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Prevalence of Selective IgA Deficiency in a Sample of Egyptian Patients with Type1 Diabetes Mellitus

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ABSTRACT

Background: Selective Immunoglobulin A deficiency (SIgAD) is known to be one of the most frequent primary immunodeficiency diseases. Several studies worldwide confirm the increased frequency of this disease among type 1 diabetes mellitus (T1DM), yet this has not been studied in Egypt.

Objective: This work aimed to define the prevalence of SIgAD among Egyptian patients with T1DM.

Patients and Methods: Fifty patients with T1DM were compared to fifty apparently healthy individuals. Serum levels of IgA, IgG, and Immunoglobulin M (IgM) levels were measured by Nephelometry to all participants.

Results: The mean age of the diabetic group was 24.5 ± 5.3 years. Thirty out of fifty patients with T1DM (60%) were diagnosed as SIgAD with, female predominance (66.7% of SIgAD). We also found a significant relationship between SIgAD and diabetic ketoacidosis (P-value<0.001). Serum IgA levels were positively correlated to IgG and IgM.

Conclusion: The current study displays 60% prevalence of SIgAD among adult Egyptians with T1DM, which is higher than stated in other countries.

Keywords: Diabetes Mellitus, SIgAD, HbA1C.

INTRODUCTION

Selective immunoglobulin A deficiency (SIgAD) is estimated to be one of the most frequent primary immunodeficiency diseases [(1)]. It is diagnosed according to international consensus when: sIgA is <0.07 g/L, provided that serum IgM and IgG are normal. Diagnosis should be confirmed after the age of four years [(2)]. SIgAD could be asymptomatic in 85% of patients, otherwise, it has diverse presentations as recurrent infections or allergic disease. Moreover, it is associated with various autoimmune diseases, such as type 1 diabetes mellitus (T1DM), celiac, autoimmune hematological diseases as anemia, and thrombocytopenia [(3)]. T1DM is a chronic autoimmune disorder, where beta cells of the pancreas are damaged by CD8+ cytotoxic T lymphocyte. Besides, CD4+ helper T cell and B lymphocytes contribute to disease pathogenesis [(4)]. Mononuclear cells invade the islets and cause "insulitis,". Soluble mediators and cytokines produced by these inflammatory cells play a pivotal role too in disease progression [(5)]. Acute diabetic complications comprise diabetic ketoacidosis and hyperosmolar coma [(6)], while long-term complications are either macrovascular as ischemic heart disease and stroke, or microvascular as nephropathy, neuropathy, and retinopathy [(7)].

In diabetic patients, glycation of immunoglobulin is noted and is directly proportional to HbA1c level. The clinical significance of this observation is not obvious since patients' response to vaccinations and infections is satisfactory in diabetic patients [(8)].

Numerous immunological mechanisms have been proposed to illustrate the emergence of autoimmunity in patients with SIgAD.

The absence of secretory IgA facilitates penetration of environmental antigens in the mucosa. Additionally, augmented autoantibody levels had been reported in patients with IgA deficiency. This could be explained in the light of molecular mimicry [(9, 10)]. The relationship between SIgAD and abnormal T-cell regulation (regulatory T-cells) could also justify the link between SIgAD and autoimmunity due to the failure of immune tolerance [(11)].

The prevalence of SIgAD in T1DM varied widely in different studies, ranging from 0.38% to 3.7%. Most of them found out higher prevalence among diabetic patients than in the general population (12). To our knowledge, scanty studies have explored the prevalence of SIgAD in adult Egyptian patients with T1DM. Hence, this work aimed to determine the prevalence of SIgAD among Egyptian patients with T1DM.

PATIENTS AND METHODS

This is an observational case-control study that included fifty adult Egyptian patients above 18 years of age, selected by systematic randomization from the Diabetes Clinic at Ain Shams University Hospital, diagnosed according to American Diabetes Association 2016 guidelines [(13)].

Exclusion criteria:Patients with type 2 diabetes mellitus, associated immunodeficiency disorders such as common variable immunodeficiency, systemic organ failure, patients on immune suppressive drugs (as steroids or cytotoxic drugs within the last 3 months), and malignancy were precluded.

A Control group of fifty apparently healthy subjects of comparable age and sex were also recruited.

Thorough history taking and clinical examination were done for all participants. Biochemical studies included: Fasting blood sugar, 2hrs postprandial blood sugar, HbA1C.

Immunoglobulin assay:

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Serum IgM, IgG, and IgA levels were determined by Nephelometry, using British kits (MININEPH, Binding site, Birmingham).

Venous blood samples were drawn by a single puncture technique of the antecubital vein. Samples were distributed into two sterile tubes: K-EDTA solution (1.2 mg/ml) was added to one tube to measure HbA1c. The second was without an anticoagulant (clotted sample) for immunoglobulin assay.

Serum was prepared at room temperature, by centrifugation for 10 minutes at 3000 rpm. Then, labeled and stored at -20°C. On analysis, day samples were diluted at a 1:11 ratio and kept at room temperature. Afterward, samples (10 µl for IgG and 40 µl for IgM and IgA) were mingled with 400 µl of buffer and 40 µl of anti-immunoglobulin in a cuvette on Nephelometer and readings were recorded.

Soluble antigen concentration was determined by nephelometric methods where a reaction with a specific antiserum was allowed to take place. Light is allowed to pass through the suspension. The amount of light dispersed (perceived by a photodiode) is proportional to the specific protein concentration in the test sample. A calibration curve within the instrument was used to calculate concentrations. Reference ranges for adults were as follows: Serum levels of IgM: 40-263 mg/dl, IgG: 658-1837 mg/dl, and IgA: 71-360 mg/dl **(14).**

Ethical consent:

The project ethical approval was obtained from the Faculty of Medicine, Ain Shams University ethical committee (Ethical committee reference number: FWA-0000-17585). Confidentiality of data was ensured to the study team. In addition, informed consent was obtained from patients following the explanation of the study rationale and procedures. This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Statistical analysis was done using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA) and JMP® version 10 (SAS© Institute Inc., Cary, NC, USA). Continuous numerical variables were described as mean and standard deviation (SD), groups were compared using the independent-samples t-test. Categorical data was presented as number and percentage and Fisher's exact test was applied to compare groups. The significance of calculated odds ratio for the association between low serum IgA level and relevant binary outcomes was examined using the Z-test. Pearson correlation was applied when needed. A receiver-operating characteristic (ROC) curve was applied to set the discriminative value of serum levels of immunoglobulins.

RESULTS

Table 1 presents an overview on demographic data of all study participants, where the mean age of patients was 24.5 ± 5.3 years compared to 26.6 ± 6.4 years in the control group. Blood sugar levels (fasting and 2 hours post prandial) and HbA1c level were significantly higher in patients than in controls (p value<0.0001 for the three measures) as demonstrated in **table 2**. **Table 3** displays disease characteristics and incidence of complications in patients with T1DM. The most striking was that diabetic ketoacidosis (DKA) was reported in 22 patients (44%).

Table 4 highlighted the level of the three immunoglobulins, as it was significantly lower in the diabetic group compared to apparently healthy group (p-value was <0.0001 in the three Igs).

Receiver-operating characteristic (ROC) curve analysis for discrimination between cases of type 1 DM and controls using serum IgA level showed that cut-off value of ≤75 mg/dl can discriminate between T1DM patients and healthy individuals with a sensitivity of 100% and specificity of 76%. AUC was 0.926 (p-value <0.0001).

Table 5 showed that low serum IgA was found in 30 patients (60%) of the diabetic group versus none in the control group.

Low serum IgA level was mainly detected among males compared to females (p-value 0.04). Surprisingly, it was also found in patients who reported previous DKA attacks than those without (p-value 0.008) **(Table 6).** Lastly, on correlating serum IgA level with other parameters, a moderate positive correlation between IgA level and IgG (r = 0.429) and a weak positive correlation with IgM were detected (r= 0.329) **(Table 7).**

Table (1): Demographic characteristics of cases of type 1 DM and controls

Variable	Type 1 DM (n=50)	Control (n=50)	95% C I	P-value
Age (years)	24.5 ± 5.3	26.6 ± 6.4	9.6 to 14.8	0.077 *
Gender (M:F)	10:40	16:34	-	0.254 #
Associated autoimmune disease				**0.027 #**
Nil	48 (96.0%)	50 (100.0%)		
Autoimmune hypothyroidism	2 (4.0%)	0 (0.0%)		

Data are mean ± standard deviation, ratio or number, and percentage (%). 95% CI = 95% confidence interval.
*Unpaired t-test. #Fisher's exact test.

Table (2): Blood sugar and HbA1c levels in cases of type 1 DM and controls

	Type 1 DM (n=50)	Control (n=50)	95% CI	P-value*
FBS (mg/dl)	177.2 ±7.0	82.7 ±8.8	-114.6 to -74.5	**<0.0001**
PPBS (mg/dl)	256.9 ±11.4	110.7 ±10.5	-177.6 to -114.8	**<0.0001**
HbA1c (%)	9.5 ±2.1	5.1 ± 0.3	-5.1 to -3.9	**<0.0001**

Data are mean and standard deviation (SD). FBS: fasting blood sugar, PPBS post prandial blood sugar. 95% CI = 95% confidence interval. *Unpaired t-test.

Table (3): Disease characteristics in cases of type 1 DM

Variable	Value
Age at onset of DM (years)	9.6 ± 3.2 (4 - 15)
Duration of DM (years)	15.0 ± 5.4 (6 - 28)
DM complications	
DKA	22 (44%)
Hypoglycemia	12 (24%)
Retinopathy	12 (24%)
Nephropathy	8 (16%)
Neuropathy	6 (12%)
CVS	2 (4%)
Foot infection	0 (0%)

Data are mean ± SD (range) or number (%).

Table (4): Results of quantitative serum IgA, IgG, and IgM assays

	Type 1 DM (n=50)		Control (n=50)		95% CI	P-value *
Variable	Mean	SD	Mean	SD		
IgA (mg/dl)	67.0±2.1		112.0±21.4		36.8 to 53.4	**<0.0001**
IgG (mg/dl)	743.8±85.6		1000.2±171.3		202.7 to 310.2	**<0.0001**
IgM (mg/dl)	88.8±9.0		126.75.1		26.7 to 49.1	**<0.0001**

Data are mean and standard deviation (SD). 95% CI = 95% confidence interval. *Unpaired t-test.

Table (1): Results of qualitative IgA assay in cases of type 1 DM and controls

Variable		Type 1 DM (n=50)	Control (n=50)	P-value
Qualitative IgA assay	*Low*	30 (60.0%)	0 (0.0%)	**<0.001 ***
	Normal	20 (40.0%)	50 (100.0%)	

Data are numbers and percentages (%). NA = test not applicable. *Fisher's exact test.

Table (6): Association between qualitative serum IgA level and other qualitative variables in diabetic patients.

		Qualitative IgA assay							
		Normal (n=20)		Low (n=30)					
Variable		**n**	**%**	**n**	**%**	**Odds ratio**	**95% CI**	**z statistic**	**P-value***
Gender	M	0	0.0%	10	33.3%	0.05	0.003 to 0.87	2.056	**0.040**
	F	20	100.0%	20	66.7%				
Associated autoimmune disease	-	18	70.0%	30	100.0%	0.04	0.002 to 0.69	2.203	0.181
	+	2	30.0%	0	0.0%				
Neuropathy	-	18	90.0%	26	86.7%	1.38	0.23 to 8.38	0.354	0.723
	+	2	10.0%	4	13.3%				
Nephropathy	-	16	80.0%	26	86.7%	0.62	0.13 to 2.81	0.626	0.531
	+	4	20.0%	4	13.3%				
CVS	-	18	90.0%	30	100.0%	0.62	0.13 to 2.81	0.626	0.531
	+	2	10.0%	0	0.0%				
DKA	-	16	80.0%	12	40.0%	6.00	1.61 to 22.39	2.667	**0.008**
	+	4	20.0%	18	60.0%				
Hypoglycemia	-	18	90.0%	20	66.7%	4.50	0.87 to 23.35	1.791	0.073
	+	2	10.0%	10	33.3%				
Retinopathy	-	14	70.0%	24	80.0%	0.58	0.16 to 2.16	0.807	0.420
	+	6	30.0%	6	20.0%				

Data are numbers and percentages (%). *Z-test.

Table (7): Correlation of serum IgA level with other quantitative variables

	IgA	
Variable	***Pearson r***	***P-value***
IgG	**0.429****	**0.002**
IgM	**0.329***	**0.020**
Age at onset of DM	0.068	0.639
Duration of DM	0.234	0.102
HbA1c	-0.083	0.566
FBS	-0.067	0.642
PPBS	-0.212	0.140

**Correlation is significant at the *P* <0.01 level.

DISCUSSION

Although SIgAD association with T1DM has been established in many studies worldwide [(15)], yet data in Egypt is scarce. Hence, this study aimed at evaluating the frequency of IgA deficiency in adult Egyptian patients with T1DM. In this case-control study, we found that 60% of patients with T1DM had SIgAD, compared to none in control. This means that there is a higher prevalence of SIgAD in T1DM patients than in the normal population, this is in line with many previous studies. **Cerutti *et al.*** [(16)], recruited 191 diabetic young patients with T1DM in Italy. SIgAD was detected in 7 participants, recording a prevalence rate of 3.7%, while it is 0.2% only among the Italian pediatric population. Also, a recent study held in Poland on 395 diabetic children showed that the most prevalent autoimmune disease is SIgAD, where it was revealed in 10% of patients [(17)]. Moreover, another study on Greek children showed prevalence in 3% of SIgAD in diabetic children compared to 0.23 % in the general population [(18)].

In Egypt, **Abo-Ali *et al.*** [(19)] studied 100 cases with diverse autoimmune diseases. Surprisingly, SIgAD was diagnosed in 67% of patients. This corroborates our findings. The high prevalence of SIgAD in comparison to worldwide records could be attributed to high consanguinity, large family size which may increase the incidence of a relatively uncommon disease. Further studies are needed on larger scale to determine prevalence in the Egyptian general population as it varies among countries.

On the contrary, a study done on the Iranian population stated that the prevalence SIgAD was 0.7% among T1DM compared to 0.15% among the general population [(20)]. Surprisingly, another study by Liberatore *et al.* encompassed 66 patients with T1DM, found no cases of SIgAD [(21)].

Both SIgAD and T1DM are related to genetic factors. They are both related to HLA B8, DR3, and DQ2 haplotype [(22-24)]. Additionally, DR15, DQ6 haplotype confers defense against IgA deficiency [(25)] and T1DM [(13)]. Based on this, **Wang *et al***. explained the higher incidence of SIgAD among T1DM by proposing evidence of common genetic predisposition between both diseases [(13)]. The high prevalence detected in this study among Egyptian patients might be attributed to the distribution of IgA Deficiency which varies significantly based on ethnicity [(3, 21)].

Furthermore, a positive correlation was proved in our study between serum IgA and serum IgG and this corroborates the results of a previous study in Greece [(18)].

Serum IgA concentration was not correlated with glycemic control. This was consistent with previous research [(16, 26, 27)]. Nevertheless, Liberatore *et al.* stated that serum IgA level was inversely proportional with HbA1c values in children and adolescents with T1DM [(21)].

Our study showed a significant relationship between SIgAD and sex which is more common in females. The predominance of females in our study may explain this, and further studies on a larger scale with an equal sex ratio might be needed. Serum IgA level and its association with age of onset, duration of illness, and glycated hemoglobin level in the diabetic group were studied and yielded no significance. This is in accordance with a study that showed that IgA level was neither correlated with the age of patients nor duration of disease [(28)].

Our study was limited by the small sample size, female predominance. Further studies on a larger scale might be needed on Egyptian patients to corroborate our results.

CONCLUSION

The current study declared that the prevalence of SIgAD among adult Egyptian patients with T1DM is 60.0% which is much higher than that detected in other populations. The prevalence of SIgAD was higher in females. Screening of all Egyptian T1DM patients for SIgAD might be needed.

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