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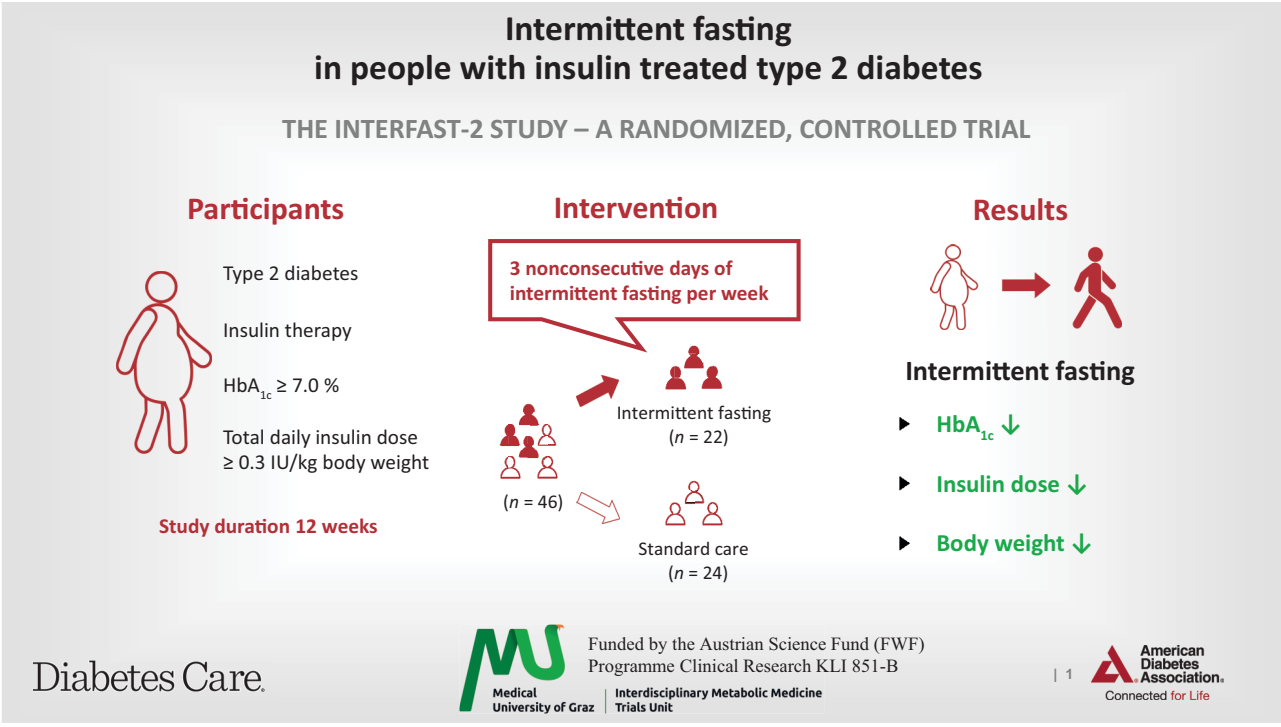

ARTICLE HIGHLIGHTS

- This study was conducted to provide robust clinical data on the effects of 12 weeks of intermittent fasting in people with insufficiently controlled insulin-treated type 2 diabetes.
- The aim of this study was to elucidate the safety and efficacy of intermittent fasting in type 2 diabetes.
- Three days of nonconsecutive intermittent fasting for 12 weeks lowered HbA_{1c}, body weight, and total daily insulin dose while improving subjective quality of life compared to a control group.
- Our findings indicate that intermittent fasting has the potential to become a promising therapy option in people with insufficiently controlled and insulin-treated type 2 diabetes.

Efficacy and Safety of Intermittent Fasting in People With Insulin-Treated Type 2 Diabetes (INTERFAST-2)—A Randomized Controlled Trial

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OBJECTIVE

To investigate the safety and feasibility of 3 nonconsecutive days of intermittent fasting (IF) per week over 12 weeks in participants with insulin-treated type 2 diabetes.

RESEARCH DESIGN AND METHODS

Forty-six people were randomized to an IF or control group. Dietary counseling and continuous glucose monitoring was provided. Coprimary end points were the change in HbA_{1c} from baseline to 12 weeks and a composite end point (weight reduction ≥2%, insulin dose reduction ≥10%, and HbA_{1c} reduction ≥3 mmol/mol).

RESULTS

The IF group showed a significant HbA_{1c} reduction (−7.3 ± 12.0 mmol/mol) compared with the control group (0.1 ± 6.1 mmol/mol) over 12 weeks ($P = 0.012$). The coprimary end point was achieved by 8 people in the IF and none in the control group ($P < 0.001$). No severe hypoglycemia occurred.

CONCLUSIONS

IF is a safe and feasible dietary option to ameliorate glycemic control while reducing total daily insulin dose and body weight in insulin-treated people with type 2 diabetes.

With the numbers of people with type 2 diabetes rising worldwide, dietary modifications provide an essential therapeutic approach for blood glucose, weight, and cardiovascular risk-factor management (1,2). Intermittent fasting (IF) has emerged as an alternative to classic daily caloric reduction (3). The approaches to IF range from limiting food consumption to certain hours of the day to alternate-day fasting (4,5). People with insulin-treated type 2 diabetes often struggle with weight gain (6), resulting in a vicious cycle of increasing insulin doses required to overcome the insulin resistance, leading to further weight gain, and ultimately resulting in higher cardiovascular risk (7). A recent meta-analysis suggested IF as an appropriate diet strategy in people with type 2 diabetes; however, the risk of hypoglycemia during fasting states in insulin-treated individuals remains a crucial barrier to adhere to diets demanding caloric restriction and further randomized controlled trials are required to verify its feasibility and safety in this population (8).

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We hypothesized that 12 weeks of IF could improve glycemic control and decrease body weight while being safe to practice in people with insulin-treated type 2 diabetes compared with a control group.

RESEARCH DESIGN AND METHODS

This open, single-center, randomized, controlled trial, Intermittent fasting in subjects with insulin-treated type 2 diabetes mellitus (INTERFAST-2), was conducted at the University Hospital Graz, Graz, Austria, and approved by the ethics committee of the Medical University of Graz, Graz, Austria (EK 30-350 ex 17/18). The detailed study protocol was published previously (9). Briefly, this study included volunteers, aged between 18 and 75 years (both inclusive), with insulin-treated type 2 diabetes, an HbA_{1c} ≥53 mmol/mol (≥7.0%), and a daily insulin dose of ≥0.3 IU/kg body wt.

The IF group practiced IF 3 days a week, reducing their calories on these days by 75% (i.e., consuming only 25% of the recommended caloric intake). Ingestion was only allowed at breakfast and/or lunch to maintain an 18-h period of fasting. Participants were asked to keep a food diary to monitor adherence. On the remaining 4 days, participants of the IF group had no caloric restriction. There was no restriction on macronutrient composition or on the consumption of water, unsweetened coffee, and tea without milk. On eating days, participants were allowed to consume any type of food or drink without any caloric restriction. Both groups had a comparable number of interactions with the study staff.

All participants were switched to the same basal insulin (insulin glargine U300) prior to the randomization. The basal insulin was administered in the morning. For fasting days, participants were instructed to reduce basal insulin by 20% and prandial insulin was only administered for glucose correctional reasons. To

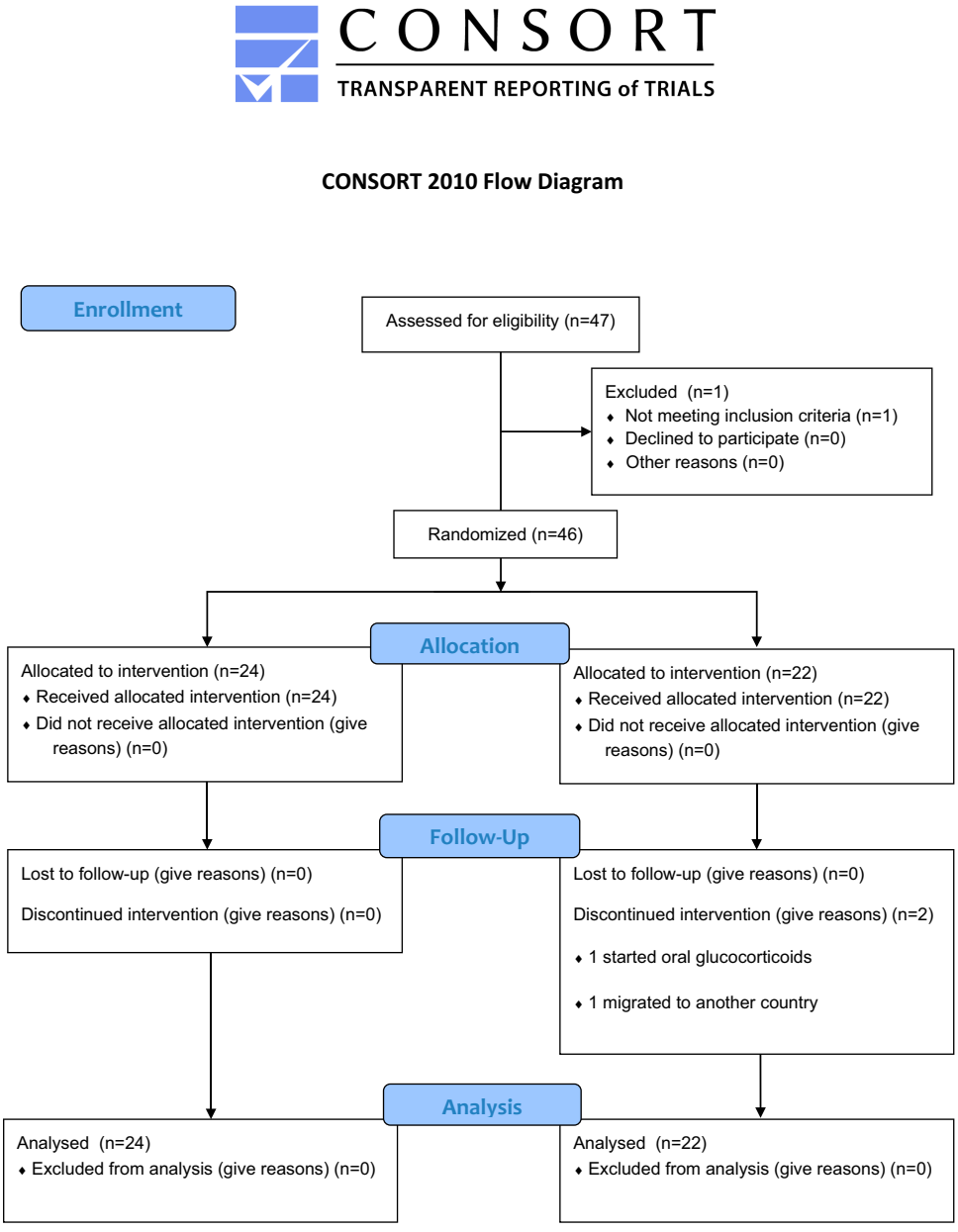

Figure 1—Trial flowchart.

reduce the risk of hypoglycemia during the IF days, participants were given an insulin dose adjustment protocol for fasting days (Supplementary Table 2). Oral nonsulfonylurea medication was continued on fasting days (9).

All participants used a FreeStyle Libre continuous glucose monitoring system (CGM; Abbott Diabetes Care, Alameda, CA) device for the 12 weeks of the study and the insulin switch phase. Data were collected using LibreView software (www.libreview.com). Lipoproteins and serum metabolites were analyzed using nuclear magnetic resonance spectroscopy (10).

We analyzed the coprimary outcomes of *1*) difference in the change in HbA_{1c} from baseline to week 12 and *2*) difference in the number of participants achieving a combined end point (weight reduction $\geq$2%, insulin dose reduction $\geq$10%, and HbA_{1c} reduction $\geq$3 mmol/mol) for the study in a hierarchical order (change in HbA_{1c} first) using an intention-to-treat approach. Continuous primary and secondary outcomes were analyzed using both unpaired *t* tests and linear mixed-effect models. A list of the predefined secondary outcomes are provided in Supplementary Table 3.

Data and Resource Availability

The data set generated during and analyzed in the study is available upon reasonable request from the corresponding author.

RESULTS

We screened 47 subjects, of whom 46 participants (22 women and 24 men) were randomized to the IF group (n = 22) or the control group (n = 24). Two participants of the IF group did not complete the intervention (Fig. 1). The mean age was 63 ± 7 years, diabetes duration was 21 ± 9 years, BMI was 34.3 ± 4.5 kg/m^2, HbA_{1c} was 67 ± 11 mmol/mol (8.3 ± 1.1%), and the mean total daily insulin dose was 56 ± 27 IU. The full details of the baseline characteristics are given in Table 1. After 12 weeks, HbA_{1c} in the IF group decreased by 7.3 ± 12.0 mmol/mol compared with an increase in the control group by 0.1 ± 6.1 mmol/mol (P = 0.012) (Fig. 2). The difference in the change in HbA_{1c} between the control and IF group remained statistically significant (P = 0.008) after adjusting for age, sex, diabetes duration, and baseline HbA_{1c}. The mean time above range over the entire 12 weeks was significantly lower in the IF group (30.4 ± 20.9%) than in the control group (42.1 ± 16.1%, P = 0.029). The mean time in range was significantly higher in the IF group (68.0 ± 20.2%) compared with the control group (56.6 ± 16.0%, P = 0.031), while the mean time below range over the 12 weeks was similar in the IF (1.6 ± 2.0%) and the control group (1.3 ± 2.2%, P = 0.334) (Supplementary Fig. 1).

Table 1—General characteristics at baseline

	All (n = 46)	Control (n = 24)	Fasting (n = 22)
Age (years)	63 ± 7	61 ± 7	65 ± 6*
Male sex	24 (52)	14 (58)	10 (46)
Duration of diabetes (years)	21 ± 9	18 ± 7	24 ± 10*
Weight (kg)	100 ± 15	104 ± 13	96 ± 16
Height (m)	1.71 ± 0.09	1.72 ± 0.09	1.70 ± 0.07
BMI (kg/m^2)	34.3 ± 4.5	35.0 ± 4.3	33.5 ± 4.7
HbA_{1c} (%)	8.3 ± 1.1	8.2 ± 1.0	8.5 ± 1.2
HbA_{1c} (mmol/mol)	67 ± 11	66 ± 10	69 ± 12
Total daily insulin dose (IU)	56 ± 27	59 ± 33	52 ± 19
Fasting glucose (mg/dL)	174 ± 44	176 ± 41	173 ± 47
Total cholesterol (mg/dL)	163 ± 45	164 ± 41	162 ± 51
HDL cholesterol (mg/dL)	48 ± 17	42 ± 15	57 ± 17*
LDL cholesterol (mg/dL)	81 ± 35	81 ± 32	80 ± 39
Blood pressure systolic (mmHg)	141 ± 22	145 ± 23	136 ± 19
Blood pressure diastolic (mmHg)	82 ± 10	85 ± 10	80 ± 10
Other glucose-lowering medication			
GLP-1RA	20 (43)	11 (46)	9 (41)
SGLT-2 inhibitors	20 (43)	9 (38)	11 (50)
DPP4-inhibitors	14 (30)	5 (21)	9 (41)
Metformin	34 (74)	17 (71)	17 (77)
Comorbidities			
Hypertension	39 (85)	18 (75)	21 (96)
Heart failure	5 (11)	1 (4)	4 (18)
Coronary artery disease	12 (26)	6 (25)	6 (27)
History of myocardial infarction	10 (22)	3 (13)	7 (32)
History of stroke	2 (4)	2 (8)	0 (0)
Retinopathy	10 (22)	5 (21)	5 (23)
Polyneuropathy	18 (39)	11 (46)	7 (32)
Amputation	2 (4)	1 (4)	1 (5)
Hyperlipidemia	41 (89)	21 (88)	20 (91)

Categorical data are presented as n (%), and continuous variables are presented as mean ± SD. DPP4, dipeptidyl peptidase 4; GLP1-RA, glucagon-like peptide 1 receptor agonist; SGLT-2, sodium–glucose linked transporter 2. *$P < 0.05$.

After 12 weeks, 8 participants (40%) in the IF group achieved the composite coprimary end point compared with none of the participants in the control group ($P < 0.001$) (Fig. 3). The same number of participants in the IF group (n = 8 [40%]) achieved the combined end point when higher thresholds were applied (at least 3% weight loss, at least 0.5% HbA_{1c} reduction, and at least 10% insulin dose reduction).

After 12 weeks of intervention, the IF group showed a significant reduction in weight (4.77 ± 4.99 kg) compared with the control group (+0.27 ± 1.34 kg, $P <$ 0.001) and in fat mass (3.5 ± 3.3 kg in the IF group and +0.1 ± 1.3 kg in the control group, $P < 0.001$). There was no statistically significant difference in the change in lean mass or bone mass between the two groups according to the DXA measurements.

The resting metabolic rate (RMR) was not different between the IF and control group, both at baseline (IF: 2,286 ± 357 kcal, control: 2,439 ± 375 kcal) and after

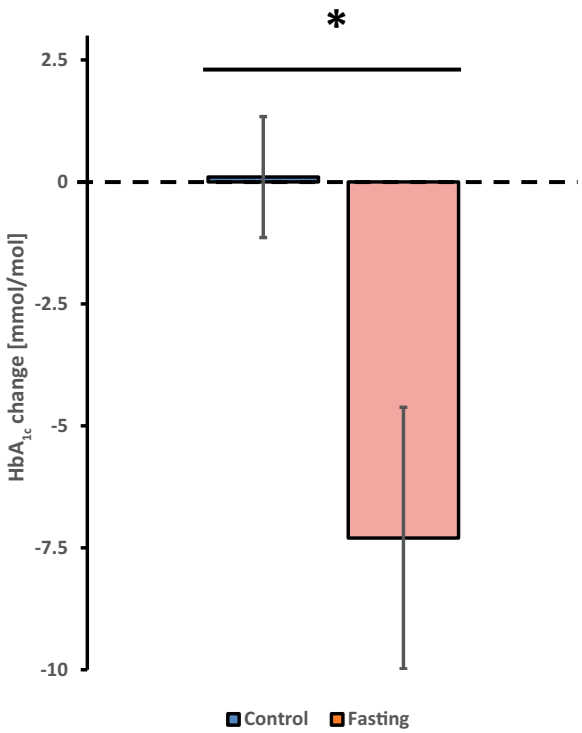

Figure 2—Change in HbA_{1c} from baseline to 12 weeks in control and IF group. Data are displayed as mean ± SEM. *P = 0.012.

12 weeks (IF: 2,248 ± 331 kcal, control: 2,429 ± 398 kcal). No difference was observed in the change of the RMR from baseline to 12 weeks between the two groups (P = 0.735). Likewise, no difference was observed in the change of the physical activity levels between the groups (P = 0.541). The mean total daily dose of insulin at baseline was 52 ± 19 IU in the IF group and 59 ± 33 IU in the control group. At 12 weeks, the IF group had an insulin dose of 45 ± 19 IU while the control group had an insulin dose of 63 ± 35 IU, resulting in a total daily insulin dose reduction in the IF group over 12 weeks by 9 ± 10 IU as opposed to the control group with an increase by 4 ± 10 IU (P = 0.008). A significant difference in the change of perceived health (EuroQol-5D visual analog scale) between the IF (from 70 ± 20 to 74 ± 21) and control group (from 70 ± 20 to 65 ± 23) was observed (P = 0.043).

Results of nuclear magnetic resonance–based metabolomics analysis showed the metabolites most contributing to the difference between fasting and control subjects included acetic acid, dimethylsulfone, and some ketone bodies (acetoacetic acid, 3-hydroxybutyric acid, and acetone). Of all 35 metabolites investigated, only acetic acid (probably derived from fatty acid metabolism) significantly increased in fasting individuals (32 ± 10 μmol/L vs. 19 ± 8 μmol/L, fold-change, 1.68; P_{adj} = 0.002) (Supplementary Fig. 2).

Of the 22 participants in the IF group, 20 (91%) achieved >75% adherence to the given fasting protocol.

During the study period, five serious adverse events leading to hospitalization were reported, two in the IF group and three in the control group. None of the serious adverse events were considered to be related to the study intervention.

CONCLUSIONS

We demonstrated that 3 days of nonconsecutive IF per week over the duration of 12 weeks improved HbA_{1c}, reduced body weight, and led to a total daily insulin dose reduction in people with insulin-treated type 2 diabetes.

Our data are in line with previous studies showing that IF was effective in HbA_{1c} reduction in people with type 2 diabetes (11). Li et al. (12) also reported data from a 7-day fasting program with a maximum intake of 300 kcal to reduce body weight in participants with type 2 diabetes; however, participants with intensified insulin treatment were excluded. Hence, our study extends previous beneficial effects on body weight and glycemic control to people with type 2 diabetes treated with insulin. Recent meta-analyses demonstrated similar HbA_{1c}-reducing potential of IF compared with continuous calorie restriction in people with type 2 diabetes, while the weight loss appeared to be more pronounced (8,13) with IF. Mechanistic studies suggest that prolonged fasting might have additional beneficial metabolic effects, independent of weight loss, by switching the metabolism to fatty acid mobilization, β-oxidation, and enhanced ketone body production or inducing autophagy (14).

From a clinical perspective, for some individuals, IF appears to be an easy to apply dietary intervention without the need for continuous caloric reductions, ultimately leading to reduced caloric intake through the time-restricted eating pattern without vigorous documentation or calorie counting (15,16). As demonstrated in our study, the risk of hypoglycemia during IF can be mitigated by reducing the insulin dose on fasting days and using a CGM system, as previously observed during Ramadan fasting (17). However, it appears critical that participants and health care personnel are instructed on insulin dose adjustments during IF.

One of the limitations of dietary studies on glycemic parameters in insulin-treated individuals with type 2 diabetes is that glucose control, body weight reduction, and insulin dose are interrelated and that changes in the insulin dose can alter the observed HbA_{1c}. For this reason, we chose a coprimary outcome besides HbA_{1c} to investigate changes in HbA_{1c} along with weight and insulin dose. A limitation of our study is the intermittently scanned (is)CGM was introduced in 16 participants in the control group and in 13 in the IF group at study start and that the isCGM use was not blinded to the participants, which might have influenced the eating behavior of the participants in both groups. Finally, participants were allowed to eat up to 25% of the recommended daily caloric intake on the fasting days as breakfast and/or lunch, which was originally introduced to reduce hypoglycemic risk and increase adherence to the study protocol in people with insulin-treated type 2 diabetes. With our study data we would feel confident to omit this caloric intake in further studies.

Strengths of the study include its randomized controlled design in people with type 2 diabetes using a basal bolus insulin regimen with a reproducible insulin

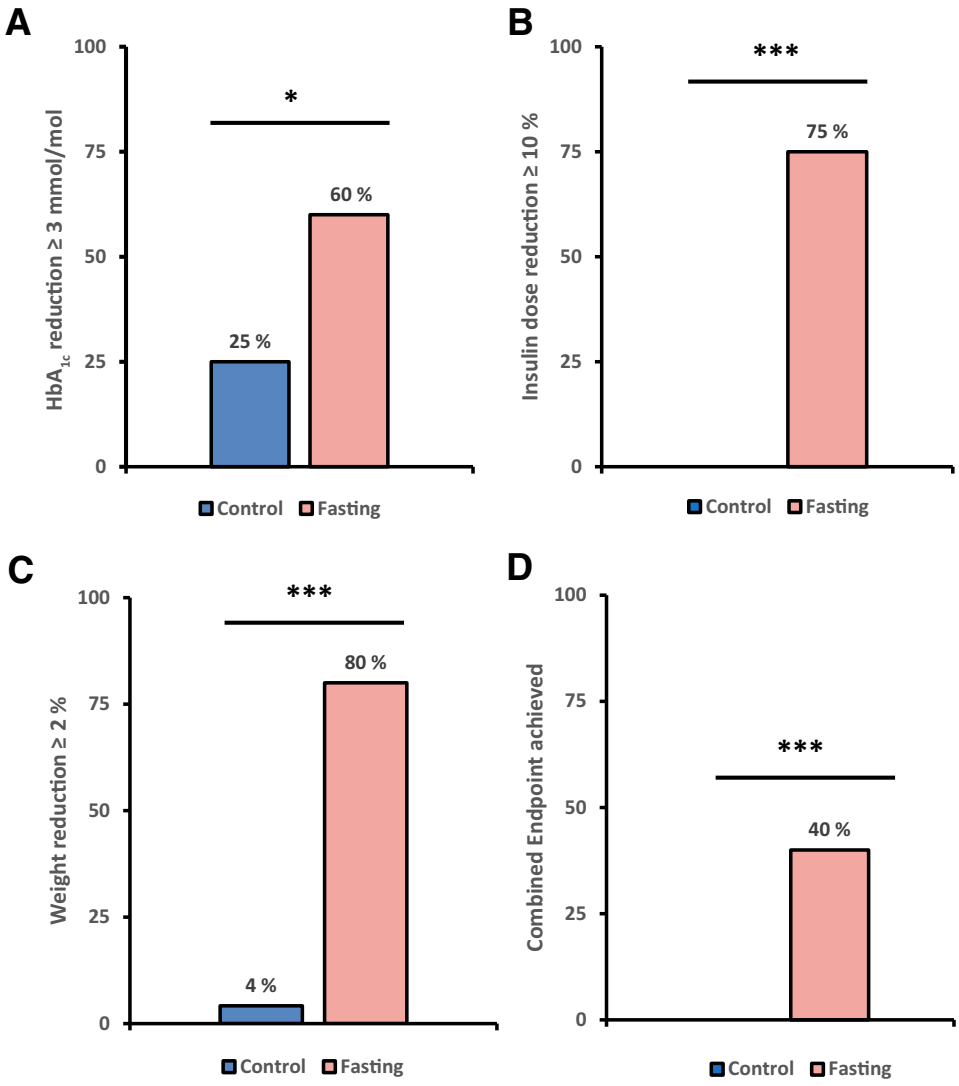

Figure 3—Coprimary end point; percentage of participants achieving each individual aspect and the combined coprimary end point. *$P < 0.05$, ***$P < 0.001$.

dosing adjustment algorithm together with isCGM data and metabolomics analysis of IF induced changes. We also monitored the RMR and physical activity throughout the study, which remained unchanged.

Our data demonstrate that IF over 12 weeks in insulin-treated people with type 2 diabetes is safe, reduces HbA_{1c}, body weight, and total daily insulin dose, while RMR and the physical activity levels remained unaltered.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. A.Ob. wrote the final manuscript. A.Ob. and N.J.T. contributed to efficient project management and day-to-day operation. A.Ob., N.J.T., P.N.P., H.K., F.Az., A.M., F.Ab., C.S., T.P., B.O.-P., and V.S. contributed to collection, analysis, and interpretation of data. A.Ob., F.Az., and A.Ou. contributed to the statistical analysis. N.J.T. and H.S. significantly contributed to development of the study protocol. N.J.T. and H.S. contributed to acquiring ethical approval for the trial. F.Az., A.M., and H.S. had access to and verified the raw data. M.S. is the dietitian of the trial. H.H. and T.M. performed the metabolomics analysis. H.S. conceived the trial. All authors reviewed and contributed to the final manuscript. A.Ob. and H.S are the guarantors of this work and, as such, had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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