RESPONSE TO COMMENT ON BRAFFETT ET AL.

Association of Insulin Dose, Cardiometabolic Risk Factors, and Cardiovascular Disease in Type 1 Diabetes During 30 Years of Follow-up in the DCCT/EDIC Study. Diabetes Care 2019;42:657–664

*Barbara H. Braffett,[1] Samuel Dagogo-Jack,[2] Ionut Bebu,[1] William I. Sivitz,[3] Mary Larkin,[4] Orville Kolterman,[5] and John M. Lachin,[1] on behalf of the DCCT/EDIC Research Group**

Diabetes Care 2019;42:e137 | https://doi.org/10.2337/dci19-0026

Snaith et al. (1) suggest that the relationship between insulin dose and adverse cardiometabolic profile might be mediated by insulin resistance and cite data linking clamp-derived measurement of insulin resistance and coronary artery calcification (2). We do not have any direct assessment of insulin resistance in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study; however, the association among weight gain, insulin resistance, and adverse cardiometabolic risk factors is well known and was discussed in our article (3). Insulin-mediated downregulation (via degradation) of insulin receptors certainly occurs and could be one of numerous receptor and postreceptor mechanisms underlying insulin resistance (4). Snaith et al. further suggest that improving insulin sensitivity in type 1 diabetes could improve cardiovascular risk, in support of which they cited the Reducing with Metformin Vascular Adverse Lesions (REMOVAL) study (5) on the effect of metformin on carotid intima-media thickness (cIMT). Notably, the REMOVAL study did not find a significant effect of metformin on the primary outcome of progression of cIMT, thus the significance of the finding regarding maximal cIMT (a tertiary end point) is unclear.

Funding. The DCCT/EDIC has been supported by cooperative agreement grants (1982–1993, 2012–2017, and 2017–2022) and contracts (1982–2012) with the Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases (current grant numbers U01 DK094176 and U01 DK094157) and through support by the National Eye Institute, the National Institute of Neurological Disorders and Stroke, the General Clinical Research Centers Program (1993–2007), and the Clinical Translational Science Center Program (2006–present), Bethesda, MD.

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

References

1. Snaith JR, Holmes-Walker DJ, Greenfield JR. Comment on Braffett et al. Association of insulin dose, cardiometabolic risk factors, and cardiovascular disease in type 1 diabetes during 30 years of follow-up in the DCCT/EDIC study. Diabetes Care 2019;42:657–664 (Letter). Diabetes Care 2019;42:e135–e136. DOI: 10.2337/dc19-0730
2. Schauer IE, Snell-Bergeon JK, Bergman BC, et al. Insulin resistance, defective insulin-mediated fatty acid suppression, and coronary artery calcification in subjects with and without type 1 diabetes: the CACTI study. Diabetes 2011;60:306–314
3. Braffett BH, Dagogo-Jack S, Bebu I, et al.; DCCT/EDIC Research Group. Association of insulin dose, cardiometabolic risk factors, and cardiovascular disease in type 1 diabetes during 30 years of follow-up in the DCCT/EDIC study. Diabetes Care 2019;42:657–664
4. Haeusler RA, McGraw TE, Accili D. Biochemical and cellular properties of insulin receptor signalling. Nat Rev Mol Cell Biol 2018;19:31–44
5. Petrie JR, Chaturvedi N, Ford I, et al.; REMOVAL Study Group. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2017;5:597–609

[1]*Biostatistics Center, The George Washington University, Rockville, MD*
[2]*Division of Endocrinology, Diabetes and Metabolism, University of Tennessee Health Science Center, Memphis, TN*
[3]*Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Iowa, Iowa City, IA*
[4]*Massachusetts General Hospital Diabetes Center, Harvard Medical School, Boston, MA*
[5]*University of California, San Diego, La Jolla, CA*

Corresponding author: Barbara H. Braffett, braffett@bsc.gwu.edu

Clinical trial reg. nos. NCT00360815 and NCT00360893, clinicaltrials.gov

**A complete list of participants in the DCCT/EDIC Research Group is presented in the Supplementary Material published online for the article in N Engl J Med 2017;376:1507–1516.*