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

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We read with great interest that Braffett et al. (1) report an association between insulin dose and adverse cardiometabolic profiles using 30 years of follow-up data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. Intensive diabetes treatment necessitating increased insulin doses became the accepted standard of care in type 1 diabetes after the DCCT/EDIC trial demonstrated cardiovascular risk benefit (mean ± SD 0.71 ± 0.21 vs. 0.65 ± 0.21 units/kg/day in the intensive vs. conventional treatment group; $P = 0.0001$). We support the authors' emphasis that this association is somewhat driven by insulin-related weight gain, especially in males. The report of no significant association between BMI and insulin dose in women indicates other contributing factors are involved. We suggest that the relationship between insulin dose and adverse cardiometabolic profile is confounded by insulin resistance, and improving insulin sensitivity in type 1 diabetes has the potential to improve cardiovascular risk.

Studies have established links between directly measured insulin resistance (using hyperinsulinemic-euglycemic clamps) and coronary atherosclerosis. In the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study, participants with insulin-resistant type 1 diabetes (with lower glucose utilization) had greater coronary artery calcification ($r = -0.42$, $P < 0.0001$) after adjusting for BMI, sex, and age (2). The study reported that individuals with type 1 diabetes were more insulin resistant than control subjects without diabetes. As body composition and adiposity were similar between groups, weight difference was not the driver of resistance but likely insulin treatment itself. This may suggest that insulin resistance in type 1 diabetes does not only affect select individuals but the entire population. Postulated causes include nonphysiologic subcutaneous insulin delivery causing portal hypoinsulinemia with peripheral hyperinsulinemia leading to insulin receptor downregulation.

Adjunctive metformin is showing cardioprotective potential in type 1 diabetes trials. In the REMOVAL (Reducing with Metformin Vascular Adverse Lesions) trial, 3 years of metformin treatment achieved greater reduction in progression of maximal carotid intima-media thickness than was achieved by 5 years of intensive glycemic control in the DCCT/EDIC trial (−0.039 mm vs. −0.013 mm) (3,4). Subsequent studies in youth treated with metformin demonstrated improved clamp-measured insulin resistance, vascular function, and cardiometabolic profiles even without a significant reduction in total daily insulin dose (5), indicating that insulin dose is an imperfect surrogate for insulin resistance.

In summary, the association between higher insulin dose and adverse cardiometabolic profiles may relate to insulin resistance, which secondarily alters systolic blood pressure, HDL cholesterol, and triglycerides. Insulin resistance is cumbersome to measure directly and was outside the scope of the DCCT/EDIC study. Metformin may offset insulin resistance in type 1 diabetes, but longer-term studies are required to determine whether insulin sensitization prevents subsequent cardiovascular events directly or through indirect improvement of blood pressure and lipid metabolism. Including clamp protocols as substudies within large type 1 diabetes longitudinal studies with hard end points will be valuable.

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

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References

1. 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

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. 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

4. Nathan DM, Lachin J, Cleary P, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. N Engl J Med 2003;348:2294–2303

5. Bjornstad P, Schäfer M, Truong U, et al. Metformin improves insulin sensitivity and vascular health in youth with type 1 diabetes mellitus. Circulation 2018;138:2895–2907