Effects of Low-Energy Diet or Exercise on Cardiovascular Function in Working-Age Adults With Type 2 Diabetes: A Prospective, Randomized, Open-Label, Blinded End Point Trial

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OBJECTIVE

To confirm the presence of subclinical cardiovascular dysfunction in working-age adults with type 2 diabetes (T2D) and determine whether this is improved by a low-energy meal replacement diet (MRP) or exercise training.

RESEARCH DESIGN AND METHODS

This article reports on a prospective, randomized, open-label, blinded end point trial with nested case-control study. Asymptomatic younger adults with T2D were randomized 1:1:1 to a 12-week intervention of *1*) routine care, *2*) supervised aerobic exercise training, or *3*) a low-energy (~810 kcal/day) MRP. Participants underwent echocardiography, cardiopulmonary exercise testing, and cardiac magnetic resonance (CMR) at baseline and 12 weeks. The primary outcome was change in left ventricular (LV) peak early diastolic strain rate (PEDSR) as measured by CMR. Healthy volunteers were enrolled for baseline case-control comparison.

RESULTS

Eighty-seven participants with T2D (age 51 ± 7 years, HbA_{1c} 7.3 ± 1.1%) and 36 matched control participants were included. At baseline, those with T2D had evidence of diastolic dysfunction (PEDSR 1.01 ± 0.19 vs. 1.10 ± 0.16 s^{-1}, $P = 0.02$) compared with control participants. Seventy-six participants with T2D completed the trial (30 routine care, 22 exercise, and 24 MRP). The MRP arm lost 13 kg in weight and had improved blood pressure, glycemia, LV mass/volume, and aortic stiffness. The exercise arm had negligible weight loss but increased exercise capacity. PEDSR increased in the exercise arm versus routine care ($\beta = 0.132$, $P = 0.002$) but did not improve with the MRP ($\beta = 0.016$, $P = 0.731$).

CONCLUSIONS

In asymptomatic working-age adults with T2D, exercise training improved diastolic function. Despite beneficial effects of weight loss on glycemic control, concentric LV remodeling, and aortic stiffness, a low-energy MRP did not improve diastolic function.

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Heart failure has emerged as one of the most common and deadly complications of type 2 diabetes (T2D) (1). This is especially the case in younger adults with T2D, who have the highest lifetime risk of cardiovascular disease, where the risk of heart failure development is four- to fivefold higher than in matched control subjects (2). Importantly, American Heart Association stage B (subclinical) heart failure is highly prevalent (present in up to one-third) in people with T2D (3,4). We have previously demonstrated that there is already evidence of subclinical diastolic impairment in young adults (mean age 32 years) with T2D, despite their young age and relatively short duration of disease (5). This is a known precursor of symptomatic heart failure (6), with the majority developing heart failure with preserved ejection fraction, a condition with no effective treatments (3). It is therefore imperative to find strategies that prevent heart failure in T2D, specifically targeting younger adults before symptoms develop and when cardiac dysfunction is likely to be reversible.

Lifestyle interventions, such as dietary modifications or exercise training, may have a pivotal role in preventing the development of clinical heart failure in younger adults with T2D. It has been established that reversal of T2D can be achieved with weight loss through a low-energy meal replacement plan diet (MRP) (7), while exercise training also leads to modest, but sustained improvements in glycemic control, improvements in insulin resistance, and improved cardiovascular fitness, even in the absence of accompanying weight loss (8,9). Whether weight loss or exercise training improve subclinical cardiac dysfunction in people with T2D, however, is not known. There have been no randomized controlled trials assessing the impact of an MRP on cardiac function in T2D, and the results of trials in exercise training have been inconsistent (10). The aims of this study were *1*) to confirm the presence and nature of subclinical cardiovascular dysfunction in working-age adults with T2D and *2*) to determine whether diastolic function can be improved by either a low-energy MRP or a supervised aerobic exercise program compared with routine care.

RESEARCH DESIGN AND METHODS

Study Design

The rationale and study design and conduct, including details of participant recruitment and planned analyses, have been published previously (11). In brief, this was a single-center, prospective, randomized, open-label, blinded end point trial with a nested case-control study at the National Institute for Health Research (NIHR) Leicester Biomedical Research Centre. Ethical approval was granted by the National Research Ethics Service (15/WM/0222).

Participants

Eligible participants were aged 18–65 years with established T2D (duration $\geq$3 months) diagnosed before age 60 years and BMI $>$30 kg/m^2 (or $>$27 kg/m^2 if South Asian or black ethnicity). Key exclusion criteria were T2D duration $>$12 years; current treatment with more than three glucose-lowering medications or insulin; history, signs, or symptoms of cardiovascular disease (including coronary artery disease, stroke, transient ischemic attack, peripheral artery disease, or heart failure); weight loss $>$5 kg in the preceding 6 months; and inability to exercise or undertake the MRP. A list of the complete study inclusion and exclusion criteria is provided in the protocol (11). Healthy volunteers free of T2D, obesity, hypertension, or prevalent cardiovascular disease were recruited for baseline case-control comparison. All participants provided written informed consent.

Participants with T2D underwent two main study assessment visits: at baseline and 12 weeks (see below). Control participants underwent the same assessments but at baseline only. Each participant was assigned a unique identification number upon recruitment. Participant details and anonymized source data were entered separately by members of the research team at site into an independent web-based database created by the Leicester Clinical Trials Unit and were only accessible to arrange follow-up visits by members of the study team.

Randomization and Blinding

Participants with T2D were randomized at the end of the baseline visit in a 1:1:1 ratio, using an independent online computerized randomization system incorporating concealed allocation (Sealed Envelope) to one of three arms: *1*) routine care as per National Institute for Health and Care Excellence (NICE) guidance (12), *2*) a supervised aerobic exercise program, or *3*) a low-energy (~810 kcal/day) MRP. Randomization was stratified by sex and baseline glucose-lowering therapy (any glucagon-like peptide 1 agonist, dipeptidyl peptidase 4 inhibitor, or sodium–glucose cotransporter 2 inhibitor vs. none of these agents). The nature of the trial interventions prevented blinding of allocation.

Assessments

Demographics, medical history, and anthropometric measures were collected at the assessment visits. A fasting blood sample was collected to obtain a biochemical profile for diabetes control, liver and kidney function, lipid profile, adiposity, insulin, and C-peptide. Insulin resistance was estimated using the HOMA for insulin resistance (HOMA-IR) method (13). Participants in the MRP arm with a fasting glucose of $<$7.0 mmol/L or HbA_{1c} $<$6.5% without taking any hypoglycemic agent postintervention were considered to have remission of T2D (14).

Cardiovascular Magnetic Resonance

Comprehensive cardiovascular magnetic resonance (CMR) scanning was performed on a 1.5T field strength scanner (MAGNETOM Aera; Siemens, Erlangen, Germany) using a standardized protocol (11). CMR images were analyzed offline while blinded to all patient details and treatment group. Cardiac chamber volumes, function, and strain were assessed by a single experienced observer (G.S.G.) using cmr42 version 5 (Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Aortic distensibility was analyzed by two experienced operators (G.S.S. and K.S.P.) using Java Image Manipulation version 6 (Xinapse Software, Essex, U.K.).

Transthoracic Echocardiography

Transthoracic echocardiography was performed and interpreted by two accredited operators (A.-M.M and J.M.) using an iE33 system with S5-1 transducer (Philips Medical Systems, Best, the Netherlands). Images were acquired and reported per American Society of Echocardiography guidelines (15). Early diastolic transmitral flow velocity (E) and early diastolic mitral annular velocity (e′) to estimate LV filling pressures were assessed by Doppler echocardiography per current recommendations (16).

Cardiopulmonary Exercise Testing

A symptom-limited incremental cardiopulmonary exercise test was performed on a stationary, electromagnetically braked cycle ergometer (eBike; GE Healthcare,

Bedford, U.K.) with expired gas analysis (GANSHORN PowerCube; GE Healthcare) to determine peak VO_2 (17).

Trial Interventions

Routine Care

Standard lifestyle advice was provided in a single coaching interview at week 0 along with signposting to freely available National Health Service resources in accordance with NICE guidance (12). Optimization of blood pressure and glucose-lowering medications was undertaken by a study clinician at baseline in accordance with NICE guidance (12).

Supervised Exercise Program

Participants attended thrice weekly, supervised, moderate-intensity aerobic exercise sessions. Exercise sessions consisted of a warm-up, stimulus, and cool-down phase. The stimulus phase included walking and/or lower-extremity cycling. Exercise intensity was titrated to ~60% baseline peak VO_2 and heart rate. The total exercise duration was gradually increased to achieve a target of 50 min per session. Objective (heart rate monitoring) and subjective (Borg Scale of Perceived Exertion) measures were used to evaluate the response to exercise sessions and to adjust exercise intensity in accordance with increasing fitness levels throughout the intervention period. Compliance was assessed by attendance at the supervised exercise sessions. Participants who attended fewer than two-thirds of the exercise sessions were considered noncompliant and excluded from the study. Participants were asked to maintain their usual dietary intake.

Low-Energy MRP

The low-energy MRP comprised an average of ~810 kcal/day (30% protein, 50% carbohydrate, and 20% fat) (Cambridge Weight Plan). Participants were asked to discontinue all glucose-lowering therapies following randomization to avoid hypoglycemia. Antihypertensive medications were stopped on the day of commencement. Blood pressure and glucose were monitored throughout the trial by a study clinician. Participants were advised to maintain their usual daily activities while on the diet and asked not to initiate any additional physical activity for the duration of the intervention. The diet was discontinued and a maintenance diet introduced once 50% excess body weight had been lost or by 12 weeks, whichever came first. Participants who did not achieve a loss of >2% body weight at week 1 and 4% at week 3 were considered noncompliant and were excluded from the study.

Outcomes

The primary outcome was a measure of diastolic function: change in left ventricular (LV) peak early diastolic strain rate (PEDSR) (an index of the speed of myocardial relaxation), as measured by CMR, from baseline to 12 weeks in the two intervention arms (MRP and exercise) compared with routine care. Key secondary outcomes were change in echocardiographic measures of diastolic function (early diastolic to late filling ratio [E/A] and noninvasive estimate of LV filling pressure [E/e']). Additional secondary outcomes were CMR measures of cardiac structure and function (LV mass and volumes, global longitudinal strain), myocardial perfusion reserve, aortic stiffness (distensibility), and peak VO_2 (11).

Power Calculation

The trial sample size calculation was determined according to published pilot data from our group (5). To detect a between-group difference in PEDSR of 0.2 s^{-1} post-intervention, at least 21 participants with T2D completing each of the three trial arms were needed to provide 80% power at $\alpha = 0.025$ (to allow for two primary comparisons, i.e., MRP vs. routine care and exercise vs. routine care). Assuming a maximum dropout rate of 30%, we targeted recruitment of 30 patients per group at baseline.

Statistical Analysis

Statistical analyses were performed by an independent trial statistician (N.B.J.) at the Leicester Clinical Trials Unit. Normality was assessed using histograms, the Shapiro-Wilk test, and Q-Q plots. Continuous data are expressed as mean ± SD if normally distributed or median (25–75% interquartile range) if not. At baseline, patient and control groups were compared by independent *t* tests or Mann-Whitney tests as appropriate. Categorical variables were compared using the χ^2 test or Fisher exact test as appropriate. For the analysis of the primary outcome, each intervention was compared with the routine care arm using linear regression adjusted for stratification factors (sex and baseline glucose-lowering therapy) and baseline PEDSR. The treatment effect was presented as a point estimate, CI, and *P* value. A Holm-Bonferroni correction was applied for the primary outcome to maintain an overall familywise error rate of 5%. If the treatment effect for the models for the two primary comparisons had $P \geq 0.025$, then they were both declared nonsignificant. If at least one model had $P < 0.025$, then the threshold for significance was $P < 0.025$ for the smaller *P* value and $P < 0.05$ for the larger *P* value. Changes in the key secondary outcomes (E/A and E/e') were also assessed using linear regression with the same stratification factors as the primary outcome. Given the large number of additional secondary outcomes, formal statistical testing was not undertaken on these parameters, but changes between baseline and follow-up are presented with 95% CIs. Statistical analysis was done using STATA 15 software (StataCorp, College Station, TX).

RESULTS

The trial profile is displayed in Supplementary Fig. 1. Between November 2015 and May 2018, 260 patients were screened of whom 93 consented and enrolled. Three were found to be ineligible after consent, and 90 were randomized as follows: 30 to routine care, 31 to the supervised exercise program, and 29 to MRP. Three of these participants (two in the exercise arm and one in the MRP arm) were found to be ineligible after laboratory test results became available and did not undertake the intervention. A total of 76 patients with T2D completed the trial (30 in the routine care arm, 22 in the exercise arm, and 24 in the MRP arm). Reasons for discontinuation are shown in Supplementary Fig. 1. Thirty-nine healthy volunteers were enrolled for baseline case-control comparison. Three of these were subsequently excluded (one because of the presence of obesity and two who were unable to undergo CMR scanning because of claustrophobia). A total of 36 healthy volunteers were therefore included in the case-control comparisons.

Baseline Characteristics

The baseline demographic characteristics of participants with T2D and control participants are shown in Table 1. Mean age of participants with T2D was 50.5 ± 6.5 years, mean BMI was 36.6 ± 5.5 kg/m^2, median duration of diabetes was 56 (32–94) months, 41% were women, and 37% were from a minority ethnic group. The control group was similar for age,

sex, and ethnicity but had lower overall body weight and BMI. Among those with T2D, 43% had a history of smoking, and 52% had a history of hypertension. None of the control participants had a history of hypertension or dyslipidemia. Antihypertensive and lipid-lowering medication use was therefore higher in participants with T2D compared with control participants.

Fasting blood test results are displayed in Table 1. Both the T2D and the healthy control groups had similar renal function. Participants with T2D had higher overall HbA_{1c} (7.3 ± 1.0 vs. 5.4 ± 0.2%, $P < 0.001$), lower total cholesterol (4.6 ± 1.0 vs. 5.7 ± 0.8 mmol/L, $P < 0.001$), and lower LDL cholesterol (2.4 ± 0.8 vs. 3.3 ± 0.8 mmol/L, $P < 0.001$) than control participants. Adiponectin levels were significantly lower and leptin levels significantly higher (both $P < 0.001$) in the T2D versus control group. Fasting C-peptide and insulin levels were significantly higher (both $P < 0.001$) in T2D versus control. Similarly, overall HOMA-IR was higher in T2D versus control (9.2 [6.2–13.5] vs. 1.6 [1.1–2.5], respectively, $P < 0.001$). Brain natriuretic peptide (BNP) levels were significantly lower in T2D versus control (10.6 [4.5–17.9] vs. 16.0 [8.7–22.6] ng/L, respectively, $P = 0.048$).

Cardiovascular Differences Between the T2D and Control Groups

Baseline CMR imaging, cardiopulmonary exercise testing, and echocardiography data comparing the T2D and control groups are displayed in Table 1. LV PEDSR was significantly lower in T2D than control (1.01 ± 0.19 vs. 1.10 ± 0.16, respectively, $P = 0.02$). Participants with T2D also had smaller indexed LV volumes, a higher LV ejection fraction, and higher LV mass than control participants. In those with T2D, there was increased concentric LV remodeling (LV mass:volume 0.82 ± 0.12 vs. 0.71 ± 0.10 g/mL, $P < 0.001$) and lower mean aortic distensibility (4.16 ± 2.05 vs. 6.56 ± 2.02 $mmHg^{-1} \times 10^{-3}$, $P < 0.001$) than control participants. There were no significant differences in indexed LV mass or global longitudinal strain between groups. Myocardial perfusion reserve was lower in the T2D group than in the control group.

Complete echocardiographic transmitral flow velocities were measurable in

Table 1—Baseline bioanthropometrics, CMR, cardiopulmonary exercise testing, and echocardiographic data in participants with T2D vs. control participants

	T2D (n = 87)	Control (n = 36)	P value
Demographics			
Age (years)	50.5 ± 6.5	48.6 ± 6.2	0.15
Sex			
Male	51 (59)	19 (53)	0.552
Female	36 (41)	17 (47)	
Ethnic origin			
Caucasian	55 (63)	25 (69)	0.51
Black or other minority ethnicity	32 (37)	11 (31)	
Anthropometrics			
Height (cm)	168 ± 10	169 ± 9	0.54
Weight (kg)	103.3 ± 16.7	70.4 ± 10.8	**<0.001**
BMI (kg/m^2)	36.6 ± 5.5	24.5 ± 2.4	**<0.001**
Systolic blood pressure (mmHg)	140 ± 15	121 ± 13	**<0.001**
Diastolic blood pressure (mmHg)	87 ± 8	76 ± 7	**<0.001**
Heart rate (beats/min)	74 ± 10	62 ± 10	**<0.001**
Medical history			
Diabetes duration (months)	56 (32–94)	NA	NA
Smoking history	39 (45)	9 (25)	**<0.001**
Hypertension	44 (51)	0 (0)	**<0.001**
Dyslipidemia	56 (64)	0 (0)	**<0.001**
Medications			
ACE inhibitor	28 (32)	0 (0)	**<0.001**
ARB	11 (13)	0 (0)	**0.025**
β-blocker	6 (7)	0 (0)	0.106
Calcium channel blocker	19 (22)	0 (0)	**0.002**
Statin	58 (67)	0 (0)	**<0.001**
Metformin	82 (94)	NA	NA
Sulfonylurea	13 (15)	NA	NA
DPP-4 inhibitor	17 (20)	NA	NA
SGLT2 inhibitor	10 (11)	NA	NA
GLP-1 receptor agonist	10 (11)	NA	NA
Fasting blood tests			
Urea (mmol/L)	5.4 ± 1.2	5.2 ± 1.4	0.59
Creatinine (mmol/L)	76 ± 15	79 ± 12	0.332
Estimated GFR ($mL/min/1.73\ m^2$)	90 (80–90)	85 (78–90)	0.122
Glucose (mmol/L)	7.6 (6.6–10.1)	5.0 (4.6–5.2)	**<0.001**
HbA_{1c} (%)	7.3 ± 1.0	5.4 ± 0.2	**<0.001**
HbA_{1c} (mmol/mol)	56 ± 11	35 ± 3	**<0.001**
Total cholesterol (mmol/L)	4.6 ± 1.0	5.7 ± 0.8	**<0.001**
Triglycerides (mmol/L)	1.88 (1.18–2.74)	0.98 (0.72–1.54)	**<0.001**
HDL (mmol/L)	1.2 (1.0–1.4)	1.7 (1.6–2.0)	**<0.001**
LDL (mmol/L)	2.4 ± 0.8	3.3 ± 0.8	**<0.001**
HDL cholesterol (mmol/L)	3.9 ± 0.9	3.3 ± 0.8	**<0.001**
Hemoglobin (g/L)	144 ± 16	141 ± 14	0.279
Adiponectin (ng/L)	3,460 (2,550–5,652)	9,514 (4,820–14,589)	**<0.001**
Leptin (pg/L)	18,911 (9,821–34,115)	4,811 (2,400–9,818)	**<0.001**
C-peptide (ng/L)	2,591 (1,865–3,371)	969 (743–1,199)	**<0.001**
Insulin (mIU/L)	26.5 (18.8–35.8)	7.4 (4.9–10.4)	**<0.001**
HOMA-IR	9.2 (6.2–13.5)	1.6 (1.1–2.5)	**<0.001**
BNP (ng/L)	10.6 (4.5–17.9)	16.0 (8.7–22.6)	**0.048**
CMR			
LV EDVi (mL/m^2)	67 ± 10	83 ± 19	**<0.001**
LV EF (%)	68 ± 7	65 ± 5	**0.016**
LV mass (g)	121 ± 25	107 ± 32	**0.011**
LV mass index (g/m^2)	55 ± 9	58 ± 14	0.133
LV mass:volume (g/mL)	0.82 ± 0.12	0.71 ± 0.10	**<0.001**
LV global longitudinal strain (%)	−16.9 ± 2.6	−17.6 ± 1.5	0.179
LV PEDSR (s^{-1})	1.01 ± 0.19	1.10 ± 0.16	**0.02**
Myocardial perfusion reserve	3.02 ± 0.98	3.98 ± 1.01	**<0.001**
Aortic distensibility ($mmHg^{-1} \times 10^{-3}$)	4.16 ± 2.05	6.56 ± 2.02	**<0.001**

Continued on p. 1304

Table 1—Continued

	T2D (n = 87)	Control (n = 36)	P value
Echocardiography			
E/A	0.95 ± 0.21	1.21 ± 0.25	**<0.001**
Average E/e′	8.1 (6.2–9.6)	6.2 (5.0–7.8)	**<0.001**
Cardiopulmonary exercise testing			
Maximum workload achieved (W)	125 ± 47	173 ± 67	**<0.001**
Peak VO_2 (mL/kg/min)	16.6 ± 4.1	27.5 ± 8.2	**<0.001**
Peak VO_2 (L/min)	1.70 ± 0.46	1.96 ± 0.73	**0.019**

Data are n (%), mean ± SD, or median (interquartile range). ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase 4; EDVi, end-diastolic volume indexed to body surface area; EF, ejection fraction; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide 1; NA, not applicable; SGLT2, sodium–glucose cotransporter 2. Bold typeface highlights P values <0.05.

84 participants with T2D and all 36 control participants. Mean E/A was significantly lower in the T2D group than in the control group (0.95 ± 0.21 vs. 1.21 ± 0.25, respectively, $P < 0.001$). Mitral annular velocities were measurable in 78 participants with T2D and all 36 control participants. Overall, average E/e′ was higher in the T2D group than in the control group (8.1 [6.2–9.6] vs. 6.2 [5.0–7.8], respectively, $P < 0.001$) (Table 1). All measures of cardiorespiratory fitness (maximum workload achieved, absolute and body weight–corrected peak VO_2) were lower in the T2D versus control group (Table 1).

Prospective, Randomized, Open-Label, Blinded End Point Trial

The baseline demographic characteristics and prescribed diabetes and antihypertensive medications of participants stratified by treatment arm in the trial are shown in Supplementary Table 1. The three groups were well balanced.

Changes in Bioanthropometric Measures, Physical Activity, and Cardiorespiratory Fitness Indices With Interventions

Changes from baseline to 12 weeks in anthropometric measures, biochemical parameters, and cardiorespiratory fitness in participants who completed the study are shown in Table 2. In the routine care arm, body weight remained stable, and there were no significant changes in body composition measures (BMI and waist-to-hip ratio). Markers of insulin resistance and glycemic control remained similar from baseline to 12 weeks. Mean systolic blood pressure dropped by 7 mmHg, driven by a guideline-directed increase in the doses of existing prescribed antihypertensive medications. Cardiopulmonary fitness did not change.

In the exercise arm, there were small reductions in body weight (median weight loss 1.6 kg) and BMI (median reduction 0.8 kg/m^2). There was no significant change in glycemic control, insulin resistance, or blood pressure. Although there was no significant change in peak VO_2 by week 12, participants' total exercise duration and maximum workload achieved did increase (by 1.2 min and 22 W, respectively).

In the MRP arm, median weight loss was 13.6 kg, BMI fell by 4.8 kg/m^2, and mean systolic blood pressure dropped by 13 mmHg, despite a reduction in the number and/or dose of antihypertensives taken. Median HbA_{1c} decreased by 0.75% (7.5 mmol/mol), with 20 (83%) participants achieving T2D remission. There was a nonsignificant trend for adiponectin to increase, and median leptin decreased by 9,873 pg/mL, median HOMA-IR decreased by 6 units, and median BNP increased by 3.5 ng/L. There was a small increase in peak VO_2 when corrected for body weight (1.9 mL/kg/min) but not in absolute peak VO_2. Other measures of cardiorespiratory fitness did not change.

Primary and Key Secondary Cardiac Outcomes

Changes in the primary end point from baseline to 12 weeks are displayed in Fig. 1. For the primary outcome measure, participants in the supervised exercise program arm demonstrated a significant improvement in PEDSR compared with those in the routine care arm of the trial ($\beta = 0.132$ [97.5% CI 0.038, 0.225], $P = 0.002$). No improvement in PEDSR was observed in participants in the MRP arm versus those in the routine care arm of the trial ($\beta = 0.016$ [95% CI −0.075, 0.106], $P = 0.731$).

Average E/e′ and E/A could be obtained in 63 (83%) and 70 (92%) participants who completed the trial, respectively. E/A and E/e′ tended to improve in both intervention arms, but these changes were not statistically significant compared with the routine care arm (average E/e′ in the exercise arm of the trial vs. the routine care arm at 12 weeks: $\beta = -0.459$ [95% CI −1.452, 0.534], $P = 0.355$; E/A: 0.028 [95% CI −0.086, 0.142], $P = 0.621$). Similarly, there was no difference in average E/e′ in the MRP arm versus routine care at 12 weeks (−0.060 [95% CI −1.099, 0.978], $P = 0.907$) or E/A (0.036 [95% CI −0.090, 0.161], $P = 0.568$).

Key secondary cardiac imaging end points are displayed in Table 3. In the routine care arm and the exercise arm, there were negligible changes in most cardiac parameters. In the MRP arm, there was a trend toward a reduction in LV mass (mean reduction 5.6 g), and indexed LV end diastolic volume increased by 5 mL/m^2, with a corresponding reduction in concentric LV remodeling (mean change −0.03 g/mL [95% CI −0.06, −0.01]). Aortic distensibility increased by 0.90 $mmHg^{-1} \times 10^{-3}$ (95% CI 0.38, 1.41). With regard to systolic function, there was a lowering of ejection fraction (−4.54% [95% CI −6.89, −2.18]) in the MRP arm. There were no significant changes in myocardial perfusion reserve in any group.

CONCLUSIONS

This is the first randomized controlled trial to compare the effects on cardiac structure and function of a low-energy diet versus an aerobic exercise program or routine care in working-age adults with T2D. Compared with control participants, individuals with T2D had reduced diastolic function, increased concentric LV remodeling, reduced myocardial perfusion, and increased aortic stiffening, consistent with asymptomatic stage B heart failure (18). A 12-week supervised aerobic exercise training program led to favorable improvements in diastolic function in the absence of any major effects on LV remodeling, perfusion, or aortic stiffening. Despite beneficial effects observed on glycometabolic profile, blood pressure, aortic stiffness, and concentric LV remodeling, a low-energy MRP did not lead to improved diastolic function.

Our T2D cohort may already have stage B heart failure (18), with clear

Table 2—Bioanthropometric measures at baseline and 12 weeks and change from baseline to 12 weeks in the three trial arms

	Routine care (n = 30)			Exercise (n = 22)			MRP (n = 24)		
	Baseline	Week 12	Median change (95% CI)	Baseline	Week 12	Median change (95% CI)	Baseline	Week 12	Median change (95% CI)
Anthropometrics									
Weight (kg)	102.6 (14.9)	100.4 (14.5)	−1.05 (−3.16, −0.01)	99.2 (16.3)	97.8 (16.6)	−1.55 (−2.51, −0.48)	106.7 (16.2)	93.0 (15.0)	−13.55 (−15.53, −11.90)
BMI (kg/m^2)	35.0 (33.0–40.7)	34.5 (32.0–41.0)	−0.25 (−1.00, 0.00)	33.0 (31.8–35.0)	33.0 (31.0–34.7)	−0.75 (−1.00, −0.09)	35.2 (33.5–40.3)	30.3 (28.1–35.5)	−4.75 (−5.17, −4.00)
Systolic BP (mmHg)	137.8 (12.7)	130.8 (14.4)	−7.07 (−10.60, −3.54)*	135.5 (16.9)	133.0 (14.3)	−2.45 (−8.94, 4.03)*	145.9 (15.9)	132.9 (18.0)	−13.00 (−21.60, −4.40)*
Diastolic BP (mmHg)	85.3 (7.3)	83.5 (10.2)	−1.83 (−4.65, 0.99)*	87.2 (8.2)	86.7 (8.5)	−0.55 (−4.08, 2.98)*	91.1 (7.4)	86.5 (9.1)	−4.67 (−9.50, 0.17)*
Heart rate (beat/min)	76.3 (7.5)	73.3 (9.6)	−3.03 (−6.06, −0.01)*	75.0 (12.7)	73.4 (9.6)	−1.55 (−4.94, 1.85)*	73.1 (8.6)	67.8 (9.8)	−5.29 (−8.55, −2.03)*
Fasting blood tests									
HbA_{1c} (mmol/mol)	56.3 (10.1)	55.2 (11.6)	−0.50 (−6.00, 1.00)	57.8 (12.1)	56.6 (12.3)	−1.00 (−3.07, 1.07)	54.8 (11.9)	44.4 (7.6)	−7.50 (−13.34, −5.00)
HbA_{1c} (%)	7.3 (0.9)	7.2 (1.1)	0.00 (−0.59, 0.10)	7.4 (1.1)	7.3 (1.1)	−0.10 (−0.31, 0.20)	7.2 (1.1)	6.2 (0.7)	−0.75 (−1.23, −0.40)
Glucose (mmol/L)	7.3 (6.7–9.1)	7.6 (6.3–9.0)	−0.19 (−0.97, 0.60)*	8.2 (7.2–10.1)	7.7 (6.4–9.0)	−0.82(−1.59, −0.05)*	7.1 (6.4–10.0)	6.3 (5.2–7.3)	−1.89 (−2.78, −1.00)*
Insulin (mIU/L)	21.5 (14.4–28.7)	18.5 (11.2–32.5)	0.07 (−5.83, 5.96)*	26.2 (19.2–35.4)	20.0 (14.3–41.4)	−3.79 (−9.92, 2.34)*	29.2 (25.1–38.1)	16.2 (11.7–19.0)	−16.15 (−21.89, −10.40)*
HOMA-IR	7.8 (4.7–9.3)	6.6 (3.3–11.7)	−0.81 (−2.07, 2.03)	9.8 (6.6–14.3)	6.5 (4.5–13.8)	−2.91 (−4.98, 0.39)	10.3 (8.0–13.6)	4.3 (3.0–6.0)	−5.98 (−9.48, −3.44)
Adiponectin (ng/mL)	4,121.3 (3,090.1–7,550.2)	4,006.9 (2,417.5–6,865.8)	17.81 (−795.87, 515.42)	3,043.2 (2,435.4–4,169.0)	2,767.5 (2,186.9–3,495.9)	−354.54 (−815.60, 256.48)	3,714.4 (2,546.3–4,681.7)	4,764.1 (3,158.4–6,159.5)	774.33 (−98.58, 2,784.91)
Leptin (pg/mL)	19,606.6 (9,617.2–34,115.0)	18,112.9 (8,544.5–27,105.2)	−2,035.80 (−4,300.81, −559.33)	16,831.1 (11,403.0–23,753.9)	12,691.9 (10,098.3–21,983.9)	−526.05 (−2,736.59, 2,248.05)	19,294.6 (9,808.7–51,040.7)	6,413.1 (3,337.4–20,558.8)	−9,873.31 (−13,360.80, −5,803.63)
BNP (ng/L)	9.4 (4.4–15.7)	8.3 (4.8–14.4)	0.00 (−1.43, 2.89)	7.4 (2.7–18.0)	7.5 (3.5–16.4)	1.05 (−3.91, 4.26)	10.8 (5.0–15.1)	13.6 (5.0–24.3)	3.45 (0.73, 8.61)
Cardiopulmonary exercise testing									
Peak VO_2 (mL/kg/min)	16.7 (3.7)	16.2 (4.1)	−0.54 (−1.55, 0.47)*	17.2 (4.5)	18.2 (4.9)	0.97 (−0.46, 2.40)*	16.4 (4.5)	18.3 (5.5)	1.93 (0.64, 3.23)*
Peak VO_2 (L/min)	1.72 (0.48)	1.63 (0.51)	−0.09 (−0.18, 0.01)*	1.67 (0.50)	1.73 (0.52)	0.06 (−0.08, 0.20)*	1.72 (0.45)	1.67 (0.46)	−0.05 (−0.16, 0.06)*
Total exercise duration (min:s)	11.3 (2.2)	11.1 (2.2)	−0.15 (−0.60, 0.25)	10.6 (2.3)	11.8 (3.1)	1.20 (0.17, 2.07)	11.4 (2.2)	11.2 (1.7)	−0.37 (−0.62, 0.47)
Maximum workload (W)	123.0 (41.9)	122.0 (47.3)	−2.50 (−8.74, 3.00)	123.2 (47.1)	141.3 (54.9)	22.00 (5.81, 32.00)	132.5 (56.4)	132.3 (50.1)	−3.50 (−9.34, 10.01)

Data are n (%), median (interquartile range), or mean (SD) unless otherwise indicated. BP, blood pressure. *Data are mean change (95% CI).

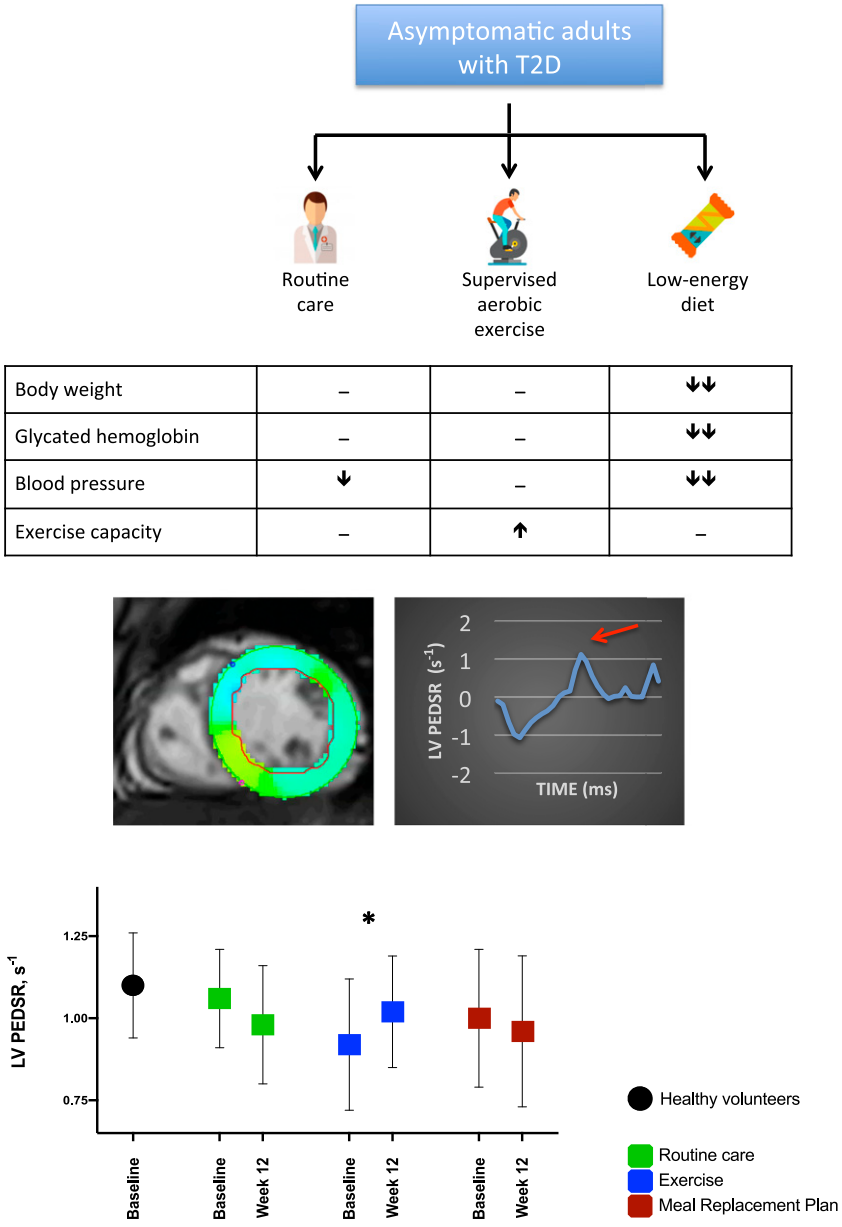

Figure 1—Summary of trial findings. Prospective, randomized, open-label, blinded end point trial of routine care vs. a supervised aerobic exercise program vs. a low-energy (~810 kcal/day) MRP. With routine care, there was a modest reduction in blood pressure. Exercise training led to improvements in exercise capacity. The dietary intervention led to dramatic reductions in body weight, glycemia, and blood pressure. The primary outcome measure was CMR-derived LV PEDSR (red arrow), a measure of the speed of myocardial relaxation. At baseline, LV PEDSR was significantly lower in participants with T2D compared with control participants ($P = 0.02$). After the 12-week interventions, PEDSR increased in the exercise arm vs. routine care ($\beta = 0.132$ [97.5% CI 0.038, 0.225], $P = 0.002$) but did not improve with MRP ($\beta = 0.016$ [97.5% CI −0.075, 0.106], $P = 0.731$). *Denotes statistically significant change with intervention versus routine care.

evidence of reduced diastolic function by both CMR and echocardiographic measures. Diastolic dysfunction and concentric LV remodeling are typically the earliest manifestations of diabetic cardiomyopathy and precursors to the onset of clinical heart failure (19). Our results suggest that supervised aerobic exercise training may improve the earliest functional consequence of T2D on the myocardium. Participants with T2D had markedly lower aerobic exercise capacity compared with control participants at baseline, and beneficial effects on diastolic function were observed even when only accompanied by small improvements in fitness.

Large cohort studies have shown that increased aerobic exercise capacity is associated with significantly lower cardiovascular and overall mortality in men (20) and women (21) with diabetes. Furthermore, diastolic function has been associated with exercise capacity in people with T2D, independent of age, sex, BMI, and HbA_{1c} (22), which suggests that improvements in exercise capacity may yield improvements in cardiac dysfunction in T2D. Several studies have assessed the effects of various exercise interventions on diastolic function in people with T2D, predominantly using echocardiography (10). The results of these studies have been inconsistent, likely because of differences in study populations, modes and duration of exercise interventions, and various measures of diastolic function being used. In general, shorter durations (~3 months) of exercise training appear to improve echocardiographic indices of diastolic function and LV filling pressures in randomized studies of exercise versus standard care, regardless of the type of exercise intervention (23–25). Trials of longer durations of exercise interventions (6–12 months), however, have not always yielded improvements in diastolic function (26, 27). This may reflect difficulties in compliance with longer-term exercise programs. Although not significant statistically, there were trends for improvement in echocardiographic markers of diastolic function, which may have been confounded by relatively poor image quality in this obese cohort where 20% had inadequate windows for complete assessment (28).

The mechanism of benefit of aerobic exercise on diastolic function in our cohort is unclear. We did not observe significant improvements in myocardial perfusion or cardiac remodeling with exercise. Even short durations of exercise training have been found to improve endothelial function and promote angiogenesis (29), though it may be that these effects were not sufficient to manifest as demonstrable improvements in myocardial perfusion in our study. It is also posited that exercise interventions cause improvements in myocyte calcium handling, mitochondrial function, inflammation, and energy metabolism (10,30,31), which are linked to impaired cardiac contraction and relaxation (32). We were not able to assess these parameters in the current study, but given the lack of improvement in cardiac energetics

Table 3—CMR and echocardiography data at baseline and 12 weeks in the three trial arms

	Routine care (n = 30)			Exercise (n = 22)			MRP (n = 24)		
	Baseline	Week 12	Mean change (95% CI)	Baseline	Week 12	Mean change (95% CI)	Baseline	Week 12	Mean change (95% CI)
CMR									
LV PEDSR (s^{-1})	1.06 (0.15)	0.98 (0.18)	−0.07 (−0.13, −0.02)	0.92 (0.20)	1.02 (0.17)*	0.10 (0.04, 0.16)	1.00 (0.21)	0.96 (0.23)	−0.05 (−0.13, 0.03)
LV global longitudinal strain (%)	−17.4 (2.2)	−16.8 (1.8)	0.63 (−0.16, 1.41)	−16.3 (2.9)	−16.1 (2.5)	0.23 (−0.79, 1.25)	−16.6 (2.9)	−16.0 (1.8)	0.61 (−0.51, 1.72)
LV mass (g)	116.1 (22.8)	117.0 (24.2)	0.90 (−2.93, 4.73)	123.1 (21.9)	122.0 (20.9)	−1.15 (−6.73, 4.44)	131.2 (26.9)	125.6 (27.0)	−5.56 (−11.53, 0.40)
LV mass/volume	0.82 (0.77–0.86)	0.83 (0.77–0.92)	0.02 (−0.01, 0.05)	0.86 (0.75–0.91)	0.85 (0.76–0.88)	−0.02 (−0.06, 0.02)	0.80 (0.74–0.91)	0.79 (0.72–0.87)	−0.03 (−0.06, −0.01)
LV EDV (mL)	133.9 (125.3–148.8)	128.7 (117.4–149.6)	−0.37 (−4.75, 4.00)	147.2 (129.3–161.3)	145.1 (132.0–159.7)	2.45 (−4.36, 9.27)	172.5 (131.7–180.7)	172.3 (116.3–188.9)	−0.15 (−5.90, 5.60)
LV EDVi (mL/m^2)	63.3 (58.1–67.8)	61.5 (56.3–69.0)	0.46 (−1.79, 2.72)	67.4 (62.0–70.6)	66.1 (62.9–72.4)	1.50 (−1.53, 4.52)	71.6 (59·9–78.4)	77.9 (64.3–87.5)	4.97 (2.22, 7.73)
LV EF (%)	67.6 (5.4)	66.2 (5.3)	−1.42 (−3.76, 0.92)	66.8 (7.9)	66.0 (6.2)	−0.79 (−3.78, 2.20)	69.8 (7.4)	65.2 (6.1)	−4.54 (−6.89, −2.18)
Myocardial perfusion reserve	2.7 (0.8)	3.2 (1.1)	0.49 (−0.03, 1.00)	3.3 (0.9)	3.4 (1.2)	0.10 (−0.54, 0.75)	3.0 (1.1)	3.2 (0.9)	0.18 (−0.44, 0.79)
Aortic distensibility ($mmHg^{-1} \times 10^{-3}$)	3.7 (2.9–5.5)	4.8 (3.0–5.8)	0.51 (−0.20, 1.21)	3.3 (2.7–5.7)	3.8 (2.9–4.6)	0.55 (−0.87, 1.97)	3.2 (2.3–4.3)	4.2 (3.1–6.1)	0.90 (0.38, 1.41)
Echocardiography									
Average E/e′	8.0 (6.5–9.7)	8.6 (7.1–9.3)	0.18 (−0.49, 0.85)	8.8 (7.0–10.6)	8.1 (6.8–9.3)	−0.70 (−1.78, 0.39)	10.1 (7.5–11.0)	8.5 (7.6–9.7)	−0.67 (−1.83, 0.48)
Average E/A	1.00 (0.21)	1.01 (0.25)	0.01 (−0.06, 0.09)	0.94 (0.19)	1.00 (0.21)	0.06 (−0.03, 0.15)	0.92 (0.20)	0.99 (0.23)	0.07 (−0.03, 0.17)

Data are mean (SD) or median (interquartile range) unless otherwise indicated. EDV, end diastolic volume; EDVi, end diastolic volume indexed to body surface area; EF, ejection fraction. *Significant difference vs. routine care.

following 12-weeks of high-intensity interval training in a previous study in people with T2D (25), it seems that this mechanism is unlikely to explain the benefit observed in diastolic function.

The ability to achieve remission of T2D by weight loss with administration of a low-energy MRP was convincingly demonstrated in the Diabetes Remission Clinical Trial (DiRECT) (7). However, improvements in cardiac function after weight loss in T2D have not been studied in a randomized controlled trial setting previously. Administration of a low-energy MRP in our patients led to dramatic improvements in body weight, blood pressure and resting heart rate, fasting triglycerides, HbA_{1c}, and markers of insulin resistance, mirroring the findings of DiRECT (7). We also observed similar rates of remission of T2D to those in DiRECT. However, PEDSR did not significantly change after MRP. This lack of improvement may have been influenced by a slightly higher baseline PEDSR in the MRP arm versus the exercise arm, although the analysis of the primary outcome measure was adjusted for baseline PEDSR. There were a small, statistically nonsignificant reduction in E/e′ and increase in E/A with the MRP that could suggest a trend toward improved diastolic function, but a much larger sample size would be required to assess this reliably.

We also observed a reduction in LV ejection fraction with a small rise in BNP levels. It is recognized that obesity is associated with increased sympathetic activity, which may result in hyperdynamic LV function (33). This is supported by our finding that LV ejection fraction was higher at baseline in those with T2D compared with healthy weight control participants. The observed reduction in ejection fraction in the MRP arm may, therefore, reflect normalization of hyperdynamic LV function with weight loss. Furthermore, obesity and T2D are both known to lower BNP levels (which may explain why baseline levels were lower in the T2D group than in the control group), and its increase in the MRP arm of the trial is also likely to be a consequence of the weight loss rather than worsening of diastolic function (34,35).

Our interpretation is that diastolic dysfunction may be irreversible with improvements in glycometabolic derangements alone. Supporting evidence includes data from interventional trials that have not shown reductions in heart failure risk with strict glycemic control (36). Although diastolic function did not improve, we did observe modest changes in cardiac remodeling and aortic distensibility in the MRP arm of the trial. Given that LV hypertrophy and smaller LV volumes are typically seen in diabetic cardiomyopathy (confirmed in our case-control analysis) and are associated with poorer cardiovascular outcomes (37,38), these changes may indicate favorable long-term effects of the dietary restriction or weight loss on the structural manifestations of heart failure in T2D. Furthermore, we have previously shown that aortic stiffening is an independent determinant of concentric LV remodeling (39), and the observed increase in aortic distensibility with MRP suggests that weight loss may ameliorate vascular stiffness in T2D and could promote reverse cardiac remodeling. It is possible that the best approach for improving stage B heart failure in people with T2D is a combination of exercise and dietary restriction to achieve weight loss, given the different effects of these interventions on diastolic function and cardiac remodeling in our study. Further trials are needed to assess the cardiovascular effects of combined exercise with dietary restriction and weight loss in people with T2D and for longer durations.

Key strengths of our trial were the randomized design, the comprehensive cardiometabolic phenotyping undertaken, the use of CMR for cardiac outcomes, the blinded image analyses, and the robust independent statistical analyses undertaken by the Leicester Clinical Trials Unit. Although the younger working-age population in this study has the highest lifetime risk of heart failure, it is underrepresented in large-scale cardiovascular outcomes trials of T2D, and no studies have demonstrated effective therapies to prevent or treat heart failure in this group.

Our trial also has some important limitations, including the small sample size, unblinded design, and short duration of follow-up. Although the sample size is modest, the trial was powered in accordance with our pilot data (5), and the excellent reproducibility of our primary outcome measure of CMR-derived PEDSR in this very T2D cohort (40) allowed us to achieve the necessary statistical power as dictated by our power calculation. However, because PEDSR is a relatively novel measure of diastolic function on CMR, no prognostic data exist regarding subclinical alterations in PEDSR. The exclusion criteria were set to maximize the probability of remission of T2D with the MRP, and therefore, the results are not generalizable to the entire population with T2D. Neither the effects of sustained weight loss on cardiac structure and function nor the possibility that detraining could lead to worsening of diastolic function were assessed in those who undertook the supervised exercise arm of the trial. Although we achieved the necessary statistical power for our trial, the relatively high rate of noncompliance (19%) with the supervised exercise intervention may hinder its real-world application.

In conclusion, in working-age adults with T2D and obesity without prevalent cardiovascular disease, there is already evidence of subclinical diastolic dysfunction, concentric LV remodeling, and aortic stiffening. A 12-week supervised aerobic exercise training program led to improvements in LV diastolic function without major effects on cardiac remodeling, weight loss, blood pressure, or glycemic control. Conversely, a low-energy MRP led to improvements in glycometabolic profiles, concentric LV remodeling, and aortic stiffness but did not improve measures of diastolic function.

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Author Contributions. G.S.G. provided clinical oversight of trial participants and drafted the report. G.S.G., D.J.S., and L.A. recruited study participants and supervised assessment visits and clinical reviews. G.S.G., G.S., A.-M.M., J.M., K.S.P., J.D.B. and M.J.D. analyzed the data. D.J.S., E.M.B., E.B., T.Y., K.K., M.J.D., and G.P.M. contributed to the design of the study. E.M.B., E.B., T.Y., K.K, M.J.D., and G.P.M critically revised the report. J.H. supervised the exercise training sessions. E.B. and S.A. initiated and oversaw administration of the MRP. N.B.J. performed the statistical analyses. Y.W. oversaw trial management. A.-M.M. and J.M. performed the echocardiograms and cardiopulmonary exercise testing. All authors read and approved the final version.

G.P.M. 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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