COMMENTARY

Can We RISE to the Challenge of Youth-Onset Type 2 Diabetes?

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Diabetes Care 2018;41:1560–1562 | https://doi.org/10.2337/dci18-0025

Over the past three decades, type 2 diabetes (T2D) in adolescents has become steadily more prevalent (1), raising the specter of increasing rates of premature micro- and macrovascular disease as affected youth move into adulthood. While T2D in adolescents is clearly linked to obesity, there is otherwise no explanation for the sudden appearance of what had previously been an adult condition in young people. Despite a steadily growing body of evidence descriptive of T2D in youth (2,3), there is a paucity of information comparing diabetic phenotypes in adults and teenagers. This issue of *Diabetes Care* contains three papers from the Restoring Insulin Secretion (RISE) Consortium (4–6) that provide the most direct examination of this question yet, with the potential for new understanding of T2D.

Present understanding of the pathophysiology of T2D holds that insulin resistance, generally a consequence related to increased adiposity, requires hyperfunction of pancreatic β-cells to maintain glucose tolerance. People whose β-cells cannot make this compensation progress to steadily worsening states of dysglycemia over time (7). Moreover, although insulin resistance does not necessarily cause β-cell failure, hyperglycemia and its associated metabolic disturbances do, such that insufficiently treated diabetes begets more severe diabetes (8). There is evidence in adults with prediabetes that interventions to alleviate insulin resistance (9) or minimize hyperglycemia (10) reduce progression to worse glucose tolerance. Similarly, intensive glucose lowering in adults with T2D can improve hyperglycemia and mitigate the typical course of disease (11). These findings provide the rationale for the RISE Consortium's efforts (12).

The RISE design paper, published in 2014, provides details of this project (12). Three intervention protocols were established, two in adults and one in children, all testing whether β-cell function and metabolic control could be effectively altered by specific interventions. All three studies recruited and randomized participants with prediabetes (impaired glucose tolerance [IGT]) or with T2D of up to 2 years duration. The three studies used similar assessments of glycemic control, β-cell function, and insulin sensitivity to allow head-to-head comparison of the effects of the interventions. The two studies in adults are ongoing. They are *1*) a medication study comparing the effects of placebo, metformin, metformin plus liraglutide, and glargine followed by metformin, and *2*) a study of gastric banding surgery versus metformin. The study that involved youth with prediabetes/diabetes, the RISE Pediatric Medication Study, compared the effects of metformin, with and without insulin, on insulin secretion and insulin sensitivity and is published in this issue (4). Also contained here are detailed comparisons of glucose metabolism, insulin sensitivity, and insulin secretion at baseline in the adolescent and adult cohorts using hyperglycemic clamps (5) and oral glucose tolerance tests (OGTTs) (6).

In the RISE Pediatric Medication Study, 91 pubertal obese youth were randomized to either 12 months of metformin titrated to 1,000 mg twice daily or 3 months of insulin glargine titrated twice a week to achieve a fasting glucose level of 4.4–5.0 mmol/L based on daily self-monitored blood glucose and followed immediately by 9 months of metformin. At 12 months, the study medications were withdrawn and patients were followed for an additional 3 months. At baseline, the adolescents had a mean age of ~14 years (range 10–19), BMI 36.7 kg/m^2, and HbA_{1c} 5.7%. Nearly 60% had IGT and the remainder had T2D of <6 months duration. Less than 30% of the patients were Caucasian. Most (77%) had received no glucose-lowering therapy, whereas 23% had taken metformin. Subjects had hyperglycemic clamps and OGTTs performed on separate

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See accompanying articles, pp. 1696, 1707, and 1717.

days at baseline, 12 months, and 15 months.

Both interventions were well tolerated and retention in the study was high, with 84/91 enrolled subjects completing the 15-month evaluation. Both treatments caused only modest changes of weight and HbA_{1c}, but both of these parameters increased between 12 and 15 months when medications were stopped. Fasting and 2-h post-OGTT glucose levels did not differ in the metformin group among the baseline and 12- and 15-month comparisons. Among the subjects receiving insulin before metformin, oral glucose tolerance was better at 12 months, but fasting glucose was higher than baseline at 15 months. β-Cell function, computed as the product of C-peptide levels and insulin sensitivity during the hyperglycemic clamp, was comparable at baseline in the two treatment groups and declined similarly at 12 and 15 months.

Thus, despite evidence in adults that metformin (9) and insulin (10) can prevent diabetes and improve insulin secretion in subjects with prediabetes, neither treatment prevented worsening β-cell function in youth with IGT or well-controlled T2D. While the outcomes of the RISE intervention trials in adults may allow more direct comparisons, the present findings suggest that the course of β-cell function differs in adolescents and adults with diabetes, consistent with previous studies of adolescent T2D (13,14). Moreover, these findings have clinical relevance in that the vast majority of teenaged T2D patients are treated with metformin and insulin, and these standard treatments do little to alter the natural history of the disease.

The other two reports from RISE in this issue provide detailed physiological data from the cohort of youth in this intervention study in comparison with an adult population with IGT and mild T2D (5,6). The two cohorts differed slightly—in gender (more females in the younger group), distribution of ethnicity (more Caucasians in the adult group), and BMI (slightly higher in the younger group). However, when studied using similar methods, they differed more dramatically in their physiological parameters. Specifically, those in the younger group were more insulin resistant and had higher fasting and stimulated levels of C-peptide than the adults. The estimates of insulin sensitivity from both the clamp and the OGTT are likely confounded by the lower hepatic insulin clearance found in the adolescents, with differences of 25% between the groups rather than the twofold differences in insulin sensitivity. Nevertheless, the results support a different pathophysiology in teens with abnormal glucose tolerance. Given the mean age of the younger cohort, it seems likely that the well-established effect of puberty to augment insulin resistance is at play here. Although the β-cell compensation for insulin resistance was comparable to that of the adults during the baseline evaluation, it is clear from the intervention study that it was not maintained in youth, an important finding that suggests a remarkably different trajectory of β-cell dysfunction in T2D presenting clinically at different ages.

What can we conclude from these carefully planned and executed studies? First, further analysis of these excellent data sets may disclose additional differences related to stage of puberty, race/ethnicity, adiposity and other aspects of body composition, or other factors. Additional insights may be provided by further measurements from stored samples, such as genomics (including epigenetics and small RNAs), metabolomics, hormones known to affect metabolism beyond insulin (including those secreted from the gut, bone, liver, fat, adrenals, and gonads), and markers of inflammation.

Second, it will be important to consider IGT and T2D separately in the group comparisons of responses to intervention, as has been done at baseline. While IGT and early T2D are close on the spectrum of dysglycemia, it is clear that many subjects will not progress from prediabetes to diabetes. This heterogeneity may cloud some additional differences present between young and older subjects with respect to potential differences in early pathophysiological mechanisms.

Third, and most notably, though both insulin and metformin showed glycemic efficacy and metformin had an effect on weight, the failure of the usual therapies used in youth-onset T2D to show any protective effect on β-cell function in this population is disappointing. The difference with early intervention studies in adults is curious and presents a serious challenge. What are we missing? If severe insulin resistance in youth, resulting from the combination of puberty and obesity, leads initially to enhanced secretion of insulin, can we find new ways to intervene? Two leading approaches are apparent. One is a renewed effort to approach the epidemic of obesity in youth as a crisis that calls for public health action as well as medical action. This could include better lifestyle programs for families and youth and, perhaps more importantly, regulatory restraints on marketing and distribution of unhealthful foods. On the medical side, better understanding of the natural history of youth-onset diabetes is needed. Cohorts including but not limited to the one studied in RISE should be observed prospectively to determine risk factors (and protective factors) for progression of β-cell dysfunction. Further, because the therapies used in RISE—metformin and basal insulin—have effects on basal glycemic control but little effect on prandial physiology, more study of neural and hormonal regulation of food intake and mealtime metabolite responses in this population is needed. Potential use of existing agents such as thiazolidinediones, glucagon-like peptide 1 receptor agonists, or sodium–glucose cotransporter inhibitors deserves consideration.

We congratulate the National Institute of Diabetes and Digestive and Kidney Diseases, the investigators, the participants, and their families. Their collaboration with a shared vision, creativity, effort, and sacrifice to bring us these new insights will drive further research and, one day, better treatments.

Funding. J.B.B. is supported by a grant from the National Institutes of Health National Center for Advancing Translational Sciences (UL1-TR-002489).

Duality of Interest. J.B.B. has received contracted consulting fees, paid to his institution, and travel support from Adocia, AstraZeneca, Dexcom, Elcelyx Therapeutics, Eli Lilly, Intarcia Therapeutics, Lexicon, Metavention, NovaTarg, Novo Nordisk, Sanofi, Senseonics, and vTv Therapeutics and grant support from AstraZeneca, Boehringer Ingelheim, Johnson & Johnson, Lexicon, Novo Nordisk, Sanofi, Theracos, and vTv Therapeutics. He holds stock options in Mellitus Health and PhaseBio. D.A.D. has received honoraria for consulting from Eli Lilly, Merck, and Novo Nordisk. M.C.R. has received honoraria for consulting from Adocia, AstraZeneca, Elcelyx Therapeutics, Eli Lilly, GlaxoSmithKline, Sanofi, and Theracos. He has received research grant

support through Oregon Health & Science University from AstraZeneca, Eli Lilly, and Novo Nordisk. These dualities have been reviewed and managed by Oregon Health & Science University. No other potential conflicts of interest relevant to this article were reported.

Prior Presentation. Parts of the article were presented at the 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, 22–26 June 2018.

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