Prevalence of selective immunoglobulin A deficiency in Greek children and adolescents with type 1 diabetes

Styliani Giza, Eleni Kotanidou, Efimia Papadopoulou-Alataki, Maria Christina Antoniou, Ioanna Maggana, Ioannis Kyrgios, Assimina Galli-Tsinopoulou

Thessaloniki, Greece

Original article

Background: **The association of selective immunoglobulin A (IgA) deficiency with type 1 diabetes (T1D) remains unclear. This study was to evaluate serum IgA concentrations in Greek children and adolescents with T1D.**

Methods: **In two hundred individuals with T1D, serum IgA concentrations were quantitatively determined using nephelometry.**

Results: **Immunoglobulin A deficiency was detected in 6 (3.0%) of 200 patients who were subjected to immunological evaluation. Recurrent infections were not recorded, but human papilloma virus infection was clinically suspected and confirmed by laboratory examination in a 5-year-old girl. In regard to coincidence of selective IgA deficiency with autoimmune diseases, celiac disease was detected in a girl and juvenile idiopathic arthritis in a boy. Serum IgA concentrations differed significantly when patients were grouped according to age at the beginning of the study (P<0.001), age at diagnosis of T1D (P=0.015) and coincidence of celiac disease (CD) (P=0.038). However, when the age of the patients was adjusted, difference in serum IgA concentrations was not statistically significant despite CD was present or not. Moreover, serum IgA concentrations were positively correlated with serum IgG (P<0.001) and IgE (P=0.001) concentrations and negatively correlated with serum anti-gliadin antibody IgG (P=0.035) concentrations. There was no association or correlation of serum IgA concentrations with glycemic control.**

Conclusions: **The prevalence of selective IgA deficiency in Greek children and adolescents with T1D is high (3.0%). The correlation of serum IgA concentrations with serum IgG, IgE and anti-gliadin antibody IgG concentrations needs further investigation.**

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Key words: **adolescents;**
children;
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Introduction

According to the diagnostic criteria for primary immunodeficiencies (PID) established by the European Society for Immunodeficiencies (ESID), selective immunoglobulin (Ig) A deficiency is considered to be present in every male or female patient greater than 4 years of age who has a serum IgA of less than 7 mg/dL (0.07 g/L) but normal serum IgG and IgM concentrations, in whom other causes of hypogammaglobulinemia have been excluded. These patients have a normal IgG antibody response to vaccination.[1,2]

Selective IgA deficiency constitutes the most frequent primary immunodeficiency.[3] The prevalence of IgA deficiency is of different distribution worldwide, varying from 1:143 in Arabian Peninsula to 1:18 500 in Japan.[4] In Greece, the prevalence of selective IgA deficiency was estimated to be 1:455 among adult blood donors[5] and1:428 among healthy children.[6]

There is a wide clinical spectrum of IgA deficiency varying from asymptomatic (85%-90%)[6] to recurrent infections (otitis media, upper respiratory tract infections, bronchitis, pneumonia, chronic diarrhea, urinary tract infections, and skin infections), allergy (allergic rhinitis/conjunctivitis, asthma, atopic dermatitis, urticaria, drug allergy, and food allergy), and autoimmune diseases (juvenile rheumatoid arthritis, systemic lupus erythematosus, Hashimoto thyroiditis, celiac disease, idiopathic thrombocytopenic purpura, and autoimmune

Author Affiliations: 4th Department of Pediatrics, Faculty of Medicine, Aristotle University of Thessaloniki, Papageorgiou General Hospital, Thessaloniki, Greece (Giza S, Kotanidou E, Papadopoulou-Alataki E, Antoniou MC, Maggana I, Kyrgios I, Galli-Tsinopoulou A)

Corresponding Author: Assimina Galli-Tsinopoulou, MD, PhD, 4th Department of Pediatrics, Faculty of Medicine, Aristotle University of Thessaloniki, Papageorgiou General Hospital, Ring Road Nea Efkarpia 56403, Thessaloniki, Greece (Tel: 00302310991537; Fax: 00302310991537; Email: gallitsin@gmail.com, agalli@auth.gr)

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hemolytic anemia) occurring more often.[7-9]

Type 1 diabetes (T1D) is a chronic autoimmune disorder characterized by destruction of insulin-producing beta cells of pancreatic islets by CD8+ cytotoxic T lymphocytes with the contribution of CD4+ helper T lymphocytes, while antibody-producing B cells play a role in the initial immunological events.[10] Although an association of IgA deficiency with T1D has been reported, the exact prevalence of IgA deficiency in children and adolescents with T1D is still under investigation. The purpose of this study was to determine serum IgA concentrations and, therefore, to estimate the prevalence of IgA deficiency in Greek children and adolescents with T1D.

Methods

Patients

This cross-sectional study was conducted in the Unit of Endocrinology, Diabetes and Metabolism, 4th Department of Pediatrics, Faculty of Medicine, Aristotle University of Thessaloniki in Papageorgiou General Hospital. Two hundred children and adolescents with T1D, diagnosed according to International Society of Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2009 Compendium,[11] were enrolled into the study. Patients aged less than 4 years were excluded from the study according to the definition of IgA deficiency. Gender, age at entry to the study, age at diagnosis, duration of T1D, severity of onset (presence or absence of ketoacidosis), history of Hashimoto thyroiditis (HT) and celiac disease (CD) were recorded. Glycosylated hemoglobin (HbA1c) was determined every 3 months for the assessment of glycemic control. The study was approved by the Ethics Committee of the Faculty of Medicine of Aristotle University of Thessaloniki. The study was performed in accordance with the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html) and informed consent to participate in the study was obtained from participants (or their parent or guardian in the case of children younger than 16 years).

All participants underwent an immunological laboratory investigation including: serum IgA, IgG, IgM, IgE as well as anti-thyroglobulin (anti-TG), anti-thyroid peroxidase (anti-TPO), endomysial (EMA), anti-gliadin IgA (AGA-IgA), AGA-IgG and tissue transglutaminase (TTG) antibodies. When IgA deficiency was identified, IgG subclasses and immunophenotype of B and T lymphocytes were determined. Furthermore, in order to assess the immunological response after vaccination, specific IgG antibodies against several viruses (hepatitis A, hepatitis B, varicella zoster, measles, rubella, and mumps virus) were tested.

Assays

Serum IgA, IgM, IgG as well as IgG subclasses were quantitatively determined using a nephelometer (IMMAGE®, Beckman Coulter Inc., Brea, CA, USA and BN II®, Siemens Healthcare Diagnostics, Marburg, Germany, respectively). Serum anti-TPO and anti-TG concentrations were determined by a solid-phase, enzyme-labeled, chemiluminescent sequential immunoassay system (IMMULITE® 2000, Siemens Healthcare Diagnostics, Marburg, Germany) and considered negative when measured <35 IU/mL and <40 IU/mL, respectively. The T- and B- lymphocytes subpopulations and CD4+/CD8+ T-lymphocytes ratio were determined by flow cytometry (COULTER® EPICS®Elite ESP, Coulter Corp., Miami, FL, USA) using monoclonal antibodies (Beckman Coulter Immunotech, Inc., Webster, TX, USA). The CD4+/CD8+ T-lymphocytes ratio was considered to be normal when the value ranged from 0.9 to 2.6, according to age. Serum EMA antibodies were semi-quantitatively measured by an indirect immunofluorescent assay system (Endomysial Primate Distal Esophagus, INOVA Diagnostics Inc., San Diego, CA, USA) and considered either positive or negative. Serum AGA-IgA, AGA-IgG and TTG antibody concentrations were semi-quantitatively determined using an enzyme-linked immunosorbent assay system (QUANTA Lite®Gliadin IgA, QUANTA Lite®Gliadin IgG II, QUANTA Lite®h-tTG IgA, INOVA Diagnostics Inc., San Diego, CA, USA) and considered negative when determined <20 IU/mL.

The concentration of glycosylated hemoglobin (HbA1c) was measured in capillary blood sample with a specialized method (DCA2000®+ Hemoglobin A1c, Siemens Healthcare Diagnostics, Marburg, Germany) and concentrations ≤7.5% or >7.5% were considered as optimal or suboptimal glycemic control respectively.

Statistical analysis

Data were analyzed using Statistical Package for Social Science software for Windows, version 18.0, (SPSS Inc, Chicago, Illinois, USA). Categorical variables were described by frequency and percentage, while continuous variables by mean±standard deviation (SD). The Kolmogorov-Smirnov test was used to investigate the normality of distributions of continuous variables. Serum IgA concentrations between groups were compared using Student's *t* test for independent samples or the non-parametric analogue Mann-Whitney *U* test. In order to search for possible correlations between serum IgA concentrations and the other variables, linear regression models were performed. One way analysis of covariance was performed in order to explore the effect of a covariate on the variability of the other variables

and thus investigate adjusted effects. Statistical significance was defined at $P<0.05$.

Results

A total of 200 patients (114 boys and 86 girls) with a mean age of 11.71±3.65 years were enrolled into the study. The sample comprised 59 (29.5%) children (<10 years old) and 141 (70.5%) adolescents (≥10 years old). The mean age at diagnosis of T1D was 7.71±3.69 years and the mean duration of T1D was 4.00±3.61 years. Ketoacidosis was present at diagnosis in 76.5% of the patients. The mean concentrations of HbA1c were 8.65%±2.23%.

Hashimoto thyroiditis was diagnosed in 19.5% of the patients based on the elevated anti-TPO and/or anti-TG concentrations. Despite the fact that positive autoantibodies for CD were detected in 32/200 (16.0%), it was a transient finding in most cases. A small intestinal biopsy was performed only in the persistence of positive autoantibodies and CD was confirmed in 4/200 (2.0%) patients according to the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines for the diagnosis of CD.[12]

The mean concentrations of serum IgA, IgG, IgM and IgE were 162.25±74.05 mg/dL, 1122.08±284.92 mg/dL, 120.77±57.23 mg/dL, and 145.58±249.90 IU/mL respectively. Serum IgA concentrations differed significantly when grouping patients according to age at entry to the study ($P<0.001$), age at diagnosis of T1D ($P=0.015$), and coincidence of CD ($P=0.038$) (Table 1). However, when participants' age was adjusted, difference in IgA concentrations according to the presence of CD or not, was not statistically significant but only with a statistical trend ($P=0.084$). Furthermore, serum IgA concentrations were positively correlated with serum IgG ($P<0.001$) and IgE ($P=0.001$) concentrations and negatively correlated with serum AGA-IgG ($P=0.035$) concentrations. Any association or correlation of serum IgA concentrations with glycemic control was not detected (Table 2).

IgA concentrations <7 mg/dL defining IgA deficiency were identified in 6/200 (3.0%) patients. All these patients fulfilled the criteria of selective IgA deficiency. Since IgG and IgM concentrations were within normal range for age, normal antibody response to vaccination was detected, other causes of congenital hypogammaglobulinemia were excluded after immunological investigation including B, T and natural killer cells and acquired causes of hypogammaglobulinemia such as medication, renal or gastrointestinal loss, B-cell-related malignancies and certain infectious diseases were excluded. Recurrent

Table 1. Serum IgA levels in subgroups of patients according to demographic, clinical and laboratory characteristics as categorical variables

Groups	Subgroup	Frequency	Mean±SD	*P* value
Gender	Male	114	160.63±74.07	0.723
	Female	86	164.40±74.40	
Age at entry (y)	<10	59	133.56±69.77	<0.001
	≥10	141	174.26±72.70	
Age at diagnosis (y)	<10	136	153.43±69.12	0.015
	≥10	64	180.57±80.87	
Duration of diabetes (y)	<1	51	156.35±67.42	0.359
	1-5	80	157.09±79.17	
	>5	69	172.61±72.51	
Diagnosis	Diabetic ketoacidosis	153	163.83±71.47	0.588
	Hyperglycemia	47	157.11±82.53	
HbA1c (%)	≤7.5	69	167.83±78.63	0.421
	>7.5	113	158.47±74.27	
IgE (IU/mL)	<87	115	156.92±74.60	0.188
	≥87	79	170.94±69.71	
EMA	Positive	4	113.07±76.16	0.169
	Negative	193	164.48±73.77	
AGA IgA (IU/mL)	Positive	6	145.27±101.89	0.552
	Negative	192	163.56±73.30	
AGA IgG (IU/mL)	Positive	19	145.12±77.88	0.827
	Negative	179	164.90±73.59	
TTG (IU/mL)	Positive	12	183.25±91.25	0.606
	Negative	186	161.70±72.89	
Celiac disease	Yes	4	86.49±92.91	0.038
	No	196	163.80±73.10	
Anti-TPO (IU/mL)	Positive	32	163.95±70.48	0.888
	Negative	168	161.93±74.91	
Anti-TG (IU/mL)	Positive	24	173.15±85.58	0.368
	Negative	176	160.76±72.48	
Hashimoto thyroiditis	Yes	39	168.68±77.15	0.694
	No	161	160.69±73.44	

HbA1c: glycosylated hemoglobin; Ig: immunoglobulin; EMA: endomysial antibody; AGA: anti-gliadin antibody; TTG: tissue transglutaminase antibody; anti-TPO: thyroid peroxidase antibody; anti-TG: thyroglobulin antibody.

Table 2. Linear regression models between serum IgA levels and quantitative demographic and laboratory parameters

Parameters	R	R^2	Gradient	Intercept	*P* value
Age at entry (y)	0.281	0.079	5.678	95.72	<0.001
Age at diagnosis (y)	0.031	0.001	-0.108	162.59	0.659
Duration of diabetes (y)	0.079	0.006	0.269	159.94	0.269
HbA1c (%)	0.035	0.001	-1.126	170.60	0.627
IgG (mg/dL)	0.296	0.088	0.076	75.97	<0.001
IgM (mg/dL)	0.034	0.001	0.044	156.10	0.629
IgE (IU/mL)	0.228	0.052	0.066	152.96	0.001
AGA IgA (IU/mL)	0.040	0.002	0.378	160.75	0.584
AGA IgG (IU/mL)	-0.152	0.023	-0.783	170.11	0.035
TTG (IU/mL)	0.091	0.008	0.579	157.49	0.213
Anti-TPO (IU/mL)	0.003	0.0001	0.001	162.16	0.965
Anti-TG (IU/mL)	0.023	0.001	0.004	161.85	0.750

HbA1c: glycosylated hemoglobin; Ig: immunoglobulin; AGA: anti-gliadin antibody; TTG: tissue transglutaminase antibody; anti-TPO: thyroid peroxidase antibody; anti-TG: thyroglobulin antibody.

Table 3. Demographic and laboratory data of IgA deficient patients

Parameters	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (y)	17.25	14.45	4.87	9.90	7.83	9.06
Gender	M	M	F	F	M	F
Diabetes duration (y)	4.02	11.22	0.02	8.14	0.01	1.27
First presentation	DKA	DKA	DKA	DKA	DKA	DKA
IgA (mg/dL)	6.67 (82-453)	6.67 (82-453)	6.67 (75-188)	6.67 (85-292)	6.67 (68-200)	6.67 (77-224)
IgM (mg/dL)	148 (46-304)	117 (99-212)	58.1 (99-212)	110 (100-252)	248 (98-235)	147 (93-248)
IgG (mg/dL)	1600 (751-1560)	2240 (751-1560)	1440 (728-1460)	1550 (934-1640)	1130 (835-1640)	1640 (830-1560)
IgE (IU/mL)	8.17 (<87)	153 (<87)	4.46 (<52)	84 (<87)	4 2 (<52)	-
IgG1 (mg/dL)	1290 (647-1231)	1800 (647-1231)	1080 (540-1000)	1060 (551-1247)	874 (549-1083)	1230 (578-1112)
IgG2 (mg/dL)	395 (111-488)	97 (11-488)	187 (85-310)	190 (92-353)	259 (90-354)	266 (86-370)
IgG3 (mg/dL)	43.3 (27-114)	136 (27-114)	74.2 (27-82)	69.9 (30-110)	17.6 (27-93)	27.1 (28-94)
IgG4 (mg/dL)	128 (13-144)	30.5 (13-144)	0.72 (8-98)	54.7 (17-113)	51.4 (8-92)	21 (16-122)
CD2 (%)	72.2 (75.9-84.9)	76.7 (75.9-84.9)	70.2 (75.9-84.9)	75.9 (75.9-84.9)	75.9 (75.9-84.9)	77.9 (75.9-84.9)
CD3 (%)	63.6 (69.2-79.8)	69.5 (52-78)	68.2 (43-76)	72.2 (52-78)	73.4 (55-78)	72.8 (60-76)
CD3+/CD4+ (%)	34.9 (39.2-50)	35.6 (25-48)	42.1 (23-48)	48.2 (25-48)	41.1 (27-53)	49.8 (31-47)
CD3+/CD8+ (%)	21.5 (19.1-31.5)	32.7 (9-35)	22.7 (14-33)	21.1 (9-35)	23.6 (19-34)	20.2 (18-35)
CD3-/16+56+ (%)	15.8 (6-13.6)	11.9 (6-27)	5.6 (4-23)	4.5 (6-27)	3.7 (4-26)	10.3 (4-17)
CD19 (%)	17 (9.2-15.4)	16.2 (8-24)	21.4 (14-44)	22.2 (8-24)	20.9 (10-31)	15.5 (13-27)
CD4/CD8 (%)	1.62 (0.9-2.9)	1.08 (0.9-3.4)	1.85 (0.9-2.9)	2.28 (0.9-3.4)	1.75 (0.9-2.6)	2.47 (0.9-2.6)
Anti-TPO	Negative	Negative	Negative	Negative	Negative	Negative
Anti-TG	Negative	Negative	Negative	Negative	Negative	Negative
EMA	Negative	Negative	Negative	Positive	Negative	Negative
AGA IgA	Negative	Negative	Negative	Negative	Negative	Negative
AGA IgG	Negative	Negative	Negative	Positive*	Negative	Positive†
TTG	Negative	Negative	Negative	Negative	Positive	Negative
HbA1c (%)	7.1	10.0	12.0	9.0	13.5	8.9

Ig: immunoglobulin; anti-TPO: thyroid peroxidase antibody; anti-TG: thyroglobulin antibody; EMA: endomysial antibody; AGA: anti-gliadin antibody; TTG: tissue transglutaminase antibody; HbA1c: glycosylated hemoglobulin; M: male; F: female; DKA: diabetic ketoacidosis. *: no compliance; †: new onset of celiac disease; (…): normal range for age. "-": no data.

infections were not recorded, whereas human papilloma virus infection was clinically suspected and laboratory confirmed in a 5-year-old girl. In regard to coincidence of selective IgA deficiency with autoimmune diseases, CD was detected in a girl and juvenile idiopathic arthritis (antinuclear antibodies, antinuclear antibodies positive) in a 17-year-old boy (Table 3).

Discussion

Although IgA deficiency has been reported to be associated with T1D,[13] data on the prevalence of IgA deficiency in patients with T1D are sparse. This study constitutes an attempt for the first time to evaluate the prevalence of IgA deficiency in Greek children and adolescents with T1D. The prevalence in this cohort was estimated to be 3.0%, higher than in other groups of patients with T1D[14-19] as well as in Greek general pediatric population (0.23%).[6] However, this comparison has several limitations, taking into account the different study design and laboratory methods used for the diagnosis. Furthermore, the prevalence of IgA deficiency in Greek children and adolescents with T1D is higher than the prevalence of IgA deficiency in general population with approximately 1:700 affected individuals worldwide.[7] The distribution of IgA deficiency varies significantly depending on the ethnic background.[4,17]

The increased prevalence of IgA deficiency in the study population is in agreement with previous studies. In a study conducted in 191 Italian children and adolescents with T1D, IgA deficiency was detected in 7 participants, giving a prevalence rate of 3.7%, higher than that in the Italian general pediatric population (0.2%).[15] Hoddinott et al[16] found 2 patients with IgA deficiency among 129 patients with T1D and disease onset before the age of 15 years (1.6%). On the other hand, in a recent study, Sayarifard et al[17] estimated the prevalence of IgA deficiency in Iranian patients with T1D at 0.7% (1/150), about 4 times higher than its prevalence in the general population of the same origin (0.15%, 1/651). Liblau et al[18] demonstrated a low prevalence rate (0.38%, 1/261) of IgA deficiency in adults with T1D, nevertheless higher than those among adult French blood donors (0.07%, 1/1400). Moreover, in the study by Liberatore et al,[19] no case of IgA deficiency was found in a group of 66 patients with T1D. Finally, an interesting finding was reported by Smith et al.[20] As they found a statistically significantly

Table 4. Characteristics of the studies concerning IgA deficiency prevalence in type 1 diabetes (T1D) and general population

Studies	Country	IgA deficiency prevalence		
		T1D population		General population
Cerutti et al, 1988[15]	Italy	7/191 (3.7%)	Children	0.2%
Hoddinott et al, 1982[16]	Canada	2/129 (1.6%)	Children, adults	Not referred
Sayarifard et al, 2012[17]	Iran	1/150 (0.7%)	Children	0.15%
Liblauet al, 1992[18]	France	1/261 (0.38%)	Adults	0.07%
Liberatore et al, 2005[19]	Brazil	0/66 (0)	Children	Not referred
Smith et al, 1978[20]	USA	9/366 (2.5%)	Children	0

Ig: immunoglobulin.

increased prevalence of IgA deficiency in children compared to adults with T1D (2.5%, 9/366 versus 0, 0/421), they concluded that the prevalence of IgA deficiency in T1D could be dependent on the age of patients. Table 4 summarizes the characteristics of the studies concerning the prevalence of IgA deficiency in T1D and general populations.

IgA deficiency has been suggested to be associated with a variety of concomitant autoimmune diseases.[14] The higher prevalence of IgA deficiency in patients with T1D compared with healthy individuals in the present study population is in agreement with the results of previous studies[15-18,20] and confirms the association of IgA deficiency with T1D. Genetic factors are implicated in the development of both IgA deficiency and T1D. IgA deficiency is strongly associated with the major histocompatibility complex (MHC) region, in particular with the human leukocyte antigen (HLA)-B8, DR3, and DQ2 (8.1) haplotype.[21,22] This haplotype is also associated with T1D.[22,23] On the other hand, the protection against IgA deficiency[24] and T1D[25] by the DR15, DQ6 haplotype further supports a possible common genetic background. In addition, common non-MHC genes are also implicated in the pathogenesis of IgA deficiency and T1D. Polymorphisms in interferon induced helicase 1 (*IFIH1*) and c-type lectin domain family 16, member A (*CLEC16A*) genes have been found to be associated with IgA deficiency in a recent study on genome-wide association.[26] Several single nucleotide polymorphisms within these genes have been found to be associated with T1D.[27,28] On this basis, Wang et al[14] presented suggestive evidence for a shared genetic predisposition between IgA deficiency and T1D, justifying the increased prevalence of IgA deficiency in patients with T1D.

In the study population, IgA concentrations were estimated to be significantly lower in patients with T1D and CD, a finding not reported by Sayarifard et al.[17] This discrepancy may be explained on the basis of the limited number of patients who concurrently have T1D and CD. As a result, studies are needed for the investigation of IgA concentrations in patients with T1D and CD. However, it is interesting that very few individuals with T1D and IgA deficiency appear to have villous atrophy on small intestinal biopsy.[29] Besides, the negative correlation between IgA and AGA-IgG concentrations may be supported by a previous study on 403 children and adolescents with T1D reporting high AGA-IgG values in 2 patients diagnosed with IgA deficiency.[30]

Furthermore, serum IgA concentrations were positively correlated with serum IgG (P<0.001) and IgE (P=0.001) concentrations. Ardawi et al[31] concluded that an abnormal IgA concentration is a very common finding among T1D patients. In the study, serum IgA concentrations were significantly increased in both patients with T1D and T2D compared with healthy individuals.[31] A similar conclusion was reported in another study in which over 41% of the patients with insulin and non-insulin dependent diabetes had abnormal serum IgA concentrations.[32] Increased serum IgA values in patients with T1D were also reported by other researchers.[33-36] In a study, the finding of elevated serum IgA concentrations at onset of T1D was reversed by insulin treatment, perhaps due to the obviation of insulinopenia and environmental factors triggering the clinical manifestation of T1D.[37] On the other hand, serum IgA concentrations in patients with T1D were reported to be either similar[16,38] or lower compared with healthy population.[39] The manner in which IgA concentrations are affected in patients with T1D deserves further study.

Some IgA deficient patients develop common variable immunodeficiency over time which predisposes to recurrent infections leading to glycemic control disturbance in T1D patients. Any association or correlation of serum IgA concentrations with glycemic control was not detected in accordance with the results of previous studies.[15,32,40] But an inverse relationship between IgA and HbA1c values was detected in a study on children and adolescents with T1D.[19] Furthermore, HbA1c was correlated with serum IgA concentrations in both T1D and T2D diabetic patients in another study.[31] This hypothesis needs further investigation.

Recurrent infections were not recorded, whereas human papilloma virus infection was clinically

suspected and laboratory confirmed in a 5-year-old girl. Such a case has not been reported in the literature. This finding may be explained on the basis that a specific IgA response known to be observed after infection with HPV 6/11, 16, or 18[41] was absent in this patient. In regard to coincidence of selective IgA deficiency with autoimmune diseases, CD was detected in a girl and juvenile idiopathic arthritis in a boy, supporting the association of IgA deficiency with autoimmune diseases.[8-10]

The immunogenetic mechanisms for IgA deficiency remain unidentified. Recently, alterations into the *TNFRSF13B/TACI* gene have been demonstrated in approximately 10% of patients with selective IgA deficiency and common variable immunodeficiency. These mutations seem to be correlated with an increased susceptibility to autoimmunity. However, *TNFRSF13B/TACI* alterations, including C104R and A181E mutations, have also been detected in healthy individuals. This indicates that *TNFRSF13B/TACI* variants may not be causative, but rather represent a modifying factor influencing the severity and/or the phenotype of hypogammaglobulinemia.[42]

In conclusion, the higher prevalence of selective IgA deficiency in Greek children and adolescents with T1D compared with the general pediatric population is in accordance with the results of previous studies. The positive correlation with serum IgG and IgE concentrations and the negative correlation with serum AGA IgG concentrations need further investigation. All children and adolescents with T1D should undergo investigation of IgA concentrations and in case of IgA deficiency, further immunological investigation is recommended. Detection of IgG subclass concentrations along with immunophenotype of T and B lymphocyte subsets is advisable. Long-term monitoring of their immune system along with appropriate treatment could offer a favorable outcome in this group of patients.

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Competing interest: None declared.

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