

Restoring Insulin Secretion (RISE): Design of Studies of β -Cell Preservation in Prediabetes and Early Type 2 Diabetes Across the Life Span

The RISE Consortium*

OBJECTIVE

The Restoring Insulin Secretion (RISE) Consortium is testing interventions designed to preserve or improve β -cell function in prediabetes or early type 2 diabetes.

RESEARCH DESIGN AND METHODS

β -Cell function is measured using hyperglycemic clamps and oral glucose tolerance tests (OGTTs). The adult medication protocol randomizes participants to 12 months of placebo, metformin alone, liraglutide plus metformin, or insulin (3 months) followed by metformin (9 months). The pediatric medication protocol randomizes participants to metformin or insulin followed by metformin. The adult surgical protocol randomizes participants to gastric banding or metformin (24 months). Adult medication protocol inclusion criteria include fasting plasma glucose 95–125 mg/dL (5.3–6.9 mmol/L), OGTT 2-h glucose ≥ 140 mg/dL (≥ 7.8 mmol/L), HbA_{1c} 5.8–7.0% (40–53 mmol/mol), and BMI 25–40 kg/m². Adult surgical protocol criteria are similar, except for fasting plasma glucose ≥ 90 mg/dL (≥ 5.0 mmol/L), BMI 30–40 kg/m², HbA_{1c} <7.0% (<53 mmol/mol), and diabetes duration <12 months. Pediatric inclusion criteria include fasting plasma glucose ≥ 90 mg/dL (≥ 5.0 mmol/L), 2-h glucose ≥ 140 mg/dL (≥ 7.8 mmol/L), HbA_{1c} $\leq 8.0\%$ (≤ 64 mmol/mol), BMI >85th percentile and ≤ 50 kg/m², 10–19 years of age, and diabetes <6 months.

RESULTS

Primary outcomes are clamp-derived glucose-stimulated C-peptide secretion and maximal C-peptide response to arginine during hyperglycemia. Measurements are made at baseline, after 12 months on treatment, and 3 months after treatment withdrawal (medication protocols) or 24 months postintervention (surgery protocol). OGTT-derived measures are also obtained at these time points.

CONCLUSIONS

RISE is determining whether medication or surgical intervention strategies can mitigate progressive β -cell dysfunction in adults and youth with prediabetes or early type 2 diabetes.

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The increase in the prevalence of obesity has contributed to the increased incidence of prediabetes (impaired glucose tolerance or impaired fasting glucose) and type 2 diabetes among youth and adults (1). Progressive decline in β -cell function is now well recognized in children and adults to be pivotal in the progression from normal to abnormal glucose tolerance (2–6). Given the increased recognition of the critical role of the β -cell in the pathogenesis of type 2 diabetes, efforts have begun to shift to prevention of the loss of insulin secretion among individuals at high risk for type 2 diabetes or early stages of the disease.

Potential Targets in Preserving Pancreatic β -Cell Function

β -Cell dysfunction impairs control of prandial and postabsorptive glucose concentrations and adipose fatty acid release, resulting in excess glucose and fatty acid exposure. This “glucolipotoxicity” in turn leads to further β -cell disruption (7), producing an accelerating cycle of β -cell dysfunction and progressive metabolic derangement. Additionally, insulin resistance, increased secretory demand on β -cells, and other obesity-related changes may be important causes of β -cell decline (4,8). Dysregulation of glucose and fat homeostasis are therefore primary targets for strategies to preserve β -cell function in prediabetes and early type 2 diabetes.

Certain of the existing glucose-lowering agents break the vicious cycle of glucolipotoxicity by stimulating insulin release, while others benefit β -cell function more indirectly. For example, metformin lowers glucose via improvements in hepatic glucose production and insulin sensitivity (9), thiazolidinediones (TZDs) improve systemic glucose and fat metabolism through improvements in handling of fatty acids, and insulin lowers glucose concentrations and fatty acid release. Insulin and medications that improve insulin sensitivity also reduce the demand on β -cells, providing β -cell “rest.” Weight loss, either from lifestyle interventions or surgical procedures, improves insulin sensitivity and reduces glycemia and fatty acid concentrations (10). Whether gastric bypass surgery activates additional mechanisms that

contribute to postsurgical changes in β -cell function is yet unclear (11,12). Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and other incretin-based therapies also improve islet function (13,14), likely by augmenting β -cell insulin release and suppressing α -cell glucagon secretion.

Preventing Progression From Prediabetes to Diabetes: Focus on the β -Cell

Studies of the prevention of progression from prediabetes to diabetes provide evidence that such strategies can improve β -cell function in adults. Pharmacologic therapies that have produced the greatest promise in these settings include TZDs, metformin, and insulin. TZDs reduced the risk of worsening hyperglycemia in several large adult prediabetes studies and showed concordant stabilization or improvement in measures of β -cell function (8,15,16). Metformin use in adults at risk for diabetes in the Diabetes Prevention Program (DPP) and Indian Diabetes Prevention Program reduced the risk of progression to type 2 diabetes (9,17) in association with improvements in insulin sensitivity and β -cell function (2). The Outcome Reduction With Initial Glargine Intervention (ORIGIN) study found that the long-acting insulin glargine reduced the risk of progression to type 2 diabetes at the conclusion of active therapy, with persistent benefits after withdrawal of therapy (18).

Other established glucose-lowering agents have been evaluated, but data are less compelling in terms of promise for improving β -cell function. Sulfonylureas initially augment β -cell function but may accelerate secondary failure (3,19) and have had mixed effects in two feasibility studies to prevent diabetes (20,21). The β -cell secretagogue nateglinide failed to prevent progression to diabetes as shown in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study (22). The α -glucosidase inhibitor acarbose decreased type 2 diabetes risk in the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) (23) but failed to prevent worsening of fasting glucose in early

diabetes in the Early Diabetes Intervention Program (EDIP) (24).

Lifestyle and weight loss interventions have been very successful in preventing or delaying progression from prediabetes to diagnosed diabetes (9,17,25–28). In the DPP, the diabetes prevention effect of lifestyle/weight loss was mediated in part through improved β -cell function, with a magnitude of effect superior to that achieved with metformin treatment (2). In the Swedish Obesity Surgery study, adults who underwent bariatric surgery were compared with historical, obesity-matched control subjects. At up to 15 years of follow-up, a persisting protective effect of gastric bypass surgery to prevent progression to diabetes was observed (26).

Limited data on durability after therapy withdrawal from adult TZD and lifestyle studies suggest that these therapies slow but do not fully arrest progression to type 2 diabetes (15,25,29). Where physiologic measurements of β -cell function have been made, the magnitude and durability of success of these interventions are related to improvements in β -cell function (4,8,26). There are no published studies of β -cell preservation in youth with prediabetes.

Preventing Progression in Established Type 2 Diabetes: Focus on the β -Cell

Small studies suggest that normalizing fasting glucose with insulin therapy can improve β -cell function (30). In a large study conducted in Chinese adults with newly diagnosed type 2 diabetes (initial HbA_{1c} of \sim 9.7%, 83 mmol/mol), aggressive insulin therapy using either mixed regular and NPH insulin or an insulin pump was compared with oral therapy (gliclazide, metformin, or the combination) (31). After an initial period of glucose lowering, treatment was withdrawn and participants were followed for glycemic progression. In both insulin treatment groups, remission was maintained for 1 year in approximately half of the participants, and limited testing suggested this was associated with improved β -cell function (31).

TZDs have been shown to stabilize falling β -cell function early in the course

of established type 2 diabetes in adults. In the A Diabetes Outcome Progression Trial (ADOPT), the effect of rosiglitazone to reduce progression of β -cell dysfunction was superior to glyburide, while metformin was intermediate (3,19). The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study of youth within 2 years of type 2 diabetes diagnosis found that metformin alone was ineffective in preventing progression to insulin requirement in half of the adolescents and that adding rosiglitazone, but not intensive lifestyle, to metformin was superior to metformin alone (32). Insulin sensitivity and β -cell function improved at 6 months with metformin plus rosiglitazone, whereas β -cell function deteriorated in the other groups (33).

Incretin-based therapies hold new promise for promoting recovery and preservation of islet function. Incretins increase glucose-stimulated insulin secretion and decrease glucagon release. In adults, improved β -cell function on GLP-1RA therapy is well established, but long-term intervention studies are few. One study examined the durability of glycemic control, comparing 3 years of the GLP-1RA exenatide to glargine in 69 adults who were also on metformin. HbA_{1c} (7.4–7.6%, 57–60 mmol/mol at baseline) was reduced similarly in both groups (6.7–6.8%, 50–51 mmol/mol) after 1 year of therapy, with the exenatide group demonstrating improved β -cell function on therapy, while the glargine group showed no change. After 1 month of washout, β -cell function reverted to pretreatment values (34). Therapy was restarted in 36 participants and continued to 3 years. After 1 month of washout, the exenatide group demonstrated modestly improved β -cell function relative to their own baseline but much reduced compared with the on-treatment measures (35). These observations highlight the potential value of GLP-1RA to improve β -cell function but leave open questions regarding the durability and magnitude of effect, which may also depend on diabetes duration at the time of the intervention. The effects of GLP-1RA in prediabetic populations are unknown.

With diet/exercise interventions and surgical approaches to weight loss, there is evidence of significant improvements in glycemic control and reversion from overt diabetes to impaired or normal glucose tolerance. Moreover, in the Action for Health in Diabetes (Look AHEAD) study of intensive lifestyle intervention versus diabetes support and education in adults with established diabetes, the lifestyle group was significantly more likely to attain normoglycemia at 1 and 4 years, and a small but significantly increased number of the intensive group had continuous, sustained normoglycemia (3.5 vs. 0.5% at 4 years in the intensive vs. control group) (36). It is unknown how these observations relate to measures of β -cell function.

These observations suggest that β -cell function can be improved in established type 2 diabetes. However, to date the trajectories of β -cell function and glycemic control suggest that regardless of differences in early effects, an underlying pattern of worsening β -cell function persists. In general, the benefits appear to be reduced with higher fasting glucose and HbA_{1c} levels and lower β -cell function at baseline, arguing for even earlier intervention (3,33).

β -Cell Preservation Strategies in Restoring Insulin Secretion (RISE)

The data reviewed above argue that progressive β -cell failure can be mitigated by reducing or preventing the adverse effects of glucolipotoxicity on β -cells (using metformin, TZDs, or insulin) or reducing the effects of excess body fat on β -cell dysfunction (using TZDs or weight loss). Also, the new class of incretin-based therapies improves glucose through direct effects on β - and α -cell biology, with potential dual effects on diabetes pathogenesis (37).

All of these approaches were considered for study in RISE. Despite evident beneficial effects of TZDs on β -cell function, the use of agents in this class has now declined owing to safety concerns (38,39). For these reasons, TZDs were excluded as a possible intervention in RISE.

At least as important as the on-treatment benefit is the durability of

beneficial effects after withdrawal of therapy, which allows assessment of the resiliency of the β -cell response. The available data suggest that durable improvements in β -cell function are less likely to be achieved in participants with established diabetes, with the important exception of the Chinese insulin treatment study (31). On the other hand, there is evidence for durable effects in people with prediabetes or early type 2 diabetes (8). On this basis, RISE will study individuals with prediabetes or early type 2 diabetes.

Finally, it appears that the phenotype of type 2 diabetes in youth differs from that of adults (32,40) and may involve unique pathophysiology. Consequently, findings in adults cannot be simply extrapolated to youth, and separate studies in youth are required.

RESEARCH DESIGN AND METHODS

In response to a National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Request for Applications (DK 10-013) for a cooperative agreement for studies of the preservation of β -cell function in prediabetes or early type 2 diabetes, study sites were selected that then together developed the study designs presented here. This process included two in-person meetings for study design but was largely performed by teleconference. The final protocols were reviewed and approved by a National Institutes of Health (NIH)-appointed independent data and safety monitoring board.

On the basis of the above rationale, the RISE Consortium will undertake exploratory studies to evaluate strategies to improve β -cell function, using glucose-lowering therapies (metformin, insulin, GLP-1RA) or obesity-reducing therapy (gastric banding surgery) in adult and pediatric participants with prediabetes or very early type 2 diabetes. RISE will assess whether applying these strategies can slow deterioration or induce improvement in β -cell function and whether the interventions produce sustained improvement in β -cell function after being discontinued.

Factors Determining Design Choices

Two main considerations dominated design choices for the RISE protocols.

First, in order to identify individuals with underlying risk of progression and existing β -cell dysfunction, a lower limit for fasting glucose was chosen. In view of data suggesting that the β -cell lesion in established diabetes may not be reversible, a conservative upper limit for measures of glycemia was also set. Second, therapies were chosen that provide a high likelihood of a beneficial response on therapy to allow assessment of the durability of this response after withdrawal of therapy. Within these limits, other design considerations produced only modest differences in study population criteria between groups or differences in the application of the interventions, as highlighted below.

Study Design

Three different protocols will be performed to assess the effect of different interventions intended to preserve or improve β -cell function in adults and children with prediabetes or recent-onset type 2 diabetes. Three adult centers (VA Puget Sound Health Care System/University of Washington, University of Chicago, and Indiana University) will together perform a randomized, partially blinded, placebo-controlled trial comparing 1) early intensive insulin treatment with insulin glargine (3 months) followed by metformin (9 months), 2) the GLP-1RA liraglutide plus metformin (12 months), and 3) metformin alone for 12 months against 4) placebo. Four centers (University of Colorado, Indiana University, University of Pittsburgh, and

Yale University) will participate in a pediatric randomized open-label clinical trial comparing insulin glargine (3 months) followed by metformin (9 months) against metformin (12 months). One adult center at the University of Southern California/Kaiser Permanente Southern California will perform a randomized open-label clinical trial comparing the effects of gastric banding with those of metformin (each 24 months).

Primary aims of the study are to determine whether these intervention strategies can produce a preservation or improvement in β -cell function lasting at least 3 months after withdrawal of therapy (medication studies) or persisting at 24 months after randomization (surgery study). Secondary aims of the study are to determine the impact of the interventions on β -cell function while on active therapy and also for up to 9 months after withdrawal of medication. Additional aims include validation of simpler fasting and oral glucose tolerance test (OGTT)-derived measures of β -cell function against hyperglycemic clamp-based measures. The adult surgical protocol will also evaluate continuous relationships between weight loss and changes in β -cell function and the role of changes in body composition (measured by dual-energy X-ray absorptiometry and abdominal magnetic resonance imaging) on β -cell function.

The inclusion criteria for the three protocols are similar (Table 1), with

some protocol-specific differences to ensure participants are appropriate to be randomized to the planned therapies and allow for differences in the presentation and physiology of early type 2 diabetes in adults versus youth. For example, fasting glucose values are normally lower in pediatric populations than in adults, prompting the selection of a lower threshold for the pediatric protocol. The lower fasting glucose limit in the surgical study was chosen to allow identification of a sufficient number of participants who meet eligibility for a surgical intervention and also have an identifiable β -cell lesion. For clean assessment of the effect of RISE therapies and for the ability to comment on their use in a prevention mode, no prior exposure to glucose-lowering therapies is permitted, with the exception of pediatric participants with recent-onset type 2 diabetes who may have received a short duration of metformin treatment or brief, acute insulin therapy at the time of presentation prior to determination of their type of underlying diabetes. Typical exclusion criteria are applied, including any features that would put adult participants in the medication protocol at increased risk from GLP-1RA therapy (prior pancreatitis, personal or family history of multiple endocrine neoplasia type 2).

The study time line is presented diagrammatically in Fig. 1. The *upper panel* depicts the time line for participants in the medication studies and the *lower panel* that for participants

Table 1—Main inclusion criteria for participants in RISE protocols

Criteria	Pediatric medication	Adult medication	Adult surgery
Fasting plasma glucose	≥ 90 mg/dL (5.0 mmol/L)	95–125 mg/dL (5.3–6.9 mmol/L)	≥ 90 mg/dL (5.0 mmol/L)
2-h OGTT	≥ 140 mg/dL (7.8 mmol/L)	≥ 140 mg/dL (7.8 mmol/L)	≥ 140 mg/dL (7.8 mmol/L)
HbA _{1c}	$\leq 8\%$ (64 mmol/mol) drug naïve $\leq 7.5\%$ (58 mmol/mol) if on metformin for <3 months $\leq 7\%$ (53 mmol/mol) if on metformin 3–6 months	5.8–7% (40–53 mmol/mol)	$\leq 7.0\%$ (53 mmol/mol)
Age	10–19 years	20–65 years	22–65 years
Tanner stage	>1	—	—
BMI	$\geq 85\%$ percentile but ≤ 50 kg/m ²	25–40 kg/m ²	30–40 kg/m ² despite 1 attempt at weight loss
Diabetes duration	<6 months	<1 year	<1 year
Diabetes drug status	Treatment with metformin <6 months, insulin <2 weeks	Glucose-lowering medication-naïve	Glucose-lowering medication-naïve

in the surgery study. The study will recruit participants over a 3-year period and follow them for a total of 21 months (medication protocols) or 24 months (surgical protocol) from randomization.

Interventions and Safety Surveillance
Run-In

Eligible volunteers in the adult and pediatric medication protocols will participate in a 3-week run-in period prior to randomization. They will be instructed by study staff in proper injection technique and will receive 3 weeks of placebo tablets and, for the adult medication protocol, 3 weeks of placebo injections. Pediatric participants already taking metformin will continue on their prestudy metformin dose during the run-in period. Final eligibility will be determined based on demonstrated compliance with medication use and attendance at scheduled study visits. Randomization and baseline study procedures (hyperglycemic clamp and OGTT) will occur after successful completion of the run-in. The surgical protocol has no run-in. In all study arms, after completing the baseline measurements, participants will receive instruction in lifestyle modification, including individualized instruction on weight loss, exercise, and diet.

Active Treatment (Medication Studies)

During their period of active and follow-up treatment, participants will be seen every three months. Adult participants randomized to metformin monotherapy or placebo will be double-blinded for scientific reasons and to minimize dropout of participants assigned to placebo. Adult participants receiving liraglutide plus metformin or insulin glargine followed by metformin will not be masked to the intervention. Similarly, pediatric participants will not be masked to the intervention.

Metformin use is the same in all treatment groups assigned to use it. For minimization of gastrointestinal side effects, patients naive to metformin will be titrated over a maximum of 8 weeks from a starting dose of 500 mg once daily to a maximum dose of 1,000 mg b.i.d. Pediatric participants already on metformin, but on a lower dose, will similarly have their dose titrated to a maximum dose of 1,000 mg b.i.d. Participants will remain on the maximum tolerated dose of metformin throughout the study. If unable to tolerate metformin, they will continue in the study but will not take the medication and will be included in the intention-to-treat analyses.

Participants randomized to insulin therapy will have once-daily insulin

glargine initiated according to fasting blood glucose values (adults, mean FBG >110 mg/dL [>6.1 mmol/L], 4 units; 100–110 mg/dL [5.6–6.1 mmol/L], 3 units; and <100 mg/dL [<5.6 mmol/L], 2 units) or by weight (pediatrics, 0.2 units/kg/day [participants with prediabetes] or 0.3 units/kg/day [participants with diabetes]). Insulin will be titrated over a period of 1 month based on daily self-blood glucose monitoring to achieve and maintain a fasting blood glucose of 80–90 mg/dL (4.4–5.0 mmol/L) without inducing significant hypoglycemia. After 3 months of insulin treatment, insulin glargine will be discontinued and metformin initiated and titrated as described above.

Adult participants randomized to liraglutide will be started at a dose of 0.6 mg subcutaneously once daily. This dose will be increased weekly by 0.6 mg daily increments to a maximum of 1.8 mg subcutaneously once daily according to the U.S. Food and Drug Administration label for the use of liraglutide. If participants cannot tolerate the increased dose, they will revert back to the previously tolerated dose. Participants will remain on the maximal tolerated daily dose for the duration of the study. After the maximal dose of liraglutide has been reached and is

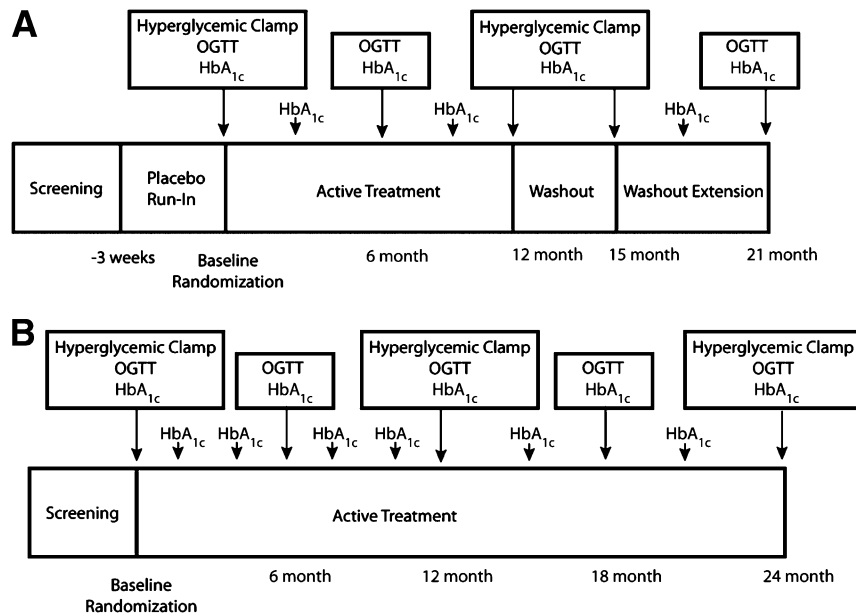


Figure 1—Time lines for screening, run-in, treatment, and washout for RISE protocols involving medications in adults and children (A) and surgery in adults (B).

tolerated, metformin will be initiated and titrated as described above. If the combination of the medications produces intolerable adverse effects, liraglutide treatment will be retained in preference to metformin.

In the medication studies, assigned therapy will be held on the morning of on-treatment procedures (hyperglycemic clamp and OGTT as detailed below). After the completion of the procedures, study medication will be recommenced, with the exception of the set of procedures performed after 12 months of the medication interventions. At this time point, study medications will be stopped and the participants will be followed off medications for a minimum of 3 months and up to 9 months, depending on the time of randomization within the 5-year study period. Fifteen-month postrandomization procedures (hyperglycemic clamp and OGTT) will be performed to determine the durability of the effects of the active interventions.

Active Treatment (Surgical Study)

In the surgical study, participants will be randomized to receive open-label metformin therapy or gastric banding surgery. Metformin therapy will be titrated and proceed as outlined above, except that active therapy will continue for the full 24 months without a study-specified period of treatment withdrawal. Adjustable gastric bands (LAP-BAND; Allergan Corporation, Irvine, CA) will be placed laparoscopically, and participants will be followed according to standard clinical practice. Participants will also meet with the bariatric nutritionist for education on dietary restrictions that apply once the band is in place. Band adjustments to achieve the therapeutic gastric restriction will commence ~4 weeks after surgery and will recur every 2 months during the first year and then every 3 months at the time of regular research visits for the remainder of the study. Adjustments will be made based on specific criteria consisting of symptoms of satiety and hunger, dietary history, and weight loss. Participants randomized to metformin will be on the same follow-up schedule as patients with gastric bands. Study outcome

procedures (hyperglycemic clamp and OGTT) will be performed at 12 and 24 months postrandomization while on active therapy.

Safety Surveillance

Glycemic status will be monitored with HbA_{1c} determinations every 2–3 months in all participants. Participants randomized to insulin therapy and those with known diabetes will also perform self-monitoring of blood glucose and will be instructed regarding the signs and symptoms of hypoglycemia and hyperglycemia and when to contact the study team. If glucose control worsens unacceptably, participants will be scheduled for final outcome assessments as soon as possible, followed immediately thereafter by institution of clinically appropriate therapy according to their primary diabetes provider.

RESULTS

Outcome Measures

RISE will use the hyperglycemic clamp to directly quantify first-phase (first 10 min after priming glucose bolus) and steady-state (at plasma glucose ~200 mg/dL; ~11.1 mmol/L) β -cell responses to intravenous glucose and the maximal arginine-stimulated β -cell response during hyperglycemia (>450 mg/dL; >25.0 mmol/L). The OGTT will also be used to evaluate β -cell responses in the context of an enterally delivered stimulus. Two primary outcome measures will be derived from the hyperglycemic clamp, namely, the mean C-peptide concentration at steady-state glucose adjusted for the prevailing insulin sensitivity at steady state and the maximal arginine plus hyperglycemia-stimulated C-peptide responses. Other prespecified outcomes of interest include the disposition index derived from clamp-based insulin sensitivity, first-phase C-peptide release in the hyperglycemic clamp, and early- and late-phase C-peptide and insulin responses after an oral glucose load. Other secondary outcomes of interest include α -cell function (glucose and arginine stimulation effects on glucagon). Relationships of circulating factors with baseline and prospective β -cell function will be assessed if resources allow. Laboratory outcome measures will be measured in a central laboratory. Stored

samples will be available for use in externally funded ancillary studies for additional evaluations of circulating factors and genetic material in relation to the RISE outcomes.

The primary focus of RISE is to evaluate whether the applied strategies produce a durable effect on β -cell function after withdrawal of therapy (medication studies) or at the end of 2 years of intervention (surgical study). The main study stages for measurement of β -cell function in the medication studies are baseline (pretreatment), at the end of 12 months of therapy (end of intervention), and at 15 months (3 months after treatment withdrawal). In the surgical study, the main study stages for measurement of β -cell function are baseline (pretreatment) and 12 and 24 months on treatment. In the adult medication study, the main comparisons of interest will be 15-month measures versus baseline, comparing active medications against placebo. In the pediatric medication study, the main comparison of interest is 15-month versus baseline, comparing insulin glargine followed by metformin versus metformin alone. In the adult surgical study, the main comparison is 24-month versus baseline, comparing gastric band versus metformin. Secondary analyses will include comparison of adult versus pediatric outcomes in the medication protocols.

Statistical Methods

Estimated effect sizes, measurement variability, and correlations between baseline and follow-up measures were estimated using unpublished datasets from studies of physiologic measures in adult and pediatric populations. Randomization is stratified by clinical center and by diabetes status as determined during the screening OGTT or by current use of metformin in the pediatric study. For the adult and pediatric protocols, the intervention groups will be compared for the primary outcome measures at 3-months postwashout, adjusted for the baseline value of each outcome. For the adult surgery protocol, the intervention groups will be compared for the primary outcome measures at 2 years, adjusted for the baseline value of each outcome. The analyses for each of the protocols

will be conducted separately under the intention-to-treat principle using the randomized treatment as assigned to each participant and using all available data from all participants, with a baseline-adjusted ANCOVA. For all three protocols, the two primary outcomes are thought to measure different aspects of β -cell function and thus will be analyzed separately with a nominal type I error probability of 0.05 for each, i.e., without an adjustment for two separate outcomes. The outcomes overall are intended as exploratory studies, and therefore the α is not corrected for multiple comparisons.

For the adult medication protocol, a sample size of 56 per arm (224 total) at the end of the washout was estimated to provide 80% power to detect a minimum effect size of 0.60 SD units between any two treatment groups in a baseline-adjusted ANCOVA when using a closed testing procedure to maintain an overall type 1 error probability $\alpha = 0.05$ for either of the two primary outcome measurements (41). Under the closed testing principle, β -cell function will first be compared across the four treatment groups using ANCOVA adjusted for baseline β -cell function. If the overall test of equality across the four treatment groups is significant at the 0.05 level, then each of the four possible sets of three interventions will be compared in four separate ANCOVA models also at the 0.05 level. The final significance testing comparing any two treatment groups is only undertaken if the *P* values for each of the two 3-intervention tests that include a particular pair of intervention groups are both significant at the 0.05 level. If the overall test across the four groups is not significant, testing concludes and no treatment group is declared different from any other. Adherence to this sequence of tests, all at the 0.05 level, ensures that the type 1 error probability for the set of tests does not exceed 0.05.

In the pediatric protocol, a sample size of 39 per arm (78 total) at the end of the washout was estimated to provide 80% power to detect a minimum effect size of 0.57 SD units favoring insulin glargine followed by metformin. In the surgery protocol, 35 participants per arm will provide 80% power to detect a minimal

effect size of 0.59 SD units (using $\alpha = 0.05$ in a baseline-adjusted ANCOVA for these protocols).

CONCLUSIONS

The RISE Consortium will provide critical information about the potential for early aggressive treatment approaches to lead to sustainable recovery of β -cell function in adults and youth after residual medication effects have dissipated and whether such approaches should be studied in larger clinical trials with longer follow-up times. Further, these studies also will provide the opportunity to determine the potential use of simpler measures of glucose metabolism and insulin responses across a wide age span, as well as identify biomarkers that can be used in future clinical studies and, possibly, in routine clinical care. Ultimately, such approaches may help to decrease the prevalence of type 2 diabetes or at least slow progress of the disease and, hopefully, reduce the long-term complications associated with progressive β -cell dysfunction.

APPENDIX

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P.J.S., and S.E.K. researched data, contributed to the discussion, and reviewed and edited the manuscript. S.L.E. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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