HHS Public Access

Author manuscript

Pediatr Diabetes. Author manuscript; available in PMC 2019 November 15.

Published in final edited form as:

Pediatr Diabetes. 2018 September ; 19(6): 1065–1072. doi:10.1111/pedi.12691.

Changes in Diabetes Medication Regimens and Glycemic Control in Adolescents and Young Adults with Youth Onset Type 2 Diabetes: the SEARCH for Diabetes in Youth Study

Cathy Anne Pinto, PhD[1], **Jeanette M. Stafford, MS**[2], **Tongtong Wang, PhD**[1], **R. Ravi Shankar, MD**[3], **Jean M. Lawrence, ScD**[4], **Grace Kim, MD**[5], **Catherine Pihoker, MD**[5], **Ralph B. D'Agostino Jr, PhD**[3], **Dana Dabelea, MD, PhD**[6]

[1]Department of Pharmacoepidemiology, Merck & Co., Inc., Kenilworth, NJ USA

[2]Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina

[3]Department of Clinical Research, Merck & Co., Inc., Kenilworth, NJ USA

[4]Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA

[5]Department of Pediatrics, University of Washington, Seattle, WA

[6]Department of Epidemiology, Colorado School of Public Health, University of Colorado Denver, Aurora, CO

Abstract

Objective—The aim of the study was to describe recent medication patterns and changes in medication patterns and glycemic control in adolescents and young adults with incident type 2 diabetes (T2D).

Methods—Using data from the SEARCH for Diabetes in Youth Study, we conducted a cross-sectional analysis of treatments for adolescents and young adults with incident T2D in two periods (2002–2005 vs. 2008/2012), and a longitudinal analysis of medications and glycemic control for a

Corresponding Author: Dana Dabelea, MD, PhD, Conrad M. Riley Professor of Epidemiology and Pediatrics, Director, Lifecourse Epidemiology of Adiposity and Diabetes (LEAD) Center, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, 13001 East 17th Ave, Box B119, Room W3110 Aurora, CO 80045, Tel: 303-724-4414, Fax: 303 724-4491, Dana.Dabelea@ucdenver.edu.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention and the National Institute of Diabetes and Digestive and Kidney Diseases.

Conflict of Interest

CAP, TW, RRS are employees and stockholders of Merck & Co., Inc., Kenilworth, NJ USA, which currently sells and distributes a DPP-4 inhibitor.

Author Contributions

- CAP, TW, RRS, and DD contributed to development of the analysis plan and wrote the manuscript.
- RBD and JMS contributed the development of the analysis plan, ran the analyses and takes responsibility for the accuracy of the data analysis.
- JML, GK, and CP contributed to interpretation of the data, reviewed, and edited the manuscript, and contributed to the discussion.
- JML, GK, CP, and DD participated in collection of SEARCH data.

subset with baseline and follow-up visits. Comparisons were performed using chi-square, Fisher's exact or ANOVA.

Results—Of 646 individuals in the cross-sectional analysis, a majority in each period received metformin (64.9% vs 70.4%) and/or insulin (38.1% vs 38.4%), while fewer used sulfonylureas (5.6% vs 3.6%) with non-significant changes over time. There was a significant reduction in thiazolidinedione use (5.0% vs 2.0%, $p<0.05$). In the longitudinal analysis, 322 participants were followed for 7 years, on average. Baseline metformin users had a lower A1C (6.4% [46.7 mmol/mol]) compared to insulin (8.4% [68.2 mmol/mol], $p<0.001$) or insulin plus any oral diabetes medication (ODM) users (7.7% [60.4 mmol/mol], $p<0.001$). Among baseline metformin users (n=138), 29.7% reported metformin at follow-up, with the remainder adding (19.6%) or switching to insulin (8.0%), ODM (15.9%), or lifestyle only (26.8%). Of those receiving insulin (±ODM) (n=129), 76% reported insulin use at follow-up. Overall, 35% were at A1C goal (<7.0%, 53 mmol/mol) at follow-up.

Conclusions—Youth-onset T2D is still largely being treated with metformin and/or insulin. The majority treated were not at ADA-recommended goal 7 years after diagnosis.

Keywords

Diabetes mellitus; type 2; adolescent; young adult; glycated hemoglobin A

INTRODUCTION

There has been an increase in prevalence of individuals diagnosed with type 2 diabetes before 20 years of age ("youth-onset" diabetes) (1). While many therapies have been tested for safety and efficacy in patients with type 2 diabetes mellitus older than 18 years of age, there are limited data for those with youth-onset diabetes (2). Currently, there are 11 different classes of medications approved for use in adults: insulin, biguanides, thiazolidinediones (TZDs), sulfonylureas (SUs), meglitinides, α-glucosidase inhibitors, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-IV inhibitors, sodium glucose co-transporter 2 inhibitors, bromocriptine, and bile acid sequestrants. Of these, only metformin and insulin are currently approved for the treatment of children and adolescents with type 2 diabetes (3).

Although the current standards for diabetes management for children and adults with type 1 and type 2 diabetes reflect the need to lower glucose as safely as possible, prior studies have shown that most youth treated with metformin and/or insulin are still not at the glycemic goal, which targets an A1C<7.5% [58.5 mmol/mol], or <7% [53 mmol/mol] if it can reasonably be achieved without excessive hypoglycemia as recommended by the American Diabetes Association (ADA) and American Academy of Pediatric Clinical Practice Guidelines (2). Data from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, a randomized multicenter trial initiated in 2004 of 699 participants with type 2 diabetes and mean duration of 7.8 months since diagnosis, demonstrated that only half receiving metformin alone maintained glycemic control (defined as <8% [64 mmol/mol] in this trial) over 3 to 4 years of treatment (4). Rates of failure were 51.7%, 38.6%, and 46.6% for metformin alone, metformin plus rosiglitazone, and metformin plus

lifestyle intervention, respectively. According to clinical guidelines, patients receiving metformin monotherapy in routine clinical practice who are not at goal would require further treatment intensification.

The SEARCH for Diabetes in Youth study reported that the majority of youth with incident type 2 diabetes (n=474) diagnosed in 2002-2005 were largely being treated with metformin and/or insulin approximately two years after diagnosis (5). Greater than 50% of the participants were not adequately controlled (A1C ≥8%, 64 mmol/mol), including >50% of those taking insulin-containing therapies alone or in combination with other therapies. With an increasing number of diabetes therapies currently approved for use in adults, the goal of the current study was to expand on the earlier SEARCH work to examine more contemporary treatment patterns and glycemic control over a longer duration of follow-up for adolescents and young adults with newly diagnosed type 2 diabetes. The specific goals of this analysis were to compare the distribution of glycemic medications among adolescents and young adults recently diagnosed with type 2 diabetes during 2002 through 2005 to those with an incident diagnosis in 2008 and 2012, and to examine longitudinal changes in medication patterns and A1C over time for a subgroup of youths who return at least 5 years after diagnosis for a subsequent SEARCH visit.

METHODS

SEARCH Design and Study Population

The SEARCH for Diabetes in Youth Study is a national, multicenter, population based study aimed at understanding more about diabetes diagnosed among children and young adults <20 years old in the United States, funded by the Centers for Disease Control and Prevention and the National Institute of Diabetes and Digestive and Kidney Diseases. SEARCH includes a registry of physician-diagnosed incident cases with type 1 and 2 diabetes in 2002-2006, 2008 and 2012, and an ongoing cohort study, which was developed by recruiting incident cases who had a baseline visit and their first cohort study follow-up visit after at least five years since their initial diagnosis. The overall SEARCH study design has been previously described in detail (6). Prior SEARCH studies have demonstrated that the physician diagnosis of type 1 and type 2 diabetes agrees well with etiologic assessments and the participants are reasonably representative of the general US population with the onset of type 1 and type 2 diabetes in childhood or adolescence (7–9).

The current report describes a cross-sectional analysis of adolescents and young adults included in the SEARCH registry with recently diagnosed type 2 diabetes in two periods: 2002-2005 (4 years) and 2008/2012 (2 years) and who had completed an in-person baseline visit (Figure 1). Incident 2006 participants were excluded from the cross-sectional analysis to provide greater balance in the number of participants contributing data during each time period and to provide a greater lapse in time between the earlier and later timeframes to assess the potential impact of real-world events on prescribing patterns occurring during the intervening years (e.g., market entry of DPP-4 inhibitors in 2006 and safety concerns raised with thiazolidinedione in 2007) (10–12). The current report also describes a longitudinal analysis of changes in medication regimens and glycemic control for a subset of patients included in the SEARCH registry, including patients with an initial diagnosis in 2002-2005,

2006, and 2008 (6 calendar years) who had completed an in-person baseline visit and who returned for a subsequent follow-up visit as part of the SEARCH cohort study (Figure 1). The longitudinal analysis did not include patients with a baseline visit in 2012 as they are not eligible for recruitment in the SEARCH cohort study. SEARCH clinical centers that contributed data for the current study included centers in Ohio, Colorado, California, Washington, and South Carolina.

Data Collection

In SEARCH, demographic information (e.g. date of birth, gender), date of diagnosis and provider–assigned diabetes type have been obtained from medical records. Race and ethnicity have been reported by the participant or their parent/guardian on the initial survey. Physical exams at the study visits have been 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. Body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) was converted to BMIz score using a standard Center for Disease Control and Prevention approach. Laboratory measurements were obtained after an overnight fast for at least 8 hours with instructions not to take diabetes medication the morning of the visit except for basal insulin administered by continuous insulin infusion pump. A1C was measured by a dedicated ion-exchange high-performance liquid chromatography instrument. Information collected from participants at the baseline and cohort visits included current use of medications to treat diabetes.

Diabetes Treatment Regimens

For the cross-sectional analysis, treatment regimens were categorized by medication class (metformin, insulin, sulfonylurea (SU), thiazolidinedione (TZD), incretin mimetics, and DPP-4 inhibitors) as the main objective for this analysis was to examine changes in specific medications patterns after the introduction of newer treatments for adults (e.g. first GLP-1 analogue in 2005, and first DPP-4 inhibitor in 2006) and potential changes related to safety concerns with TZDs. For the longitudinal analysis, medication use was categorized more broadly as metformin only, insulin only, insulin plus any oral diabetes medication (ODM), other ODM only, and no diabetes medication use (lifestyle only).

Statistical Analysis

Descriptive summaries were presented with continuous variables described as mean values, ± standard deviation, or median (IQR) values, and categorical variables described as the count and percentage per subgroup of interest. Data not available were reported as missing, with no imputation of missing data. Between group and within group comparisons were performed using chi-square or Fisher’s exact test (categorical data) or one-way ANOVA (continuous data) with a type 1 error rate of 0.05. Statistical analyses were conducted using SAS (version 9.4; SAS Institute, Cary, NC).

RESULTS

The cross-sectional analysis included 646 adolescents and young adults with incident type 2 diabetes (age at diagnosis [SD] 14.4 [2.6] years, 62% female, 41% African American, BMI-

z [median (IQR)] 2.3 (1.9, 2.5)) with a mean duration (SD) of 12.4 (8.2) months between diagnosis and the SEARCH baseline visit, with comparable baseline characteristics for the subset of SEARCH participants (n=322) included in the longitudinal analysis (Table 1). Participants in the longitudinal analysis (N=322), which included participants with a baseline and follow-up cohort visit, completed their follow-up visit on average (SD) 7.1 (2.1) years after their baseline visit.

Cross-Sectional Analysis of Diabetes Medication Regimens (2002-2005 versus 2008/2012)

During the earlier (2002–2005) and latter (2008/2012) time periods, the majority of adolescents and young adults with newly diagnosed type 2 diabetes received metformin and/or insulin. (Table 2) There was a significant ($p<0.05$) reduction in TZD use from 5% in 2002-2005 to 2% in 2008/2012. All reported TZD use in 2008/2012 was reported for the 2008 baseline cases. Other notable changes, which did not reach statistical significance, included a numerical increase in the proportion of metformin users (65% versus 70%, $p=0.14$) and metformin plus insulin users (18% versus 23%, $p=0.09$), with fewer participants reporting SU use (5.6% versus 3.6%, $p=0.22$), in 2002-2005 and 2008/2012, respectively.

Longitudinal Analysis of Diabetes Medication Use and Glycemic Control

The longitudinal analysis included a total of 322 adolescents and young adults with newly diagnosed type 2 diabetes. At the time of the baseline visit, the majority were receiving metformin and/or insulin, with approximately 10% reporting lifestyle only (Table 3). At the baseline visit, those reporting use of metformin monotherapy had a significantly lower unadjusted A1C (6.4±1.4%) compared to those on insulin monotherapy (8.4±2.2%, $p<0.001$), insulin plus an ODM (7.7±2.2%, $p<0.001$), or other ODM (7.3% ±2.1%, $p<0.05$), and comparable unadjusted A1C levels to those with no use of diabetes medications (6.6% ±2.4%) (Table 3).

At follow-up, a larger proportion of participants had changed medication category than were on the same medication they were on at their baseline visit ($p<0.001$) (Table 3). Among 138 participants on metformin monotherapy at baseline, 29.7% reported metformin monotherapy at follow-up, with the remainder either adding (19.6%) or switching (8.0%) to insulin, another ODM (15.9%), or lifestyle only (26.8%) (Table 3). Of those receiving insulin (±ODM) at baseline (n=129), 76% were on insulin (±ODM) at follow-up. Overall, 35% of the 322 participants were at A1C goal (<7.0%, 64 mmol/mol) at the follow-up visit including 44.1% of those on metformin monotherapy at baseline, 20.6% of those on insulin (±ODM) baseline, and 64.5% of those with no reported medication use at baseline (Figure 2). Of those receiving metformin monotherapy at baseline and follow-up visit, approximately 50% had an A1C ≥7% (53 mmol/mol) at the time of the follow-up visit (Table 3). Overall, approximately 15% of the 322 participants included in the longitudinal analysis were not receiving any diabetes medications at the time of the follow-up visit and had an A1C<6.5% (47.5 mmol/mol). When comparing this subgroup to those taking medication at follow-up (regardless of A1c level) or with an A1C≥6.5% (47.5 mmol/mol) at follow-up without medication, no significant difference was found in gender, race/ethnicity, or BMI z-score (data not shown). There was a significant difference in age (15.0 ±2.4 vs. 14.0 ±2.7, $p=0.13$) and mean baseline A1C level (5.9 ±0.9 vs. 7.3 ±2.1 [40.8 ± 10.0 vs. 56.4

± 22.9 mmol/mol], p<0.0001), respectively, for those with an A1C less than 6.5% (47.5 mmol/mol) without medication vs. those either taking medication or with an A1C ≥ 6.5% at follow-up. Of the 267 adolescents and young adults receiving metformin and/or insulin at baseline, 13% were not using a diabetes medication at follow-up with an A1C<6.5% (47.5 mmol/mol), including 18% of participants receiving metformin only and approximately 7% in the insulin (±ODM) groups.

DISCUSSION

The current cross-sectional analysis confirms earlier SEARCH findings that the majority of youth with type 2 diabetes are largely being treated with metformin and/or insulin, which are the only two diabetes medications approved for use in children (5). There was little to no use of other ODMs, such as DPP-4 inhibitors or incretin mimetics which have been more recently approved for use in adults. The current analysis also reveals a significant decrease in TZD use over time, mirroring a similar pattern observed in adults, which may be attributed to an increased awareness of safety concerns reported for adults in association with the use of this medication class (10–12).

Expanding on the earlier SEARCH analysis by Badaru et. al (4), the current analysis also examined longitudinal changes in medication patterns and glycemic control over time, with an additional follow-up of 7 years, on average, after the baseline visit. The results show that only 35% of participants were at A1C goal (<7.0%, 53 mmol/mol) at follow-up, including approximately 50% of those who reported use of metformin monotherapy at both baseline and follow-up. Although our findings are generally consistent with the TODAY study results in that a large proportion of youths with type 2 diabetes being treated with metformin monotherapy did not achieve glycemic goal, a direct comparison between the results of these two studies is difficult given differences in eligibility criteria, study design, and oversight (1). Even so, our study results provide further evidence that a large proportion of children and adolescents with youth onset diabetes are not being treated to goal, which is of significant concern given the increased risk of vascular complications.

The failure of to achieve A1C goal may be multifactorial in nature, with some factors difficult to identify and not all amenable to modification. The current study does not address the question of whether poor glycemic control in adolescents and young adults is attributable to lack of adherence, persistence, or access issues (e.g. lack of nutritional counseling). Similarly, we were not able to assess the contribution of lack of treatment intensification by healthcare professionals (sometimes referred to as ‘clinical inertia’), such as inaccurate perceptions by healthcare providers about optimal A1C treatment goals in primary care centers. There are patient-level barriers due to comorbidities and system-level barriers (particularly time constraints). (14) Although the reasons for poor glycemic control were not evaluated in the current study, it should be noted that a majority of participants in the longitudinal cohort study were adults at the time of follow-up, yet there was very limited use of medications approved for adults other than metformin and/or insulin. Given the age of participants at follow-up, one possible explanation could be a lack of tailored clinical programs and policies to support transitioning of care for pediatric patients and loss to the healthcare system. A recent SEARCH study of factors associated with transfer from

pediatric to adult care revealed a substantial worsening of glycemic control and loss to follow-up during healthcare transfer (13). A substantial proportion (15%) of those transitioning from pediatric care reported no medical care after 18 years of age. Insurance status was a major difference between the groups at follow-up with 74% in the no care group being uninsured compared with 15% in the adult care group and only 1.6% of pediatric participants at baseline being uninsured.

Another important finding of the present study is that the approximately 15% of participants at the time of the follow-up visit were not taking glycemic medications and had an A1C<6.5% (47.5 mmol/mol). The percentage of participants not taking any glycemic medications is higher compared with expert consensus that fewer than 10% of youth with type 2 diabetes will attain glycemic goals through lifestyle intervention alone (2). For participants receiving baseline metformin and/or insulin, approximately 13% in the current study were not taking a diabetes medication at follow-up with an A1C within non-diabetic range (<6.5%, 47.5 mmol/mol). These findings may be explained by an initial need for diabetes therapy to stabilize glycemic levels impacted by increased growth hormones and increased insulin resistance that occur during puberty but that over time, lifestyle alone may be sufficient to reduce glycemic levels within normal range in a subset of patients (17–19).

There are several limitations of the study. First, the use of diabetes medications was self-reported which may bias the assessment of medication use. However, there is no reason to suspect systematic differences in the accuracy of self-reporting between treatment groups. We were also unable to evaluate lifestyle efforts or adherence, persistence, and switching of medications, so treatment patterns during the course of long-term follow-up for participants with youth-onset type 2 diabetes may be different than those observed at the time of a single follow-up visit. As well, treatment decisions by healthcare providers, participants, or parents, and external barriers to treatment are unknown which may impact our interpretation of the findings regarding clinical inertia. Finally, the timing for initiation of therapy in relation to the timing of the study visits when A1C was measured was not collected as part of the study protocol. Caution should be exercised when interpreting A1C results obtained from longitudinal analysis; relationships between regimens and A1C control should not be inferred from this study. Strengths of the current study include the population-based approach of SEARCH with a sample that is representative of adolescents and young adults with youth-onset type 2 diabetes in the US, and the consistency of data collection using a common protocol among recruitment centers during each study period (6–9).

Despite the growing number of diabetes medications available for adults, youth with type 2 diabetes are still largely being treated with metformin and/or insulin, which are the only medications approved for pediatric use in the US, with a recent decline in TZD use as seen in adults. We found that a majority of youth receiving treatment for an average of 7 years were not at the ADA-recommended A1C goal. Further research is warranted to continue to evaluate changes in treatment patterns and outcomes over time, particularly as the present study may not account for other evidence-based treatment changes currently occurring with accumulating evidence from other recently published clinical and observational studies of youths. It is also important to continue to improve our current understanding of barriers to suboptimal therapy (e.g. access to healthcare providers and lack of medication adherence or

persistence) as well as underlying factors that may be contributing to clinical inertia and failure to intensify treatment for youth with diabetes who are sub optimally treated. Equally important is the need to examine why so few medications have been approved for pediatric use: 75% of the currently completed randomized clinical controlled registration trials in pediatric patients have not resulted in approvals from the FDA, while ongoing clinical and translational research studies are facing significant recruitment challenges (15,16). Greater attention needs to be placed on addressing the challenges and approaches for developing new treatments for youth-onset diabetes so there are more therapeutic options available.

Acknowledgments

The SEARCH for Diabetes in Youth Study is indebted to the many youth and their families, and their health care providers, whose participation made this study possible.

Grant Support: SEARCH for Diabetes in Youth is funded by the Centers for Disease Control and Prevention (PA numbers 00097, DP-05-069, and DP-10-001) and supported by the National Institute of Diabetes and Digestive and Kidney Diseases.

Site Contract Numbers: Kaiser Permanente Southern California (U48/CCU919219, U01 DP000246, and U18DP002714), University of Colorado Denver (U48/CCU819241-3, U01 DP000247, and U18DP000247-06A1), Children's Hospital Medical Center (Cincinnati) (U48/CCU519239, U01 DP000248, and 1U18DP002709), University of North Carolina at Chapel Hill (U48/CCU419249, U01 DP000254, and U18DP002708), University of Washington School of Medicine (U58/CCU019235-4, U01 DP000244, and U18DP002710-01), Wake Forest University School of Medicine (U48/CCU919219, U01 DP000250, and 200-2010-35171).

The authors wish to acknowledge the involvement of the South Carolina Clinical & Translational Research Institute, at the Medical University of South Carolina, NIH/National Center for Advancing Translational Sciences (NCATS) grant number UL1 TR000062; Seattle Children's Hospital and the University of Washington, NIH/NCATS grant number UL1 TR00423; University of Colorado Pediatric Clinical and Translational Research Center, NIH/NCATS grant Number UL1 TR000154; the Barbara Davis Center at the University of Colorado at Denver (DERC NIH grant number P30 DK57516); the University of Cincinnati, NIH/NCATS grant number UL1 TR000077; and the Children with Medical Handicaps program managed by the Ohio Department of Health. This study includes data provided by the Ohio Department of Health, which should not be considered an endorsement of this study or its conclusions.

References

1. Dabelea D, Mayer-Davis EJ, Saydah S, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001–2009. Jama. 2014; 311(17):1778–1786. [PubMed: 24794371]
2. Copeland KC, Silverstein J, Moore KR, Prazar GE, Raymer T, Shiffman RN, et al. Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. Pediatrics. 2013; 131:364–82. [PubMed: 23359574]
3. Rosenbloom AL, Silverstein JH, Amemiya S, Zeitler P, Klingensmith GJ. Type 2 diabetes in children and adolescents. Pediatr Diabetes. 2009; 10(Suppl. 12):17–32. [PubMed: 19754615]
4. Study Group TODAY. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med. 2012 Jun 14; 366(24):2247–2256. [PubMed: 22540912]
5. Badaru A, Klingensmith GJ, Dabelea D, Mayer-Davis EJ, Dolan L, Lawrence JM, Marcovina S, Beavers D, Rodriguez BL, Imperatore G, Pihoker C. Correlates of treatment patterns among youth with type 2 diabetes. Diabetes Care. 2014; 37(1):64–72. [PubMed: 24026554]
6. Hamman RF, Bell RA, Dabelea D, D'Agostino RB Jr, Dolan L, Imperatore G, Lawrence JM, Linder B, Marcovina SM, Mayer-Davis EJ, Pihoker C, Rodriguez BL, Saydah S, SEARCH for Diabetes in Youth Study Group. The SEARCH for Diabetes in Youth Study: Rationale, Findings, and Future Directions. Diabetes Care. 2014; 37:3336–44. [PubMed: 25414389]
7. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA. 2014; 311(17):1778–1786. [PubMed: 24794371]

8. Dabelea D, Stafford JM, Mayer-Davis EJ, D'Agostino R Jr, Dolan L, Imperatore G, et al. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. JAMA. 2017; 317(8):825–835. [PubMed: 28245334]

9. Dabelea D, Pihoker C, Talton JW, D'Agostino RB Jr, Fujimoto W, Klingensmith GJ. Etiologic approach to characterization of diabetes type. Diabetes Care. 34:1628–1633.2011; [PubMed: 21636800]

10. Ahuja V, Sohn M, Birge JR, et al. Geographic variation in rosiglitazone use surrounding FDA warnings in the department of veterans affairs. J Manag Care Spec Pharm. 2015; 21(12):1214–1234. DOI: 10.18553/jmcp.2015.21.12.121411 [PubMed: 26679970]

11. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence, and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. BMJ Open. 2016; 6:e010210. doi: 10.1136/bmjopen-2015-010210

12. Nissen S, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007; 356:2457–71. [PubMed: 17517853]

13. Agarwal, et al. Diabetes Medicine 2018. Transfer to paediatric to adult care for young adults with Type 2 diabetes: the SEARCH for Diabetes in Youth Study.

14. Zafar A, Stone MA, Davies J, Khunti K. Acknowledging and allocating responsibility for clinical inertia in the management of Type 2 diabetes in primary care: a qualitative study. *Diabet.* Med. 2015; 32:407–413.

15. Nadeau KJ, Anderson BJ, Berg EG, Chiang JL, Chou H, Copeland KC, et al. Youth-Onset Type 2 Diabetes Consensus Report: Current Status, Challenges, and Priorities. Diabetes Care. 2016; 39:1635–1642. [PubMed: 27486237]

16. Christensen ML, Franklin BE, Momper JD, Reed MD. Pediatric Drug Development Programs for Type 2 Diabetes: A Review. J Clin Pharmacol. 2015; 55(7):731–738. [PubMed: 25781151]

17. Bloch CA, Clemons P, Sperling MA. Puberty decreases insulin sensitivity. J Pediatr. 1987; 110(3):481–487. [PubMed: 2950219]

18. Jeffery AN, Metcalf BS, Hosking J, et al. Age Before Stage: insulin resistance rises before the onset of puberty: a 9-year longitudinal study (EarlyBird 26). Diabetes Care. 2012; 35:536–541. [PubMed: 22279034]

19. Hannon TS, Janosky J, Arslanian SA. Longitudinal study of physiologic insulin resistance and metabolic changes of puberty. Pediatr Res. 2006; 60:759–763. [PubMed: 17065576]

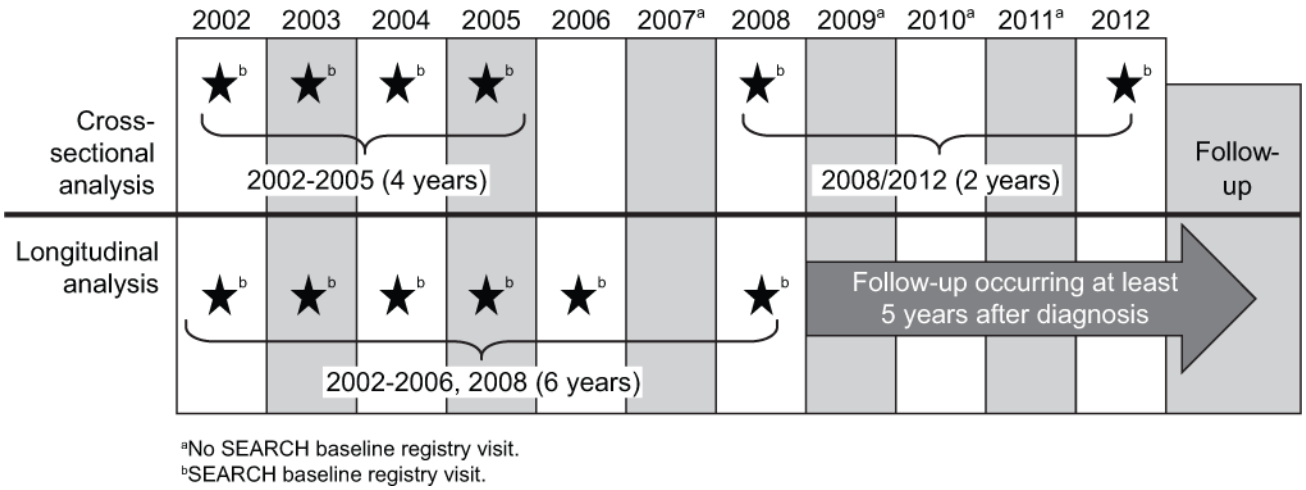

Figure 1.

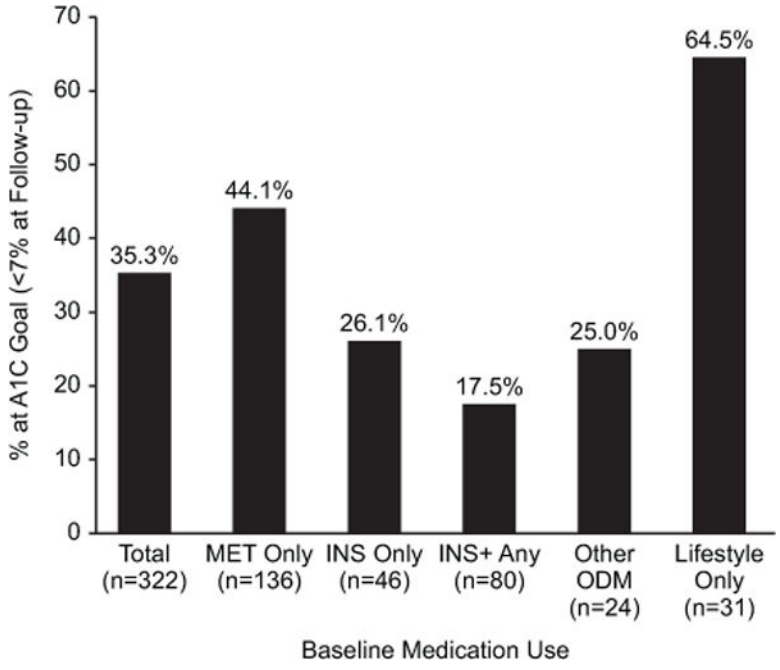

Figure 2.

Table 1

Demographic and clinical characteristics of adolescents and young adults with type 2 diabetes included in the cross-sectional and longitudinal analyses

	Cross-Sectional Analysis			Longitudinal Analysis*					
	ALL (N=646)	2002-2005 (N=339)	2008/2012 (N=307)	ALL (N=322)	MET only† (N=138)	INS only† (N= 46)	INS + Any† (N=83)	Other ODM† (N=24)	Lifestyle only† (N=31)
Baseline Registry Visit‡									
Age at diagnosis (years)	14.4±2.6	14.3 ± 2.5	14.5 ± 2.7	14.2 ±2.7	14.2 ± 2.5	13.6 ± 3.0	13.8 ± 2.5	15.0 ± 2.6	15.6 ± 2.6
Female gender %	401 (62.1)	204 (60.2)	197 (64.2)	206 (63.9)	90 (65.2)	27 (58.7)	56 (67.5)	15 (62.5)	18 (58.1)
Race/Ethnicity, %									
• African American	266 (41.2)	137 (40.4)	129 (42.0)	142 (44.1)	55 (39.9)	23 (50.0)	48 (57.8)	9 (37.5)	7 (22.6)
• Hispanic	180 (27.9)	83 (24.5)	97 (31.6)	78 (24.2)	38 (27.5)	10 (21.7)	15 (18.1)	7 (29.2)	8 (25.8)
• Non-Hispanic White	122 (18.9	78 (23.0)	44 (14.3)	71 (22.0)	38 (27.5)	10 (21.7)	16 (19.3)	2 (8.3)	5 (16.1)
• Other/unknown	78 (12.1)	41 (12.1)	37 (12.1)	31 (9.6)	7 (5.1)	3 (6.5)	4 (4.8)	6 (25.0)	11 (35.5)
BMI z-score [median(IQR)]	2.3 (1.9, 2.5)	2.3 (1.9, 2.5)	2.2 (1.9, 2.5)	2.3 (1.9, 2.5)	2.3 (1.9, 2.6)	2.2 (1.3, 2.5)	2.3 (2.0, 2.6)	2.4 (1.9, 2.7)	2.1 (1.9, 2.5)
Duration of diabetes since diagnosis (months)	12.4±8.2	11.2±7.4	13.8±8.8	11.2 ±7.3	11.2 ± 7.1	10.4 ± 7.8	10.0 ± 6.6	12.6 ± 9.1	14.5 ± 6.9
Cohort Follow-up Visit‡									
Duration since baseline (years)	N/A	N/A	N/A	7.1 ±2.1	7.1 ± 2.0	7.5 ± 2.2	6.9 ± 2.0	7.2 ± 2.1	7.0 ± 2.5
Duration of diabetes since diagnosis (years)	N/A	N/A	N/A	8.0±2.0	8.0 ± 2.0	8.4 ± 2.1	7.7 ± 2.0	8.3 ± 2.1	8.2 ± 2.3
Age at follow-up (years)	N/A	N/A	N/A	22.2±3.5	22.2 ± 3.3	22.0 ± 3.7	21.5 ± 3.4	23.3 ± 2.8	23.9 ± 3.9

*, †, ‡, §, ||, ¶, #, **, ††, ‡‡.

*Participants with a baseline and follow-up cohort visit

†Medication categories at the baseline visit

‡Results are presented as mean ±standard deviation unless otherwise noted

3N/A = not applicable; MET= metformin, INS=insulin, INS+Any= insulin plus oral diabetes med, ODM= oral diabetes medication, Lifestyle only= no diabetes medication use, IQR=interquartile range. There were no users of incretin mimetics included in the longitudinal analysis.

Table 2

Distribution of medication use for adolescents with incident type 2 diabetes during two time periods

Type 2 Diabetes Baseline Treatment *	Incident Cases		p-value difference†
	2002-2005 (N=339)	2008/2012 (N=307)	
Metformin, n (%)	220 (64.9)	216 (70.4)	0.1389
• Metformin alone, n (%)	141 (41.6)	136 (44.3)	0.4876
Insulin, n (%)	129 (38.1)	118 (38.4)	0.9202
• Insulin alone, n (%)	54 (15.9)	44 (14.3)	0.5721
Metformin and insulin, n (%)	61 (18.0)	72 (23.5)	0.0866
• Metformin and insulin alone, n (%)	54 (15.9)	65 (21.2)	0.0860
• Metformin and insulin + other, n (%)	7 (2.1)	7 (2.3)	0.8512
Sulfonylurea, n (%)	19 (5.6)	11 (3.6)	0.2227
TZDs, n (%)	17 (5.0)	6 (2.0) ‡	0.0361
Incretin Mimetics, n (%)	1 (0.3)	1 (0.3)	0.9999
DPP-4 inhibitors, n (%)	0 (0)	1 (0.3)	0.4752
Lifestyle only	39 (11.5)	41 (13.4)	0.4758

TZD=thiazolidinedione; DPP= dipeptidyl peptidase; lifestyle only= no diabetes medication use;

*unless otherwise listed as monotherapy, treatment categories are not mutually exclusive;

†p-values from chi-square or Fisher's exact tests comparing 02-05 vs 08/12 groups;

‡all 6 cases in 2008

Table 3

Changes in diabetes medication regimens and glycemic control for adolescents and young adults with type 2 diabetes, SEARCH baseline and follow-up visits

	Baseline Medication (N=322)				
	MET only (n=138)	**INS only (n=46)**	**INS + ANY (n=83)**	**Other ODM [a] (n=24)**	**Lifestyle Only (n=31)**
Baseline HbA1c, mean (std)	**6.4 ± 1.4**	**8.4 ± 2.2**	**7.7 ± 2.2**	**7.3 ± 2.1**	**6.6 ± 2.4**
Baseline HbA1c (mmol/mol), mean (std)	**46.7 ± 15.3**	**68.2 ± 23.8**	**60.4 ± 24.0**	**56.3 ± 23.0**	**48.4 ± 26.3**
Medication At Follow-up[b]					
MET only use, n %[c]	**41 (29.7)**	**5 (10.9)**	**7 (8.4)**	**5 (20.8)**	**5 (16.1)**
• Duration (years) since diagnosis	7.7 ± 1.8	8.5 ± 3.0	7.5 ± 2.9	10.3 ± 1.9	7.5 ± 1.9
• A1C<6.5% (47.5 mmol/mol) [d]	18 (43.9)	2 (40.0)	1 (14.3)	2 (40.0)	3 (60.0)
• A1C<7% (53.0 mmol/mol) [d]	20 (48.8)	3 (60.0)	1 (14.3)	2 (40.0)	4 (80.0)
• A1C<8% (64.0 mmol/mol)[d]	24 (58.5)	3 (60.0)	2 (28.6)	2 (40.0)	5 (100)
INS only use, n, %[c]	**11 (8.0)**	**19 (41.3)**	**27 (32.5)**	**4 (16.7)**	**0**
• Duration (years) since diagnosis	8.1 ± 1.4	8.9 ± 2.0	7.8 ± 1.8	6.8 ± 2.3	—
• A1C<6.5% (47.5 mmol/mol) [d]	3 (27.3)	1 (5.3)	2 (7.4)	0 (0)	—
• A1C<7% (53.0 mmol/mol) [d]	3 (27.3)	3 (15.8)	3 (11.1)	1 (25.0)	—
• A1C<8% (64.0 mmol/mol) [d]	3 (27.3)	7 (36.8)	4 (14.8)	1 (25.0)	—
INS + Any use, n, %[c]	**27 (19.6)**	**14 (30.4)**	**38 (45.8)**	**4 (16.7)**	**5 (16.1)**
• Duration (years) since diagnosis	8.1 ± 2.0	7.1 ± 1.7	7.5 ± 2.1	8.1 ± 2.0	9.3 ± 2.7
• A1C<6.5% (47.5 mmol/mol) [d]	0 (0)	1 (7.1)	2 (5.7)	0 (0)	0 (0)
• A1C<7% (53.0 mmol/mol) [d]	1 (4.0)	1 (7.1)	4 (11.4)	0 (0)	1 (20.0)
• A1C<8%(64.0 mmol/mol) [d]	2 (8.0)	3 (21.4)	6 (17.1)	1 (25.0)	1 (20.0)
Other ODM use, n, %[c]	**22 (15.9)**	**3 (6.5)**	**2 (2.4)**	**4 (16.7)**	**2 (6.5)**
• Duration (years) since diagnosis	7.9 ± 2.0	7.5 ± 0.9	8.3 ± 0.4	7.1 ± 1.8	7.0 ± 4.4
• A1C<6.5% (47.5 mmol/mol) [d]	6 (27.3)	0 (0)	0 (0)	1 (25.0)	1 (50.0)

	Baseline Medication (N=322)				
	MET only (n=138)	**INS only (n=46)**	**INS + ANY (n=83)**	**Other ODM [a] (n=24)**	**Lifestyle Only (n=31)**
• A1C<7% (53.0 mmol/mol) [d]	9 (40.9)	1 (33.3)	0 (0)	1 (25.0)	1 (50.0)
• A1C<8% (64.0 mmol/mol) [d]	15 (68.2)	2 (66.7)	0 (0)	2 (50.0)	1 (50.0)
Lifestyle only, n, % [c]	**37 (26.8)**	**5 (10.9)**	**9 (10.8)**	**7 (29.2)**	**19 (61.3)**
• Duration (years) since diagnosis	8.4 ± 2.3	10.3 ± 0.5	8.3 ± 1.5	8.4 ± 1.6	8.3 ± 2.2
• A1C<6.5% (47.5 mmol/mol) [d]	25 (67.6)	4 (80.0)	5 (55.6)	1 (14.3)	14 (73.7)
• A1C<7% (53.0 mmol/mol) [d]	27 (73.0)	4 (80.0)	6 (66.7)	2 (28.6)	14 (73.7)
• A1C<8% (64.0 mmol/mol) [d]	28 (75.7)	4 (80.0)	6 (66.7)	4 (57.1)	14 (73.7)

[a] 10 (41.7%) in the other ODM baseline category were receiving sulfonylurea

[b] at follow-up, a larger proportion of participants had changed medication category than remained on their baseline therapy (p<0.001)

[c] percent of cases within baseline medication use category

[d] percent of cases within baseline/follow-up treatment subgroup

Treatment groups presented at baseline and follow-up are mutually exclusive categories

MET= metformin, INS=insulin, INS+Any= insulin plus oral diabetes med, ODM= oral diabetes medication, lifestyle only= no diabetes medication use. There were no users of incretin mimetics included in the longitudinal analysis.