Pediatric Diabetes

ISPAD International Society for Pediatric and Adolescent Diabetes

Pediatric Diabetes 2017: 18: 222–229
doi: 10.1111/pedi.12377
All rights reserved

© 2016 John Wiley & Sons A/S.
Published by John Wiley & Sons Ltd.
Pediatric Diabetes

Original Article

A cross-sectional view of the current state of treatment of youth with type 2 diabetes in the USA: enrollment data from the Pediatric Diabetes Consortium Type 2 Diabetes Registry

Nambam B, Silverstein J, Cheng P, Ruedy KJ, Beck RW, Paul Wadwa R, Klingensmith G, Willi SM, Wood JR, Bacha F, Thomas IH and Tamborlane WV, for the Pediatric Diabetes Consortium†. A cross-sectional view of the current state of treatment of youth with type 2 diabetes in the USA: enrollment data from the Pediatric Diabetes Consortium Type 2 Diabetes Registry. Pediatric Diabetes 2017: 18: 222–229.

Objective: To describe the clinical characteristics, treatment approaches, clinical outcomes, and co-morbidities of youth with type 2 diabetes (T2D) enrolled in the Pediatric Diabetes Consortium (PDC) T2D Registry.
Methods: PDC enrolled 598 youth <21 yr of age with T2D from February 2012 to July 2015 at eight centers. Data were collected from medical records and interviews with participants and/or parents and included glycated hemoglobin (HbA1c), diabetes treatments, prevalence of diabetes comorbidities (hypertension (HTN), dyslipidemia (DL), microalbuminuria (MA), and nonalcoholic fatty liver disease (NAFLD).
Results: Insulin use was observed in 45% of those with T2D duration <1 yr, 44% for 1–<2 yr, 55% for 2–3 yr and 60% for ≥4 yr. Median HbA1c was 6.7% (50 mmol/mol), 8.5% (69 mmol/mol), 9.6% (81 mmol/mol), and 9.7% (82 mmol/mol) in those with disease duration <1, 1–<2, 2–3 and ≥4 yr, respectively. Only 33 and 11% of those with HTN and DL respectively, were being treated. MA and NAFLD were observed in 5–6% of the participants. Prevalence of HTN was associated with higher BMI ($p < 0.001$), DL with higher HbA1c ($p < 0.001$), and MA with longer diabetes duration ($p = 0.001$).
Conclusions: Frequency of insulin therapy in youth with T2D was associated with increased disease duration and those with longer duration rarely achieve target HbA1c level. This highlights the aggressive course of T2D in youth and adolescents. Additionally, co-morbidities are not being adequately treated. Follow up data from the PDC will provide additional important information about the natural history of T2D and patterns of gaps in treatment.

Bimota Nambam[a], Janet Silverstein[a], Peiyao Cheng[b], Katrina J Ruedy[b], Roy W Beck[b], R Paul Wadwa[c], Georgeanna Klingensmith[c], Steven M Willi[d], Jamie R Wood[e], Fida Bacha[f], Inas H Thomas[g] and William V Tamborlane[h] for the Pediatric Diabetes Consortium*

[a]Pediatric Endocrinology, University of Florida, Gainesville, FL, USA; [b]Jaeb Center for Health Research, Tampa, FL, USA; [c]Department of Pediatrics, Barbara Davis Center for Childhood Diabetes, University of Colorado, Aurora, CO, USA; [d]Children's Hospital of Philadelphia, Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [e]Center for Endocrinology, Diabetes, and Metabolism, Children's Hospital Los Angeles, Los Angeles, CA, USA; [f]USDA/ARS Children's Nutrition Research Center, and Pediatric Diabetes and Endocrinology, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA; [g]Pediatric Endocrinology, University of Michigan, Ann Arbor, MI, USA; and [h]Pediatric Endocrinology, Yale University, New Haven, CT, USA

Key words: pediatric endocrinology and diabetes – treatment – type 2 diabetes

Corresponding author: Katrina Ruedy,
Jaeb Center for Health Research,
15310 Amberly Drive,
Suite 350,

Tampa,
FL 33647,
USA.
Tel: (813) 975-8690;
fax: (888) 795-2858;
e-mail: pdc@jaeb.org;
kruedy@jaeb.org

*A complete listing of the members of the study group is included in the Appendix.

Submitted 14 August 2015.
Accepted for publication 16 February 2016

Type 2 diabetes (T2D) is an increasingly serious health problem in children and adolescents in the USA, with complications that extend beyond the difficulty in achieving optimal glycemic control (1–8). It has emerged as an increasingly serious health problem with complications that extend beyond the difficulty in achieving optimal glycemic control (1–8). The young age of patients and the prevalence of co-morbidities, such as hypertension (HTN) and dyslipidemia (DL), contribute to the early development of retinopathy, nephropathy, and increase the risk for future cardiovascular disease (CVD), the major cause of death in adults with T2D (2, 6–8). These co-morbidities occur earlier and progress rapidly in children and adolescents (6–8) even in those with good metabolic control (2, 6–8).

The Pediatric Diabetes Consortium (PDC) T2D Registry was established in 2012 to improve the care of children with T2D through sharing of best practices, collecting outcome data with a common database and collectively advocating for improvements in pediatric diabetes care focused on evidence. In this paper, the clinical characteristics, treatment approaches, clinical outcomes, and co-morbidities of the first 598 youth with T2D enrolled in the Registry are described.

Methods

The PDC enrolled 598 patients with T2D between February 2012 and July 2015. The protocol was approved by the Institutional Review Boards (IRB) at each of the eight participating centers at following locations: Houston, TX; Los Angeles, CA; Stanford, CA; Denver, CO; Gainesville, FL; New Haven, CT; Ann Arbor, MI; Philadephia, PA. Informed consent was obtained from participants ≥18 yr and from parents of participants <18 yr. Assent was obtained from participants per local IRB regulations at each center. Participants had to be <21 yr of age and diagnosed with using the criteria of the American Diabetes Association to be eligible for enrollment in the study.

Diagnostic criteria for diabetes included a glycated hemoglobin (HbA1c) ≥6.5% (≥48 mmol/mol), random glucose >200 mg/dL (11.1 mmol/L), 2 h postchallenge glucose ≥200 mg/dL (11.1 mmol/L) or a fasting glucose ≥126 mg/dL (7.0 mmol/L). Diagnostic criteria for T2D, once diabetes was diagnosed, included negative diabetes associated autoantibodies. If diabetes autoantibodies were not available at diagnosis, an elevated C-peptide (above the normal fasting level for the laboratory) and/or absence of insulin requirement at 6 months postdiagnosis were used to determine T2D. For enrollment, participants also had to have a weight percentile of ≥85% for age and sex either at the time of diagnosis or prior to the weight loss associated with unrecognized diabetes.

Data collection

Data were collected from medical records and from interviews with the participants and/or parents. Participant age, diagnosis information (presentation and diagnostic criteria, diabetic ketoacidosis (DKA) status with associated lab results including HbA1c and physical examination results), treatment following diagnosis including insulin use, DKA, and severe hypoglycemia events since diagnosis, frequency of home blood glucose monitoring, laboratory results including HbA1c, kidney function, and lipid profile from the time of diagnosis were obtained. The most recent laboratory results, physical examination findings, other medical conditions and medications also were recorded.

Body mass index (BMI) was computed from height and weight measured by the health care provider within ±28 d of enrollment. BMI percentile and standard deviation score adjusted for age and gender were calculated using the 2000 Center for Disease Control (CDC) population growth chart data (9). Similarly, blood pressure (BP) percentiles adjusted for age, gender, and height were calculated from the CDC charts (10). HTN was defined as a medical problem

noted in the medical record as not resolved, currently being treated for HTN during enrollment, or a systolic or diastolic BP measurement $\geq 95^{th}$ percentile for those age <18 yr and systolic BP ≥140 or diastolic BP ≥ 90 for those age ≥18 yr within ±28 d of enrollment. DL was defined as any of the following as noted in the medical record: unresolved hypertriglyceridemia, elevated low-density lipoprotein (LDL) cholesterol, or decreased high-density lipoprotein (HDL) cholesterol (based on descriptions from medical records, cut-points not available); currently being treated with medication for dyslipidemia; or a non-HDL cholesterol ≥145 mg/dL within ±28 d of enrollment (fasting status not available). Microalbuminuria (MA) and non-alcoholic fatty liver disease (NAFLD) were defined as the patient having each respectively as an ongoing medical condition at the time of enrollment.

Statistical analysis

Prevalence of DL was calculated among those participants who participated an ancillary study during enrollment where blood samples were taken for multiple lab tests (n = 298) in order to reduce bias caused by large amount of missing data in laboratory results. Prevalence of the other three comorbidities was calculated among all the T2D participants enrolled (n = 598).Both univariable and multivariable logistic regression models were used to determine the association between each of the comorbidities specified above with age, diabetes duration, BMI, and HbA1c as continuous variables. These factors were selected based on clinical factors that have been suggested as contributing to the development of HTN, DL, and MA in diabetes, including the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study in adolescents with T2D (6).

No formal adjustment was made for multiple comparisons; only p-values <0.01 were considered to be statistically significant. All reported p-values are two-sided. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

As shown in Table 1, the 598 participants included in the analyses had a median (interquartile range) age of 16.0 yr (14.0–17.7 yr) during enrollment. Median (interquartile range) diabetes duration was 2.0 (0.7–4.2) yr during enrollment. The majority was female (63%), Hispanic (55%) and had a family history of diabetes (92%). Only 31% had a parent with education beyond high school and 64% had Children's Health Plan or other government health insurance. A total of 85% of the participants were obese (BMI >95th percentile for age and gender) and 41% had a BMI >99th percentile for age and gender. A total of 11% had at least one episode of DKA since diagnosis. Only 2% had a severe hypoglycemic (SH) event that resulted in loss of consciousness or seizure.

During enrollment, 35% (n = 208) of participants were being treated with metformin alone, 19% (n = 111) with insulin alone, 31% (n = 186) with both metformin and insulin, 13% (n = 75) with lifestyle modification alone, and only 3% (n = 18) were treated with other glucose-lowering medications with/without metformin or insulin. Overall, 51% of participants were using insulin during enrollment. The overall median (interquartile range) HbA1c was 7.3% (56 mmol/mol) [interquartile range: 6.0–9.4% (42–79 mmol/mol)], 46% were <7% (53 mmol/mol) and 29% were ≥9% (75 mmol/mol). As shown in Fig. 1 and Table 2, HbA1c levels were lower in participants treated with lifestyle or metformin alone. For those treated with lifestyle modifications alone in the <1 and 1–<2 yr duration group, median HbA1c levels were in high prediabetic and diabetic range, respectively.

However, insulin use increased with increasing duration of T2D. Insulin use was observed in 45% of those with disease duration <1 yr and 44% of those with diabetes duration 1–<2 yr; this increased to 55% for 2–3 yr and 60% for ≥4 yr. HbA1c levels also increased from 6.7% (50 mmol/mol) to 8.5% (69 mmol/mol), 9.6% (81 mmol/mol) and 9.7% (82 mmol/mol) among those using insulin with T2D duration <1, 1–<2, 2–3, and ≥4 yr, respectively.

At the time of enrollment, 31% had HTN, 44% had DL, 6% had MA, and 5% had NAFLD (Table 3). However, only 33% of the participants who had HTN and 11% of those who had DL were being treated with medication for the respective condition at the time of enrollment. HTN was associated with higher BMI ($p < 0.001$) while DL was associated with higher HbA1c ($p < 0.001$), and MA with longer diabetes duration ($p = 0.001$). The prevalence of DL also trended higher among those participants with older age ($p = 0.02$). No associations were detected with NAFLD. Results from multivariate regression models were similar.

Discussion

Enrollment data from the PDC T2D Registry provide a cross-sectional view of the current clinical management and outcomes of treatment of youth with T2D. Consistent with previous studies (11), this disease disproportionally affects girls from disadvantaged Black and Hispanic/Latino families. While all participants were required to have a BMI ≥85th percentile around the time of diagnosis to qualify for entry in the Registry, very few of the participants

Table 1. Participant characteristics at enrollment (n = 598*)

	#	%
Age (yr)		
<13	95	16
13–<15	129	22
15–<18	251	42
18–<21	123	21
Median (25th, 75th percentiles)	16.0 (14.0–17.7)	
Gender		
Male	222	37
Female	376	63
Race/ethnicity		
White	50	8
Hispanic or Latino	328	55
Black/African American	175	30
Other/multiple race	39	7
Parent education		
High school or less	382	69
Associate	76	14
Bachelor	64	12
Master/professional degree	30	5
Health insurance		
Private	166	28
Children's health plan or other government	382	64
Military	4	<1
None	46	8
Family history of diabetes	538	92
Diabetes duration (yr)		
<1	185	31
1–<2	118	20
2–<4	134	22
≥4	161	27
Median (25th, 75th percentiles)	2.0 (0.7–4.2)	
BMI percentile† (%)		
<85	18	3
85–<95	66	12
95–<99	242	44
≥99	229	41
Median (25th, 75th percentiles)	99 (97–99)	
HbA1c % (mmol/mol)		
<6.0 (<42)	133	25
6.0–<7.0 (42–<53)	117	22
7.0–<8.0 (53–<64)	77	14
8.0–<9.0 (64–<75)	57	11
≥9.0 (≥75)	158	29
Median (25th, 75th percentiles)	7.3 (6.0–9.4) [56 (42–79)]	
Participants with any DKA event since diagnosis	66	11
DKA events rate (# events/100 person-yr)	19.8	
Participants with any severe hypoglycemia (SH) events since diagnosis	11	2
SH events rate (# events/100 person-yr)	1.3	
Insulin use	306	51
Insulin delivery modality		
Pump	1	<1
1 daily injection	72	24
2–3 daily injections	147	49
≥4 daily injections	82	27
Insulin dose (units/kg/d)		
<0.3	81	27
0.3–<0.5	65	22
0.5–<0.8	80	27
≥0.8	71	24
Median (25th, 75th percentiles)	0.5 (0.3–0.8)	
Self-monitoring blood glucose (# tests/d)‡		
0	83	14
1	119	20
2–3	276	46
≥4	120	20
Median (25th, 75th percentiles)	2 (1–3)	

BMI, body mass index; CDC, Center for Disease Control; DKA, diabetes ketoacidosis; HbA1c, glycated hemoglobin.
*Number of participants with missing or 'unknown' data: race/ethnicity (6), parent education (46), family history (12), BMI (43), HbA1c (56), insulin delivery modality (4), and insulin dose (9).
†BMI percentiles adjusted for age and gender based on 2000 CDC growth charts and excluded those >20 yr of age.
‡Self-reported values.

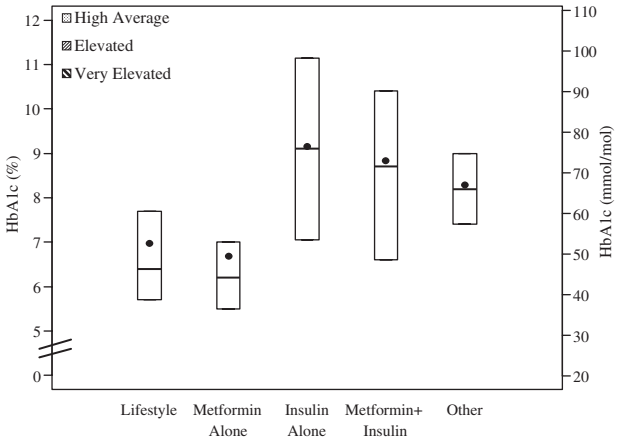

Fig. 1. HbA1c levels by diabetes treatment at enrollment. The bottom and top of each box denote the 25th and 75th percentiles, the line inside the box denotes the median and the dot is the mean.

had lowered their BMI percentiles into the normal range at the time of enrollment.

Treatment with insulin was common in the early phase of the disease (<1 yr), which was likely being employed to rapidly reverse gluco-toxicity around the time of diagnosis. This interpretation is consistent with the relatively low mean A1c levels in these subjects and with the results of the run-in phase of the TODAY study, where the majority of adolescents during the first 1–2 yr could be weaned off insulin treatment without adversely affecting metabolic control (12). However, most of our subjects with longer disease duration who were treated with insulin either alone or in combination with metformin had mean A1c levels that were ≥9.0%; values that were much higher than the target A1c levels of <7.5% currently recommended by the American Diabetes Association and the International Society for Pediatric and Adolescent Diabetes (13). This observation may be reflective of a decline of β-cell function previously reported in youth with T2D, which appears to be much more rapid than in adults with T2D (4, 14, 15).

A majority of the participants treated with lifestyle modifications alone had A1c ≥6% and those with A1c in the diabetic range, who could have clearly benefitted from pharmacological intervention, were not prescribed metformin. The reason behind the undertreatment is not clear but could be multifactorial including poor follow up. It should also be noted that many of our subjects were enrolled in the registry prior to publication of the ISPAD clinical practice guidlelines (2014) for treatment of youth with T2D,

Table 2. HbA1c levels at enrollment by diabetes duration and treatment (n = 542)

		HbA1c % [mmol/mol]	
Diabetes duration	Diabetes treatment	n*	Median (25th, 75th percentiles)
0–<1 yr	Overall	167	6.5 (5.7–7.9) [48 (39–63)]
	Life-style alone – no meds	27	6.4 (5.7–7.9) [46 (39–63)]
	Metformin alone	62	6.5 (5.7–7.1) [47 (39–54)]
	Insulin alone	26	6.9 (6.0–9.1) [52 (42–76)]
	Metformin + insulin	52	6.6 (5.7–8.5) [49 (39–69)]
	Other med. ± insulin/metformin	0	NA
1–<2 yr	Overall	110	7.3 (6.1–8.9) [56 (43–74)]
	Life-style alone – no meds	14	7.0 (6.1–7.8) [53 (43–62)]
	Metformin alone	44	6.2 (5.6–7.0) [44 (38–53)]
	Insulin alone	17	7.6 (6.5–10.1) [60 (48–87)]
	Metformin + insulin	32	8.9 (7.5–10.3) [74 (58–89)]
	Other med† ± insulin/metformin	3	7.9 (7.7–7.9) [63 (61–63)]
2–<4 yr	Overall	125	7.8 (5.8–10.2) [62 (40–88)]
	Life-style alone – no meds	15	5.8 (5.5–8.2) [40 (37–66)]
	Metformin alone	41	5.8 (5.4–6.3) [40 (36–45)]
	Insulin alone	28	9.6 (8.3–12.6) [81 (68–114)]
	Metformin + insulin	38	9.5 (7.8–10.7) [80 (62–93)]
	Other med‡ ± insulin/metformin	3	8.8 (7.3–8.9) [73 (56–74)]
≥4 yr	Overall	140	8.4 (6.3–10.6) [68 (45–90)]
	Life-style alone – no meds	7	6.0 (5.9–6.2) [42 (41–44)]
	Metformin alone	36	6.2 (5.6–7.3) [44 (38–57)]
	Insulin alone	28	9.3 (8.2–11.3) [78 (66–100)]
	Metformin + insulin	58	9.7 (7.7–11.9) [82 (61–107)]
	Other med.§ ± insulin/metformin	11	8.2 (7.1–10.2) [66 (54–88)]

HbA1c, glycated hemoglobin.
*Number with HbA1c data available.
†Other diabetes medications including liraglutide and exenatide.
‡Other diabetes medications including glipizide, glyburide, and pioglitazone.
§Other diabetes medications including exenatide, glipizide, glyburide plus metformin, liraglutide, pioglitazone, and repaglinide.

Table 3. Factors associated with comorbidities during enrollment

	N	HT	DL	MA	NAFLD
Overall	598	31%	44%	6%	5%
Age					
<13 yr	95	26%	28%	2%	5%
13–<15 yr	129	30%	39%	9%	2%
15–<18 yr	251	33%	49%	5%	6%
18–<21 yr	123	31%	48%	10%	7%
p-value*		0.41	0.02	0.12	0.33
T2D duration					
<1 yr	185	23%	40%	3%	4%
1–<2 yr	118	38%	31%	8%	5%
2–<4 yr	134	39%	58%	6%	4%
≥4 yr	161	29%	46%	10%	7%
p-value†		0.43	0.47	0.001	0.46
BMI‡,§					
<85%	18	17%	36%	22%	6%
85%- < 95%	66	20%	48%	3%	3%
95%- < 99%	242	30%	46%	6%	4%
≥99%	229	39%	43%	7%	7%
p-value†		<0.001	0.76	0.06	0.28
HbA1c§,¶% (mmol/mol)					
<6.0 (<42)	133	31%	28%	5%	6%
6.0–<7.0 (42–<53)	117	25%	37%	3%	5%
7.0–<8.0 (53–<64)	77	34%	52%	10%	8%
8.0–<9.0 (64–<75)	57	39%	65%	9%	5%
≥9.0 (≥75)	158	35%	58%	9%	3%
p-value†		0.51	<0.001	0.08	0.24

CDC, Center for Disease Control; DL, dyslipidemia; HbA1c, glycated hemoglobin; HT, hypertension; MA, microalbuminuria; NAFLD, non-alcoholic fatty liver disease.
*Not adjusted for multiple comparisons. p-value from logistic regression model using continuous variable as predictor.
†BMI percentiles adjusted for age and gender based on 2000 CDC growth charts and excluded those <2 and >20 yr of age. Missing for n = 42 cases.
‡Within ±28 d from enrollment.
§HbA1c missing for n = 56 cases.

which recommended early treatment with metformin along with lifestyle modifications for all youth with T2D (16). Physical activity remains imperative in management of T2D in adolescents (17) and barriers to better compliance with lifestyle modifications must be recognized and addressed.

As seen in other pediatric T2D populations (6–8, 18–20), co-morbidities and other risk factors for microvascular and macrovascular disease were prevalent in a large proportion of participants in the PDC T2D Registry. Another theme that emerges from these data is that many of the participants with elevated blood pressure and abnormal lipid levels at the time of enrollment in the Registry were not being treated for hypertension or dyslipidemia. The same trend of low treatment rates of hypertension in children with T2D has also been reported in other studies (15, 20). In the SEARCH study, 9% of T2D patients were diagnosed with dyslipidemia but only 5% of the cohort was on lipid lowering medications (19). It is of concern that in the TODAY study, deterioration of both the atherogenic lipid profile and inflammatory markers occurred rapidly over the course of 3 yr despite treatment with statins and intensive intervention by study personnel to attempt to achieve adherence to taking their lipid-lowering medication (8). It is anticipated that adherence to prescribed medications, will be even lower in a non-study setting.

The prevalence of MA in the PDC T2D Registry is similar to that seen at study onset in the TODAY Study (6.4 vs. 6.3%, respectively) but lower than the 16.6% prevalence of MA at the end of the TODAY study 3 yr later (6). However, similar to the TODAY participants, the prevalence of MA in our cohort increased with increasing duration of the disease.

The strengths of the PDC T2D Registry include the size of the cohort as well as the inclusion of a cohort that provides a snap shot of real life practices. The data were obtained from eight academic pediatric diabetes treatment centers in the USA and thus reflect the current outpatient management of pediatric T2D. This contrasts with many clinical trials in pediatric T2D, in which clinical outcomes in highly selected cohorts of patients managed with structured treatment protocols are described.

However, certain limitations of this study should also be noted. As the cohort was enrolled only from large pediatric centers, the results of the analyses may not be wholly representative of the entire US pediatric T2D population. In addition, as diagnosis of T2D of the participants was obtained from medical records, there is a small possibility of missing undiagnosed T2D adolescents. The presence of co-morbidities was determined from the medical record 'problem list' which is dependent on the medical provider recording this. Therefore we may be underestimating the frequency of co-morbidities in this population. Also, fasting status and medication report were not available for all participants and may have affected the data interpretation at enrollment. Finally, this is a cross-sectional analysis, and one cannot infer longitudinal trends from the data even though duration of diabetes varies among the participants. Nonetheless, the findings of these initial analyses serve to underscore many of the special challenges that clinicians face in treating children and adolescents with T2D. Many patients are from disadvantaged, minority families, where socio-economic factors make compliance with treatment regimens more difficult. Moreover, metformin and insulin remain the only pharmacological treatment options approved for treatment of youth with T2D and, because of the difficulties in performing pharmaceutical trials in this population, it is unlikely that new drugs will be approved for treatment of pediatric T2D in the near future (21). Hopefully, the collaborative efforts of the PDC will facilitate well-controlled studies to evaluate novel therapies and strategies for T2D and associated comorbidities in this population.

Lastly, the observation of low rates of treatment of hypertension and dyslipidemia in the PDC T2D Registry is of concern. Despite clear guidelines from the ADA with respect to identification and treatment of co-morbidities in children with T2D, it does not appear that these co-morbidities are being adequately treated even in academic pediatric diabetes centers. The reason for the low treatment rates needs further study. As atherosclerosis begins in childhood (22, 23), increased screening and an aggressive approach to glycemic control and treating co-morbidities should be encouraged in order to delay or prevent cardiovascular disease during the lifetime of our patients.

Acknowledgements

The Pediatric Diabetes Consortium and its activities are supported by an unrestricted grant from NovoNordisk. BN, JS, PC, WT, and KR researched data, contributed to discussion, wrote manuscript, and reviewed/edited manuscript. RB, SW, RW, GK, JW, FB, and IT researched data, contributed to discussion, and reviewed/edited manuscript. RB is the guarantor of this work and, as such, had complete access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. GK reports payment for educational consultation to Eli Lilly as the planner and participant in a CME course for the Eli Lilly Company, and also is a paid consultant for Novo Nordisk. SMW has grant funding from Novo Nordisk and Veroscience. WT is a paid consultant for Novo Nordisk, AstraZeneca, Boehringer Ingelheim, Takeda, and JBN, JS, KR, RB, PC, RW, JW, FB, and IT report no conflict of interest.

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 to 2009. JAMA 2014: 311: 1778–1786.
2. Fox CS, Coady S, Sorlie P et al. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation 2007: 115: 1544–1550.
3. Pettitt DJ, Talton J, Dabelea D et al. for the SfDiYSG: Prevalence of diabetes in U.S. youth in 2009: the SEARCH for diabetes in youth study. Diabetes Care 2014: 37: 402–408.
4. Bacha F, Gungor N, Lee S, Arslanian SA. Progressive deterioration of Î²-cell function in obese youth with type 2 diabetes. Pediatr Diabetes 2013: 14: 106–111.
5. TODAY Study group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med 2012: 366: 2247–2256.
6. TODAY Study group. Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial. Diabetes Care 2013: 36: 1735–1741.
7. TODAY Study group. Retinopathy in youth with type 2 diabetes participating in the TODAY clinical trial. Diabetes Care 2013: 36: 1772–1774.
8. TODAY Study Group. Lipid and inflammatory cardiovascular risk worsens over 3 years in youth with type 2 diabetes: the TODAY clinical trial. Diabetes Care 2013: 36: 1758–64.
9. Kuczmarski R, Ogden C, Grummer-Strawn L et al. CDC growth charts: United States. Adv Data 2000: 314: 1–27.
10. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004: 114: 557–559.
11. Copeland KC, Zeitler P, Geffner M et al. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. J Clin Endocrinol Metab 2011: 96: 159–167.
12. Laffel L, Chang N, Grey M et al. R: Metformin monotherapy in youth with recent onset type 2 diabetes: experience from the prerandomization run-in phase of the TODAY study. Pediatr Diabetes 2012: 13: 385–391.
13. Chiang JL, Kirkman MS, Laffel LMB, Peters AL. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care 2014: 37: 2034–2054.
14. Kahn SE, Lachin JM, Zinman B et al. Effects of rosiglitazone, glyburide, and metformin on Î²-cell

function and insulin sensitivity in ADOPT. Diabetes 2011: 60: 1552–1560.
15. Group TS. Effects of metformin, metformin plus rosiglitazone, and metformin plus lifestyle on insulin sensitivity and [beta]-cell function in TODAY. Diabetes Care 2013: 36: 1749–1757.
16. Zeitler P, Fu J, Tandon N et al. Type 2 diabetes in the child and adolescent. Pediatr Diabetes 2014: 15: 26–46.
17. Herbst A, Kapellen T, Schober E, Graf C, Meissner T. Holl RW, for the DPVS-I: impact of regular physical activity on blood glucose control and cardiovascular risk factors in adolescents with type 2 diabetes mellitus – a multicenter study of 578 patients from 225 centres. Pediatr Diabetes 2015: 16: 204–210.
18. Eppens MC, Craig ME, Cusumano J et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. Diabetes Care 2006: 29: 1300–1306.
19. Kershnar AK, Daniels SR, Imperatore G et al. Lipid abnormalities are prevalent in youth with type 1 and type 2 diabetes: the search for diabetes in youth study. J Pediatr 2006: 149: 314–319.
20. Rodriguez BL, Dabelea D, Liese AD et al. Prevalence and correlates of elevated blood pressure in youth with diabetes mellitus: the search for diabetes in youth study. J Pediatr 2010: 157: 245–251.e241.
21. Tamborlane WV, Klingensmith G. Crisis in care: limited treatment options for type 2 diabetes in adolescents and youth. Diabetes Care 2013: 36: 1777–8.
22. Berenson GS, Srinivasan SR, Bao W, Newman WP III, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. N Engl J Med 1998: 1650–6.
23. McGill HC, McMahan CA, Zieske AW et al. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. Arterioscler Thromb Vasc Biol 2000: 20: 1998–2004.

Appendix

The Pediatric Diabetes Consortium Study Group

Clinical Centers: [Listed clinical center name, city, and state. Personnel are listed as (PI) for Principal Investigator, (I) for co-Investigator and (C) for Coordinators.] (1) Baylor College of Medicine, Houston, TX: Fida Bacha, MD (PI); Morey Haymond, MD (I); Maria J. Redondo, MD, PhD (I); Elizabeth Johnson (C); Andrene McDonald (C) (2) Children's Hospital of Los Angeles, Los Angeles, CA: Jamie Wood, MD (PI); Brian Ichihara, BA (C); Megan Lipton, MA, CCRP (C); Marisa Cohen, MPH (C); (3) Stanford University, Stanford, CA: Bruce Buckingham, MD (PI); Breanne Harris, BS (C); Satya Shanmugham, BS (C); (4) Barbara Davis Center for Childhood Diabetes, University of Colorado School of Medicine, Aurora, CO: Georgeanna J. Klingensmith, MD (PI); Eric Cruz, BA (C); Heidi Haro, BA, BS (C); Maria King, BA (C); Katherine Manseau (C); (5) University of Florida, Gainesville, FL: Desmond Schatz, MD (PI); Janet Silverstein, MD (I); Michael J. Haller, MD (I); Erica Dougherty, BS (C); (6) Yale University, New Haven, CT: William V. Tamborlane, MD (I); Eda Cengiz, MD (PI); Melody Martin, CCRP (C); Amy Steffen, BA (C); Lori Carria, MS (C); Darryll Cappiello (C); (7) University of Michigan, Ann Arbor, MI: Joyce M. Lee, MD, MPH (PI); Surair Bashir (C); Ashley Eason (C); (8) Children's Hospital of Philadelphia, Philadelphia, PA: Steven M. Willi, MD (PI); Tammy Mawson (C); Coordinating Center: Jaeb Center for Health Research, Tampa, FL: Roy W. Beck, MD, PhD; Katrina J. Ruedy, MSPH; Craig Kollman, PhD; Crystal G. Connor, MS, MPH; Beth Stevens; TJ Mouse.