

The Type 2 Family

A Setting for Development and Treatment of Adolescent Type 2 Diabetes Mellitus

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Objective: To identify physical, behavioral, and environmental features of adolescents (aged 11-17 years) with type 2 diabetes mellitus and their families to define the involvement of known risk factors and to define a profile of at-risk individuals.

Design and Methods: A total of 42 subjects from 11 families with an adolescent in whom type 2 diabetes was previously diagnosed participated. All subjects underwent anthropometric measurement and completed food frequency and eating disorder questionnaires, and were classified according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. In addition, laboratory tests to determine levels of hemoglobin A_{1c}, fasting glucose, C peptide, insulin, and proinsulin were performed.

Results: Type 2 diabetes had been diagnosed in 5 of 11 mothers and 4 of 11 fathers before the study. Type 2 diabetes was diagnosed in 3 of the remaining 7 fathers during the study. In 3 families, both parents were affected with type 2 diabetes. As a group, participants were obese, with a body mass index higher than the 95th percentile for probands and fathers, and higher than the 85th percentile for mothers and siblings. The sum of skin fold measurements was above the 95th percentile for the probands, their siblings, and the parents. All groups had high

fat intake and low fiber intake. None of the subjects participated in a structured or routine exercise program, and most reported no regular physical activity. Three of the probands met the criteria for binge-eating disorder, and 6 additional patients had notable characteristics of the disorder. Mothers affected with type 2 diabetes had markedly abnormal hemoglobin A_{1c} levels, indicating poor control. There were no group differences in fasting concentrations of insulin, proinsulin, or C peptide. However, a third of the mothers with type 2 diabetes, and all but 1 of the siblings, had evidence of insulin resistance.

Conclusions: Adolescents in whom type 2 diabetes has been diagnosed, as well as their first-degree family members, are obese. In addition, the incidence of diagnosed and undiagnosed type 2 diabetes or of insulin resistance in the families of adolescents with type 2 diabetes is striking. Probands and other family members have lifestyles characterized by high fat intake, minimal physical activity, and a high incidence of binge eating. These findings indicate that the families of adolescents with type 2 diabetes share many anthropometric and lifestyle risk factors. The design of treatment programs for adolescents with type 2 diabetes will need to address the lifestyle and health habits of the entire family.

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Editor's Note: The families described in this study seem to be walking time bombs for serious morbidity and worse. What would it take to stop the ticking? Next study, please.

Catherine D. DeAngelis, MD

WE REPORTED a 10-fold increase in the incidence of type 2 diabetes mellitus among adolescents in Cincinnati, Ohio, during the past decade.¹ Most startling is the observation that type 2 diabetes accounted for nearly 40% of new-onset diabetes cases among adolescents presenting to the diabetes clinic of the Children's Hospital Medical Center, Cincinnati. When initially seen, patients with type 2 diabetes were obese and pubertal and had strong family histories

of type 2 diabetes. Similar observations have been made in other parts of the United States, and with rising rates of obesity among the young,²⁻⁴ this problem can be expected to worsen.

Among adults, type 2 diabetes is associated with genetic, environmental, and lifestyle risk factors, such as obesity, low physical activity, and the high caloric intake typical of the western "supermarket diet."^{5,6} However, little detailed information is available regarding the role of these factors in the development of early type 2 diabetes among adolescents. The goal of this study was to identify physical, behavioral, and environmental features of adolescents (aged 11-17 years) with type 2 diabetes and their families to define the involvement of known risk factors and to define a profile of at-risk individuals to allow selection of patients for early intervention.

The affiliations of the authors appear in the acknowledgment section at the end of the article.

RESEARCH DESIGN, SUBJECTS, AND METHODS

SUBJECTS

All families containing an adolescent in whom type 2 diabetes was previously diagnosed at Children's Hospital Medical Center, Cincinnati, Ohio,¹ were contacted by letter and subsequent telephone call. Twenty-six families had both parents able to participate in the study, of which 11 families (42%) agreed to participate. The mean age and weight, sex, race, duration of diabetes, and incidence of parental diabetes did not differ between probands who participated and those who did not. There were no other exclusion criteria for participation. These studies were approved by the Institutional Review Board of Children's Hospital Medical Center. Participants aged 18 years and older signed informed consent forms before participation in this study. Parents of participants younger than 18 years signed informed consent forms for their children after written assent was obtained from the child.

PHYSICAL EXAMINATION AND ANTHROPOMETRIC MEASUREMENTS

Skin fold thickness was measured using Lange calipers at the triceps and subscapular regions. For skin fold thickness greater than 65 mm (the maximum opening of the calipers), greater than 65 mm was recorded. Waist and hip circumference measurements were taken with a calibrated nonstretchable tape at the narrowest part when viewed from the front and the widest part when viewed laterally, respectively.

FOOD FREQUENCY QUESTIONNAIRE

A dietary questionnaire⁷ was administered by a dietitian and used to determine individual fat and fiber intake. For fat

content, a score less than 17 is desirable, a score from 22 to 24 represents a typical American diet, and a score higher than 27 indicates a diet high in fat. For fiber content, a score less than 30 is desirable, while a score less than 20 indicates a diet deficient in fiber.

EATING AND ACTIVITY PATTERNS

Patients were questioned about their eating habits and body image in a structured interview using a standard eating disorder questionnaire and were classified according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.⁸ In addition, participants were asked to describe and quantify their leisure time activities.

LABORATORY EVALUATION

The plasma glucose level was measured using the glucose oxidase method (Glucose Analyzer II; Beckman, Brea, Calif). The insulin level was measured using an equilibrium radioimmunoassay (Linco, St Louis, Mo) with an antibody having less than 1% cross-reactivity for proinsulin and proinsulin-related peptides.⁹ Proinsulinlike material was measured using antiserum 11E in a nonequilibrium assay, as previously described.^{9,10} The level of C peptide was measured using antiserum M1280, as previously described.⁹ Intra-assay and interassay coefficients of variation were 9% and 9% for insulin, 9% and 6% for proinsulin, and 2% and 7% for C peptide, respectively. The reference range was based on 27 nondiabetic mixed lean and obese subjects.⁹

STATISTICAL ANALYSIS

Comparisons between groups were tested for significance using analysis of variance followed by Newman-Keuls testing. Descriptive data are expressed as mean \pm SEM.

RESULTS

Eleven probands, 9 siblings, and their parents participated. The age, race, and sex of the participants are summarized in **Table 1** and **Table 2**. The mean age of the participating probands was not different from the entire population¹ of adolescents with type 2 diabetes (14.50 ± 1.70 vs 14.08 ± 1.81 years) at Children's Hospital Medical Center; their mean body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) (39.60 ± 11.20 vs 38.50 ± 9.58), female-male ratio (1.75 vs 1.60), and percentage of African Americans (72% vs 68%) were not different either.

Type 2 diabetes was diagnosed in 5 of 11 mothers and 4 of 11 fathers before the study. During the study, type 2 diabetes was suspected in 3 of the remaining 7 fathers based on an elevated hemoglobin A_{1c} level, and confirmed by the subjects' personal physicians. Nine of 11 probands had at least 1 parent with type 2 diabetes. In 3 families, both parents were affected with type 2 diabetes. Type 2 diabetes was not diagnosed in any siblings before or during the study.

ANTHROPOMETRIC MEASUREMENTS

Participants were obese (mean BMI, 37 ± 11) (Table 1). The mean BMI, corrected for age, sex, and race, was higher than the 95th percentile for the probands and the fathers and higher than the 85th percentile for the mothers and siblings.¹¹ The sum of skin fold measurements (at the triceps and subscapular regions) was above the 95th percentile for all subgroups.¹¹ There was no statistically significant difference between probands and siblings for waist-hip ratio (Tables 1 and 2). However, among probands, the waist-hip ratio was in the third tertile in 5 and in the first tertile in 2 (**Figure**), whereas among their siblings the opposite pattern was observed.

EATING HABITS

All subgroups had high fat intake and low fiber intake (Tables 1 and 2). There were no differences in mean scores on either questionnaire between the subgroups or between parents with type 2 diabetes and those without.

Table 1. Anthropometric and Behavioral Characteristics of Adolescent Probands*

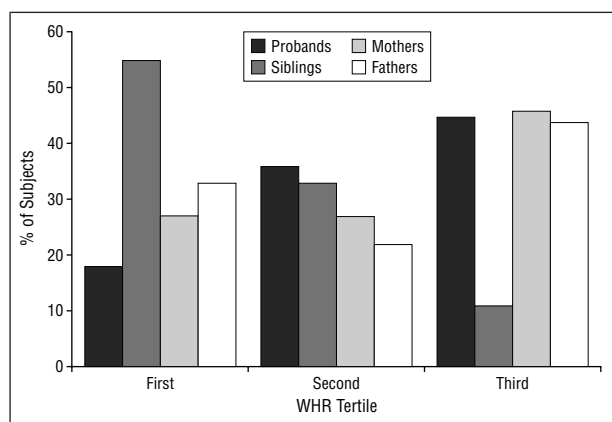
Subject No./Race/ Sex/Age, y	Hemoglobin A _{1c} Level	BMI, kg/m ² †	Circumference, cm		WHR	Skin Fold Thickness, mm			Television Viewing, h/d	Fat Score	Fiber Score
			Waist	Hip		Triceps	Subscapular Region	TRI/SC			
1/AA/M/14	0.063	63	144.3	176.0	0.82	65	65	1.00	5	18	19
2/W/M/13	0.082	30	101.5	115.2	0.88	40	46	0.87	9	25	19
3/AA/M/13	0.075	41	116.7	123.3	0.95	44	52	0.85	2	18	19
4/W/F/11	0.060	32	91.2	117.5	0.78	51	57	0.89	8	35	24
5/AA/F/15	0.171	33	95.7	117.0	0.82	49	55	0.89	6	25	22
6/AA/F/16	0.156	32	97.7	113.7	0.86	47	65	0.72	2	27	19
7/AA/F/17	0.192	40	112.0	125.3	0.89	65	65	1.00	1	13	16
8/W/F/15	0.077	38	118.7	124.6	0.95	65	65	1.00	5	15	19
9/AA/F/14	0.102	33	99.6	117.6	0.85	42	55	0.76	5	42	13
10/AA/M/16	0.056	59	148.9	145.5	1.02	65	65	1.00	6	31	28
11/AA/F/15	0.070	33	97.0	118.4	0.82	55	61	0.90	8	19	20

*AA indicates African American; W, white; BMI, body mass index; WHR, waist-hip ratio; TRI/SC, triceps-subscapular region ratio; and ellipses, data not applicable.

Table 2. Anthropometric and Behavioral Characteristics of Family Members*

Family Member	Age, y	Hemoglobin A _{1c} Level	BMI, kg/m ² †	Circumference, cm		WHR	Skin Fold Thickness, mm			Television Viewing, h/d	Fat Score	Fiber Score
				Waist	Hip		Triceps	Subscapular Region	TRI/SC			
Siblings (n = 9)	14.0 ± 3.4	0.060 ± 0.002	29 ± 8	89 ± 22	107 ± 21	0.83 ± 0.10	42 ± 19	42 ± 22	1.1 ± 0.2	3.0 ± 2.4	27 ± 8	16 ± 6
Mothers (n = 11)	40.5 ± 7.1	0.094 ± 0.013	38 ± 14	102 ± 18	124 ± 16	0.74 ± 0.30	49 ± 11	55 ± 13	0.9 ± 0.2	3.0 ± 1.3	25 ± 12	19 ± 11
Fathers (n = 11)	47.0 ± 14.0	0.070 ± 0.004	39 ± 7	120 ± 19	129 ± 15	0.93 ± 0.10	43 ± 7	51 ± 16	0.8 ± 0.2	4.2 ± 3.4	22 ± 7	15 ± 6

*Data are given as mean ± SEM. BMI indicates body mass index; WHR, waist-hip ratio; and TRI/SC, triceps-subscapular region ratio.



Waist-hip ratio (WHR) in families of adolescents with type 2 diabetes mellitus. Waist and hip circumference measurements were taken using standard procedures with a calibrated nonstretchable tape. Data are presented as percentage of members of each group whose WHR falls into first, second, and third tertiles for age and sex.¹²⁻¹⁴

EXERCISE

None of the probands participated in a structured or routine exercise program. Indeed, 9 of 11 probands reported no physical activity at all. Siblings were more likely to exercise than any other group, although 4 of 9 siblings also reported little to no physical activity. The patients reported an average time spent in sedentary activities (watching television, playing video games, or playing computer games) of 5.0 ± 2.7 h/d, whereas their siblings reported an average of 3.0 ± 2.4 h/d.

EATING DISORDER

Three probands met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria for binge-eating disorder. Six of the remaining patients had notable characteristics of the binge-eating disorder but did not meet strict criteria for binge-eating disorder. None reported self-induced vomiting or misuse of laxatives. One sibling, 2 mothers, and 1 father met these criteria. An additional sibling showed characteristics of the disorder without meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria.

LABORATORY EVALUATION

The probands and mothers had hemoglobin A_{1c} values above the normal range for the assay (0.04-0.08) (Tables 1 and 2). For mothers and fathers affected with type 2 diabetes, hemoglobin A_{1c} values were 0.134 ± 0.016 (range, 0.09-0.18) and 0.076 ± 0.007 (range, 0.05-0.10), respectively.

There were no significant group differences in fasting concentrations of insulin (P = .49), proinsulin (P = .41), or C-peptide (P = .24). However, among the 9 siblings, none of whom had an elevated fasting serum glucose level, 3 had fasting insulin levels greater than 179 pmol/L and 8 had C-peptide levels above the upper limit of normal (0.46 ± 0.03 nmol/L; mean, 0.69 ± 0.13 nmol/L). Proinsulin levels in these siblings were also elevated (**Table 3**). Each of the siblings with elevated insulin, proinsulin, and C-peptide values had a BMI at or greater than the 95th percentile for age, race, and sex. There was a positive correlation between BMI and C-peptide levels (r = 0.93, P = .002).

Table 3. Biochemical Characteristics of Family Members*

Family Members	Fasting Insulin Level, pmol/L	Fasting Proinsulin Level, pmol/L	Fasting C-Peptide Level, nmol/L
Siblings (n = 9)	169 ± 49	20.1 ± 5.1	0.70 ± 0.10
Mothers (n = 11)	201 ± 34	22.2 ± 5.7	0.80 ± 0.10
With type 2 diabetes mellitus (n = 5)	153 ± 47	28.7 ± 9.5	0.67 ± 0.08
Without type 2 diabetes mellitus (n = 6)	240 ± 43	17.1 ± 6.9	0.85 ± 0.12
Fathers (n = 11)	172 ± 44	20.2 ± 5.4	1.10 ± 0.20
With type 2 diabetes mellitus (n = 4)	146 ± 22	17.1 ± 9.5	0.97 ± 0.31
Without type 2 diabetes mellitus (n = 7)	192 ± 78	22.4 ± 2.3	1.26 ± 0.31

*Data are given as mean ± SEM. The normal fasting insulin level was less than 108 pmol/L; fasting proinsulin level, 8.60 ± 0.64 pmol/L; and fasting C-peptide level, 0.46 ± 0.03 nmol/L.

Of the 6 mothers in whom type 2 diabetes had not been previously diagnosed and who did not have an elevated fasting serum glucose level, 4 had fasting insulin levels greater than 179 pmol/L (range, 187-380 pmol/L). Of these 4, three had a BMI greater than the 95th percentile for age, sex, and race, and the fourth was at the 85th percentile. C-peptide levels were elevated in mothers, regardless of whether type 2 diabetes had previously been diagnosed (Table 3). Proinsulin levels were higher in mothers in whom type 2 diabetes was previously diagnosed compared with mothers in whom type 2 diabetes was not previously diagnosed (Table 3).

Three fathers had fasting insulin levels greater than 179 pmol/L: type 2 diabetes had previously been diagnosed in 1, and type 2 diabetes was diagnosed in 2 as part of their participation in this study. The mean C-peptide level of those in whom type 2 diabetes was previously diagnosed and those in whom type 2 diabetes was diagnosed during the study was 1.41 ± 0.17 nmol/L, and the mean proinsulin level was 23.8 ± 6.2 pmol/L.

COMMENT

We report that adolescents with type 2 diabetes have marked central obesity, poor dietary habits, including a high prevalence of binge-eating disorder, and a sedentary lifestyle. These findings, each of which is an independent risk factor for obesity-related morbidity, are similar to anthropometric and behavioral characteristics described among adult patients with type 2 diabetes.¹²⁻¹⁴ Most important, however, the data also indicate that adolescents with type 2 diabetes come from families in which parents and siblings share many or all of these high-risk features.

Not only did the parents of these adolescents have a high prevalence of central obesity, increased rates of type 2 diabetes, and insulin resistance, their otherwise healthy siblings also displayed marked central obesity and nearly all demonstrated elevated levels of C peptide and proinsulin. Among adolescents, a BMI higher than the 85th percentile for age and sex has been associated with a significant health risk, particularly if there is the additional feature of a family history of type 2 diabetes.¹⁵ Similarly, the odds ratio for the development of type 2 diabetes more than doubles from the first to the third waist-hip ratio tertile.¹⁴ Furthermore, fasting plasma proinsulin levels have a linear relationship with cumulative incidence of type 2 diabetes.¹⁶ These data indicate that

first-degree family members of adolescents with type 2 diabetes, including apparently healthy siblings, represent a group at high risk for development of the disorder.

Families of adolescents with type 2 diabetes eat diets high in fat ($P = .49$) and low in fiber ($P = .56$). The lack of a significant difference among the subgroups suggests that poor eating habits are characteristic of the family unit. This is troubling given that the patients and their parents had been given nutrition education at the time of the original diagnosis of diabetes. Furthermore, many of the families had an adult member with type 2 diabetes who had undergone his or her own dietary education and been prescribed an appropriate diet. Difficulty with the diet was not due to lack of understanding on the part of the parents; families expressed good understanding of the desired diet but had been unable to carry it out.

Short food questionnaires can be used to rank nutrient intake, and they have a high degree of correlation with complete assessments of food frequency.⁷ The specific screening questionnaire used in these studies has been validated against National Health and Nutrition Examination Survey dietary information in a multiage, multiethnic population representative of the US population.^{17,18} Although the questionnaire relies on recall, reports¹⁹ indicate that obese patients underestimate actual energy intake. Thus, it is likely that the true dietary habits in our study patients are worse than suggested by the self-report questionnaires.

Binge-eating behavior was prevalent in our study population, in agreement with previous reports²⁰ that approximately 30% of patients seeking weight control treatment have binge-eating disorder. While the prevalence of binge-eating disorder in adult patients in whom type 2 diabetes was newly diagnosed was not greater than in matched nondiabetic control subjects, 14% of subjects with type 2 diabetes reported occasional episodes of binge eating.²¹ Binge eating and binge-eating disorder have also been reported to be increased among women with type 1 diabetes.²² Unfortunately, our data do not indicate whether binge eating was present at diagnosis or developed as a result of rigid standards of dietary restraint. Recent reports²³ of an association between disordered eating behavior and diabetic retinopathy in adolescent girls with type 1 diabetes strongly indicate that this problem warrants further attention.

The finding of poor diabetes control among affected mothers suggests that conventional education and follow-up, aimed primarily at the adolescents, may not be sufficient. Failure of the mother to control her own disorder

may bode poorly for diabetes control in the child. Unlike patients with type 1 diabetes, in whom mismanagement has immediate effects on health, patients with type 2 diabetes do not necessarily have immediate feedback regarding their compliance with recommendations and may not recognize the future risks of their neglect and poor control.

To our knowledge, these results represent the first report of the lifestyle characteristics of adolescents with type 2 diabetes and their families. Although the generalization of the results of the present study to the adolescent population with type 2 diabetes is limited by the small sample size, we believe that these results have important implications for this population. First, no exclusion criteria that would bias the profile of the participants were used, and the participants accurately reflected the Children's Hospital Medical Center population with type 2 diabetes for age, race, sex, and body habitus. Second, these findings are in agreement with similar large population-based studies^{12-14,24} among adults with type 2 diabetes and, therefore, make sense clinically and biologically. While the specific extrapolation of these results to other centers must be undertaken with caution, we believe that the prevalence of risk factors among the probands and their families in this study accurately reflects the adolescent population with type 2 diabetes at large. Although a large population-based study of the etiology and treatment of type 2 diabetes in adolescents is highly desirable, no such study is under way. Therefore, we hope that the findings in this small representative group will be useful in guiding clinicians caring for obese adolescents, as well as in aiding in the design of larger studies.

In summary, our findings indicate that adolescents in whom type 2 diabetes has been diagnosed, as well as their first-degree family members, are obese, with anthropometric measurements characteristic of central obesity. Along with obesity, the incidence of diagnosed and undiagnosed diabetes or insulin resistance in the families of adolescents with type 2 diabetes is striking. In addition, probands and other family members, with or without type 2 diabetes, lead lifestyles characterized by high fat intake and minimal physical activity. Finally, clinicians need to be aware of the high prevalence of binge eating among probands and family members. Taken together, these findings indicate that the families of adolescents with type 2 diabetes represent a high-risk group and share many of the same anthropometric and lifestyle risk factors as the proband. Therefore, it may be appropriate to screen family members for insulin resistance or overt type 2 diabetes. Furthermore, the design of effective treatment programs for adolescents with type 2 diabetes will need to take into account the lifestyle and health habits of the entire family.

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