

Changing Prevalence of Overweight Children and Adolescents at Onset of Insulin-Treated Diabetes

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OBJECTIVE — The aim of this study was to compare the prevalence of being overweight in black and white children and adolescents at onset of insulin-treated diabetes during two time periods: 1979–1989 (period I) and 1990–1998 (period II).

RESEARCH DESIGN AND METHODS — All black children <19 years of age diagnosed with diabetes and treated with insulin at onset admitted to the Children's Hospital of Pittsburgh between January 1979 and December 1998 were matched with white children by sex, age at onset, and year of diagnosis. Data were obtained from a review of medical records. Overweight was defined as BMI \geq 85th percentile for age and sex. Islet cell autoantibodies were measured.

RESULTS — The prevalence of being overweight increased from 12.6% (period I) to 36.8% (period II) ($P = 0.0003$); in whites from 2.9 to 16.6% ($P = 0.04$) and in blacks from 22 to 55% ($P = 0.001$); and in the age-group <11 years from 7.3 to 22.2% ($P = 0.04$) and age 11–18 years from 20 to 50% ($P = 0.006$). In children with at least one antibody, the prevalence of being overweight increased from 5.1 to 24.4% ($P = 0.001$). In the multivariate logistic regression, period of diagnosis (period II), race (black), age at onset (\geq 11 years old), and absence of autoimmunity were associated with being overweight.

CONCLUSIONS — At onset of the disease, the prevalence of being overweight has tripled from the 1980s to the 1990s, following the trend in the general population. Weight gain may be an accelerating factor for onset of insulin-treated diabetes and may have contributed to the increased incidence of diabetes in youth seen in some populations.

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It is generally believed that children and adolescents with insulin-treated diabetes (previously known as insulin-dependent diabetes, now type 1 diabetes) are not overweight at onset. Rather, overweight children are generally thought to have type 2 diabetes (formerly known as non-insulin-dependent diabetes) (1), as

obesity is a well-established risk factor for type 2 diabetes. However, two reports (2,3) have shown that young children who developed type 1 diabetes were heavier during their pre-diabetes infancy period than control children. The concept of excessive weight gain as a risk factor for type 1 diabetes among siblings was sup-

ported by a study from Finland (4), and it has recently been expanded as the “accelerator hypothesis” (5) with some evidence from a preliminary report of an inverse relationship between age at onset and BMI at diagnosis (6). The prevalence of being overweight has increased steadily for the last 20–30 years in children and adolescents, both in the U.S. (7,8) and around the world (9–13), which is concurrent with a rising incidence of insulin-treated diabetes in many populations (14–17). There are no data, to our knowledge, regarding changes in the prevalence of excess weight in children and adolescents at the diagnosis of insulin-treated diabetes. The Children's Hospital of Pittsburgh insulin-dependent diabetes (IDDM) registry includes all children <19 years of age diagnosed with diabetes and treated with insulin at onset since 1979. It has been shown to be representative of the larger population-based Allegheny County IDDM registry (18), which demonstrated an increase in the incidence of diabetes over the period of this study (15). The purpose of the present study was to compare the prevalence of being overweight at diabetes onset in children and adolescents in Children's Hospital of Pittsburgh IDDM registry over 2 decades.

RESEARCH DESIGN AND METHODS

Subjects

All patients treated with insulin at the onset of diabetes were admitted to Children's Hospital of Pittsburgh. As part of an ongoing study, all 130 black patients diagnosed between 1 January 1979 and 31 December 1998 were matched by sex, age (within 1 year), and year of diagnosis (within 1 year) to an equal number of white patients. The criteria for inclusion in this study were as follows: 1) being assessed to have diabetes and require insulin by a physician, 2) <19 years of age at diagnosis, and 3) treated with insulin therapy at the time of hospital discharge. All cases of secondary diabetes and type 2 diabetes, diagnosed on the basis of clinical

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Abbreviations: IA-2, insulinoma-associated protein 2; IAA, insulin autoantibodies; ICA, islet cell antibody; JDF, Juvenile Diabetes Foundation.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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See accompanying editorial, p. 2954.

Table 1—Characteristics of the study group

| Characteristics | Black | White | P |
|----------------------------|----------|----------|--------|
| n | 96 | 89 | |
| Age at onset (years) | 10 ± 4.2 | 10 ± 4.1 | 0.84 |
| Sex (male/female) | 46/54 | 45/55 | 0.90 |
| Period (I/II) | 38/62 | 40/60 | 0.79 |
| Family history of diabetes | 80 | 75 | 0.35 |
| Diabetic ketoacidosis | 42 | 38 | 0.33 |
| Ketosis | 69 | 78 | 0.12 |
| ≥1 autoantibody | 68 | 89 | 0.0005 |

Data are means ± SD and percent.

cal criteria, were excluded. The initial management of new patients with diabetes, which did not change over the time period of this study, involved starting insulin therapy in all patients with a presumptive diagnosis of type 1 diabetes, irrespective of obesity, if they had ketosis and/or severe hyperglycemia and/or marked weight loss. If obese patients improved dramatically or became euglycemic on small insulin doses while on diet, insulin was stopped within a few days and they were treated with diet and oral hypoglycemic agents. These patients and those treated without insulin at onset were not included in this study.

Demographic and clinical data

Data were obtained from review of medical records and included sex, race, date and age at onset, height, weight (measured in all children at diagnosis), family history of diabetes, bicarbonate level, presence of ketosis, and diabetic ketoacidosis. BMI was expressed as body weight in kilograms divided by the square of height in meters (kg/m^2) (19), and overweight was defined as BMI \geq 85th percentile for age and sex. Period I was defined as 1 January 1979 to 31 December 1989 and period II as 1 January 1990 to 31 December 1998.

Autoantibodies assays

Blood samples were obtained within 1 week of diagnosis for insulin autoantibodies (IAA) or within 3 months for autoantibodies other than IAA. Blood was stored frozen at 20°C before antibody testing. Antibody positivity was defined as having at least one of the four conventional autoantibodies present, either islet cell antibody (ICA) measured on human pancreas ($n = 184$), IAA ($n = 95$), GAD65 autoantibodies ($n = 175$), or insulinoma-

associated protein 2 (IA-2) autoantibodies ($n = 184$).

ICAs were detected by a modification of an immunoperoxidase method on human blood group 0 (H) fresh frozen pancreas (20). This assay is sensitive to Juvenile Diabetes Foundation (JDF) units using the JDF serum as standard. The specificity of this assay was 77–100%, and sensitivity varied between 88 and 99% in the JDF proficiency workshops conducted by the University of Florida in Gainesville from 1991 to 1996.

The insulin autoantibody assay was performed only on those subjects with serum available within 5 days of diagnosis. The radioimmunoassay used I^{125} -monoiodinated insulin obtained from New England Nuclear and protein A separation using the assay described by Williams et al. (21). This assay detected 16% of subsets of type 1 diabetes and was 100% specific in the Diabetes Autoantibody Standardization Program workshop in 2000, which was average for participating laboratories. The intra-assay coefficient of variation was 8% and the interassay coefficients of variation (CVs) were 8.9, 6.5, and 21.6%, respectively, for low, medium, and high controls.

GAD65 autoantibodies were detected by a radiobinding assay using ^{35}S -[Met]-labeled recombinant human GAD65 produced in vitro with the TNT reticulocyte R transcription/translation kit as described by Grubin et al. (22). The GAD65 construct used for this study was donated by Dr. Åke Lernmark, whereas the IA-2 construct (ICA512bdc) was provided by Dr. George Eisenbarth. The results were expressed as an index (index = sample cpm – negative control cpm/positive control cpm – negative control cpm) as previously reported (23). Of the results from the proficiency workshops orga-

nized by the University of Florida in Gainesville (1995, 1996, and 1997) and the Diabetes Autoantibody Standardization Program workshop (2000) organized by the World Health Organization, the data were 76–100% sensitivity, 90–100% specificity (100% specificity three times), and 100% validity for GAD autoantibodies; and 48–78.5% sensitivity, 98–100% specificity, 87.5% validity, and 91.6% consistency in the 1996 and 2000 workshops for IA-2 autoantibodies.

Statistical analysis

Student's *t* test was used to compare continuous variables and the χ^2 test to compare proportions. When the expected values were <5 , Fisher's exact test was used. *P* values <0.05 were deemed statistically significant. Logistic regression analysis was used to determine which variables were associated with presence of overweight. Variables introduced into the regression analysis included sex, race, age at diagnosis, time period, presence of at least one autoantibody to the islet cells, and presence of ketosis. Computations were done using the SPSS statistical software package (SPSS, Chicago, IL).

RESULTS— Complete data including blood for antibody testing were available for 185 (71%) of the 260 subjects, of whom 96 were black and 89 were white. Their characteristics are presented in Table 1. Of the 96 black subjects, 38% ($n = 36$) were diagnosed during period I and 62% ($n = 60$) during period II. Similarly, 40% ($n = 35$) of the white subjects presented during period I, whereas 60% ($n = 54$) were diagnosed during period II ($P = 0.79$), which is consistent with the increased number of newly diagnosed patients in the Children's Hospital of Pittsburgh Registry from 50–60 per year in the early 1980s to 120–150 per year at the end of the 1990s.

The prevalence of being overweight through the 20-year period was 27.5%. There was no significant difference by sex (females vs. males, 26.7 vs. 28.5%, $P = 0.91$). However, blacks had a higher prevalence of overweight than whites (42 vs. 11%, $P = 0.0001$), and adolescents (aged ≥ 11 years) had a higher prevalence of overweight than children aged <11 years (40 vs. 16%, $P = 0.0002$). Among those with autoimmunity, the prevalence of being overweight was 16%, but it was less

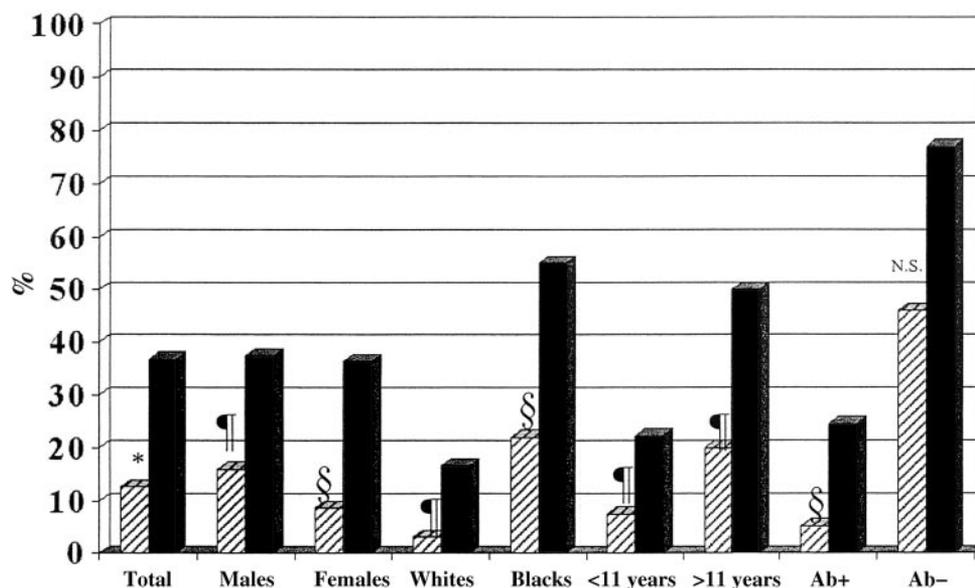


Figure 1—Prevalence of being overweight by period. ▨, period I; ■, period II. * $P < 0.0005$; § $P < 0.005$; ¶ $P < 0.05$. NS, not significant.

than in the group with no evidence of autoimmunity (66%, $P = 0.00001$).

When comparing the two periods, the prevalence of being overweight increased threefold, from 12.6% in the decade of the 1980s to 36.8% in the decade of the 1990s ($P = 0.0003$) (Fig. 1). This increase was seen in both males (16–37.5%, $P = 0.036$) and females (8.5–36.4%, $P = 0.002$). In whites, the prevalence rose five times, from 2.9 to 16.6% ($P = 0.04$), whereas in blacks it more than doubled from 22 to 55% ($P = 0.001$). In younger children (aged <11 years at onset), the prevalence of being overweight increased from 7.3 to 22.2% ($P = 0.04$), whereas in the group ≥ 11 years of age, it increased from 20 to 50% ($P = 0.006$).

In the group with islet autoantibodies ($n = 144$), who by definition have type 1a diabetes, the prevalence of obesity increased almost five times, from 5.1% in the 1980s to 24.4% in the 1990s ($P = 0.002$). The increase was statistically significant among blacks (7.4 vs. 36.8%, $P = 0.006$), males (6.8 vs. 28.2%, $P = 0.02$), females (3.4 vs. 21.2%, $P = 0.04$), and the adolescent group (5 vs. 33.3%, $P = 0.02$). In the group without autoantibodies, the prevalence of being overweight was higher and also increased from 46.1 to 75% without reaching statistical significance ($P = 0.07$), which was likely due to the small numbers ($n = 41$).

Table 2 shows the biochemical data at presentation and frequency of autoantibodies by race and period. No differences were seen in the severity of presentation

between periods in either blacks or whites. In period I, 39% of the group presented in diabetic ketoacidosis compared with 35% in period II ($P = 0.99$). There were also no significant differences in prevalence of ketosis (81 vs. 73%, $P = 0.2$), mean bicarbonate level (16.7 vs. 17.5 meq/l, $P = 0.3$), or venous pH (7.29 vs. 7.27, $P = 0.3$). There was also no statistically significant difference in severity of presentation (presence of diabetic ketoacidosis) between the overweight patients with and without evidence of autoimmunity (29 vs. 15%, $P = 0.37$).

In the logistic regression, being black (odds ratio 5.84; 95% CI 4.94–6.74), older (2.52; 1.61–3.38), diagnosed during the 1990s (5.95; 4.97–6.97), and not having islet antibodies (7.39; 6.51–8.27) were significantly associated with being overweight.

CONCLUSIONS— These data demonstrate that being overweight is increasingly prevalent in children and adolescents

with new-onset insulin-treated diabetes similar to the increasing prevalence of obesity observed in the general population (7,8). This increase was seen irrespective of sex, race, and age at onset, but it was more striking among whites and those with islet autoantibodies. The most dramatic increase was seen in those with autoimmune-associated type 1 diabetes, with a fivefold increase in the prevalence of being overweight. In the children without these autoantibodies, which is usually associated with type 2 diabetes and described in studies of “atypical diabetes” (24–26), the initially high prevalence of overweight in period I also almost doubled. This weight excess was obvious despite the frequent weight loss during the prodromal phase of the disease and was unlikely to have accounted for differences between the two periods as the frequency of ketosis and diabetic ketoacidosis were not different.

These observations provide further evidence that there may be a link between

Table 2—Biochemical data at presentation and frequency of autoantibodies by race and period

| | Black | | | White | | |
|---------------------------|-------------|-------------|----------|-------------|-------------|----------|
| | Period I | Period II | <i>P</i> | Period I | Period II | <i>P</i> |
| Diabetic ketoacidosis (%) | 53 | 36 | 0.12 | 37 | 38 | 0.95 |
| Ketosis (%) | 72 | 66 | 0.57 | 85 | 74 | 0.19 |
| Bicarbonate (meq/l) | 16.1 ± 7.8 | 17.6 ± 7.9 | 0.29 | 17.4 ± 6.6 | 17.4 ± 7.8 | 0.95 |
| Venous pH | 7.30 ± 0.14 | 7.25 ± 0.23 | 0.38 | 7.28 ± 0.17 | 7.29 ± 0.16 | 0.92 |
| ≥1 antibody | 75 | 65 | 0.31 | 89 | 88 | 0.83 |
| ≥3 antibodies | 32 | 29 | 0.72 | 52 | 51 | 0.95 |

Data are means ± SD unless otherwise indicated.

the prevalence of childhood weight excess and the rising incidence of childhood type 1 diabetes. The incidence of insulin-treated diabetes in adolescents in Allegheny County, Pennsylvania, increased more than threefold from the early 1980s to 1994 (15), which is concurrent with an increase in incidence of type 1 diabetes in children reported around the world (27). Our data from the Children's Hospital of Pittsburgh Registry, which has previously been shown to be representative of the Allegheny County population, reveal an apparent continued increase in these numbers. This requires validation by an update of the population-based registry. The BMI data demonstrate an increase in the prevalence of excess weight in children diagnosed with diabetes, as is also seen in the general population and is contemporaneous with the worldwide increased incidence of type 1 diabetes (27).

Our data support a potential mechanistic link between excess weight gain and increasing frequency and earlier onset of type 1a diabetes with the age decreasing to include most of early childhood (28). Obesity-associated insulin resistance increases insulin secretory demands on β -cells and may accelerate autoimmune damage in these metabolically upregulated cells by increasing antigen presentation (29). Also, the clinical presentation of autoimmune-mediated diabetes can probably occur earlier in the face of relative insulin deficiency, which otherwise may not become clinically apparent until later in life in susceptible individuals. These concepts are included in the recently described "accelerator hypothesis" (5). The theory of obesity-induced acceleration of type 1 diabetes is supported by the reports of an inverse correlation between age at onset and BMI at diagnosis in a group of children <16 years of age (6) as well as the studies that have shown that children who develop type 1 diabetes were heavier in their pre-diabetes infancy and childhood periods than control children (2–4).

In summary, this study shows that the prevalence of being overweight at onset of insulin-treated diabetes has tripled in children and adolescents from the 1980s to the 1990s, which follows the trend seen in the general population. The rate of this increase is most dramatic among those with type 1 diabetes. This leads to the speculation that excess weight gain may be an accelerating factor for onset of the

disease and that it may have contributed to the increase in incidence seen in some populations. This implication of mixed ethiopathogenesis may impact classification, treatment, and prevention of childhood diabetes. Moreover, these data raise a cautionary note in the general assumption that all overweight children with diabetes have type 2 diabetes. Instead, children with type 1 diabetes are increasingly likely to present with a phenotype that is similar to that of type 2 diabetes. Thus, both autoimmunity and insulin resistance may play a role in the precipitation of clinical disease.

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