HHS Public Access

Author manuscript

Lancet Diabetes Endocrinol. Author manuscript; available in PMC 2023 May 01.

Published in final edited form as:

Lancet Diabetes Endocrinol. 2022 May ; 10(5): 303–304. doi:10.1016/S2213-8587(22)00075-4.

Dapagliflozin in young people with type 2 diabetes

Kalie L. Tommerdahl, M.D.[a], **Robert G. Nelson, M.D., Ph.D.**[b], **Petter Bjornstad, M.D.**[a]

[a] Section of Endocrinology, Department of Pediatrics, Division of Nephrology, Department of Medicine, University of Colorado School of Medicine, Aurora, CO 80045-7106, USA

[b] National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, AZ, USA

Commentary:

Clinical trials in young persons with type 2 diabetes (T2D) are scarce, which is why the trial data presented by Tamborlane *et al.* evaluating the effects of a novel adjunctive T2D medication provide important therapeutic insight into this burgeoning, high-risk and understudied population.[1] Nearly 14 million youth in the United States are obese and at increased risk for youth-onset T2D.[2] Rising rates of obesity and other metabolic conditions are projected to increase the incidence of youth-onset T2D by 600% between 2017 and 2060.[2,3] The more severe metabolic phenotype observed in youth-onset vs. adult-onset T2D, including greater insulin resistance and more rapid deterioration of pancreatic β-cell function,[4] increases their risk for the micro- and macrovascular complications of diabetes.[5] Indeed, kidney biopsies obtained from Pima Indians with T2D document more severe kidney structural lesions in youth than adult-onset T2D irrespective of age and diabetes duration.[6] Despite the burden of complications in youth-onset T2D, current therapeutic options are limited.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are highly effective therapies that significantly reduce the risk of heart and kidney disease in adults with T2D,[7] but at present these medications are not approved by the FDA for persons younger than 18 years old. The Treatment Options for T2D in Adolescents and Youth (TODAY) and Restoring Insulin Secretion (RISE) trials have demonstrated differing physiology in adult-onset vs. youth-onset T2D indicating that dedicated clinical trials in young persons with youth-onset T2D are needed.[4]

Corresponding Author: Petter Bjornstad, M.D., Section of Endocrinology, Department of Pediatrics, Division of Nephrology, Department of Medicine, University of Colorado School of Medicine, 13123 E 16th Ave, Box B265, Aurora, CO 80045-7106, Office: 720-777-4659, Fax: 720-777-7301, petter.m.bjornstad@cuanschutz.edu.

Conflicts of interest

P.B. reports serving as a consultant for AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eli-Lilly, LG Chemistry, Sanofi, Novo Nordisk, and Horizon Pharma. P.B. also serves on the advisory boards of AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, and XORTX.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute of Health.

Tamborlane *et al.* presented data from the first phase 3 placebo-controlled randomized trial of the SGLT2 inhibitor dapagliflozin, when added to standard of care (i.e., metformin, insulin, or both) in young persons with T2D (16.1 ± 3.4 years). The primary outcome of the trial was change in hemoglobin A1c (HbA1c) over 24 weeks. The intention-to-treat analysis did not demonstrate a statistically significant change in HbA1c between the dapagliflozin and placebo groups (−0.75 [95% CI −1.64, 0.15] %, p=0.10), but a pre-specified analysis of protocol-compliant participants documented a statistically significant decrease in HbA1c in response to dapagliflozin (−1.13 [−1.99, −0.26] %, p=0.01). This relative decrease in HbA1c was clinically significant and in line with that observed in adults with T2D. The incongruent results between the intention-to-treat and compliance-based analyses are not unexpected, since young persons with T2D face several barriers to medical adherence including high rates of depression and poor motivation.[8] Hypoglycemia was documented in 28% of the participants receiving dapagliflozin and in 18% of those receiving placebo. The authors did not report any episodes of diabetic ketoacidosis (DKA). In contrast with adult trials, no statistically significant effects were noted in this study for secondary endpoints including changes in body mass index or blood pressure. These differences could be ascribed in part to normal growth fluctuations related to puberty and/or the low baseline prevalence of hypertension in this trial.

Considering the strong kidney protective effects of SGLT2 inhibition, a limitation of the trial was the absence of serial measures of albuminuria and estimated glomerular filtration rate (eGFR). A previous study in youth with T2D found that a single dose of SGLT2 inhibitor increased natriuresis and attenuated eGFR, findings consistent with adult data and demonstrating the need for long-term evaluation in pediatrics.[9] Ongoing SGLT2 inhibitor trials in young persons with T2D that include changes in albuminuria and eGFR as additional endpoints will help establish the efficacy of SGLT2 inhibitors in mitigating diabetic kidney disease risk in this population.

The recently completed Treatment Options for Type 2 Diabetes in Adolescents and Youth follow-up study (TODAY/TODAY2) documented poor glycemic control and a high burden of vascular complications as adolescents with T2D enter young adulthood, a time that otherwise could be the most productive period of their lives.[5] These serious data underscore the need for additional therapies, such as SGLT2 inhibitors, to improve metabolic and vascular health in these young persons with T2D. Future studies should leverage advances in integrative biology to define the mechanisms of benefit afforded by SGLT2 inhibition. This approach will help inform strategies for combination therapy and target the treatment to individuals with T2D who will most likely respond to these therapies.

Acknowledgement

K.L.T. receives salary and research support from the NIH/NHLBI (K23 HL159292), Children's Hospital Colorado Research Institute Research Scholar Award, University of Colorado Diabetes Research Center (P30 DK116073), Ludeman Family Center for Women's Health Research at the University of Colorado, and the Department of Pediatrics, Section of Endocrinology at the University of Colorado School of Medicine. R.G.N. is supported by the Intramural Research Program of NIDDK. P.B. receives salary and research support from NIDDK (R01 DK129211, R21 DK129720, K23 DK116720, UC DK114886, and P30 DK116073), JDRF (2-SRA-2019–845-S-B, 3-SRA-2017–424-M-B, 3-SRA-2022–1097-M-B), Boettcher Foundation, American Heart Association (20IPA35260142), Ludeman Family Center for Women's Health Research at the University of Colorado, the

Department of Pediatrics, Section of Endocrinology and Barbara Davis Center for Diabetes at University of Colorado School of Medicine.

References:

1. Tamborlane W EFFICACY AND SAFETY OF DAPAGLIFLOZIN IN CHILDREN AND YOUNG ADULTS WITH TYPE 2 DIABETES: A PROSPECTIVE, MULTICENTRE, RANDOMIZED, PARALLEL GROUP PHASE 3 STUDY. Lancet Diabetes Endocrinol (2022).
2. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, Imperatore G, Linder B, Marcovina S, Pettitt DJ, Pihoker C, Saydah S, Wagenknecht L & Study S. f. D. i. Y. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002–2012. N Engl J Med 376, 1419–1429, doi:10.1056/NEJMoa1610187 (2017). [PubMed: 28402773]
3. TÖNnies T, Saydah S, Isom S, Dabelea D, Divers J, Mayer-Davis EJ, Pihoker C, Dolan LM, Brinks R, Dagostino R, Hoyer A & Imperatore G 156-OR: Projections of Type 1 and Type 2 Diabetes Burden in the U.S. Population Aged <20 Years through 2060. Diabetes 70, doi:10.2337/db21-156-OR (2021).
4. Consortium R & Investigators RC Effects of Treatment of Impaired Glucose Tolerance or Recently Diagnosed Type 2 Diabetes With Metformin Alone or in Combination With Insulin Glargine on beta-Cell Function: Comparison of Responses In Youth And Adults. Diabetes, doi:10.2337/db19-0299 (2019).
5. Group TS, Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, Nathan DM, Tesfaldet B, Tryggestad J, White NH & Zeitler P Long-Term Complications in Youth-Onset Type 2 Diabetes. N Engl J Med 385, 416–426, doi:10.1056/NEJMoa2100165 (2021). [PubMed: 34320286]
6. Looker HC, Pyle L, Vigers T, Severn C, Saulnier PJ, Najafian B, Mauer M, Nelson RG & Bjornstad P Structural Lesions on Kidney Biopsy in Youth-Onset and Adult-Onset Type 2 Diabetes. Diabetes Care 45, 436–443, doi:10.2337/dc21-1688 (2022). [PubMed: 35006272]
7. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW & Investigators CT Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med 380, 2295–2306, doi:10.1056/NEJMoa1811744 (2019). [PubMed: 30990260]
8. Katz LL, Anderson BJ, McKay SV, Izquierdo R, Casey TL, Higgins LA, Wauters A, Hirst K, Nadeau KJ & Group TS Correlates of Medication Adherence in the TODAY Cohort of Youth With Type 2 Diabetes. Diabetes Care 39, 1956–1962, doi:10.2337/dc15-2296 (2016). [PubMed: 27352955]
9. Bjornstad P, Laffel L, Tamborlane WV, Simons G, Hantel S, von Eynatten M, George J, Marquard J & Cherney DZI Acute Effect of Empagliflozin on Fractional Excretion of Sodium and eGFR in Youth With Type 2 Diabetes. Diabetes Care 41, e129–e130, doi:10.2337/dc18-0394 (2018). [PubMed: 29941496]