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

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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% of 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 antibody 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 American Diabetes Association criteria in subjects with normal glucose tolerance, with impaired fasting glycaemia (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-Ab¹²⁵I-Radioassay, IA2-Ab¹²⁵I-Radioassay, and IAA-Ab¹²⁵I-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

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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 IGF 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 glycemia (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 individu-
als 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 Diabe-

tes 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 evi-
dence that excess body weight and insul-
in resistance do not influence the frequencies of autoantibodies as postu-

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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) (%)  | 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/m²)    | 25.1 ± 2.3 | 28.9 ± 4  | <0.0001                 | 27.7 ± 4.5       | 17.9 ± 2.7    | <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 (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 χ² or Fischer’s exact tests.
lated by the accelerator hypothesis, which is therefore not supported by our data. It also shows that an obese child can be at risk for type 1 diabetes as much as a normal-weight child. However, the hypothesis of the “overload” of β-cells as a result of increased insulin demands linked to obesity warrants further study.

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