Piloting a Remission Strategy in Type 2 Diabetes: Results of a Randomized Controlled Trial

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Context: Medical strategies targeting remission of type 2 diabetes have not been systematically studied.

Objective: This trial assessed the feasibility, safety, and potential to induce remission of a short-term intensive metabolic strategy.

Design: A randomized, parallel, open-label pilot trial with 83 participants followed for 52 weeks.

Participants: Patients with type 2 diabetes of up to 3 years in duration.

Interventions: Participants were randomized to: (1) an 8-week intensive metabolic intervention, (2) a 16-week intensive metabolic intervention, or (3) standard diabetes care. During the intensive intervention period, weight loss and normoglycemia were targeted using lifestyle approaches and treatment with metformin, acarbose, and insulin glargine. Diabetes drugs were then discontinued in the intervention groups and participants were followed for hyperglycemic relapse.

Primary Outcome: On-treatment normoglycemia.

Results: At 8 weeks, 50.0% of the 8-week intervention group vs 3.6% of controls achieved normoglycemia on therapy (relative risk [RR], 14.0; 95% confidence interval [CI], 1.97 to 99.38), and at 16 weeks, these percentages were 70.4% in the 16-week group and 3.6% in controls (RR, 19.7; 95% CI, 2.83 to 137.13). Twelve weeks after completion of the intervention, 21.4% of the 8-week group compared with 10.7% of controls (RR, 2.00; 95% CI, 0.55 to 7.22) and 40.7% of the 16-week group compared with 14.3% of controls (RR, 2.85; 95% CI, 1.03 to 7.87) met hemoglobin A1C criteria for complete or partial diabetes remission.

Conclusions: A short course of intensive lifestyle and drug therapy achieves on-treatment normoglycemia and promotes sustained weight loss. It may also achieve prolonged, drug-free diabetes remission and strongly supports ongoing studies of novel medical regimens targeting remission. (J Clin Endocrinol Metab 102: 1596–1605, 2017)
diabetes is the first step on the path of chronic, increasingly complex therapeutic regimens. Recent data suggest that this may not be inevitable and that diabetes may be partially or even completely reversed, at least in some patients. For example, short-term intensive insulin therapy (1–12), oral diabetes drugs (9–11), intensive lifestyle therapy (13–15), a low-carbohydrate Mediterranean diet (16), or a very-low-calorie diet (17) can reverse diabetes in up to 40% of patients, and bariatric surgery can induce diabetes remission in up to 95% of patients (18–23). These data highlight the importance of considering and testing alternative treatment paradigms for type 2 diabetes that focus on reversing the disease rather than simply controlling progressive hyperglycemia. They also suggest that achieving normoglycemia on therapy using one or more approaches may be an important component of any remission strategy. We therefore conducted a pilot trial to determine whether a short-term intensive metabolic approach that targeted fasting and postprandial normoglycemia and weight loss using a combination of pharmacological and lifestyle approaches was feasible and safe, and whether it showed the potential to induce sustained diabetes remission.

Methods

Study design

This is a randomized, parallel, open-label pilot trial that was conducted at the Hamilton Health Sciences in Hamilton, Ontario, Canada. The trial was approved by Health Canada and the Hamilton Integrated Research Ethics Board.

Participants

Participants were recruited through the Diabetes Care and Research Program at Hamilton Health Sciences. They were included if they were between 30 and 80 years of age with a body mass index (BMI) ≥ 23 kg/m² and type 2 diabetes diagnosed within 3 years prior to enrollment, and if they had a hemoglobin A1C (HbA1C) ≤ 8.5% (69 mmol/mol) on no oral diabetes drugs or ≤7.5% (58 mmol/mol) on either one diabetes drug or half-maximal doses of two drugs at stable doses for at least 8 weeks, had a negative pregnancy test and an agreement to use a reliable method of birth control (in all females with childbearing potential), were able to self-monitor capillary blood glucose and willing to self-inject insulin, and when they had metformin, acarbose, or insulin glargine. We have expanded the HbA1C inclusion criterion from 6.5% to 8.0% (48 to 64 mmol/mol) on no oral diabetes drugs to ≤8.5% (69 mmol/mol) on no oral diabetes drugs in February 2012 to increase recruitment. All participants provided written informed consent and had a baseline electrocardiogram to screen for any evidence of ischemic heart disease or arrhythmia.

Randomization and masking

Eligible participants were randomized 1:1:1 to three groups: (1) an 8-week intensive metabolic intervention followed by cessation of all diabetes drugs; (2) a 16-week intensive metabolic intervention followed by cessation of all diabetes drugs; or (3) standard diabetes therapy using random permuted blocks of six and nine. A randomization schedule was prepared by an independent statistician using a computer-generated random number sequence. Allocation was performed through a central computerized system to ensure concealment. Owing to the nature of the study interventions, participants and research staff were not blinded to treatment allocation. Laboratory personnel were blinded to group assignment.

Procedures

Intervention groups

The two interventions only differed in their duration. They comprised an intensive follow-up schedule during which lifestyle therapy and treatment with insulin glargine, metformin, and acarbose were reinforced. All other diabetes drugs were discontinued. Participants met with the research nurse every week for the first 8 weeks, and then every 2 weeks during weeks 9 to 16 in the 16-week intervention group. They were also contacted by phone between study visits.

Lifestyle therapy comprised dietary and physical activity intervention. A dietician estimated participants’ baseline daily energy requirements using the Mifflin–St. Jeor equation (24) and activity level, encouraged participants to reduce their daily caloric intake by 500 to 750 kcal/d by providing a suggested meal plan, and reinforced caloric reduction during subsequent meetings. A kinesiologist prescribed an individualized moderate-intensity exercise program, encouraged participants to achieve ≥150 min of moderate intensity physical activity per week by week 16 of the trial and to maintain it for the duration of the trial, and led weekly small-group gym sessions. Participants were also provided with a pedometer (Accusplitt Eagle AE120XLM) and encouraged to work toward a goal of 10,000 steps/d. The overall lifestyle goal was to achieve and maintain ≥5% reduction in baseline weight by week 28 of the trial.

Insulin glargine was started at 2 to 6 U subcutaneously at bedtime and titrated daily in 1-U increments by the participant and twice weekly in 2- to 4-U increments by the research nurse to achieve a fasting capillary glucose between 4.0 and 7.0 mmol/L; active liver disease, alanine transaminase ≥ 2.5-fold the upper limit of normal, or excessive alcohol intake; cardiovascular disease, pulmonary disease with dependence on oxygen, inflammatory bowel disease, colonic ulcers, recent or significant bowel surgery, predisposition to bowel obstruction, any disease requiring systemic glucocorticoid treatment, or any major illness with a life expectancy of <3 years; history of any condition that significantly limited participant’s ability to achieve moderate levels of physical activity; or a history of hypersensitivity to metformin, acarbose, or insulin glargine. We have expanded the HbA1C inclusion criterion from 6.5% to 8.0% (48 to 64 mmol/mol) on no oral diabetes drugs to ≤8.5% (69 mmol/mol) on no oral diabetes drugs in February 2012 to increase recruitment. All participants provided written informed consent and had a baseline electrocardiogram to screen for any evidence of ischemic heart disease or arrhythmia.

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glucose of 4.0 to 5.3 mmol/L by week 4 and to maintain this target for the remaining duration of the intensive metabolic intervention.

After completing the intensive metabolic intervention, participants in both intervention groups stopped oral diabetes drugs and tapered insulin to zero during a 5-day period. They were encouraged to continue with lifestyle modifications and regular glucose monitoring (at least three times per week) during the maintenance phase of the trial. A 75-g oral glucose tolerance test (OGTT) was done at 12 weeks after randomization in the 8-week intervention group and at 20 and 28 weeks in all groups. An OGTT was done earlier when fasting capillary glucose levels rose to >7 mmol/L on ≥50% of home glucose readings in the absence of an acute illness. Hyperglycemia relapse was defined as a fasting plasma glucose ≥ 6.1 mmol/L or a 2-hour plasma glucose ≥7.8 mmol/L on the OGTT. Participants who met criteria for hyperglycemia relapse returned to standard glycemic care by their usual diabetes care provider and did not have further OGTTs.

Control group

Control group participants received standard lifestyle advice and were also provided with a pedometer as an incentive to be active. They received standard glycemic management by their usual diabetes care provider for the duration of the trial. They had a scheduled OGTT at 20 and 28 weeks and were asked to hold diabetes drugs for 48 hours prior to the OGTT.

Follow-up

All participants were seen at 8, 16, 20, and 28 weeks after randomization and were contacted by telephone at least once a month between these visits. After week 28, all study participants returned to their regular diabetes care provider who continued to manage their diabetes and came back for one last study visit at 52 weeks after randomization. HbA1C was measured at 8, 20, 28, and 52 weeks. The European Quality of Life five-dimension questionnaire (25–27) was collected at baseline, 20 weeks, and 28 weeks. It is a two-part instrument that includes a (1) five-item descriptive system from which a weighted health utility index score is derived ranging from 0 (death) to 1 (perfect health state), and (2) a visual analog scale of perceived health status that is ranked by the participant from 1 (poor) to 100 (perfect) at the time of completion of the questionnaire.

Outcomes

Table 1 summarizes the various definitions of glycemic response used in the study. The primary outcome was normoglycemia on therapy defined as a mean fasting capillary glucose ≤ 5.4 mmol/L and a mean 2-hour postprandial glucose ≤ 6.8 mmol/L calculated from two 7-point glucose profiles collected during week 8 (8-week group) and week 16 (16-week group) of therapy. Secondary outcomes included HbA1C, fasting plasma glucose, changes in weight, BMI, waist circumference, waist/hip ratio from baseline, hypoglycemic episodes, quality of life, recruitment rate, retention rate, and adherence to therapy. We also evaluated diabetes remission and regression outcomes based on the results of an OGTT and HbA1C in participants remaining off glucose-lowering drugs (see Table 1 for definitions). The OGTT-based definition of complete diabetes remission was included in the study protocol. Other definitions of remission and regression were added before any statistical analyses were carried out by treatment group.

OGTTs were performed after a minimum of an 8-hour fast. Blood samples for plasma glucose were collected in a fluoride-containing tube at 0 and 120 minutes after administration of a 75-g oral glucose load and submitted to the hospital laboratory within 20 minutes of collection. HbA1C was measured in a clinical laboratory using methods calibrated to the International Federation of Clinical Chemistry and Laboratory Medicine method.

Statistical analyses

All analyses were performed using the intention-to-treat principle. Participants lost to follow-up (N = 2) were presumed not to have achieved any diabetes remission. A χ² test (or Fisher’s exact test) was used to compare dichotomous outcomes, and a two-sample t test (or a nonparametric equivalent) was used to compare continuous outcomes. A sample size of 126 participants was estimated to provide 90% power to show a risk difference of ≥30% for achieving normoglycemia on therapy in each intervention group vs the control group, assuming this would be achieved in ≤5% of the control group. SAS version 9.2 (SAS Institute, Cary, NC) was used to perform statistical analyses. The trial was registered at ClinicalTrials.gov, identifier NCT01181674.

Results

A total of 132 participants were screened and 83 (mean age, 57 years; 52% females) were randomly allocated to the 8-week metabolic intervention group (N = 28), 16-week metabolic intervention group (N = 27), and

### Table 1. Definitions of Glycemic Response to Therapy

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Glycemic Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMBG criteria</td>
<td>Normoglycemia on therapy</td>
<td>A mean fasting capillary glucose ≤ 5.4 mmol/L and a mean 2-hour postprandial glucose ≤ 6.8 mmol/L calculated from two 7-point glucose profiles</td>
</tr>
<tr>
<td>OGTT criteria</td>
<td>Complete diabetes remission</td>
<td>A fasting plasma glucose &lt; 6.1 mmol/L and 2-hour plasma glucose &lt; 7.8 mmol/L on an OGTT and no chronic diabetes drugs</td>
</tr>
<tr>
<td></td>
<td>Partial or complete diabetes remission</td>
<td>A fasting plasma glucose &lt; 7.0 mmol/L and 2-hour plasma glucose &lt; 11.1 mmol/L on an OGTT and no chronic diabetes drugs</td>
</tr>
<tr>
<td>HbA1C criteria</td>
<td>Complete diabetes remission</td>
<td>HbA1C &lt; 6.0% (42 mmol/mol) and no chronic diabetes drugs</td>
</tr>
<tr>
<td></td>
<td>Partial or complete diabetes remission</td>
<td>HbA1C &lt; 6.5% (48 mmol/mol) and no chronic diabetes drugs</td>
</tr>
<tr>
<td></td>
<td>Diabetes regression or remission</td>
<td>HbA1C &lt; 7.0% (53 mmol/mol) and no chronic diabetes drugs</td>
</tr>
</tbody>
</table>
control group (N = 28) between 11 February 2011 and 9 January 2014. Overall, two (2.4%) control group participants did not complete the study and had no follow-up glucose tolerance tests or HbA1C results available (Fig. 1). At baseline, the mean [standard deviation (SD)] duration of diabetes was 14.6 (10.6) months, HbA1C was 6.6% (0.6%) [49 (6.6) mmol/mol], BMI was 33.2 (5.8) kg/m², and 66 (79.5%) participants were taking oral glucose-lowering drugs. Baseline characteristics of the study participants are summarized in Table 2, and they were not significantly different when compared between each intervention group and the control group.

Glycemic outcomes in the 8-week group

The mean (SD) fasting and 2-hour capillary glucose levels during week 8 of therapy were 5.3 (0.6) and 6.4 (0.9) mmol/L in the intervention group and 7.3 (1.5) and 8.3 (1.7) mmol/L in the control group. Normoglycemia on therapy was achieved in 14 (50.0%) of participants in the intervention group and one (3.6%) in the control group [relative risk (RR), 14.0; 95% confidence interval (CI), 1.97 to 99.38].

Four weeks after completion of the intervention (Fig. 2), two (7.1%) participants in both the intervention and control groups met the OGTT criteria for complete diabetes remission (RR, 1.00; 95% CI, 0.15 to 6.61). At this time, 10 (35.7%) participants in the intervention group and two (7.1%) in the control group had either partial or complete diabetes remission (RR, 5.00; 95% CI, 1.20 to 20.79).

Twelve weeks after completion of the intervention (Fig. 2), two (7.1%) participants in both the intervention and control groups met the OGTT criteria for complete remission as well as for partial or complete remission (RR for both, 1.00; 95% CI, 0.15 to 6.61). At this time, the HbA1C diabetes remission criteria (Fig. 3) indicated that three (10.7%) intervention participants vs one (3.6%) control participant maintained complete diabetes remission (RR, 3.00; 95% CI, 0.33 to 27.12); six (21.4%) vs three (10.7%) participants maintained partial or complete remission (RR, 2.00; 95% CI, 0.55 to 7.22); and eight (28.6%) vs four (14.3%) participants had either diabetes regression or remission (RR, 2.00; 95% CI, 0.68 to 5.89).

At 52 weeks (44 weeks after completion of the intervention), four (14.3%) intervention participants vs two (7.1%) control participants maintained complete diabetes remission (RR, 2.00; 95% CI, 0.40 to 10.05); seven (25.0%) vs three (10.7%) maintained either partial or complete remission (RR, 2.33; 95% CI, 0.67 to 8.12); and eight (28.6%) vs four (14.3%) had either diabetes regression or remission (RR, 2.00; 95% CI, 0.68 to 5.89) based on the HbA1C criteria.
The mean (SD) fasting and 2-hour capillary glucose levels during week 16 of therapy were 4.9 (0.5) and 6.0 (0.7) mmol/L in the intervention group and 6.8 (1.1) and 7.8 (1.9) mmol/L in the control group. Normoglycemia on therapy was achieved in 19 (70.4%) of participants in the intervention group and one (3.6%) in the control group (RR, 19.7; 95% CI, 2.83 to 137.13). Four weeks after completion of the intervention, four (14.8%) participants in the intervention group and two (7.1%) in the control group met the OGTT criteria for complete diabetes remission (RR, 2.07; 95% CI, 0.41 to 10.41; Fig. 2). At this time, 12 (44.4%) participants in the intervention group and two (7.1%) in the control group had either partial or complete diabetes remission (RR, 6.22; 95% CI, 1.53 to 25.24).

Twelve weeks after completion of the intervention (Fig. 2), two (7.4%) participants in the intervention group vs one (3.6%) in the control group met the OGTT criteria for complete remission (RR, 2.07; 95% CI, 0.41 to 10.41); 11 (40.7%) vs four (14.3%) participants maintained partial or complete remission (RR, 2.85; 95% CI, 1.03 to 7.87); and 13 (48.2%) vs four (14.3%) participants had either diabetes regression or remission (RR, 3.37; 95% CI, 1.25 to 9.05) based on the HbA1C criteria.

At 52 weeks (36 weeks after completion of the intervention), one (3.7%) intervention participant vs two (7.1%) control participants maintained complete diabetes remission (RR, 0.52; 95% CI, 0.05 to 5.39); six (22.2%) vs three (10.7%) maintained either partial or complete remission (RR, 2.07; 95% CI, 0.58 to 7.47); and seven (25.9%) vs four (14.3%) had either diabetes regression or remission (RR, 1.81; 95% CI, 0.60 to 5.50) based on the HbA1C criteria.

**Other outcomes**

Figure 4 illustrates the change in weight and waist circumference during the trial. During 28 weeks of follow-up, 10 (35.7%) participants in the 8-week group and 17 (63.0%) in the 16-week group achieved target ≥ 5% weight loss from baseline compared with 3 (10.7%) in the control group [RR, 3.33 (1.03 to 10.84) and 5.88
The mean (SD) percentage weight loss from baseline peaked at 20 weeks after randomization and was 3.1% (3.4%) in the 8-week group, 5.1% (3.3%) in the 16-week group, and 1.4% (2.4%) in controls. The mean (SD) decrease in waist circumference observed at 20 weeks was 3.2 (2.4) cm in the 8-week group, 4.3 (3.5) cm in the 16-week group, and 1.3 (2.3) cm in controls.

During the induction phase of the trial (intensive metabolic intervention period), 21 (38.2%) participants in the intervention groups required a reduction in dose or temporary withholding of at least one study medication. Seven (12.7%) participants stopped one study medication permanently due to side effects (six participants stopped acarbose and one stopped insulin glargine). The mean (SD) daily insulin glargine doses at the end of the induction phase were 27.5 (16.5) U in the 8-week group and 21.2 (12.8) U in the 16-week group. The mean daily insulin doses were 17.2 (14.8) U in participants who achieved remission 12 weeks after stopping diabetes drugs and 27.8 (14.1) U in those who did not achieve remission.

At 28 weeks or at the time of hyperglycemia relapse if it occurred earlier, intervention group participants returned to their regular diabetes care provider. At 52 weeks after randomization, eight (28.8%) of participants were on no diabetes drugs, 16 (57.1%) were on one agent, and four (14.3%) were on two agents in the 8-week group; 11 (40.7%) were on no drugs, 14 (51.9%) were on one agent, and two (7.4%) were on two agents in the 16-week group; and 10 (35.7%) were on no drugs, 11 (39.3%) were on one agent, six (21.4%) were on two agents, and one (3.6%) was on three agents in the control group (see Supplemental Table 1 for details). There were no serious adverse events related to the study drugs and no severe

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time since completion of intervention</th>
<th>Time since randomization</th>
<th>Treatment</th>
<th>Control</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission</td>
<td>4 weeks</td>
<td>12 wks in 8-week group; 20 wks in controls</td>
<td>2 (7.1%)</td>
<td>2 (7.1%)</td>
<td>1.00 (0.15-6.61)</td>
</tr>
<tr>
<td>Partial or Complete Remission</td>
<td>10 (35.7%)</td>
<td>12 weeks</td>
<td>2 (7.1%)</td>
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</tr>
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<td>12 weeks</td>
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</tr>
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<td>2 (7.1%)</td>
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(1.94 to 17.8), respectively). The mean (SD) percentage weight loss from baseline peaked at 20 weeks after randomization and was 3.1% (3.4%) in the 8-week group, 5.1% (3.3%) in the 16-week group, and 1.4% (2.4%) in controls. The mean (SD) decrease in waist circumference observed at 20 weeks was 3.2 (2.4) cm in the 8-week group, 4.3 (3.5) cm in the 16-week group, and 1.3 (2.3) cm in controls.

Figure 2. RR of diabetes remission in the intervention groups compared with the control group based on the OGTT criteria. Complete diabetes remission was defined as a fasting plasma glucose < 6.1 mmol/L and 2-hour plasma glucose < 7.8 mmol/L on an OGTT and no chronic diabetes drugs. Partial or complete diabetes remission was defined as a fasting plasma glucose < 7.0 mmol/L and 2-hour plasma glucose < 11.1 mmol/L on an OGTT and no chronic diabetes drugs.

[Image of a table showing RR of diabetes remission]
hypoglycemic episodes among study participants. Non-severe symptomatic hypoglycemic episodes were observed in nine (32.1%) participants in the 8-week group, 10 (37.0%) participants in the 16-week group, and one (3.6%) participant in the control group. Other events observed during the trial are summarized in the Supplemental Table 2. The European Quality of Life five-dimension health utility index and visual analog scale baseline scores and changes in scores from baseline to 20 and 28 weeks were not significantly different when compared between each intervention group and the control group (see Supplemental Table 3).

Discussion

This randomized controlled pilot trial showed that a short-term, intensive metabolic intervention targeting fasting and postprandial normoglycemia and weight loss was feasible and safe, and capable of achieving normoglycemia in >50% of patients and inducing ≥5% weight loss in >35% of patients with recently diagnosed type 2 diabetes. The intervention was implemented by a nurse, dietitian, and kinesiologist and included frequent visits, individualized dietary, physical activity, and drug titration advice, and assistance with setting and attaining lifestyle goals. The recruitment rate of two to three participants per month at one site and no losses to follow-up in the intervention groups suggest that the intervention was highly accepted. The finding that up to 41% of the intervention group participants maintained partial or complete diabetes remission 12 weeks after stopping diabetes drugs challenges the notion that type 2 diabetes is a permanent and progressive disease as previously thought (28–30), and it suggests that it might be possible to achieve diabetes remission by using a combination of lifestyle and pharmacological approaches. Future trials with at least 1 year of active follow-up off drugs will be able to provide 1-year remission rates when using the

![Figure 3](https://academic.oup.com/jcem/article-abstract/102/5/1596/3070517)
The proposed therapeutic approach. The trial findings also suggest that an 8-week course of intensive metabolic therapy may not be sufficient for inducing remission, and an induction therapy of a longer duration might be needed.

Previous trials of medical interventions for diabetes have yielded results that are consistent with the present findings related to the feasibility of achieving remission of type 2 diabetes. One trial (10) with 382 participants with newly diagnosed type 2 diabetes reported that 45% to 51% of patients who achieved tight glycemic goals with short-term intensive insulin therapy and 27% of those who achieved glycemic goals with oral agents maintained remission after 1 year of follow-up. Similarly, 20.9% of newly diagnosed patients who achieved tight glycemic goal with short-term oral drug therapy and 37.9% of those who achieved this glycemic goal with oral drugs plus insulin maintained good glycemic control without medication for 1 year (11). In another trial in people with a longer duration of diabetes, intensive lifestyle approaches vs standard diabetes support and education achieved partial or complete diabetes remission in 11.5% vs 2% of participants during the first year of follow-up (13).

The strengths of our study include a randomized controlled design with predefined outcomes, intention-to-treat analyses, high adherence, few losses to follow-up, and inclusion of people with new and established diabetes. Limitations include conducting the study at one site, the short follow-up period, and the fact that participants returned to usual diabetes care as soon as they had evidence of abnormal glucose tolerance. Nevertheless, this trial clearly shows that a multifaceted intensive metabolic strategy that targets normoglycemia and weight loss using pharmacological and lifestyle approaches may achieve remission, is acceptable to patients, and may be easily translated into clinical practice. The trial supports further research focused on identifying the most efficacious combinations of therapies to induce diabetes remission, and testing whether these approaches can reduce adverse health consequences of type 2 diabetes, improve quality of life, and reduce the burden of illness associated with type 2 diabetes.

Figure 4. Anthropometric outcomes. (a) Percentage weight change from baseline (---, 8-week group; —△—, 16-week group; ○○○, control group). Means and standard errors of the means are shown. For the 8-week intervention group compared with the control group, \( P = 0.001 \) at 8 weeks and \( P = 0.007 \) at 16 weeks. For the 16-week intervention group compared with the control group, \( P = 0.001 \) at 8 weeks, \( P = 0.0001 \) at 20 weeks, and \( P = 0.006 \) at 28 weeks. (b) Change in waist circumference from baseline (---, 8-week group; —△—, 16-week group; ○○○, control group). Means and standard errors of the means are shown. For the 8-week intervention group compared with the control group, \( P < 0.0001 \) at 8 weeks, \( P = 0.002 \) at 16 weeks, and \( P = 0.007 \) at 20 weeks. For the 16-week group compared with the control group, \( P = 0.002 \) at 8 weeks, \( P = 0.002 \) at 16 weeks, \( P = 0.001 \) at 20 weeks, and \( P = 0.01 \) at 28 weeks.

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Author contributions: N.M. designed the study jointly with H.C.G. and Z.P., led study implementation and acquisition of data, oversaw the analyses and data interpretation, and drafted the original manuscript. A.S. implemented the study and acquired data. R.O. and J.V. delivered lifestyle intervention. Z.P. contributed to study design, D.S. contributed to study implementation, and S.H. assisted with data acquisition and analyses. K.B. conducted study analyses. H.C.G. conceived the study idea, designed the study together with N.M. and Z.P., contributed to study implementation, analyses, and interpretation of the data, and revised the manuscript. All authors contributed to critical review and revision of the manuscript.

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References


