Further RISE'ing to the Challenge of Type 2 Diabetes in Youth

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Despite three decades of increasing prevalence of type 2 diabetes (T2D) in adolescents (1), the diabetes community continues to grapple with the pathophysiology of youth-onset T2D. Accumulating evidence indicates that when compared with T2D in adults, T2D in youth follows a more aggressive course (2–4). Adolescents are therefore entering adulthood with an advanced and perhaps misunderstood disease that puts them at risk for morbidity from micro- and macrovascular complications. Moreover, as the susceptibility of individuals with diabetes to poor outcomes during the coronavirus pandemic became increasingly apparent (5), the urgency to address the health crisis of T2D in youth has been amplified.

The Restoring Insulin Secretion (RISE) study, designed in 2014, tested interventions in both adolescents and adults to determine whether β-cell decline could be halted in people with prediabetes or early T2D (6). The primary analyses were overall disheartening regarding slowing the progression of T2D in youth (7–12). However, the RISE study provides the most direct opportunity yet to examine differences between T2D in youth and adults. In this issue of *Diabetes Care*, the RISE Consortium delivers three articles that offer mechanistic insights into the pathogenesis of T2D and potentially a path forward for the treatment of T2D in youth (13–15). A summary of these articles is presented in Table 1 and discussed in subsequent paragraphs.

RISE was predicated on the critical role of progressive β-cell decline in the pathogenesis of T2D, where β-cell dysfunction results in excessive glucose and fatty acid exposure, termed glucolipotoxicity (6). Glucolipotoxicity coupled with insulin resistance compounds β-cell stress and contributes to β-cell failure. Previous data in adults suggest that early intensive intervention may delay β-cell dysfunction and slow the course of T2D (16–18). Prior to RISE, no study had directly tested this hypothesis in youth or performed a head-to-head comparison between youth and adults with similar levels and duration of dysglycemia.

The RISE study design has previously been described (6). RISE utilized three protocols in participants with impaired glucose tolerance (IGT) or recent-onset T2D. Whereas adults were glucose-lowering medication naive, children with diabetes were eligible if they had been on metformin for $<$6 months or insulin for $<$2 weeks. Each group underwent similar assessments at specific time points to provide direct comparisons of the interventions. Adults in the medication cohort were randomized to placebo, metformin, liraglutide + metformin (L+M), or glargine for 3 months followed by metformin (G/M). Adults in the surgical intervention arm received laparoscopic gastric band surgery (LB) or metformin. In children, the intervention compared G/M with metformin alone. In adults, active treatment, including LB, produced improvements in glycemia, but L+M provided the most benefit for β-cell function (10,11). On-treatment improvements observed in adults dissipated within 3 months of washout from medical intervention (10). Conversely, in children with IGT or T2D, neither metformin nor G/M prevented worsening of β-cell function (7,12). The big questions thus remained: why do children have such aggressive decline in β-cell function, and can this decline be prevented? The secondary analyses published in this issue characterize the individuals at most risk for β-cell decline and test the hypothesis that α-cell dysfunction contributes to the rapid deterioration of β-cells in youth.

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See accompanying articles, pp. 1938, 1948, and 1961.

Table 1—Summary of RISE papers in this issue

Article	Primary objective	Participants and intervention	Findings
Baseline Predictors of Glycemic Worsening in Youth and Adults With Impaired Glucose Tolerance or Recently Diagnosed Type 2 Diabetes in the Restoring Insulin Secretion (RISE) Study (13)	Identify baseline predictors of glycemic worsening in youth and adults with IGT or recently diagnosed T2D	Youth: 10–19 years of age with IGT or T2D <6 months' duration and treated with metformin alone or insulin for <2 weeks; randomized to MET or G/M for 12 months. Adults: 20–65 years of age with IGT or drug-naive T2D <12 months' duration; randomized to placebo, MET, G/M, or L+M.	Youth: β-cell dysfunction at baseline appeared to be the primary predictor of glycemic worsening in youth. Treatment had no impact on glycemic worsening. Adults: both β-cell dysfunction at baseline and insulin sensitivity were predictive of glycemic worsening. Dysglycemia was not. Significant benefits with L+M vs. placebo largely disappear after drug withdrawal. Takeaway: differences in baseline predictors of glycemic worsening highlight potential pathophysiologic differences between youth- and adult-onset T2D.
Hyperglucagonemia Does Not Explain the β-Cell Hyperresponsiveness and Insulin Resistance in Dysglycemic Youth Compared With Adults: Lessons From the RISE Study (14)	Determine whether β-cell hyperresponsiveness and insulin resistance in youth are related to hyperglucagonemia	Youth: 10–19 years of age with IGT or T2D <6 months' duration. No intervention; baseline only. Adults: 20–65 years of age with IGT or drug-naive T2D <12 months' duration. No intervention; baseline only.	Fasting and steady-state glucagon levels were not different between youth and adults. While data in adults demonstrated a positive correlation between glucagon levels and fasting glucose, data in youth suggested a negative correlation. Takeaway: α-cell dysfunction cannot account for β-cell hyperresponsiveness observed in youth compared with adults.
Effect of Medical and Surgical Interventions on α-Cell Function in Dysglycemic Youth and Adults in the RISE Study (15)	Compare the effects of medical and surgical interventions on alpha-cell function in youth and adults.	Youth: 10–19 years of age with IGT or T2D <6 months' duration and treated with metformin alone or insulin for <2 weeks; randomized to MET or G/M. Adult Medication Study: 20–65 years of age with IGT or drug-naive T2D <12 months' duration; randomized to placebo, MET, G/M, or L+M. Adult Surgery Study: 20–65 years of age with BMI 30–40 kg/m^2 despite at least 2 months on a lifestyle modification program; randomized to MET or LB.	No change in glucagon levels was observed in youth. In adults, L+M and LB reduced glucagon. Statistical adjustments suggest that glucagon-lowering effects were largely mediated by weight loss. Takeaway: weight loss appears to preserve α-cell function in adults. Medical or surgical weight management trials may be essential to halt the progression of T2D in vulnerable youth.

MET, metformin G/M, glargine for 3 months, followed by metformin for 9 months; LB, laparoscopic gastric band surgery; L+M, liraglutide + metformin.

The first report compares the glycemic worsening between youth and adult RISE participants to identify baseline characteristics that predict worsening in each group at the end of the treatment period (month 12) and 9 months following withdrawal (month 21) (13). Treatment did not impact glycemic worsening in youth, 17.8% and 36.7% of whom experienced a 0.5% increase in HbA_{1c} from baseline at month 12 and month 21, respectively. Only 7.5% of adults worsened while on treatment, primarily driven by placebo treatment (14.3% progression). Following withdrawal of intervention, 20% of adults had glycemic worsening. Subjects randomized to L+M experienced attenuated glycemic worsening at month 12 but only demonstrated a trend toward improvement after withdrawal. In both adults and

youth, lower baseline clamp- and oral glucose tolerance test–derived β-cell responses predicted glycemic worsening. Interestingly, though insulin sensitivity predicted progression in adults, it did not predict progression in children. While it is not clear why insulin sensitivity in youth was not predictive, the significantly increased baseline insulin resistance observed in youth likely plays a role. The RISE authors hypothesize that because of the severe insulin resistance observed in youth, β-cell function acts as the key factor to differentiate children who will develop diabetes. Indeed, in the setting of such severe insulin resistance, perhaps modest increases in insulin sensitivity make little difference.

The other two reports examine the role of the α-cell. Prior RISE data demonstrate that at every matched degree of insulin sensitivity, youth release greater amounts of C-peptide and insulin than adults. The RISE Consortium thus concluded that youth have hyperresponsive β-cells (8,9), though the mechanisms surrounding this enhanced insulin release are not understood. α-cell dysfunction and resultant glucagon dysregulation have been accepted as a plausible culprit, due to glucagon effects on the β-cell. Therefore, glucagon levels were assessed to determine whether α-cell dysfunction in youth compared with adults accounted for the β-cell hyperresponsiveness. Unexpectedly, fasting and steady-state glucagon were not different between youth and adults at baseline (14). Fasting glucose and glucagon were positively correlated in adults but trended toward a negative correlation in youth. These data indicate that α-cell dysfunction cannot account for the hyperresponsiveness of the β-cell but also emphasize potential pathophysiologic differences between adults and children.

No change in fasting or steady-state glucagon was observed following treatment with metformin or G/M in youth (15). Thus, while β-cell function declines rapidly in children, α-cell function appears to be preserved. The trajectories of these two cell types have been thought to be parallel, due to proximity and paracrine regulation. These data suggest that, at least in youth, the fates of these cell types are not as connected as hypothesized.

Adults also showed no improvement in α-cell function with metformin, G/M, or placebo. However, L+M and LB demonstrated durable reductions in fasting and steady-state glucagon levels. But adjustments for baseline and change in weight eliminated any difference in fasting glucagon concentration across the treatment subgroups. Adjustments for insulin sensitivity did not impact the results. The importance of weight loss for α-cell function observed in adulthood thus must be acknowledged. Interventions that induce weight loss were not attempted in children.

With sequential and frequent measures of glucose response and insulin sensitivity, the RISE study has provided substantial mechanistic data. Regardless, direct comparison of adults and children will always be fraught with confounders. It is impossible to account for social, epigenetic, and age-related differences between youth and adulthood. However, the degree of insulin resistance at baseline for youth and adults stands out as a major difference. Statistical adjustments for insulin resistance cannot account for all concurrent pathophysiologic effects. Fundamentally one must wonder: are we comparing apples to oranges? Diabetes in youth is different from diabetes in adults.

There is little way to get around these issues, and, thus, making observations and understanding their caveats are essential. RISE offers us the first formal prospective randomized trial to directly compare parameters of α- and β-cells at baseline and in the setting of common interventions in adults and youth. Thus far, RISE reminds us that β-cell function remains the most important marker of risk for diabetes in youth in the setting of severe insulin resistance. Addressing insulin resistance seems paramount to the treatment of T2D in the vulnerable youth. Without addressing peripheral resistance, it seems likely that no matter the intervention, β-cell stress will lead to eventual β-cell failure.

Longitudinal studies, like RISE, are essential for identifying the most vulnerable. Given that puberty is such a tenuous period, pinpointing the most specific parameters for progression to diabetes may allow for early and aggressive intervention. Perhaps, if β-cell function is protected during puberty, T2D onset could be significantly delayed. These are the questions that must be answered in order to protect youth from poor long-term outcomes.

Interventions in adults provide some hope. Surgical or medical weight loss with liraglutide or LB improve many parameters. More aggressive weight loss interventions in youth should be explored. Liraglutide has been shown to be safe and effective in children (19). Metabolic surgery has an evolving role in youth (20). Novel pharmaceuticals under development provide for outstanding reductions in weight. The optimal timing of intervention is also likely to be very different in youth and adults. In youth, intervention prior to puberty might be essential, but we must first understand on whom to intervene. It will be interesting to see what, if any, impact GLP-1 receptor agonists and near-at-hand related medications have on progressive β-cell decline in youth and whether surgical approaches in the very young provide extended protection from T2D.

Designing the right experiment to understand youth T2D pathophysiology is an incredible challenge. Adult T2D serves as guide, and though the diseases mirror each other, youth-onset T2D has unique characteristics. Further analysis from RISE will undoubtedly provide additional insights (21). Progress remains slow, but with well-designed and executed studies like RISE, understanding accumulates and the path toward effective intervention in youth with T2D becomes clearer.

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