Remission of Type 2 Diabetes Following a Short-term Intensive Intervention With Insulin Glargine, Sitagliptin, and Metformin: Results of an Open-label Randomized Parallel-Design Trial

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OBJECTIVE

The aim of the study was to evaluate remission of type 2 diabetes following a short-term intervention with insulin glargine, sitagliptin/metformin, and lifestyle approaches.

RESEARCH DESIGN AND METHODS

In this open multicenter trial, 102 patients with type 2 diabetes were randomized to *1*) a 12-week intervention with sitagliptin/metformin, insulin glargine, and lifestyle therapy or *2*) control group. Participants with HbA_{1c} <7.3% (<56 mmol/mol) at 12 weeks were asked to stop diabetes medications and were followed for evidence of relapse over 52 weeks. Diabetes relapse criteria included HbA_{1c} ≥6.5% (≥48 mmol/mol), ≥50% of capillary glucose readings >10 mmol/L over 1 week, and reinitiation of diabetes medications with or without abnormal fasting plasma glucose (FPG) or 2-h plasma glucose on an oral glucose tolerance test (OGTT). Time-to-relapse analysis was conducted to compare the treatment groups with (primary analysis) and without (supplementary analysis) FPG/OGTT relapse criteria.

RESULTS

With the FPG/OGTT relapse criteria included, the hazard ratio (HR) of relapse was 0.72 (95% CI 0.47–1.10) in the intervention group compared with the control group (primary analysis), and the number of participants remaining in remission was not significantly different between treatment groups at 24, 36, 48, and 64 weeks. In the supplementary analyses without these criteria, HR of relapse was 0.60 (95% CI 0.39–0.95), and the number of participants remaining in remission was significantly higher (26 vs. 10%) in the intervention group at 36 weeks.

CONCLUSIONS

Although our primary outcome was not statistically significant, the tested approach deserves further study with further optimization of its components.

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**Members of the REMIT-sita Collaborative Group are listed in the supplemental material online.*

Type 2 diabetes is traditionally considered to be a permanent progressive disease requiring a stepwise escalation of glucose-lowering therapy over time. However, several randomized controlled trials have shown that it can be reversed with bariatric surgery (1–3). Emerging evidence also suggests that a variety of nonsurgical approaches including several diets (4–6), intensive lifestyle approaches (7), and intensive glucose-lowering therapies (8,9) may also promote remission of type 2 diabetes. Thus far, the only nonsurgical approaches that have been shown to achieve sustained diabetes remission in patients with newly diagnosed or early diabetes are intensive glucose-lowering therapy (8) and weight loss induced by a prolonged very-low-calorie diet (5,6). Other approaches that combine lifestyle and pharmacotherapy clearly need to be systematically studied to identify additional effective regimens.

One such approach builds on evidence that glucose normalization may restore pancreatic function in people with type 2 diabetes (8–13), and this normoglycemia or near-normoglycemia can be achieved using various combinations of therapies. We recently reported that a combination of lifestyle approaches and intensive glucose-lowering therapy with insulin glargine, metformin, and either acarbose (14) or dapagliflozin (15) achieved a short-term remission of type 2 diabetes in participants with early diabetes. In the Remission Evaluation of a Metabolic Intervention in Type 2 diabetes with sitagliptin (REMIT-sita) trial, we tested the effect of a combination of lifestyle approaches with insulin glargine, metformin, and sitagliptin on inducing remission of type 2 diabetes in recently diagnosed individuals.

RESEARCH DESIGN AND METHODS

Study Participants

This trial was conducted in six Canadian centers and recruited 30- to 80-year-old participants with type 2 diabetes diagnosed within the prior 5 years whose HbA_{1c} was ≤9.5% (≤80 mmol/mol) on no diabetes medications or ≤8.0% (≤64 mmol/mol) on one agent or half-maximal doses of two agents. Main exclusion criteria were current use of insulin, history of pancreatitis, alanine transferase ≥2.5 times the upper limit of normal, creatinine ≥124 μmol/L, and previous history of cardiovascular disease. Full inclusion/exclusion criteria are listed in the Supplementary Table 1. The trial was approved by research ethics boards at all sites, and all participants signed written informed consent.

Study Design

This was an open-label parallel randomized controlled trial. Eligible participants were centrally randomized with an online system with stratification by center and random permuted blocking to ensure concealment of allocation to two treatment groups: *1*) 12 weeks of remission induction therapy with insulin glargine, sitagliptin/metformin, and lifestyle therapy and 52 weeks of posttreatment follow-up or *2*) 12 weeks of standard diabetes treatment and 52 weeks of posttreatment follow-up. The 12-week duration of the intervention period was selected based on data from our REMIT pilot trial (14). At 12 weeks, all participants with HbA_{1c} <7.3% (<56 mmol/mol) were asked to discontinue their diabetes medications and continue with lifestyle modifications. This HbA_{1c} cutoff was selected because changes in HbA_{1c} lag behind improved glycemic status as a result of changes in lifestyle and/or medications. Participants who were not on diabetes medications or who stopped them at 12 weeks were assumed to be in diabetes remission at 12 weeks and were followed for evidence of relapse (see below) until 64 weeks after randomization. Although it was not possible to blind participants or investigators to treatment allocation, all outcomes were ascertained according to prespecified criteria. Moreover, the study statistician was masked to treatment group until the statistical analysis plan was finalized and the database was closed.

Treatment Period

Participants assigned to the intervention group were asked to stop their baseline diabetes medications at the randomization visit and start sitagliptin/metformin 50/500 mg orally for 4 days and then increase to 50/500 mg twice a day for 4 days, then 50/850 mg twice a day for 4 days, and then 50/1,000 mg twice a day. The dose was adjusted if participants developed side effects. Participants also concurrently started insulin glargine 2–6 units subcutaneously at bedtime, and the dose was titrated over 2–4 weeks to achieve a fasting capillary glucose of 4.0–5.3 mmol/L. This target was maintained for the duration of the intervention period. The insulin dose was adjusted if there was a concern regarding hypoglycemia. Intervention group participants were also provided with a pedometer (either AE120XLGM Enhanced DigiWalkerXL Pedometer, ACCUSPLIT, Livermore, CA, or 4×3runner, Ozeri, Compton, CA) and asked to increase their moderate-intensity physical activity to ≥150 min/week by week 12. They were also counseled regarding decreasing their caloric intake while maintaining a healthy diet with a goal of achieving ≥5% weight loss by 36 weeks. Research staff met with the intervention group participants weekly for the first 6 weeks of the trial and then every 2 weeks during weeks 6–12 to assist with medication titration, review any side effects, help with setting individualized lifestyle goals, and address any barriers. Participants were also contacted via telephone between in-person study visits.

Participants assigned to the control group continued their diabetes medications as prescribed by their usual diabetes care providers. They were counseled on the current dietary recommendations and the importance of regular physical activity and were also provided with a pedometer. They met with study staff at 6 and 12 weeks for study-related measurements and were encouraged to continue to meet with their usual diabetes care providers including allied health professionals.

Posttreatment Follow-up Period

HbA_{1c} was measured at 12 weeks, and all participants with an HbA_{1c} <7.3% (<56 mmol/mol) were asked to discontinue their glucose-lowering medications. Participants taking insulin were asked to taper it to zero over 5 days. Participants were asked to continue with their lifestyle modifications and monitor their fasting capillary glucose levels at least three times per week. Participants met with study staff at 16, 24, 36, 48, and 64 weeks and were contacted by telephone monthly between the clinic visits to review their capillary glucose values and adherence to the lifestyle recommendations. Participants

were also asked to contact research staff between study visits if they had fasting capillary glucose readings >10 mmol/L. Participants who did not stop their diabetes medications at 12 weeks or who experienced diabetes relapse after the 12-week visit (see criteria below) were asked to continue or restart their baseline glucose-lowering medications and return to their usual diabetes care providers for further glycemic care as informed by the Canadian Diabetes Guidelines (16).

Two glucose profiles were collected for each participant at 6 and 12 weeks. FPG was measured at baseline and 16 weeks, and a standard 75-g oral glucose tolerance test (OGTT) was conducted at 24 weeks. Participants on glucose-lowering medications were asked to hold them for 48 h prior to these tests unless fasting capillary glucose levels rose above 12 mmol/L. HbA_{1c} was measured at baseline and 12, 24, 36, 48, and 64 weeks. The short version of the International Physical Activity Questionnaire (17,18) was administered at baseline and at 12, 24, 36, 48, and 64 weeks. The EuroQol 5-Dimension (EQ-5D) questionnaire (19–21) was administered at baseline and at 12 and 64 weeks.

Outcomes

The primary outcome in the original protocol was diabetes remission at 24 weeks after randomization. However, based on data from a trial with a similar design (15), a decision was made prior to seeing any study data to modify the analytic strategy from the calculation of relative risk of diabetes remission at 24 weeks to a calculation of the hazard of relapse throughout the whole study period. Relapse could occur at any time at or after the 12-week visit and was defined in two ways (Table 1). The primary definition was based on the following: a capillary glucose level >10 mmol/L on ≥50% of measurements over 1 week in the absence of an acute illness, $HbA1_c$ ≥6.5% (≥48 mmol/mol), use of any glucose-lowering medication, FPG ≥7 mmol/L, or a 2-h postprandial plasma glucose ≥11.1 mmol/L during an OGTT. A prespecified supplementary definition of relapse that was consistent with that used in our other remission trials (14,15) excluded the results of the FPG levels and the 2-h plasma glucose levels on OGTT.

Main secondary outcomes included the number of participants remaining in remission (defined as not satisfying any criteria for relapse) at 24, 36, 48, and 64 weeks. The remission status of participants who missed any study visit was classified as the same as that at the subsequent visit. Participants who did not have a subsequent visit were assumed to have relapsed at the first missed visit. The main safety outcome was the number of severe hypoglycemic episodes during 64 weeks of follow-up.

Statistical Analyses

Sample size calculations suggested that 50 participants per treatment group would provide 80% power to show a 2.9-fold higher proportion of diabetes remission in the intervention group compared with the control group at 24 weeks. These estimates assumed that 10% of participants in the control group and 29% in the intervention group would achieve remission at that time with type I error of 5% and a one-sided test (14,22).

All analyses were done according to the intention-to-treat principle. A Cox proportional hazards model was used to analyze time to diabetes relapse. Participants who were lost to follow-up prior to the 12-week visit or right after stopping drugs at the 12-week visit, or those who did not experience relapse by the end of the study, were censored at their last visit. Proportionality of the model was assessed by confirming nonsignificance of the treatment × time interaction term. Kaplan-Meier curves were compared with a log-rank test.

Continuous variables were compared with a two-sample *t* test or Wilcoxon signed rank test and categorical variables with a Pearson χ^2 test or the Fisher exact test. A linear mixed model was used to compare changes in repeated measurements over time between the treatment groups using restricted maximum likelihood. Prior to the EQ-5D analysis, the questionnaire responses were used to derive a weighted health utility index score ranging from 0 (death) to 1 (perfect health) as well as a visual analog scale score of participants' perceived health status ranging from 1 (poor) to 100 (perfect).

SAS, version 9.4 (SAS Institute, Cary, NC), was used to conduct statistical analyses. The level of significance was set at

Table 1—Definitions of diabetes relapse and remission

Definition	Diabetes remission	Diabetes relapse
Primary	Absence of relapse	Any of the following:
		1) ≥50% of capillary glucose values in any week >10 mmol/L in absence of illness
		2) HbA_{1c} ≥6.5%
		3) Use of diabetes drugs
		4) FPG ≥7.0 mmol/L
		5) 2-h postprandial plasma glucose ≥11.1 mmol/L on an OGTT
Supplementary	Absence of relapse	Any of the following:
		1) ≥50% of capillary glucose values in any week >10 mmol/L in absence of illness
		2) HbA_{1c} ≥6.5%
		3) Use of diabetes drugs

FPG, measured at 16 and 24 weeks; HbA_{1c}, measured at 24, 36, 48, and 64 weeks; OGTT (75 g), administered at 24 weeks.

$\alpha = 0.05$. All secondary analyses were considered as exploratory. This trial was registered at www.ClinicalTrials.gov (NCT02561130).

RESULTS

Study Population

In this trial 130 participants were screened and 102 with type 2 diabetes were enrolled at six Canadian academic and community diabetes centers between 20 July 2016 and 29 May 2018. Recruited participants (37% women) were of mean (SD) age 55.5 (9.0) years, with BMI 31.6 (4.7) kg/m^2 and duration of diabetes 24 (16.9) months. Mean baseline HbA_{1c} was 6.6% (0.7%) [49 (7.7) mmol/mol], 15 (14.7%) participants were on no diabetes medications, 72 (70.6%) were on one agent, and 12 (11.8%) were on two agents. (See Table 2.) A total of 50 participants were randomized to the intervention group and 52 to the control group. (See Supplementary Fig. 1.)

Achievement of Glycemic and Lifestyle Targets

At the end of the 12-week treatment period, six control group participants were not taking any diabetes medications. At that time, all intervention group participants were taking metformin and sitagliptin and 49 (98%) were taking insulin, at a mean (SD) daily dose of 21.6 (15.1) units. Fasting and 2-h postprandial capillary glucose levels on glucose profiles were 5.0 (0.4) mmol/L and 6.4 (0.9) mmol/L, respectively, in the intervention group and 7.0 (1.1) mmol/L and 7.3 (1.1) mmol/L in the control group. Forty-one (82%) intervention group and 13 (25%) control group participants achieved a mean fasting capillary glucose $\leq$5.3 mmol/L, and 40 (80.0%) intervention group participants and 25 (48.1%) control group participants reported $\geq$150 min/week of vigorous and moderate physical activity at 12 weeks. Achievement of other glycemic and lifestyle targets is summarized in Supplementary Table 2.

Table 2—Baseline characteristics in the study groups

	Intervention group	Control group
N	50	52
Age (years)	56.4 (8.7)	54.7 (9.3)
Female sex, *n* (%)	18 (36.0)	20 (38.5)
Ethnicity, *n* (%)		
Caucasian	42 (84.0)	47 (90.4)
Non-Caucasian	8 (16.0)	5 (9.6)
Duration of diabetes (months)	26.4 (17.3)	21.7 (16.3)
Use of antidiabetes medications at baseline, *n* (%)		
None	8 (16.0)	7 (13.5)
One agent	35 (70.0)	37 (71.2)
Two agents	7 (14.0)	5 (9.6)
Use of specific antidiabetes medications at baseline, *n* (%)		
Sulfonylurea	3 (6.0)	4 (7.7)
Biguanide	42 (84.0)	41 (78.8)
Meglitinide	1 (2.0)	0
DPP-4 inhibitor	2 (4.0)	5 (9.6)
GLP-1 agonist	1 (2.0)	1 (1.9)
SGLT2 inhibitor	0	2 (3.8)
Weight (kg)	91.3 (15.6)	93.9 (17.8)
BMI (kg/m^2)	30.9 (4.7)	32.2 (4.8)
Waist circumference (cm)	103.9 (12.2)	105.3 (12.4)
FPG (mmol/L)	7.5 (1.6)	7.4 (1.8)
HbA_{1c} (%)	6.6 (0.6)	6.6 (0.8)
HbA_{1c} (mmol/mol)	49 (6.6)	49 (8.7)

Data are means (SD) unless otherwise indicated. There were no significant differences between the treatment groups in the listed characteristics. DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SGLT2, sodium–glucose cotransporter 2.

Discontinuation of Diabetes Medications and Follow-up for Relapse

All intervention group participants and 37 control group participants had an HbA_{1c} <7.3% at the 12-week visit and stopped their glucose-lowering medications as planned. These individuals and the six control group participants who were not on any glucose-lowering medications at the 12-week visit were assumed to be in remission and were followed for relapse. The remaining nine control group participants did not stop diabetes medications.

Six control group participants who were either not eligible to stop their diabetes medications or refused to stop were assumed to have relapsed at the 12-week visit. One participant was lost to follow-up and one died in the intervention group after stopping drugs at the 12-week visit, and one participant in the control group was lost to follow-up prior to the 12-week visit. They were censored for the time-to-event analyses and presumed to have relapsed for analyses at 24, 36, 48, and 64 weeks. Additionally, one participant in the intervention group and three participants in the control group who did not provide an HbA_{1c} at 12 weeks or a subsequent visit were assumed to have relapsed at those visits.

The criteria for the primary definition of relapse (Table 1) were met by 41 (82%) intervention group participants and 48 (92%) control group participants during follow-up (hazard ratio [HR] 0.72, 95% CI 0.47–1.1, $P = 0.13$) (Fig. 1*A*). Analysis of the number of participants remaining in remission at prespecified time points revealed nonsignificant differences between treatment groups when the same relapse definition was used (Fig. 2*A*). The criteria for the supplementary definition of relapse were met by 37 (74%) intervention group participants and 46 (88%) control group participants during follow-up (HR 0.60, 95% CI 0.39–0.95, $P = 0.03$) (Fig. 1*B*). With these criteria, 13 (26%) intervention group participants and 5 (10%) control group participants were in remission at 36 weeks (relative risk (RR) 2.70, 95% CI 1.04–7.03, $P = 0.04$) with no significant differences at other time points (Fig. 2*B*). Removing the 2-h plasma glucose from the primary definition of relapse in an exploratory analysis did not change the overall results (HR 0.75, 95% CI 0.49–1.15, $P = 0.19$).

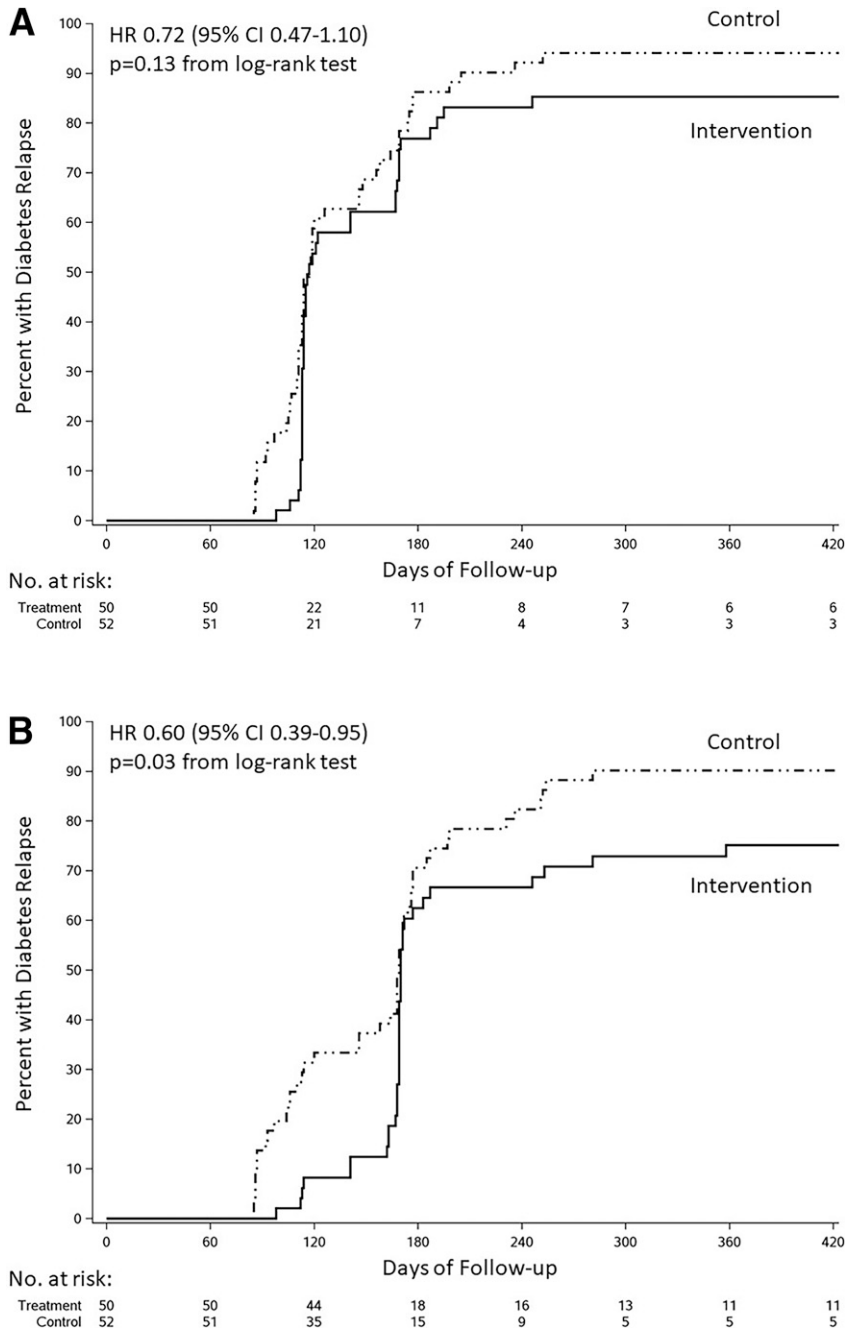

Figure 1—Kaplan-Meier curves for diabetes relapse in the intervention group and the control group. Diabetes medications were stopped at 12 weeks after randomization in participants with HbA_{1c} <7.3% (<56 mmol/mol). *A*: Diabetes relapse when FPG and OGTT results were included in the relapse criteria. *B*: Diabetes relapse when FPG and OGTT results were not included in the relapse criteria.

Other Outcomes

Least squares mean differences in glycemic and anthropometric outcomes between the treatment groups during study follow-up are summarized in Supplementary Table 3. In comparisons with the control group, HbA_{1c} and percent weight loss were significantly lower in the intervention group. The EQ-5D analyses revealed no statistically significant differences in the utility index scores but a significantly higher visual analog scale score in the intervention group compared with the control group at 12 weeks (Supplementary Table 4).

There were no severe hypoglycemic episodes during study follow-up. Non-severe symptomatic hypoglycemic episodes were observed in 35 (70.0%) participants in the intervention group and 12 (23.1%) in the control group ($P < 0.0001$). There was one death unrelated to the study in the intervention group between week 12 and 24 of follow-up, which was due to hemorrhagic/septic/cardiogenic shock. Other collected adverse events were not significantly different between the treatment groups and are summarized in Supplementary Table 5.

CONCLUSIONS

In this diabetes remission trial, a 3-month remission induction regimen targeting fasting normoglycemia on therapy, increased physical activity, and modest weight loss with a combination of lifestyle therapy, metformin/sitagliptin, and insulin glargine did not significantly reduce the hazard of diabetes relapse compared with usual diabetes care after the glucose-lowering medications were discontinued. It also did not significantly increase the proportion of participants in remission at various follow-up times. These findings were based on criteria for relapse that included results of two FPG levels and one 2-h glucose level from an OGTT. When the supplementary definition of relapse that was only based on HbA_{1c}, persistently high capillary glucose values, or initiation of glucose-lowering drugs was used, a larger 40% reduction in the hazard of relapse was observed with a 95% CI that excluded 1. Moreover, this definition suggested a 2.7-fold higher proportion in remission 6 months after the treatment period ended.

Our fasting glucose target of 4.0–5.3 mmol/L on therapy was achieved in 82% of the intervention group participants compared with 25% in the control subjects; however, our intervention did not achieve lasting improvements in the fasting and postprandial glucose levels on OGTT when the glucose-lowering medications were discontinued, as reflected in the primary outcome. This was likely due to the modest observed weight loss as well as high day-to-day variability in measurements of FPG and 2-h plasma glucose on OGTT. However, when in our supplementary analyses the definition of relapse was based on the HbA_{1c} as suggested in the recent American Diabetes Association consensus report (23), the hazard of relapse was lower in the intervention group compared with the control group, and 20% of participants in the intervention

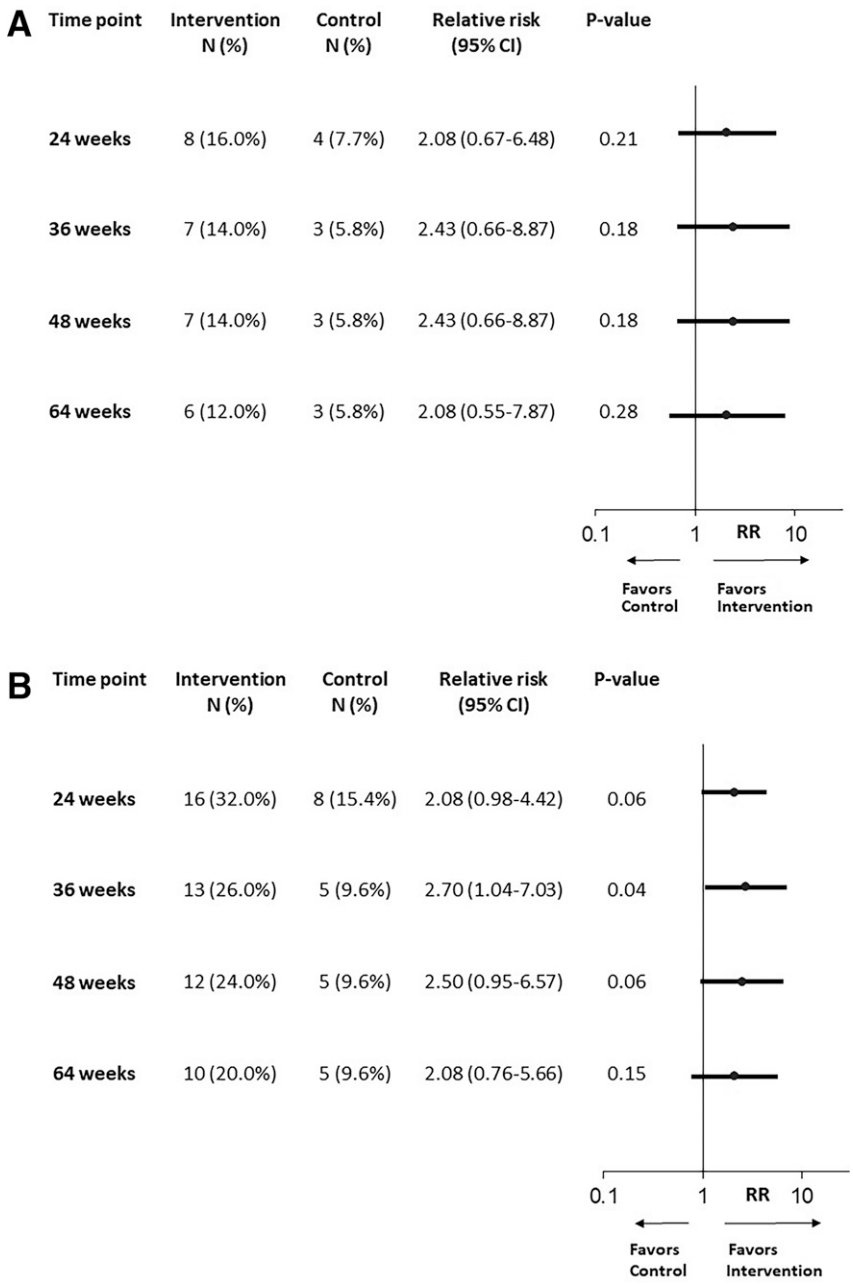

Figure 2—Diabetes remission in the intervention group and the control group at 24, 36, 48, and 64 weeks after randomization. Diabetes medications were stopped at 12 weeks after randomization in participants with HbA_{1c} <7.3% (<56 mmol/mol). Diabetes remission was defined as HbA_{1c} <6.5% (<48 mmol/mol) and no evidence of diabetes relapse. *A*: Diabetes remission when the relapse criteria included FPG and OGTT results. *B*: Diabetes remission when the relapse criteria did not include FPG and OGTT results.

group and 10% in the control group remained in remission after 1 year. We previously reported that up to 41% of patients with type 2 diabetes remained in remission at 3 months following a short-term treatment with insulin glargine, metformin, and acarbose vs. 14% in the control group (14) and also that up to 14% met similar criteria for remission at 1 year after completing a short course of treatment with insulin glargine, metformin, and dapagliflozin compared with 8% in the control group (15). The observation of similar effect sizes with overlapping CIs in both the primary and supplementary analyses in the current trial and our previous trials (14,15) supports the therapeutic strategy of combining lifestyle and medical therapies that was used and the need for further assessment of this multifaceted approach to inducing remission.

Several nonsurgical therapeutic strategies focused on inducing and maintaining remission of type 2 diabetes have been assessed in randomized controlled trials (5,6,8,14,15). Weng et al. (8) observed remission in 27–51% of newly diagnosed patients treated with a short course of oral hypoglycemic agents or intensive insulin therapy and followed for 1 year. In Diabetes Remission Clinical Trial (DiRECT), 46% of the intervention group participants treated with very-low-calorie diet vs. 4% in the control group met criteria for remission at 1 year (5), and 36% in the intervention group and 3% in the control group had remission of diabetes at 2 years (6). The observed differences in remission outcomes between treatment groups in our trial were less pronounced than in our pilot trial (14) as well as in DiRECT (5) and the trial of Weng et al. (8). This could be because of a longer duration of diabetes in our participants than in the trial of Weng et al. (up to 5 years vs. newly diagnosed), a shorter duration of induction therapy than in one intervention arm of our three-arm pilot trial (12 vs. 16 weeks), and less weight loss achieved in the current trial than with a very-low-calorie (825–853 kcal/day) liquid formula diet for 3–5 months in DiRECT (0.9% vs. 10% weight loss at 1 year). Furthermore, different combinations of medications used during induction therapy in our trials may influence the magnitude of the observed remission response and its sustainability.

Our combined intervention is thought to work by acting on multiple physiological pathways. Insulin has been shown to improve β-cell function by multiple mechanisms (24–27). Metformin inhibits gluconeogenesis in the liver (28), increases insulin sensitivity in peripheral tissues (29), and increases incretin release (30,31). Sitagliptin has been shown to increase insulin secretion (32,33) and may also have cytoprotective effects on β-cells as suggested by animal studies (34–38). Normalization of plasma glucose with intensive glucose-lowering therapy is also thought to reverse glucotoxicity and improve pancreatic β-cell function and insulin sensitivity (8–13). Weight loss and exercise have been shown to be associated with reductions in liver and visceral fat and an

improvement in insulin sensitivity and insulin secretion (39–42).

Strengths of our trial include randomization of individual patients, proper concealment of allocation, low losses to follow-up, ascertainment of relapse/remission outcomes based on predefined criteria, and intention-to-treat analysis. We also ascertained remission/relapse similarly in the two treatment groups by asking eligible participants to discontinue diabetes medications at 12 weeks and evaluating whether they underwent remission similarly. In other published trials, diabetes medications were only stopped in the intervention group, which likely led to overestimation of the efficacy of the studied interventions in establishing remission (5,22,43,44). Our intervention was well accepted by participants and led to an increase in health-related quality of life at 12 weeks as measured by the EQ-5D visual analog scale. Limitations of our trial include overestimation of the intervention effects during sample size calculation and the inability to blind participants and research staff to the study treatments due to the nature of the intervention.

The growing prevalence of diabetes strongly supports the search for a variety of novel, easily implemented nonsurgical approaches to diabetes remission. This trial tested the hypothesis that targeting fasting normoglycemia and modest weight loss with a combination of metformin/sitagliptin, insulin glargine, and lifestyle modifications would induce sustained remission of type 2 diabetes. Although our overall results were not statistically significant, the data suggest that the tested approach may partially but not completely restore glucose homeostasis. Future studies need to focus on selecting and testing the most optimal combinations of medications that can induce durable improvements in metabolic pathways even after the medications are discontinued, and maximizing the benefits of existing and new lifestyle approaches to achieve sustained weight loss.

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