaminase <7 U/mL. Both IgE deficient patients had antithyroid peroxidase antibody >5.6 UI/mL and antithyroglobulin antibody >4.1 UI/mL, therefore were diagnosed with thyroiditis.

The one patient with IgM deficiency had no other diagnosed autoimmune or non-autoimmune diseases, no history of infection-related hospitalizations, and had previous history of one urinary tract infection only.

Discussion

Our study showed that immunoglobulin deficiency is relatively frequent in pediatric patients with T1D, as six of the forty children (15%) studied had one type of immunoglobulin bellow age-adjusted reference range. This is in line with previous studies carried out on the same topic.[10-12] Partial selective IgA deficiency was the most frequent, followed by selective IgE deficiency, and lastly selective IgM deficiency.

To gain more knowledge about the topic, a literature search was performed on the matter. IgA deficiency prevalence ranges from 1 in 100 to 1 in 1000 in Caucasians,[23] which represents a much rarer prevalence than we found in this study. There are no large-scale studies reporting the prevalence of IgM, IgE or IgG deficiencies worldwide. A study performed in a group of 3436 healthy adults from Iran determine a prevalence of 0.37% of selective IgM deficiency.[24] A prevalence of 0.03% was observed on another community-based study from an unselected group of 3213 individuals.[25] Goldstein MF *et al* described that the prevalence of selective IgM deficiency on a pediatric group of symptomatic patients followed in an allergy and immunology practice was 0.03%.[26] Therefore, the prevalence of IgM deficiency found in this study is higher. The prevalence of selective IgE deficiency varies depending on the cohort under study, with previous investigations reporting a prevalence of 0.8% in blood donors, 3.1% in allergy-immunology patients, and 1.3% in rheumatology practice patients.[27] Other study found IgE deficiency in 2.7% of the patients included, although some of these individuals had other concomitant immunodeficiencies diagnosed, such as common variable immunodeficiency.[28] In our study, 5% of the patients presented with selective IgE deficiency. The frequency of selective IgG deficiency is not known with certainty, as most studies evaluate the prevalence of each specific IgG subclass deficiency, which were not measured in this study. Nevertheless, the real prevalence of antibody deficiencies might be underestimated worldwide, as many individuals may be asymptomatic or go undiagnosed.[29]

Hogendorf A *et al* performed a study on antibody deficiency among 395 pediatric patients with T1D, which demonstrated that hypogammaglobulinemia is frequent among these patients, with 22.8% presenting at least one class of immunoglobulin deficiency. Nevertheless, this study established that patients with hypogammaglobulinemia of any kind had higher risk of infection-related hospitalization, and subgroup analysis by specific immunoglobulin deficiency showed that patients with IgA or IgE deficiency had higher risk of non-autoimmune comorbidities. Patients with partial selective IgA deficiency also had higher risk of autoimmune comorbidities.[11] In our study, such relations were not found, which might be related to the smaller sample size and thus lower statistical power of this study.

Other reports obtained similar findings in this topic, suggesting that low levels of IgA are more common among patients with T1D.[10-12] In a study carried out by Greco D *et al* , in Western Sicily, which included 150 subjects with T1D, 5.3% of subjects had IgA deficiency, a prevalence similar to what was found in this study.[10] Previous studies show that IgA deficiency is also associated with other autoimmune diseases like autoimmune thyroiditis, systemic lupus erythematosus, celiac disease, psoriasis, between others.[13] The haplotype 8.1 is the most frequently found among IgA deficient patients. Also, it is often linked to several autoimmune diseases highly associated with low IgA levels, such as autoimmune thyroiditis, systemic lupus erythematosus, celiac disease, rheumatoid arthritis, T1D and myasthenia gravis.[13] This associations might suggest shared genetic background that predispose subjects to both autoimmune manifestations and immunoglobulin deficiency. The previous observation of familial predominance with clustering of IgA deficit supports the importance of the genetic influence.[13,30] Other hypothesis are that autoimmune processes responsible for T1D might also influence other components of the immune system, like immunoglobulin formation, or that IgA protects against autoimmunity, with low IgA favoring the development of autoimmune diseases.[13] In our study, no autoimmune disorders had been diagnosed among patients with abnormally low levels of IgA, other than T1D.

Antithyroid peroxidase antibody above normal was associated with selective IgE deficiency. Both IgE deficient patients included in the study had autoimmune thyroiditis. This goes along with the findings of Picado C *et al*, whose study described an association between selective IgE deficiency and autoimmune diseases, thyroiditis included, although in that study none of the IgE deficient patients were diagnosed with T1D.[31]

In this study, patients with T1D and immunoglobulin deficiency did not seem to have increased risk of any type of infection or infection-related hospitalization, when compared to patients with T1D and normal values of immunoglobulins. This is congruent to the fact that patients with immunoglobulin deficiency may be asymptomatic.[13,14] Previous studies report an association between poor glycemic control and higher risk of infection or other comorbidities in diabetic patients, especially if longer duration of diabetes.[4,5,32] In this study, this evaluation was not considered.

Our study has several limitations, the most relevant being the small sample size and consequent low statistical power that limits its conclusions. A small number of subjects were included, which may be related to the lack of association between immunoglobulin deficiency and the risk of infections and other comorbidities found in this study. Plus, the clinical history of the individuals was reported by their caregivers, and thus subjective. To obtain more reliable clinical information, questionnaires were complemented with electronic medical records, which showed us that some caregivers forgot to mention relevant antecedents such as infection-related hospitalizations, especially older episodes. Therefore, old intercurrences for which there is no clinical record may have been ignored. Also, insulin requirements were not assessed, and the quality of glycemic control was evaluated based only on a single measurement of glycated hemoglobin, while time in range was not considered. Continuous glucose monitoring and time in range would reflect more truthfully the dynamic nature of long-term glucose control, and the variability of glucose concentrations, which could be valuable additional information.[33]

Given the fact that immunoglobulin deficiencies appear to be more common in patients with T1D, more research is required to better understand the relation between T1D and immunoglobulin deficit, to decide if patients with T1D should be regularly screened for immunoglobulin deficiency, especially if it is a patient with history of recurrent infections, frequent need for intravenous antibiotic treatment or other alarm signs of immunodeficiency.

Conclusion

This study demonstrated that immunoglobulin deficiency is relatively frequent among pediatric patients with T1D, suggesting a potential common background. Plus, in concordance to previous studies, selective IgE deficiency may be associated with positive antithyroid antibodies.[31]

Although in this study immunoglobulin deficit did not seem to be related to specific outcomes such as higher risk of infection, autoimmune or non-autoimmune comorbidities, further investigation is needed to clarify this relation, and to assess the potential benefit from screening immunoglobulin deficiency among pediatric patients with T1D.

Contributorship Statement / Declaração de Contribuição:

TF: Study conception and design, data collection, analysis and interpretation of results, draft manuscript preparation. CC: Study conception and design, data collection, interpretation of results, supervision.
All authors reviewed and approved the final version of the manuscript.

Responsabilidades Éticas

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