

Correlates of Treatment Patterns Among Youth With Type 2 Diabetes

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OBJECTIVE

To describe treatment regimens in youth with type 2 diabetes and examine associations between regimens, demographic and clinical characteristics, and glycemic control.

RESEARCH DESIGN AND METHODS

This report includes 474 youth with a clinical diagnosis of type 2 diabetes who completed a SEARCH for Diabetes in Youth study visit. Diabetes treatment regimen was categorized as lifestyle alone, metformin monotherapy, any oral hypoglycemic agent (OHA) other than metformin or two or more OHAs, insulin monotherapy, and insulin plus any OHA(s). Association of treatment with demographic and clinical characteristics (fasting C-peptide [FCP], diabetes duration, and self-monitoring of blood glucose [SMBG]), and A1C was assessed by χ^2 and ANOVA. Multiple linear regression models were used to evaluate independent associations of treatment regimens and A1C, adjusting for demographics, diabetes duration, FCP, and SMBG.

RESULTS

Over 50% of participants reported treatment with metformin alone or lifestyle. Of the autoantibody-negative youth, 40% were on metformin alone, while 33% were on insulin-containing regimens. Participants on metformin alone had a lower A1C ($7.0 \pm 2.0\%$, 53 ± 22 mmol/mol) than those on insulin alone ($9.2 \pm 2.7\%$, 77 ± 30 mmol/mol) or insulin plus OHA ($8.6 \pm 2.6\%$, 70 ± 28 mmol/mol) ($P < 0.001$). These differences remained significant after adjustment ($7.5 \pm 0.3\%$, 58 ± 3 mmol/mol; $9.1 \pm 0.4\%$, 76 ± 4 mmol/mol; and $8.6 \pm 0.4\%$, 70 ± 4 mmol/mol) ($P < 0.001$) and were more striking in those with diabetes for ≥ 2 years (7.9 ± 2.8 , 9.9 ± 2.8 , and $9.8 \pm 2.6\%$). Over one-half of those on insulin-containing therapies still experience treatment failure (A1C $\geq 8\%$, 64 mmol/mol).

CONCLUSIONS

Approximately half of youth with type 2 diabetes were managed with lifestyle or metformin alone and had better glycemic control than individuals using other therapies. Those with longer diabetes duration in particular commonly experienced treatment failures, and more effective management strategies are needed.

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Over the last two decades, type 2 diabetes has emerged as a pediatric condition. As a result, there are few randomized controlled trials assessing the safety and efficacy of various treatment modalities in youth with type 2 diabetes (1–3). In addition, there is also a paucity of data on the management strategies used in clinical practice, with few data on how these strategies are associated with clinical course in youth with type 2 diabetes. Furthermore, analyses of reports on treatment of youth with type 2 diabetes may be complicated by the inclusion of overweight youth clinically diagnosed with type 2 diabetes but who actually have autoimmune diabetes concomitant with their obesity (4–6). The latter will result in a study population with a mixture of type 1 and type 2 diabetes.

Metformin is the only approved oral pharmacologic agent for the treatment of type 2 diabetes in the pediatric population, and there is only a limited number of evidence-based guidelines for management of type 2 diabetes in youth (7). Recently, the Treatment Options for Type 2 Diabetes in Youth (TODAY) study (3), a multicenter trial of youth with type 2 diabetes, examined the long-term safety and efficacy of metformin alone or in combination with either rosiglitazone or intensive lifestyle modification. In the metformin monotherapy group, only half of the participants maintained optimal glycemic control over 3–4 years, suggesting a more rapid deterioration in glycemic control in adolescents than in adults with type 2 diabetes (8–10).

To provide further information about treatment of youth with type 2 diabetes, we analyzed cross-sectional data from the SEARCH for Diabetes in Youth study (SEARCH) to describe diabetes treatment regimens used in a large cohort of youth 10–20 years old with provider-diagnosed type 2 diabetes. We examined whether type of treatment regimen varied by demographic factors, as is the case with treatment regimens for type 1 diabetes (11). We also assessed whether treatment regimen was associated with glycemic control and explored whether this association varied with diabetes duration. Finally

we tested whether, as in observational studies of adults with type 2 diabetes, lifestyle changes and metformin were associated with lower A1C than other therapies, including insulin (12,13).

RESEARCH DESIGN AND METHODS

Overview of SEARCH

SEARCH is an ongoing multicenter observational study that conducts population-based ascertainment of youth <20 years of age newly diagnosed with diabetes (14). Youth with diabetes were identified in geographically defined populations in Colorado, Ohio, South Carolina, and Washington; among managed health care plan enrollees in Hawaii and California; and among Indian Health Service beneficiaries in selected American Indian populations. Cases were considered valid if diagnosed by a health care provider. For all validated cases, core demographic and diagnostic information, including date of birth, sex, date of diabetes diagnosis, and clinical diabetes type, was obtained from medical records. All youth or their parents/guardians were asked to complete a short initial survey. Youth who completed the initial survey and whose diabetes was not secondary to another condition were invited to a study visit.

Data Collection

Study visits were conducted when participants were metabolically stable (no episode of diabetic ketoacidosis during the previous month). Written informed consent and assent (when appropriate) were obtained at the start of the visit in accordance with the guidelines established by the local institutional review boards. Participants were instructed to fast overnight for at least 8 h and not to take diabetes medications the morning of the visit except for basal insulin administered by a continuous insulin infusion pump. Blood was drawn, and a urine sample was collected. Specimens were processed locally and shipped within 24 h to the central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories).

Physical examinations at the study visits were conducted according to standardized protocols by trained and

certified staff members. Height and weight were measured to the nearest 0.5 cm and 0.1 kg. BMI was calculated as weight in kilograms divided by the square of height in meters and converted to BMI z score using a standard Centers for Disease Control and Prevention approach (15). Waist circumference was measured to the nearest 0.1 cm following the National Health and Nutrition Examination Survey (NHANES) protocol (16). Information collected at the visit included current use of medications to treat diabetes and other conditions, frequency of self-monitoring of blood glucose (SMBG), type of health care provider delivering diabetes care, household structure (one vs. two parents), household income, highest level of parent education, and insurance status. This was collected from parents or guardians for participants <18 years of age and from the participant themselves if they were age 18 years or older. Self-reported race and ethnicity were collected as part of the initial survey using the 2000 U.S. Census questions (17).

Diabetes Treatment Regimens and SMBG

Diabetes treatment regimen was categorized as follows: 1) lifestyle alone (no pharmacologic treatment and/or diet and exercise), 2) metformin alone, 3) any oral hypoglycemic agent (OHA) (e.g., sulfonyleureas, thiazolidinediones, acarbose) other than metformin or two or more OHAs (e.g., metformin plus acarbose), 4) insulin alone, and 5) insulin plus any OHA(s), including metformin. For participants on insulin therapy, information on frequency, mode of administration, and type(s) of insulin was collected. Frequency of SMBG was self-reported and categorized as testing less than once a day, one to three times a day, and four times a day or more.

Laboratory Analyses

Samples were analyzed for GAD65 and insulinoma-associated protein-2 diabetes autoantibodies (DAs) using a standardized assay protocol and a common serum calibrator developed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-

sponsored standardization group. Results were expressed as NIDDK units (NIDDKU) per milliliter (18). Fasting C-peptide (FCP) was measured by a two-site immunoassay (Tosoh Bioscience, San Francisco, CA). The assay sensitivity is 0.05 ng/mL. A1C was measured by a dedicated ion-exchange high-performance liquid chromatography instrument (Tosoh).

Selection of the Study Population

Sample selection for inclusion in these analyses is based on clinical diabetes type, participation in a baseline study visit, and availability of a fasting blood sample. Clinical diabetes type was defined as the diabetes type assigned by the health care professional around the time of diagnosis. This was obtained from medical records or physician reports and categorized as type 1 (combining type 1, type 1a, and type 1b), type 2, secondary diabetes, and other types (such as “hybrid,” maturity-onset diabetes of the young, other type, and unknown/missing). Of the 548 youth whose clinically diagnosed type 2 diabetes was prevalent in 2001 or incident in 2002 through 2005 who attended a baseline SEARCH visit, we excluded 74 youth who did not have a fasting blood sample, which resulted in a final sample size of 474 youth for these analyses.

Statistical Analyses

Because we were interested in treatments used by youth with clinically diagnosed type 2 diabetes, we initially present data on all SEARCH participants with a clinical diagnosis of type 2 diabetes in our analytic sample. Then, to avoid possible effects of immune-mediated β -cell destruction on specific key clinical outcomes, we limit some analyses to those youth with a clinical diagnosis of type 2 diabetes who had negative results for both GAD65 and insulinoma-associated protein-2 DAs ($n = 428$ of the 474 participants with measured DA).

Statistical analyses were conducted using SAS (version 9.2; SAS Institute, Cary, NC) with a type I error rate of 0.05. Outcome variables with right-skewed distributions (FCP, A1C) are presented with P values based on log-transformed values. Associations between DA status

and demographic and clinical characteristics were analyzed using χ^2 statistics and t tests for categorical and continuous variables, respectively. Comparisons of treatment regimens were analyzed using χ^2 statistics and one-way ANOVA for categorical and continuous variables, respectively. We used multiple linear regression analyses to evaluate independent associations of treatment regimens and A1C, adjusting for age, diabetes duration, race/ethnicity, household income, and structure (one- vs. two-parent household), parental education, study site, FCP, and frequency of SMBG. All underlying assumptions for normality and equal variances in residuals for linear regression and group variances in ANOVA were confirmed. Further analyses explored the association between A1C/FCP and treatment regimen across subgroups by diabetes duration (<2 years vs. ≥ 2 years), SMBG (<1 time daily, 1–3 times daily, ≥ 4 times daily), and sex. All analyses are adjusted for age and sex, with the exception of the sex-subgroup model, which was adjusted for diabetes duration. We used logistic regression to model the odds of A1C $\geq 8\%$ vs. <8% across treatment and duration subgroups, adjusted for age and sex, to allow comparisons with the TODAY study, where treatment failure was defined as A1C $\geq 8\%$.

RESULTS

The study sample was comprised of 474 youth with a clinical diagnosis of type 2 diabetes with a mean (SD) duration of 24.2 (22.3) months and a mean age of 16.3 (2.8) years at the study visit. The majority (63%) were female and from minority racial and ethnic groups (35% black, 24% Hispanic, 10% Native American, and 9% Asian/Pacific Islander). A majority (64%) reported a family income of <50,000 USD (16% missing data), and over half (61%) received their diabetes care from a pediatric endocrinologist. Mean BMI z score was 1.96 (0.79).

Comparison of DA-Negative and DA-Positive Participants

Of the total sample, 46 (9.7%) were positive for at least one of the two DAs measured by the study. Sex, race/

ethnicity, socioeconomic indices, diabetes duration, and A1C at the study visit were not significantly different between DA-negative and DA-positive participants (data not shown). However, mean FCP levels were significantly higher (3.6 ng/mL vs. 2.7 ng/mL, $P < 0.0001$) in DA-negative participants. Treatment regimens were significantly different by DA status ($P < 0.0001$) with insulin use less common in DA-negative participants than DA-positive participants (33 vs. 70%). Management was lifestyle only in 12.7% of DA-negative vs. 8.7% of DA-positive and metformin only medication in 38.2% of DA-negative vs. 17.4% of DA-positive participants. Frequency of SMBG differed significantly ($P = 0.003$) by DA status, with DA-positive participants performing SMBG more frequently (45.5% ≥ 4 times daily, 40.9% 1–3 times daily, and 13.6% more than once daily) compared with DA-negative participants (53% 1–3 times daily and 23.2% more than once daily).

Analyses Restricted to DA-Negative Participants

Demographic, clinical, and laboratory characteristics of the 428 DA-negative participants by diabetes treatment regimen are shown in Table 1. Metformin monotherapy was the most common (40%) treatment; however, a substantial proportion of youth (33%) were on regimens that included insulin. The distribution of treatment regimens differed significantly by race/ethnicity ($P = 0.001$), although the use of metformin monotherapy was not significantly different among non-Hispanic whites, blacks, and Hispanics ($P = 0.25$). Treatment regimens also varied by their type of diabetes care provider, with participants whose primary diabetes care provider was a pediatric endocrinologist most likely to be on metformin monotherapy (44%).

There were significant differences in A1C by treatment regimen. Participants on lifestyle and metformin monotherapy had lower A1C than all other groups ($P < 0.001$). These differences remained significant after adjustment for age, duration, race/ethnicity, sex, socioeconomic measures (parental education, household income, and composition), BMI z score, FCP, and

Table 1—Demographic and social characteristics of youth with type 2 diabetes who were DA negative (n = 428) by diabetes treatment regimen: SEARCH, 2001–2005

	Total (N = 428)	Lifestyle	Metformin only	Insulin only	Other OHA**/multiple OHAs***	Insulin and OHA	P†
N (%)		56 (13.1)	173 (40.4)	48 (11.2)	59 (13.8)	92 (21.5)	
Age at in-person visit (years)	16.25 (2.8)	17.4 (2.6)	15.7 (2.5)	16.1 (3.3)	17.6 (2.7)	16.0 (2.3)	<0.001
Female sex, N (%)	272 (63.6)	37 (13.6)	107 (39.3)	32 (11.8)	36 (13.2)	60 (22.1)	0.93
Diabetes duration (months)	24.6 (22.5)	23.6 (22.9)	20.1 (18.0)	32.0 (30.4)	32.5 (23.6)	24.6 (22.3)	<0.001
Race/ethnicity, N (%)							<0.001
Asian/Pacific Islander	39 (9.1)	11 (28.2)	14 (35.9)	5 (12.8)	5 (12.8)	4 (10.3)	
Non-Hispanic black	154 (36.0)	12 (7.8)	59 (38.3)	17 (11.0)	16 (10.4)	50 (32.5)	
Hispanic	105 (24.5)	18 (17.1)	44 (41.9)	14 (13.3)	15 (14.3)	14 (13.3)	
Native American	44 (10.3)	7 (15.9)	13 (29.6)	2 (4.6)	17 (38.6)	5 (11.4)	
Non-Hispanic white	83 (19.4)	8 (9.6)	41 (49.4)	10 (12.1)	6 (7.2)	18 (21.7)	
Household income (USD), N (%)							0.28
<25,000	173 (40.7)	15 (8.7)	73 (42.2)	24 (13.9)	22 (12.7)	39 (22.5)	
25,000–49,000	103 (24.2)	17 (16.5)	40 (38.8)	8 (7.8)	13 (12.6)	25 (24.3)	
≥50,000	80 (18.8)	15 (18.8)	34 (42.5)	6 (7.5)	10 (12.5)	15 (18.8)	
Parental education, N (%)							0.46
<High school graduate	65 (15.6)	9 (13.9)	20 (30.8)	11 (16.9)	9 (13.9)	16 (24.6)	
High school graduate	147 (35.3)	14 (9.5)	62 (42.2)	18 (12.2)	21 (14.3)	32 (21.8)	
Some college through associate degree	135 (32.4)	20 (14.8)	62 (45.9)	9 (6.7)	20 (14.8)	24 (17.8)	
Bachelor's degree or more	70 (16.8)	10 (14.3)	26 (37.1)	9 (12.9)	7 (10.0)	18 (25.7)	
Household composition, N (%)							0.52
Single parent	199 (46.8)	21 (10.6)	84 (42.2)	24 (12.1)	22 (11.1)	48 (24.1)	
Two parents	181 (42.6)	28 (15.5)	72 (39.8)	20 (11.1)	26 (14.4)	35 (19.3)	
Other	45 (10.6)	6 (13.3)	17 (37.8)	4 (8.9)	10 (22.2)	8 (17.8)	
Health insurance, N (%)							<0.001
Private	216 (51.2)	29 (13.4)	90 (41.7)	24 (11.1)	25 (11.6)	48 (22.2)	
Medicaid/Medicare	162 (38.4)	13 (8.0)	74 (45.7)	20 (12.4)	18 (11.1)	37 (22.8)	
None/other	44 (10.5)	12 (27.3)	9 (20.5)	4 (9.1)	15 (34.1)	4 (9.1)	
Provider type, N (%)							<0.001
Pediatric endocrinologist	260 (61.3)	30 (11.5)	114 (43.9)	27 (10.4)	28 (10.8)	61 (23.5)	
Adult endocrinologist	26 (6.1)	4 (15.4)	11 (42.3)	5 (19.2)	2 (7.7)	4 (15.4)	
Generalist	67 (15.8)	11 (16.4)	24 (35.8)	4 (6.0)	18 (26.9)	10 (14.9)	
Nurse practitioner/physician assistant	35 (8.3)	2 (5.7)	13 (37.1)	7 (20)	0 (0.0)	13 (37.1)	
Other/none	36 (8.5)	8 (22.2)	11 (30.6)	5 (13.9)	10 (27.8)	2 (5.6)	

Data are means (SD) unless otherwise indicated. **OHA = yes to any of the following: sulfonylureas (n = 39), thiazolidinedione (n = 18), acarbose (n = 0), other (n = 6). In the other OHA/multiple OHAs category, 23 participants were taking a single OHA only (not metformin) and 36 reported multiple OHAs. ***Multiple OHAs = two or more OHAs of metformin, sulfonylureas, thiazolidinedione, acarbose, or other. †P value for association between the variable and the 5 treatment groups. Comparisons of continuous outcomes, ANOVA; comparisons of categorical outcomes, χ^2 tests.

frequency of SMBG. When adjusted for these covariates, A1C was 6.8% for lifestyle alone, which was significantly lower ($P < 0.001$) than all other groups except metformin monotherapy (A1C 7.5%, $P = 0.10$). The adjusted mean A1C was significantly higher in those treated with insulin monotherapy than in those treated with lifestyle alone (9.1 vs. 6.8%) ($P < 0.001$) or metformin monotherapy (7.5%, $P = 0.003$) but it was not significantly different for the other regimens. When regimens were combined to compare those on insulin-containing regimens and those who were not on insulin, participants on non-insulin-

containing regimens had a lower A1C than those on insulin (7.4 vs. 8.8%, $P < 0.001$; data not shown). Adjustment for diabetes duration, FCP, and demographic and socioeconomic measures did not change the significant A1C differences by regimen (Table 2).

Frequency of SMBG and Glycemic Control

Frequency of SMBG varied by treatment regimen and was associated with A1C. Participants who reported being treated with lifestyle or on metformin monotherapy reported testing less frequently than those on more intense

regimens (Table 2); 45% of participants on insulin-containing treatment regimens reported testing four or more times, while 64% of participants on metformin monotherapy tested one to three times daily and 52% of participants on lifestyle tested less than once a day.

Increased frequency of SMBG was associated with lower A1C in those on insulin-containing regimens, with mean A1C significantly lower in participants on insulin who reported testing four or more times daily compared with those who tested less frequently ($P = 0.01$). In

Table 2—Predictors and effects of treatment modality of youth with type 2 diabetes who were DA negative (n = 428) by diabetes treatment regimen: SEARCH, 2001–2005

	Total (N = 428)	Lifestyle	Metformin only	Insulin only	Other OHA**/ multiple OHAs***		P†
A1C							<0.001
%	7.9 (2.5)	7.0 (2.3)	7.0 (2.0)	9.2 (2.7)	9.0 (2.7)	8.6 (2.6)	
mmol/mol	63 (27)	53 (25)	53 (22)	77 (30)	75 (30)	70 (28)	
A1C adjusted for duration, FCP, and socioeconomic variables, mean (SE) [^]							<0.001
%	8.3 (0.24)	6.8 (0.4)	7.5 (0.3)	9.1 (0.4)	9.0 (0.4)	8.6 (0.4)	
mmol/mol	67 (3)	51 (4)	58 (3)	76 (4)	75 (4)	70 (4)	
FCP (ng/mL)	3.6 (2.1)	3.9 (2.1)	3.9 (2.1)	2.4 (1.8)	3.4 (2.1)	3.3 (2.3)	<0.001
Fasting serum glucose (mg/dL)	160.5 (80.9)	138.4 (77.6)	138.8 (60.8)	188.0 (89.1)	195.5 (100.1)	182.1 (85.0)	<0.001
Frequency of SMBG, N (%)							<0.001
<Once a day	91 (24.3)	21 (23.1)	39 (42.9)	7 (7.7)	18 (19.8)	6 (6.6)	
1–3 times daily	200 (53.3)	15 (7.5)	98 (49.0)	16 (8.0)	27 (13.5)	44 (22.0)	
≥4 times daily	84 (22.4)	4 (4.8)	15 (17.9)	24 (28.6)	5 (6)	36 (42.9)	
Insulin dose (units/kg/day)	0.60 (0.46)	—	—	0.52 (0.28)		0.57 (0.43)	0.47

Data are means (SD) unless otherwise indicated. **OHA = yes to any of the following: sulfonylureas (n = 39), thiazolidinedione (n = 18), acarbose (n = 0), other (n = 6). In the other OHA/multiple OHAs category, 23 participants were taking a single OHA only (not metformin) and 36 reported multiple OHAs. ***Multiple OHAs = two or more OHAs of metformin, sulfonylureas, thiazolidinedione, acarbose, or other. †P value for association between the variable and the 5 treatment groups. Comparisons of continuous outcomes, ANOVA; comparisons of categorical outcomes, χ^2 tests. [^]Socioeconomic variables include age at initial patient visit, health insurance status, sex, parental education, household income, and household composition.

participants on non-insulin-containing regimens, although A1C trended lower in those who tested four or more times daily, this was not significant ($P = 0.06$) (data not shown).

A1C and FCP Stratified by Duration of Diabetes and Insulin Use

Additional model-adjusted analyses were conducted exploring the associations between measured A1C and FCP and treatment regimen across subgroups based on diabetes duration (<2 years and ≥2 years), SMBG frequency, and sex (Table 3). Overall, participants with duration of diabetes ≥2 years (n = 156, 36%) had significantly higher mean A1C (8.5 vs. 7.8%, $P = 0.03$) and significantly lower mean FCP (2.8 vs. 3.8 ng/mL, $P < 0.001$) compared with participants with shorter diabetes duration of diabetes (n = 272, 64%) (Table 3). A1C was significantly lower in participants who were on non-insulin-containing regimens compared with those on insulin regardless of duration (Table 3). All models in Table 3 were adjusted by age and sex except for sex comparisons, which were adjusted by age and duration.

We analyzed A1C as a continuous variable (Table 3) as well as a categorical variable (Table 4). In unadjusted

analysis, a duration of diabetes >2 years was associated with a significantly higher frequency of an A1C >8% for those on metformin monotherapy (14.7 vs. 39.2% with duration <2 vs. ≥2 years, $P < 0.001$) and for those on insulin plus an OHA (42.4 vs. 73.7% with duration <2 years vs. ≥2 years, $P = 0.009$). For those with diabetes duration ≥2 years, participants using lifestyle alone (21.4%) or metformin alone (39.2%) were less likely to have an A1C ≥8% compared with those on more intensive regimens.

Odds ratios (ORs) were calculated to determine the likelihood of having an A1C ≥8% (which we define as treatment failure) comparing participants with diabetes duration ≥2 years with those with duration <2 years. The OR for having an A1C ≥8% were also compared across treatment groups using metformin alone as the reference group. Among those with a duration ≥2 years, the OR was 2.18 (95% CI 1.32–3.60) for an A1C ≥8% compared with the reference group of those with duration <2 years. Among the participants with a duration <2 years, all groups had a greater OR of having an A1C ≥8% (OR 1.45–6.86) compared with those on metformin alone, although lifestyle alone was not

statistically significantly different. In those with a duration ≥2 years, those on lifestyle alone had a nonsignificant OR <1 of having an A1C ≥8% (0.27) compared with those on metformin alone, while all other groups continued to have a greater OR of an A1C ≥8% (OR 2.45–3.88). As expected, those on insulin-containing regimens had a higher OR of treatment failure (A1C ≥8%) than those on non-insulin treatment regimens in both the duration categories of <2 years and ≥2 years (3.53 and 3.23, respectively).

For participants with duration of diabetes <2 years, mean FCP was not significantly different between those not on insulin compared with those using insulin (4.2 ng/mL vs. 3.7 ng/mL, $P = 0.13$). However, for those with duration of diabetes ≥2 years, mean FCP was significantly lower in participants who were on insulin compared with those who were not (2.0 ng/mL vs. 3.2 ng/mL, $P < 0.001$).

A1C and FCP Stratified by Sex

A1C was different across treatment regimens for both females and males, but these results did not differ by sex (Table 3). Likewise, the A1C for females and males was different for those on

Table 3—Least squares means of A1C and FCP among youth with type 2 diabetes by treatment regimen, frequency of SMBG, sex, and duration of diabetes: SEARCH, 2001–2005

	Overall		Noninsulin therapy				Insulin therapy		P for noninsulin vs. insulin therapy	
	Total	Noninsulin therapy	Insulin therapy	Lifestyle	Metformin only	Other OHA/multiple OHA	Insulin only	Insulin and metformin/insulin and other OHA		
n	428	288	140	56	173	59	48	92		
A1C by duration (%; mmol/mol)										
<2 years	7.81 (0.17); 62 (2)	7.01 (0.17); 53 (2)	8.45 (0.26); 69 (3)	<0.001	6.84 (0.35); 51 (4)	6.85 (0.21); 51 (2)	8.15 (0.46); 66 (5)	9.01 (0.44); 75 (5)	8.20 (0.30); 66 (3)	<0.001
≥2 years	8.45 (0.22); 70 (2)	8.01 (0.24); 64 (3)	9.49 (0.32); 80 (4)	<0.001	6.49 (0.62); 47 (7)	7.72 (0.31); 61 (3)	9.03 (0.39); 75 (4)	9.49 (0.49); 80 (5)	9.50 (0.39); 80 (4)	<0.001
<i>P</i>	0.03	0.001	0.01	0.62	0.02	0.14	0.47	0.01		
A1C by glucose-monitoring frequency (%; mmol/mol)										
<Once a day	7.91 (0.30); 63 (3)	7.18 (0.26); 55 (3)	8.79 (0.64); 73 (7)	0.02	6.42 (0.48); 47 (5)	6.93 (0.35); 52 (4)	8.80 (0.53); 73 (6)	10.89 (0.84); 95 (9)	6.52 (0.90); 48 (10)	<0.001
1–3 times a day	8.21 (0.20); 66 (2)	7.42 (0.20); 58 (2)	9.39 (0.30); 79 (3)	<0.001	6.42 (0.57); 47 (6)	7.19 (0.23); 55 (3)	8.79 (0.43); 73 (5)	9.14 (0.55); 76 (6)	9.50 (0.33); 80 (4)	<0.001
≥4 times a day	7.59 (0.34); 59 (4)	7.01 (0.47); 53 (5)	8.28 (0.31); 67 (3)	0.02	6.44 (1.10); 47 (12)	6.80 (0.57); 51 (6)	8.02 (0.98); 64 (11)	8.78 (0.45); 72 (5)	7.89 (0.38); 63 (4)	0.0550
<i>P</i>	0.26	0.63	0.03	0.99	0.71	0.76	0.09	<0.001		
A1C by sex (%; mmol/mol)										
Female	8.26 (0.15); 67 (2)	9.06 (0.24); 76 (3)	7.55 (0.17); 59 (2)	<0.001	7.18 (0.38); 55 (4)	7.26 (0.22); 56 (2)	8.61 (0.37); 71 (4)	9.43 (0.39); 80 (4)	8.83 (0.29); 73 (3)	<0.001
Male	8.04 (0.21); 64 (2)	8.84 (0.33); 73 (4)	7.48 (0.22); 58 (2)	<0.001	6.58 (0.52); 48 (6)	7.31 (0.28); 56 (3)	8.63 (0.47); 71 (5)	8.98 (0.56); 75 (6)	8.72 (0.40); 72 (4)	<0.001
<i>P</i>	0.38	0.82	0.58	0.34	0.90	0.98	0.51	0.82		
FCP by duration (ng/mL)										
<2 years	3.81 (0.17)	4.19 (0.16)	3.70 (0.24)	0.08	4.11 (0.31)	4.26 (0.20)	3.86 (0.49)	2.81 (0.45)	4.04 (0.28)	0.06
≥2 years	2.82 (0.21)	3.23 (0.23)	2.08 (0.29)	0.001	3.46 (0.63)	3.15 (0.30)	3.32 (0.37)	2.07 (0.45)	2.11 (0.36)	0.03
<i>P</i>	<0.001	<0.001	<0.001	0.36	0.002	0.38	0.26	<0.001		
FCP by sex (ng/mL)										
Female	3.16 (0.14)	3.55 (0.16)	2.71 (0.22)	0.002	3.56 (0.36)	3.61 (0.21)	3.36 (0.35)	2.38 (0.39)	2.87 (0.27)	0.03
Male	3.51 (0.20)	3.79 (0.21)	3.20 (0.30)	0.10	3.65 (0.48)	3.74 (0.26)	4.16 (0.49)	2.43 (0.52)	3.60 (0.37)	0.16
<i>P</i>	0.14	0.34	0.19	0.89	0.70	0.18	0.94	0.11		

All means (SE) are estimated from multivariable general linear models, adjusted by age and sex except for sex comparisons, which were adjusted by age and duration.

Table 4—ORs (95% CI) of A1C \geq 8.0% (64 mmol/mol)† among youth with type 2 diabetes by treatment regimen and duration of diabetes: SEARCH, 2001–2005

	Total (N = 428)	Noninsulin therapy			Insulin therapy	
		Lifestyle (n = 56)	Metformin only (n = 173)	Other OHA/ multiple OHAs (n = 59)	Insulin only (n = 48)	Insulin and metformin/insulin and other OHA (n = 92)
DM duration <2 years	1.00 (–)	1.45 (0.60–3.54)	1.00 (–) 1.00 (–)	4.85 (1.84–12.81)	6.86 (2.68–17.60) 3.53 (1.56–6.68)	4.45 (2.14–9.23)
DM duration \geq 2 years	2.18 (1.32–3.60)	0.27 (0.06–1.12)	1.00 (–) 1.00 (–)	2.45 (0.98–6.14)	3.55 (1.16–10.89) 3.23 (1.99–6.24)	3.88 (1.48–10.19)

†ORs for A1C \geq 8% are organized as follows: overall duration \geq 2 years vs. duration <2 years (reference), within-duration category odds of each of 4 treatments (lifestyle, other OHA/multiple OHAs, insulin only, insulin plus metformin/OHA) vs. metformin only (reference), and odds of insulin vs. noninsulin (reference).

non-insulin-containing regimens and insulin-containing regimens, but the mean A1C did not differ by sex.

Females had significantly different treatment regimens across FCP levels, and those on insulin-containing regimens had lower mean FCP than those who were not on insulin ($P = 0.002$) (Table 3). Males did not have different regimens based on FCP ($P = 0.10$). In comparing FCP in females to males, there was no significant difference within treatment groups or between those on non-insulin-containing regimens versus insulin-containing regimens ($P = 0.34$ and 0.19 , respectively, for noninsulin vs. insulin-containing regimens).

CONCLUSIONS

In this SEARCH cohort of youth with DA-negative type 2 diabetes, treatment regimens at the time of their study visit were associated with the participants' race/ethnicity and clinical factors including glycemic control, FCP, and diabetes care provider. Metformin and lifestyle were the most commonly used regimens (50% when combined) and were generally associated with better glycemic control, regardless of diabetes duration. Other/multiple OHAs and/or insulin were more commonly used by those with higher A1C levels, particularly among youth with longer diabetes duration. Regardless of diabetes duration, youth who were not on insulin (67% of participants) had lower A1C than those who were on insulin (33% of participants). Most likely, youth on more intensive regimens, e.g., insulin or multiple agents, had already failed less intensive

regimens. However, the cross-sectional design of this observational study does not allow us to confirm this assumption.

Of great concern is that >50% of these youth with type 2 diabetes had an A1C \geq 8% only 2 years after diabetes diagnosis. While the mean A1C of those treated with lifestyle alone or on metformin monotherapy was <8%, less than half of the participants were on only these regimens after diabetes duration of \geq 2 years; in each of the other regimen groups, mean A1C was >9%. The percent of youth with an A1C \geq 8% at 2 years' duration (55.8%) in the SEARCH study was higher than that observed in the TODAY study, where A1C \geq 8% was observed in 52% of youth on metformin alone, 39% on metformin plus rosiglitazone, and 47% on metformin plus lifestyle 3–4 years after being diagnosed with diabetes. This difference is most likely due to the selective entry criteria for the TODAY trial as well as to the increased attention provided to participants in the TODAY study treatment trial compared with participants in SEARCH, an observational study.

As expected, longer duration of diabetes was associated with lower FCP in youth on insulin-containing regimens, a reflection of declining endogenous insulin secretion. Participants treated with lifestyle alone or on metformin monotherapy had lower A1C values and higher FCP, and these differences in A1C remained after adjusting for multiple covariates including demographics, FCP, BMI, frequency of SMBG, and duration of diabetes. The higher OR for experiencing treatment failure (A1C

\geq 8%) in those on more intensive regimens most likely reflects a decline in FCP noted in these youth and points out the need for additional effective therapy for adolescents and young adults with type 2 diabetes as endogenous insulin secretion wanes.

Current recommendations for SMBG in youth with type 2 diabetes are not evidence based. Among youth with DA-negative type 2 diabetes treated with insulin in our study, we observed that increased frequency of SMBG was significantly associated with lower A1C, while no association was observed among youth who were on regimens that did not include insulin. There is controversy over the effect of SMBG on glycemic control in adults with type 2 diabetes, with a recent meta-analysis showing that more frequent SMBG was not associated with lower A1C (19). However, our results emphasize the importance of SMBG among youth with type 2 diabetes treated with insulin showing that SMBG is an important correlate of A1C. Additional data are needed on the efficacy of SBGM for improving glycemia in youth with T2D according to treatment regimen.

Approximately 10% of youth in this report with clinically diagnosed type 2 diabetes were positive for at least one of the two DA measured in this study. These youth were similar to DA-negative youth in terms of their A1C, demographic, and many clinical characteristics but had lower FCP and were more likely to be on insulin-containing regimens. This is consistent with other reports, including youth with clinically diagnosed type 2 diabetes screened for

potential participation in the TODAY study (6). As we have described in an earlier SEARCH publication on etiological classification of diabetes in youth, DA-positive youth with clinically diagnosed type 2 diabetes likely represent obese youth with autoimmune diabetes (4).

There are several limitations that should be considered when interpreting the findings of our study. We are unable to take into consideration the treatment decisions made by the health care providers treating these youth, the study participants, or their parents that may have influenced the selection of their regimens. Similarly, we do not know the timing of the initiation of the regimens in relation to the timing of the study visit, when the blood was collected for A1C measurement. The information on how regimens were selected or timing of initiation was not collected as part of the study protocol. Because these analyses are cross-sectional and timing of regimen initiation is unknown, causal relationships between regimens and A1C cannot be inferred. Similarly, we are not able to assess adherence to the prescribed pharmacological regimens or lifestyle efforts to treat type 2 diabetes or health care and diabetes education received by these youth. Finally, data on treatment regimen and SMBG are self-reported. However, the strengths of this report include the relatively large size and multiracial and ethnic composition of the cohort of youth with type 2 diabetes and the consistency of data collection using a common protocol across the six centers and over time. These results are based on the treatment regimens of youth with type 2 diabetes diagnosed through 2005 who were seen from 2002 through 2007—a relatively contemporary cohort. As newer therapies, such as glucagon-like peptide-1 agonists, are introduced into clinical therapies in the care of youth, it will be of great interest to follow this cohort and further assess changes in regimens and outcomes.

Over half of the youth with type 2 diabetes with a duration of ≥ 2 years had an A1C $\geq 8\%$, representing a failure of their diabetes treatment, despite almost 60% being on more “intensive” management regimens; $>50\%$ of those

on intensive regimens still experience treatment failures. These data indicate that current management strategies are not resulting in adequate glycemic control in these youth. More effective therapies and/or therapeutic strategies are needed for youth with type 2 diabetes that will lead to better glycemic control and thus lower risk of diabetes complications as adults.

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