FEATURE ARTICLE

Characteristics of Type 2 Diabetes in Female and Male Youth

Beatriz Castillo Rodriguez,[1] Marcela Astudillo,[2] Mustafa Tosur,[2] Ahmad Rafaey,[2] Siripoom McKay,[2] Fida Bacha,[2,3] Ashok Balasubramanyam,[4] and Maria J. Redondo[2]

The incidence of type 2 diabetes in children is rising and carries a worse prognosis than in adults. The influence of sex on pediatric type 2 diabetes outcomes has not been well investigated. We studied 715 youth with type 2 diabetes diagnosed at a median age of 13.7 years and compared sex differences in demographic, clinical, and laboratory characteristics within the first year of diagnosis. Females diagnosed with type 2 diabetes were younger and at a higher stage of pubertal development than males, yet presented with lower A1Cs, a lower prevalence of diabetic ketoacidosis, and higher HDL cholesterol levels.

KEY POINT

» In this cohort study of 715 youth with type 2 diabetes, females were diagnosed at a younger age than males and presented with a milder clinical phenotype characterized by lower glucose, A1C, and frequency of diabetic ketoacidosis and higher HDL cholesterol.

Type 2 diabetes is described as developing from progressive loss of adequate β-cell insulin secretion on a background of insulin resistance (1,2). However, the heterogeneity of type 2 diabetes physiopathology and clinical presentation (3) is increasingly recognized as a barrier to optimal prevention and treatment. In adults with diabetes, differences in clinical characteristics have been noted between the sexes. Adult women have a higher predisposition to type 2 diabetes than adult men (4), whereas type 1 diabetes predominates in males, particularly in regions of high type 1 diabetes prevalence (5). Adult women with type 2 diabetes are also at higher risk of cardiovascular disease than their male counterparts (6).

The frequency of pediatric type 2 diabetes is increasing rapidly, and its prevalence increased by 95.3% between 2001 and 2017 (7,8). The prevalence of pediatric type 2 diabetes varies across races and ethnicities. In the United States, the overall prevalence in youth is 0.67/1,000, yet among ethnic minorities it is as high as 0.85/1,000 (4,9). In addition, type 2 diabetes is associated with worse outcomes in children than in adults (10), in part because of a faster rate of β-cell deterioration in youth (11,12). The incidence of type 2 diabetes in female patients aged 10–14 years has been found to be up to twice as high as in their male counterparts (13). Although sex differences in the epidemiology of pediatric type 2 diabetes have been reported, less is known about sex-based clinical differences. Hence, we aimed to compare clinical and biochemical characteristics between male and female youth with type 2 diabetes. Better understanding of the differences between males and females could shed light on the pathogenesis of pediatric type 2 diabetes and offer the potential for targeted therapy.

Research Design and Methods

Participants

We identified 716 youth <19 years of age with a clinical diagnosis of type 2 diabetes who were seen in our center between July 2016 and July 2019. Steroid-induced and cystic fibrosis–related diabetes were not included. We also excluded one child who tested positive for islet autoantibodies, resulting in a final sample of 715. The

[1]Baylor College of Medicine, School of Medicine, Houston, TX; [2]Division of Diabetes and Endocrinology, Texas Children's Hospital, Baylor College of Medicine, Houston, TX; [3]USDA/ARS Children's Nutrition Research Center, Texas Children's Hospital, Baylor College of Medicine, Houston, TX; [4]Division of Diabetes, Endocrinology and Metabolism, Baylor College of Medicine, Houston, TX

Corresponding author: Beatriz Castillo Rodriguez, beatrizr@bcm.edu

https://doi.org/10.2337/cd22-0057

study protocol was approved by the Baylor College of Medicine Institutional Review Board (H-45325).

Procedures

We collected demographic, clinical, and laboratory characteristics by electronic medical record review. Physical exam information included Tanner staging for pubertal development (I–V) within 3 months of diabetes diagnosis, performed by a pediatric endocrinologist using breast development staging for girls and testicular size for boys.

Laboratory data included random serum glucose and C-peptide levels measured simultaneously at the time of diabetes diagnosis, A1C within 1 month of diagnosis, history of clinician-diagnosed dyslipidemia and/or nonalcoholic fatty liver disease (NAFLD), lipid profile, and urine albumin-to-creatinine ratio obtained within 1 year of diagnosis.

Definitions

Microalbuminuria was defined as two consecutive abnormal spot urine results with microalbumin-to-creatinine ratio >30 mg/g. Diabetic ketoacidosis (DKA) was defined using the standard criteria of the International Society for Pediatric and Adolescent Diabetes 2018 clinical practice consensus guidelines (2) in those with available biochemical data or by documentation of DKA in the medical record.

Statistical Analysis

We first conducted a univariable comparison of males and females for each of the characteristics of interest, using χ^2, Fisher exact, and Wilcoxon rank sum tests as appropriate. To adjust for potential confounding, we conducted multivariable logistic regression analysis with the variables that were statistically significant in the univariable analysis. With Bonferroni correction for the number of independent comparisons, $P < 0.0045$ was considered statistically significant in the univariable analyses, and $P < 0.05$ was considered statistically significant for multivariable analyses. All analyses were conducted using STATA, v. 12 statistical software (StataCorp, College Station, TX).

Results

We studied 715 children (448 female and 267 male) with type 2 diabetes who presented to the clinic within the 3-year study period. At diagnosis, their mean age was 13.7 years (SD 2.4 years), glucose was 13.9 mmol/L (SD 7.60 mmol/L) (250.5 mg/dL [SD 136.9 mg/dL]), and A1C 9.6% (SD 2.6%). Puberty was assessed at stage IV or V in 60.4% of the patients. The mean BMI *z* score at diagnosis was 2.25 (SD 0.48). Within 1 year of diagnosis, mean HDL cholesterol was 0.98 mmol/L (SD 0.26 mmol/L) (37.9 mg/dL [SD 10.1 mg/dL]), and the mean triglyceride level was 5.52 mmol/L (SD 6.35 mmol/L) (488.9 mg/dL [SD 562.4 mg/dL]) (Table 1).

In univariable analysis, female patients were younger (13.4 vs. 14.1 years of age), had lower A1C (9.3 vs. 10.1%), and had lower blood glucose (13.2 vs. 15.0 mmol/L [237.8 vs. 270.3 mg/dL]) at diagnosis. A larger percentage of female patients were at Tanner stages IV or V than male patients (68.4 vs. 44.9%). Additionally, 5.2% of females presented with DKA at diagnosis, compared with 12.6% of males. HDL cholesterol levels measured within 1 year of diagnosis were higher in female patients (1.02 vs. 0.92 mmol/L [39.4 vs. 35.6 mg/dL]) (Table 1).

Race/ethnicity, family history of type 2 diabetes, age- and sex-adjusted BMI *z* score, and C-peptide levels at diagnosis were not significantly different between females and males. Non-HDL cholesterol, LDL cholesterol, triglycerides, history of NAFLD, history of retinopathy, and microalbuminuria collected within 1 year of diagnosis were also not significantly different between the sexes.

In multivariable analyses, female sex was significantly associated with both younger age after adjusting for Tanner stage ($P < 0.0001$) and more advanced Tanner stage ($P < 0.0001$) after adjusting for age. Male sex was statistically associated with both DKA after adjusting for A1C ($P = 0.035$) and A1C after adjusting for DKA ($P = 0.006$) at diagnosis. The significant association between female sex and higher HDL levels persisted ($P = 0.001$) after adjusting for age and Tanner stage at diagnosis.

Discussion

We studied sex differences in a large cohort of youth with type 2 diabetes and observed that females are diagnosed at a younger age and with more advanced pubertal development than males and present with milder clinical characteristics as indicated by lower A1C, lower frequency of DKA, and higher HDL cholesterol levels.

The earlier age at type 2 diabetes diagnosis in females is possibly the result of higher insulin resistance from earlier pubertal development than males. This hypothesis is supported by the higher percentage of females who presented at Tanner stages IV and V and previous

TABLE 1 Characteristics of Female and Male Patients With Type 2 Diabetes

Characteristic	Overall (N = 715)	Males (n = 267)	Females (n = 448)	P
Age, years*	13.7 ± 2.4	14.1 ± 2.2	13.4 ± 2.5	**0.0002**
Race/ethnicity				0.045
Non-Hispanic White	8.9 (62)	9.5 (25)	8.5 (37)	
Hispanic	57.4 (402)	61 (161)	55.3 (241)	
Black	30.6 (214)	25 (66)	33.9 (148)	
Other	3.1 (22)	4.6 (12)	2.3 (10)	
C-peptide, nmol/L*	1.27 ± 1.01 (466)	1.17 ± 1.01 (188)	1.34 ± 1.02 (278)	0.0082
Glucose, mmol/L [mg/dL]*	13.9 ± 7.60 [250.5 ± 136.9] (618)	15.0 ± 8.49 [270.3 ± 153.0] (238)	13.2 ± 6.94 [237.8 ± 125.0] (380)	0.0055
A1C, %*	9.6 ± 2.6 (627)	10.1 ± 2.7 (241)	9.3 ± 2.5 (386)	**0.0014**
Puberty stage*				**<0.0001**
Tanner I	9.2 (34)	13.4 (17)	6.97 (17)	
Tanner II	10.8 (40)	20.5 (26)	5.74 (14)	
Tanner III	19.7 (73)	21.3 (27)	18.9 (46)	
Tanner IV	22.9 (85)	26.8 (34)	20.9 (51)	
Tanner V	37.5 (139)	18.1 (23)	47.5 (116)	
Tanner stage IV or V*	60.4 (224)	44.9 (57)	68.4 (167)	**<0.0001**
Family history of diabetes	93.8 (645)	95.4 (247)	92.8 (398)	0.173
First-degree relative with diabetes	67.2 (462)	67.2 (174)	67.2 (288)	0.990
BMI, z score*	2.25 ± 0.48 (538)	2.29 ± 0.53 (212)	2.23 ± 0.45 (326)	0.0277
DKA*	8.0 (56)	12. (33)	5.2 (23)	**0.001**
Non-HDL cholesterol, mmol/L [mg/dL]†	3.47 ± 0.98 [134.0 ± 37.8] (464)	3.50 ± 1.09 [135.1 ± 42.1] (181)	3.44 ± 0.93 [132.8 ± 35.9] (283)	0.8675
HDL cholesterol, mmol/L [mg/dL]†	0.98 ± 0.26 [37.9 ± 10.1] (530)	0.92 ± 0.24 [35.6 ± 9.28] (205)	1.02 ± 0.27 [39.4 ± 10.4] (325)	**0.0001**
LDL cholesterol, mmol/L [mg/dL]†	2.54 ± 0.77 [98.2 ± 29.8] (490)	2.47 ± 0.80 [95.5 ± 30.9] (186)	2.59 ± 0.75 [100.2 ± 29.0] (304)	0.0569
Triglycerides, mmol/L [mg/dL]†	5.52 ± 6.35 [488.9 ± 562.4] (529)	6.29 ± 8.81 [557.1 ± 780.3] (206)	5.02 ± 4.04 [444.6 ± 357.8] (323)	0.1558
NAFLD history	12.6 (90)	11.2 (30)	13.4 (60)	0.400
Microalbuminuria†	21.3 (105)	21.8 (33)	21.0 (61)	0.827
Retinopathy†	1.4 (3)	1.2 (1)	1.4 (2)	0.889

Data are mean ± SD, mean ± SD (n), or % (n). Bold type indicates statistical significance. *At diagnosis. †Within 1 year of diagnosis.

studies demonstrating that diagnosis of type 2 diabetes is rare before the onset of puberty (14). Puberty is characterized by a growth spurt driven by a marked increase in growth hormone secretion that results in growth velocities averaging 9.5 cm/year in males and 8.25 cm/year in females (15). Growth hormone is known to induce insulin resistance, with a consequent rise in serum glucose levels, through complex mechanisms related in part to growth hormone's facilitation of adipose tissue lipolysis (16) and hepatic gluconeogenesis (17). It is also possible that female sex hormones have a greater influence on type 2 diabetes risk through their influence on adiposity or other mechanisms, further contributing to the earlier age of onset in females. Girls are more insulin resistant than boys during early to midpuberty (16,18). This sex difference is

partially explained by differences in adiposity (16,18), IGF-1 levels (16), as well as lower physical activity in females (16). On the other hand, obesity is associated with higher androgens, which relate to insulin resistance during puberty only in girls (19). These factors may explain some of the sex differences in age of onset of type 2 diabetes. An additional potential explanation for the milder presentation in females could be earlier medical attention prompted by health concerns related to the earlier pubertal development that is typically observed in girls compared with boys. However, longitudinal studies are needed to examine these relationships and account for additional confounders, including race/ethnicity and physical activity.

In addition to the implications for current knowledge of the physiopathology of type 2 diabetes, the observation that girls develop type 2 diabetes earlier has clinical significance. Screening guidelines for diabetes and prediabetes may need to be stratified by sex, and females with risk factors for type 2 diabetes should be monitored starting earlier in life than males.

We also observed that serum A1C was higher in males than in females. Given the well-known associations between A1C and diabetes outcomes, this finding suggests that males may be at risk for worse diabetes outcomes than females. The mechanisms underlying these sex differences are not clear.

HDL cholesterol levels were higher in females than in males. This finding may be related to known sex differences in HDL cholesterol levels. Pubertal development has been reported to improve the lipid profile, but, in the present data, the difference in HDL cholesterol was present after adjustment for pubertal development. However, we cannot exclude incomplete adjustment because we did not have Tanner stage information for all of the children in the study. Additionally, we could not account for the potential effect of glucose control on the lipid profile at the time of the assessment. The observed sex differences in HDL cholesterol are in contradistinction to findings from the TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) study, in which females had lower HDL cholesterol than males, whereas males were more likely to have elevated blood pressure early in the disease course (20). Interestingly, in the TODAY study, males were more likely than females to have been born large for gestational age and to have been exposed to maternal gestational diabetes (20). This finding supports the importance of more studies to gain a better understanding of the underpinnings of these observations.

Limited studies have compared clinical characteristics in males and females with type 2 diabetes. Strengths of our study include the large sample size in a single-center study and the availability of Tanner stage information evaluated by a pediatric endocrinologist for a large percentage of the sample. Our study has some limitations, however. Because of the cross-sectional design, we did not have follow-up information on the trajectory of glucose control or other diabetes outcomes. We were not able to assess birth history or other environmental, physical activity, or nutritional factors that may contribute to sex differences in diabetes risk. Additionally, we lacked detailed information on specific relatives and diabetes types (e.g., gestational diabetes or established type 2 diabetes in mothers of participants), which could be helpful in identifying genetic patterns in this multifactorial disease. Longitudinal studies with comprehensive assessment of in utero exposures, lifestyle factors, and the hormonal milieu in childhood will increase our understanding of pathophysiologic and prognostic differences between male and female youth with type 2 diabetes. Extended follow-up of participants will allow determination of whether the observed differences between males and females persist over time. In addition, it will be important to evaluate potential differences in diabetes outcomes such as risks for and types of chronic diabetes complications and comorbidities.

In conclusion, we observed that females are diagnosed with type 2 diabetes at a younger age, at a more advanced pubertal stage, and with milder disease characteristics than males. There are likely sex-specific factors affecting the development and progression of type 2 diabetes in children that are not yet well understood. Continued efforts to understand these processes could lead to more precise approaches to the diagnosis and treatment of type 2 diabetes in children.

FUNDING

This work was supported by a U.S. Department of Agriculture-Agricultural Research Service Current Research Information System award (F.B.) and National Institutes of Health grant R01 DK124395 (M.J.R.).

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

B.C.R. contributed to the study design, data analysis, and interpretation; communicated results at local and international meetings; and wrote the first draft of the manuscript. M.A. collected the data, contributed to data analysis and

interpretation, and edited the manuscript. M.T., S.M., F.B., and A.B. contributed to data interpretation and edited the manuscript. A.R. contributed to data collection and edited the manuscript. M.J.R. conceptualized the study; contributed to the study design, data analysis, and interpretation; and edited the manuscript. All the authors approved the final version of the manuscript. M.J.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PRIOR PUBLICATION

Parts of the content of this article were presented in abstract form at the European Academy of Paediatric Societies' virtual 8th Congress, 16–19 October 2020.

REFERENCES

1. American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes—2022*. Diabetes Care 2022;45(Suppl. 1):S17–S38

2. Abraham MB, Jones TW, Naranjo D, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes 2018;19(Suppl. 27):178–192

3. Merino J, Udler MS, Leong A, Meigs JB. A decade of genetic and metabolomic contributions to type 2 diabetes risk prediction. Curr Diab Rep 2017;17:135

4. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, et al. Sex and gender: modifiers of health, disease, and medicine. Lancet 2020;396:565–582

5. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. Endocrinol Metab Clin North Am 2010;39:481–497

6. Kannel WB, Wilson PW. Risk factors that attenuate the female coronary disease advantage. Arch Intern Med 1995;155:57–61

7. Hamman RF, Bell RA, Dabelea D, et al.; SEARCH for Diabetes in Youth Study Group. The SEARCH for Diabetes in Youth study: rationale, findings, and future directions. Diabetes Care 2014;37:3336–3344

8. Lawrence JM, Divers J, Isom S, et al.; SEARCH for Diabetes in Youth Study Group. Trends in prevalence of type 1 and type 2 diabetes in children and adolescents in the US, 2001–2017. JAMA 2021;326:717–727

9. Liese AD, D'Agostino RB Jr, Hamman RF, et al.; SEARCH for Diabetes in Youth Study Group. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth study. Pediatrics 2006;118:1510–1518

10. Constantino MI, Molyneaux L, Limacher-Gisler F, et al. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. Diabetes Care 2013;36:3863–3869

11. RISE Consortium. Impact of insulin and metformin versus metformin alone on β-cell function in youth with impaired glucose tolerance or recently diagnosed type 2 diabetes. Diabetes Care 2018;41:1717–1725

12. TODAY Study Group; Zeitler P, Hirst K, Pyle L, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med 2012;366:2247–2256

13. Lawrence JM, Mayer-Davis EJ, Reynolds K, et al.; SEARCH for Diabetes in Youth Study Group. Diabetes in Hispanic American youth: prevalence, incidence, demographics, and clinical characteristics: the SEARCH for Diabetes in Youth study. Diabetes Care 2009;32(Suppl. 2):S123–S132

14. Astudillo M, Tosur M, Castillo B, et al. Type 2 diabetes in prepubertal children. Pediatr Diabetes 2021;22:946–950

15. Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for North American children. J Pediatr 1985;107:317–329

16. Jeffery SC, Hosking J, Jeffery AN, et al. Insulin resistance is higher in prepubertal girls but switches to become higher in boys at age 16: a cohort study (EarlyBird 57). Pediatr Diabetes 2018;19:223–230

17. Corbit KC, Camporez JPG, Tran JL, et al. Adipocyte JAK2 mediates growth hormone-induced hepatic insulin resistance. JCI Insight 2017;2:e91001

18. Moran A, Jacobs DR Jr, Steinberger J, et al. Insulin resistance during puberty: results from clamp studies in 357 children. Diabetes 1999;48:2039–2044

19. Chynoweth J, Hosking J, Jeffery A, Pinkney J. Contrasting impact of androgens on male and female adiposity, fat distribution and insulin resistance in childhood and adolescence (EarlyBird 75). Pediatr Obes 2020;15:e12685

20. Copeland KC, Zeitler P, Geffner M, et al.; TODAY Study Group. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. J Clin Endocrinol Metab 2011;96:159–167