Prevalence of Type 1 Diabetes Autoantibodies (GADA, IA2, and IAA) in Overweight and Obese Children

Valentina M. Cambuli, md[1]
Michela Incani, bsc[1]
Efisio Cossu, md[1]
Tiziana Congiu, md[1]
Francesca Scano, md[1]
Sabrina Pilia, md[2]
Federica Sentinelli, bsc, phd[1]
Claudio Tiberti, ata[3]
M. Gisella Cavallo, md, phd[4]
Sandro Loche, md[2]
Marco G. Baroni, md, phd[1]

OBJECTIVE — Little is known about the prevalence of β-cell autoantibodies in children with excess body weight. The prevalence of type 1 diabetes autoantibodies and its relation with hyperglycemia was analyzed in 686 overweight/obese children and adolescents.

RESEARCH DESIGN AND METHODS — All children underwent an oral glucose tolerance test, and anti-GAD, anti-IA2, and anti-IAA autoantibodies were measured. Autoantibody prevalence was evaluated in 107 normal-weight children for comparison.

RESULTS — A single autoantibody was present in 2.18% of overweight/obese subjects and 1.86% normal-weight subjects (*P* = NS). Postload glycemia was significantly higher in antibody-positive children (133 ± 69.9 vs. 105.4 ± 17.7 mg/dl, *P* < 0.0001) compared with autoantibody-negative subjects. No difference in autoantibody distribution was seen when our cohort was stratified by age, sex, SDS-BMI, pubertal stage, and homeostasis model assessment–insulin resistance (HOMA-IR).

CONCLUSIONS — The 2.18% prevalence of type 1 diabetes autoantibodies is similar to that reported in nonobese children. This study provided evidence that excess body weight and insulin resistance do not influence autoantibody frequency.

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Over the last 60 years, a striking increase in the incidence of childhood type 1 diabetes has been observed consistently in almost all populations. EURODIAB (1) reported an overall increase of 3.2% per annum in Europe between 1989 and 1998. There have also been considerable changes in childhood nutrition, which have resulted in changes in growth. Increased weight, height, and BMI in children have all been associated with a higher risk of type 1 diabetes (2). The so-called "accelerator hypothesis" argues that obesity causing overworked β-cells underlies both type 1 and type 2 diabetes and that these "types" are only distinguished by how the body responds to this growth-induced β-cell stress. This hypothesis therefore attributes the rise in type 1 diabetes to an increase in child obesity (3). A variation of the hypothesis suggests that, once initiated, islet autoimmunity progresses more rapidly in the context of "overload" of the β-cells due to increased insulin resistance (4).

Sardinia has one of the highest incidences of type 1 diabetes worldwide, second only to Finland (5). Moreover, Sardinian children and adolescents are experiencing the same increase in obesity as other European populations (6). To date, little is known on the prevalence of autoantibodies against β-cells in children with excess body weight.

The aim of our study was to analyze the prevalence of type 1 diabetes autoantibodies in a cohort of Sardinian overweight/obese children and adolescents and to evaluate their distribution in relation to the presence of glucose abnormalities.

RESEARCH DESIGN AND METHODS

A total of 686 overweight/obese Italian children and adolescents were studied, all attending the Pediatric Endocrine Unit for the presence, in all cases, of excess body weight. Exclusion criteria were the presence of endocrine disorders or genetic syndromes, including syndromic obesity. A second group of normal-weight children (*n* = 107) was collected for antibody prevalence comparison. Clinical characteristics of all 793 subjects are shown in Table 1.

Clinical and metabolic parameters

All overweight/obese subjects underwent an oral glucose tolerance test (OGTT). The OGTT was performed according to clinical recommendations for children (1.75 g/kg body wt, up to 75 g). Plasma glucose and insulin were measured at 0 and 120 min. Subjects were classified according to American Diabetes Association criteria in subjects with normal glucose tolerance, with impaired fasting glycemia (IFG), impaired glucose tolerance (IGT), or diabetes. Impaired glucose regulation (IGR) defined the presence of any category of glucose abnormality (IFG, IGT, and diabetes). Diagnosis of type 1 diabetes was made in the presence of diabetic hyperglycemia and at least one β-cell autoantibody.

In all 793 children, anti-GAD, anti-IA2, and anti-IAA autoantibodies (GAD-Ab[125]I-Radioassay, IA2-Ab[125]I-Radioassay, and IAA-Ab[125]I-Radioassay) were assessed (all from DLD Diagnostika, Germany). The upper normal limit for anti-GAD and anti-IA2 is ≤1 unit/ml and for anti-IAA is ≤0.4 units/ml. Anti-GAD assay has an intra-assay coefficient of variation (CV) of 3.6% and an

Table 1—*Clinical and biochemical characteristics of overweight/obese and normal-weight children and adolescents*

	Overweight	Obese	P (overweight vs. obese)	Overweight/obese	Normal weight	P (overweight/obese vs. normal weight)
n	217	469		686	107	
Age (years)	10.6 ± 3	10.2 ± 3.2	NS	10.3 ± 3.2	11.4 ± 3.2	<0.01
Sex (F/M) (n)	124/93	236/233	NS	360/326	49/58	NS
Prepubertal/pubertal (n)	150/67	329/240	NS	479/207	68/39	NS
BMI (kg/m^2)	25.1 ± 2.3	28.9 ± 4	<0.0001	27.7 ± 4.5	17.9 ± 2.7	<0.0001
SDS-BMI	1.9 ± 0.7	3.2 ± 1.2	<0.0001	2.8 ± 1.2	-0.46 ± 0.8	<0.0001
Systolic blood pressure (mmHg)	104.19 ± 13.4	107.53 ± 15.5	<0.017	106.4 ± 14.9	105 ± 10.6	NS
Diastolic blood pressure (mmHg)	61.35 ± 7.9	62.38 ± 9.4	NS	62 ± 9	61.1 ± 5.4	NS
Glycemia 0′ (mg/dl)	90.1 ± 7.8	89.4 ± 7.6	NS	89.6 ± 7.7	88.4 ± 8.4	NS
Insulin (μU/ml)	15.7 ± 7.2	16.9 ± 9.7	NS	16.6 ± 9	11.7 ± 6	<0.0001
HOMA-IR	3.5 ± 1.6	3.7 ± 2.3	NS	3.7 ± 2	2.6 ± 1.4	<0.0001
Total cholesterol (mg/dl)	168 ± 34.1	165.9 ± 32.2	NS	166.6 ± 32.8	165 ± 26.3	NS
HDL (mg/dl)	51.4 ± 11.8	49.8 ± 11	NS	50.3 ± 11.3	59.4 ± 12.2	<0.0001
LDL (mg/dl)	105.1 ± 28.9	103.3 ± 28.2	NS	103.9 ± 28.4	96.4 ± 24	<0.02
Triglycerides (mg/dl)	57.2 ± 39.2	60.8 ± 32.8	NS	59.7 ± 35	45.7 ± 29.5	<0.0001
Autoantibody positive [n (%)]	7 (3.22)	8 (1.70)	NS	15 (2.18)	2 (1.86)	NS
Anti-GAD positive [n (%)]	6 (2.76)	7 (1.49)	NS	13 (1.89)	2 (1.86)	NS
Anti-IA2 positive [n (%)]	1 (0.46)	5 (1.06)	NS	6 (0.87)	2 (1.86)	NS
Anti-IAA positive [n (%)]	2 (0.92)	1 (0.21)	NS	3 (0.43)	0	NS

Data are means ± SD unless otherwise indicated. Overweight, obesity, and SDS-BMI were defined according to Italian growth charts in people aged 2–20 years (12). 1 SD of BMI defines overweight, 2 SD of BMI defines obesity. Pubertal developmental stages were determined according to Tanner. Differences between variables were evaluated by two-tailed Student's *t* test or Mann-Whitney test. Categorical variables were compared by χ^2 or Fischer's exact tests.

interassay CV between 4.9 and 7.0%. Anti-IA2 assay has intra- and interassay CVs between 2.5 and 2.8% and between 3.3 and 5.3%, respectively. Anti-IAA assay has intra- and interassay CVs between 3.0 and 5.8% and 4.2 and 6.7%, respectively.

Our laboratory achieved 76% sensitivity and 95.7% specificity for anti-GAD and 64% sensitivity and 98.9% specificity for anti-IA2 at the latest Diabetes Antibody Standardization Program (DASP2009). Anti-IAA results were confirmed by a second method based on a competitive fluid-phase radioimmunoassay (7).

RESULTS

Type 1 diabetes autoantibodies
In the 686 overweight/obese children, a single autoantibody (either anti-GAD, anti-IA2, or anti-IAA) was present in 15 subjects (2.18%). Anti-GADs were detectable in 13 of 686 (1.89%) children, anti-IA2s were present in 6 of 686 (0.87%) children, and anti-IAAs were found in 3 of 686 (0.43%) children. Two antibodies were found together in five (0.7%) subjects. All three autoantibodies were found in only one subject. In the 107 normal-weight children, anti-GAD and anti-IA2 were found together in two subjects (1.86%, *P* = NS vs. overweight/obese children).

No difference in autoantibody distribution was observed when our cohort was stratified by age, sex, SDS-BMI, pubertal stage, and the homeostasis model assessment–insulin resistance (HOMA-IR) (data not shown).

IGR and autoantibodies in overweight/obese children
Overall prevalence of IGR in our cohort of overweight/obese children was 11.37% (78/686). The frequency of IFG was 8.16% (56/686), IGT 3.2% (22/686), and diabetes 0.6% (4/686).

When divided on the basis of glucose regulation, the presence of autoimmunity was three times more prevalent in children with IGR (5.12%) than in children with normal glucose tolerance (1.80%). The prevalence of glucose abnormalities in antibody-positive subjects was 27%, compared with 11% in antibody-negative children.

In the whole group, anti-IAA titers correlated with postload glycemia (*P* < 0.03), which was significantly higher in antibody-positive children (133 ± 69.9 vs. 105.4 ± 17.7 mg/dl; *P* < 0.0001) when compared with antibody-negative subjects. Antibodies titers were not correlated to fasting glucose (93.5 ± 16.2 vs. 89.6 ± 7.4; *P* = NS).

CONCLUSIONS
In the present study, we found that the prevalence of autoantibodies in overweight/obese children was similar (2.18%) to that found in our cohort of normal-weight–matched subjects (1.86%, *P* = NS), as well as to that reported in the general population of schoolchildren (8,9). When our cohort was stratified in subjects with normal and impaired glucose regulation, prevalence of autoantibodies was higher in individuals with IGR (5.12%). This prevalence is similar to that reported in nonobese hyperglycemic children (10).

We also found that antibody-positive subjects had a significantly higher 2-h glycemia. Our results are in line with those recently demonstrated in the Diabetes Prevention Trial–Type 1 (DPT-1) study (11), where the majority of subjects diagnosed with type 1 diabetes had impaired post-OGTT glucose levels, thus suggesting that OGTT in antibody-positive subjects may help to prevent acute-onset disease. With regards to this point, the prevalence of glucose abnormalities in our antibody-positive subjects was nearly 30%, and in all cases, IGR was diagnosed by the 2-h value.

In conclusion, this study provides evidence that excess body weight and insulin resistance do not influence the frequencies of autoantibodies as postu-