A High-Protein Diet With Resistance Exercise Training Improves Weight Loss and Body Composition in Overweight and Obese Patients With Type 2 Diabetes

**OBJECTIVE** — To evaluate the effects of two low-fat hypocaloric diets differing in the carbohydrate-to-protein ratio, with and without resistance exercise training (RT), on weight loss, body composition, and cardiometabolic risk outcomes in overweight/obese patients with type 2 diabetes.

**RESEARCH DESIGN AND METHODS** — A total of 83 men and women with type 2 diabetes (aged 56.1 ± 7.5 years, BMI 35.4 ± 4.6 kg/m²) were randomly assigned to an isocaloric, energy-restricted diet (female subjects 6 MJ/day, male subjects 7 MJ/day) of either standard carbohydrate (CON) diet (carbohydrate:protein:fat 53:19:26) or high protein (HP: 43:33:22), with or without supervised RT (3 days/week) for 16 weeks. Body weight and composition, waist circumference (WC), and cardiometabolic risk markers were assessed.

**RESULTS** — Fifty-nine participants completed the study. There was a significant group effect (P ≤ 0.04) for body weight, fat mass, and WC with the greatest reductions occurring in HP+RT (weight [CON: −8.6 ± 4.6 kg, HP: −9.0 ± 4.8 kg, CON+RT: −10.5 ± 5.1 kg, HP+RT: −13.8 ± 6.0 kg], fat mass [CON: −6.4 ± 3.4 kg, HP: −6.7 ± 0.4 kg, CON+RT: −7.9 ± 3.7 kg, HP+RT: −11.1 ± 3.7 kg], and WC [CON: −8.2 ± 4.6 cm, HP: −8.9 ± 3.9 cm, CON+RT: −11.3 ± 4.6 cm, HP+RT: −13.7 ± 4.6 cm]). There was an overall reduction (P < 0.001) in fat-free mass (−2.0 ± 2.3 kg), blood pressure (−15/8 ± 10/6 mmHg), glucose (−2.1 ± 2.2 mmol/L), insulin (−4.7 ± 5.4 mU/L), A1C (−1.25 ± 0.94%), triglycerides (−0.47 ± 0.81 mmol/L), total cholesterol (−0.67 ± 0.69 mmol/L), and LDL cholesterol (−0.37 ± 0.53 mmol/L), with no difference between groups (P ≥ 0.17).

**CONCLUSIONS** — An energy-restricted HP diet combined with RT achieved greater weight loss and more favorable changes in body composition. All treatments had similar improvements in glycemic control and CVD risk markers.

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physical exercise (more than two 30-min sessions/week of moderate/vigorous aerobic exercise or one 30-min session/week of RT) during the 6 months prior to study were also excluded. Participants provided written informed consent. The study was approved by the human research ethics committees of the Commonwealth Scientific and Industrial Research Organisation (CSIRO) and the University of Adelaide.

In a parallel study, participants were blocked matched for age, sex, and weight, then randomized to one of four lifestyle interventions: an energy-restricted standard carbohydrate, low-protein, low-fat diet alone (CON) or with RT (CON+RT); or an isocaloric higher-protein, moderate-carbohydrate, low-fat diet alone (HP) or with RT (HP+RT) for 16 weeks. At baseline (week 0) and week 16, participants attended the CSIRO research clinic after an overnight fast for assessment. At the clinic testing visits, height (week 0 only), body weight, blood pressure, waist circumference (WC), and body composition were measured before a venous blood sample was drawn and muscle strength was assessed. Prior to the clinical assessments, a 24-h urine sample was collected.

Medications at baseline and changes throughout the study were documented. Lipid-lowering and antihypertensive medications were encouraged to remain constant throughout the intervention. Participants were asked not to modify their lifestyle patterns other than necessary during the intervention to comply with the study protocol.

**Diet interventions**
The diets were designed to be isocaloric with moderate energy restriction (~6,000 kJ/day for women, ~7,000 kJ/day for men). The planned macronutrient profile of the CON diet was 53% of total energy as carbohydrate, 19% (~0.7 g · kg⁻¹ · day⁻¹) protein, and 26% fat. The target profile for the HP diet was 43% carbohydrate, 33% (~1.2 g · kg⁻¹ · day⁻¹) protein, and 22% fat. To facilitate dietary compliance, detailed dietary advice, meal planning, and recipe information were provided at baseline and every 2 weeks by a qualified dietitian. Key foods representative of each diet’s macronutrient profile (~50% total energy) were supplied every 2 weeks. Diets were structured to include specific food quantities/weights to ensure correct macronutrient and energy profile were achieved. These foods were listed in a quantitative food record completed daily by participants. Participants were asked to weigh and measure their food using scales provided. Dietary composition was assessed by a qualified dietitian based on the analysis of 7 consecutive days from the semiquantitative food record of each 2-week period using a computerized database (Foodworks Professional Edition, version 4, 1998; Xyris Software, Highgate Hill, Australia). Participants who did not complete the food records were excluded as noncompliers.
Exercise intervention
The CON+RT and HP+RT group participants followed a progressive RT program. Eight separate exercises (leg press, knee extension, chest press, shoulder press, lat pull down, seated row, triceps press, and sit-ups) were performed using weight-stacked machines (Maxim Health Fitness, Adelaide, Australia), except sit-ups, on 3 nonconsecutive days/week. The weight loading was set at 70–85% one repetition maximum (1RM, protocol described below), determined for each exercise at Week 0. This allowed ~8–12 reps to volitional fatigue with two sets per exercise and 1–2 min rest between sets to be performed. Once participants could successfully perform two sets of >12 repetitions, the weight load was increased to maintain the training load. Resistance exercise training sessions lasted ~45 min and were conducted at the CSIRO gymnasium under professional supervision. Participants completed a training diary, and if a scheduled session was missed, they were encouraged to attend a makeup session as soon as possible.

Outcomes, body weight, composition, blood pressure, and muscle strength
Body mass was measured using calibrated electronic digital scales (Mercury; AMZ 14, Tokyo, Japan), and body composition was measured using dual-energy X-ray absorptiometry (DXA; Lunar Prodigy; General Electric, Madison, WI) to assess total body fat mass and total body fat-free mass (FFM). WC was measured on a horizontal plane 2 cm proximal to the uppermost lateral border of the right iliac crest. Seated blood pressure was measured using an automated sphygmomanometer (DYNAMAP 8100; Criticon, Tampa, FL).

Muscle strength (1RM) was assessed pre- and postintervention for chest press and lat pull down according to standard guidelines (11). 1RM of the other five weight-stacked exercises were also assessed in the participants in the exercise groups at baseline only to set initial training loads. To determine 1RM, following a low-intensity warm-up, participants performed four to five trials (separated by a 2-min resting interval) using varying moderate-heavy weights to determine the highest weight that could be lifted with only one repetition through the full range of motion with correct technique.

Biochemical analyses
Serum lipids and insulin, plasma glucose, C-reactive protein (CRP), and creatinine were measured using standard methods (12). A1C, measured using high-performance liquid chromatography, and 24-h urinary urea, creatinine, and albumin were assessed at a commercial laboratory (IMVS, Adelaide, Australia). Creatinine clearance was calculated as (urine creatinine [μmol/l] × urine volume [ml]/plasma creatinine [μmol/l] × minutes) and corrected for body surface area (13).

Statistical analyses
Statistical analyses were performed using SPSS for Windows (version 17.0; SPSS, Chicago, IL). Prior to hypothesis testing, data were examined for normality. Non-normally distributed variables (insulin, CRP, and urinary albumin) were logarithmically transformed before analysis. Differences in baseline characteristics were compared by one-way ANOVA for continuous variables and χ² tests for categorical variables. This investigation represents an efficacy trial to determine the physiological/metabolic effects of the treatments. Primary analysis was conducted on participants who completed the study per protocol. Secondary intention-to-treat (ITT) analysis was also conducted for the primary outcome measures (body weight and composition, cardio-metabolic and glycemic control), including participants who completed the study irrespective to protocol adherence. Changes over time in the groups were assessed using repeated-measures ANOVA. The effects of the treatments on changes were assessed using one-way ANOVA, with group (CON, HP, CON+RT, and HP+RT) as a between-subject factor. Where there was a significant main effect, post hoc tests with Dunnett adjustment for multiple comparisons were performed to determine differences between group means compared with HP+RT; based on a prior hypothesis, the HP+RT group would achieve greater changes compared with the other treatments. Age and sex were included as covariates. No significant effect of sex or age was observed for any of the outcomes. To compare the magnitude of change between the two diets (CON and CON+RT versus HP and HP+RT) and exercise versus nonexercise (CON and HP versus CON+RT and HP+RT), planned contrasts were used in the statistical model. Pearson correlation coefficients were used to determine the relationships between variables. Statistical significance was set at P < 0.05. Data are means ± SD.

RESULTS
Participants
Of 83 randomized participants, 18 withdrew and 6 participants were excluded for dietary noncompliance (failure to complete food records); 59 participants completed the study per protocol (Fig. 1). There was no difference between treatment groups, diets, or exercise versus nonexercise groups in the number of participants who withdrew (P ≥ 0.34) or who were excluded (P ≥ 0.17). At baseline, there were no significant differences in age, weight, BMI, A1C, and sex distribution between groups (P ≥ 0.12). These characteristics were also similar between participants who completed or did not complete the study (P ≥ 0.09), except for age in which completers were on average 5 years younger (completers: aged 50.8 ± 10.4 years, dropouts: aged 56.1 ± 7.4 years; P = 0.02).

Dietary composition and exercise compliance
Based on the food records, participants showed good compliance with the prescribed diets (Table 1). Total energy intake was similar across treatment groups, while macronutrient composition was different between the diet groups; the HP and HP+RT groups consumed significantly more protein and less carbohydrate and fat compared with the CON and CON+RT groups. There was a significant diet effect for the urinary urea-to-creatinine excretion ratio (P = 0.003), which decreased in the CON diet groups (CON: 30.8 ± 8.6 to 26.7 ± 3.8, CON+RT: 25.9 ± 5.1 to 24.2 ± 4.0) and increased in the HP diet groups (HP: 31.1 ± 9.8 to 33.6 ± 11.2, HP+RT: 28.3 ± 9.5 to 31.5 ± 7.7), indicating higher protein intakes in the HP diet groups.

Compliance with RT was defined as the number of exercise sessions completed at the prescribed training loads per total number of prescribed sessions. All participants in the CON+RT and HP+RT groups achieved compliance with the prescription (defined as 75% of prescribed sessions), on average completing 93% (43.5 ± 4.0 of 47) of the prescribed sessions. There was a significant effect of exercise treatment for 1RM lat pull down and chest press (P < 0.001) such that in-
creases occurred in the diet+RT groups, with no change in the diet-only groups (Table 2), indicating compliance with the prescribed RT.

**Body weight and composition**

Overall, body weight was reduced ($P < 0.001$), with a significant group effect ($P = 0.04$), such that HP+RT achieved greatest weight loss (CON: $-8.9\%$, HP: $-8.7\%$, CON+RT: $-10.0\%$, HP+RT: $-12.7\%$) (Table 2). Post hoc analysis showed that the greater weight loss in HP+RT was statistically significant compared with CON and HP groups ($P < 0.05$), but compared with CON+RT statistical significance was not reached ($P = 0.20$). Overall, weight loss was not different between the two diets ($P = 0.18$); however, the exercise groups (HP+RT and CON+RT) lost more weight compared with the diet-only groups (CON and HP) (diet+RT: $-12.0 \pm 5.7$ kg, diet only: $-8.8 \pm 4.6$ kg; $P = 0.02$). ITT analysis showed a similar weight loss pattern, albeit the magnitude of effect was reduced (CON: $-9.4 \pm 6.5$ kg, HP: $-8.0 \pm 4.8$ kg, CON+RT: $-10.5 \pm 5.1$ kg, HP+RT: $-12.6 \pm 6.5$ kg; $P = 0.16$ group effect).

Similarly, fat mass and WC reduced in all groups ($P < 0.001$) (Table 2), with a significant group effect ($P = 0.006$) such that HP+RT had greatest reductions. Post hoc analysis showed that HP+RT had significantly greater reductions compared with CON and HP ($P \leq 0.02$), but compared with CON+RT, statistical significance was not reached (fat mass: $P = 0.06$, WC: $P = 0.32$). Overall, compared with the diet-only groups, the exercising groups had greater reductions in fat mass (diet+RT: $-9.6 \pm 4.1$ kg, diet only: $-6.7 \pm 3.8$ kg; $P < 0.01$) and WC (diet+RT: $-12.4 \pm 4.7$ cm, diet only: $-8.5 \pm 4.3$ cm; $P < 0.01$). Overall, more fat mass loss occurred in participants consuming the HP diet ($-9.4 \pm 4.5$ kg) compared with the CON diet ($7.3 \pm 3.8$ kg; $P = 0.06$). There was an overall reduction in FFM (Table 2), with no effect of treatment group ($P = 0.91$), diet composition ($P = 0.80$), or exercise participation ($P = 0.51$). ITT analysis confirmed these results, with a significant group effect evident for fat mass and WC ($P \leq 0.02$) but not for FFM ($P = 0.75$).

**Cardiometabolic outcomes and glycemic control**

Overall, blood pressure, lipids, glucose, A1C, and CRP were reduced ($P \leq 0.02$) (Table 2) with no difference between treatment groups ($P \geq 0.37$), diet composition ($P \geq 0.27$), or exercise participation ($P \geq 0.21$). Insulin concentrations also decreased ($P < 0.001$) with a differential (nonsignificant) effect evident between treatment groups ($P = 0.11$), such that HP+RT experienced approximately twofold greater reductions compared with the other groups. No differential insulin response between diet compositions ($P = 0.19$) or exercise participation ($P = 0.29$) were observed. Changes in insulin were significantly correlated with changes in weight ($r = 0.35$, $P < 0.01$) and fat mass ($r = 0.36$, $P = 0.005$). ITT analysis also showed no significant differences in the changes of these parameters between the groups.

**Creatinine clearance and urinary albumin**

Overall, creatinine clearance was reduced ($P < 0.001$) (Table 2), with no differential effect between treatments ($P = 0.68$), diet composition ($P = 0.55$), or exercise participation ($P = 0.46$). At week 0, 45 participants (CON diet: 27, HP diet: 18) had normoalbuminuria (urinary albumin excretion $<20 \mu g/min$), and values remained in the normoalbuminuria range at week 16, except in 1 participant in the CON group whose urinary albumin excretion increased ($33.4 \mu g/min$) to microalbuminuria classification (urinary albumin excretion $20–200 \mu g/min$). At baseline, 14 participants (24%; CON diet: $n = 6$, HP diet: $n = 8$) had microalbuminuria; at week 16, 4 participants (CON: $n = 2$, HP: $n = 2$) remained in the microalbuminuria range and 10 participants decreased to normoalbuminuria classification (CON: $n = 4$, HP: $n = 6$).

**Medication changes**

A total of 33 participants were on hypoglycemic medication at baseline (CON: $n = 11$, HP: $n = 7$, CON+RT: $n = 10$, HP+RT: $n = 5$), and during the intervention, medication dose was reduced in 9 participants (CON: $n = 2$, HP: $n = 1$, CON+RT: $n = 4$, HP+RT: $n = 2$) and increased in 1 participant in the HP group. There were no significant differences between the treatment groups. At baseline, 36 and 29 participants were on antihypertensive medication (CON: $n = 9$, HP: $n = 4$, CON+RT: $n = 14$, HP+RT: $n = 9$) and lipid-lowering medication (CON: $n = 9$, HP: $n = 5$, CON+RT: $n = 9$, HP+RT: $n = 6$), respectively.

| Table 1— Macronutrient composition of the treatment groups |
|-----------------------------------------------------------|
|              | CON     | HP     | CON+RT | HP+RT  |
| n             | 16      | 12     | 17     | 14     |
| Energy (kJ)   | 6,278 ± 648 | 6,321 ± 763 | 6,199 ± 696 | 6,339 ± 649 |
| Carbohydrate (g) | 197.4 ± 16.3 | 176.3 ± 23.7 | 195.0 ± 21.5 | 170.0 ± 23.1 |
| Carbohydrate (% of energy) | 53.6 ± 2.6 | 47.4 ± 1.6 | 53.6 ± 3.9 | 45.5 ± 2.4 |
| Protein (g)   | 68.4 ± 5.9 | 119.0 ± 7.8 | 68.0 ± 8.3 | 117.1 ± 6.7 |
| Protein (% of energy) | 18.6 ± 0.9 | 32.3 ± 2.8 | 18.7 ± 1.3 | 31.6 ± 2.2 |
| Fat (g)       | 38.5 ± 7.7 | 30.5 ± 8.2 | 37.3 ± 9.6 | 33.7 ± 5.5 |
| Fat (% of energy) | 22.6 ± 3.0 | 17.7 ± 3.0 | 22.3 ± 4.5 | 19.6 ± 1.9 |
| Saturated fat (% of total fat) | 34.1 ± 5.5 | 33.9 ± 5.0 | 33.2 ± 2.8 | 34.3 ± 4.3 |
| Polyunsaturated fat (% of total fat) | 19.8 ± 4.5 | 22.3 ± 3.6 | 21.4 ± 4.5 | 21.0 ± 4.2 |
| Monounsaturated fat (% of total fat) | 46.1 ± 6.6 | 43.9 ± 4.1 | 45.5 ± 5.4 | 44.8 ± 5.1 |
| Diet fiber (g) | 31.1 ± 2.9 | 24.7 ± 4.0 | 30.5 ± 4.4 | 22.6 ± 4.1 |

Data are means ± SD. The treatment groups were a standard carbohydrate, low-protein, low-fat diet alone (CON) or with resistance exercise training (CON+RT), or an isocaloric higher-protein, low-fat diet alone (HP) or with resistance exercise training (HP+RT). *Differences between groups (one-way ANOVA). †Comparison of the difference between the diets (CON and CON+RT vs. HP and HP+RT) (planned contrast).
Table 2—Body weight, composition, muscle strength, cardiometabolic risk factors, and glycemic control before and after 16 weeks of either an energy-restricted standard carbohydrate, low-protein, low-fat diet alone (CON) or with resistance exercise training (CON+RT), or an isocaloric higher-protein, low-fat diet alone (HP) or with resistance exercise training (HP+RT)

|                  | CON  | HP   | CON+RT | HP+RT | Time effect* | Group effect† | Diet comparison‡ | Exercise comparison§ |
|------------------|------|------|--------|-------|--------------|---------------|-------------------|----------------------|
| **Body weight (kg)** |      |      |        |       |              |               |                   |                      |
| Week 0           | 97.0±10.6 | 102.7±15.4 | 105.0±15.3 | 107.6±15.5 | <0.001 | 0.04 | 0.18 | 0.02 |
| Week 16          | 88.4±11.2 | 93.7±13.8 | 94.5±15.4 | 93.8±13.5 | <0.001 | 0.06 | 0.17 | 0.03 |
| Change           | −8.6±6.6 | −9.0±4.8 | −10.5±5.1 | −13.8±6.0 | <0.001 | 0.06 | 0.17 | 0.03 |
| **BMI (kg/m²)**  |      |      |        |       |              |               |                   |                      |
| Week 0           | 34.8±4.9 | 35.6±3.8 | 34.9±4.9 | 36.6±5.0 | <0.001 | 0.06 | 0.17 | 0.03 |
| Week 16          | 31.7±5.1 | 32.5±3.1 | 31.4±4.3 | 31.9±4.3 | <0.001 | 0.06 | 0.17 | 0.03 |
| Change           | −3.1±1.6 | −3.2±1.7 | −3.5±1.7 | −4.7±2.1 | <0.001 | 0.06 | 0.17 | 0.03 |
| **Total body fat mass (kg)** |      |      |        |       |              |               |                   |                      |
| Week 0           | 38.5±8.0 | 40.4±8.4 | 40.4±10.0 | 42.9±11.6 | <0.001 | 0.06 | 0.06 | <0.01 |
| Week 16          | 32.1±9.5 | 33.2±6.9 | 32.3±10.7 | 31.5±11.6 | <0.001 | 0.06 | 0.19 | 0.48 |
| Change           | −6.5±3.7 | −7.1±4.0 | −8.1±3.8 | −11.4±3.9 | <0.001 | 0.06 | 0.19 | 0.48 |
| **WC (cm)**      |      |      |        |       |              |               |                   |                      |
| Week 0           | 111.3±10.7 | 114.3±6.8 | 113.7±8.5 | 116.2±12.7 | <0.001 | 0.06 | 0.06 | <0.01 |
| Week 16          | 103.2±12.8 | 105.4±6.7 | 102.4±9.6 | 102.5±11.8 | <0.001 | 0.06 | 0.19 | 0.48 |
| Change           | −8.2±4.6 | −8.9±3.9 | −11.3±4.6 | −13.7±4.6 | <0.001 | 0.06 | 0.06 | <0.01 |
| **Total FFM (kg)** |      |      |        |       |              |               |                   |                      |
| Week 0           | 58.5±10.7 | 62.3±13.0 | 64.6±12.4 | 64.7±11.5 | <0.001 | 0.19 | 0.08 | 0.51 |
| Week 16          | 56.3±10.6 | 60.4±13.2 | 62.2±12.0 | 62.3±10.7 | <0.001 | 0.19 | 0.08 | 0.51 |
| Change           | −2.2±1.9 | −1.9±1.9 | −2.4±2.5 | −2.4±3.1 | <0.001 | 0.01 | <0.001 | 0.78 |
| **Single repetition bench press (kg)** |      |      |        |       |              |               |                   |                      |
| Week 0           | 60.0±18.1 | 68.5±27.4 | 67.1±22.4 | 64.6±25.5 | <0.001 | <0.001 | 0.78 | <0.001 |
| Week 16          | 58.1±17.7 | 66.0±25.1 | 76.2±23.6 | 75.5±28.9 | <0.001 | <0.001 | 0.78 | <0.001 |
| Change           | −1.9±4.8 * | −2.5±8.0 ** | 9.1±8.5 | 10.9±8.2 | <0.001 | <0.001 | 0.78 | <0.001 |
| **Single repetition lat pull down (kg)** |      |      |        |       |              |               |                   |                      |
| Week 0           | 49.8±15.1 | 56.7±15.4 | 55.0±14.8 | 55.7±18.7 | <0.001 | <0.001 | 0.51 | <0.001 |
| Week 16          | 50.4±14.9 | 57.2±15.9 | 66.2±17.4 | 65.0±20.7 | <0.001 | <0.001 | 0.51 | <0.001 |
| Change           | 0.6±4.9 * | 0.6±3.7† | 11.2±6.0 | 9.3±4.9 | <0.001 | <0.001 | 0.51 | <0.001 |
| **Systolic blood pressure (mmHg)** |      |      |        |       |              |               |                   |                      |
| Week 0           | 137±12 | 141±11 | 137±10 | 138±9 | <0.001 | 0.90 | 0.86 | 0.943 |
| Week 16          | 124±11 | 125±11 | 122±9 | 124±9 | <0.001 | 0.90 | 0.86 | 0.943 |
| Change           | −13±11 | −16±13 | −16±7 | −14±9 | <0.001 | 0.90 | 0.86 | 0.943 |
| **Diastolic blood pressure (mmHg)** |      |      |        |       |              |               |                   |                      |
| Week 0           | 79±9 | 83±9 | 81±8 | 79±8 | <0.001 | 0.49 | 0.56 | 0.346 |
| Week 16          | 72±6 | 74±9 | 74±6 | 72±8 | <0.001 | 0.49 | 0.56 | 0.346 |
| Change           | −7±6 | −10±6 | −8±5 | −7±6 | <0.001 | 0.49 | 0.56 | 0.346 |
| **Plasma glucose (mmol/l)** |      |      |        |       |              |               |                   |                      |
| Week 0           | 9.2±2.7 | 9.5±2.9 | 8.7±3.2 | 8.2±2.1 | <0.001 | 0.90 | 0.79 | 0.483 |
| Week 16          | 7.1±1.0 | 7.0±1.0 | 6.8±1.5 | 6.3±1.0 | <0.001 | 0.90 | 0.79 | 0.483 |
| Change           | −2.2±2.2 | −2.5±2.7 | −1.9±2.3 | −1.9±1.6 | <0.001 | 0.90 | 0.79 | 0.483 |
| **Glycosylated hemoglobin (%)** |      |      |        |       |              |               |                   |                      |
| Week 0           | 7.6±1.0 | 8.0±1.8 | 7.3±1.4 | 6.8±1.0 | <0.001 | 0.21 | 0.16 | 0.179 |
| Week 16          | 6.4±0.7 | 6.3±0.9 | 6.2±1.0 | 5.6±0.6 | <0.001 | 0.21 | 0.16 | 0.179 |
| Change           | −1.1±0.6 | −1.8±1.6 | −1.1±0.7 | −1.1±0.7 | <0.001 | 0.21 | 0.16 | 0.179 |

(continued)
Table 2—Continued

|                          | CON        | HP         | CON+RT     | HP+RT      | Time effect* | Group effect† | Diet comparison‡ | Exercise comparison§ |
|--------------------------|------------|------------|------------|------------|--------------|----------------|---------------------|---------------------|
| Serum insulin (mU/l)     |            |            |            |            |              |                |                     |                     |
| Week 0                   | 15.8 ± 10.0| 12.4 ± 8.6 | 12.3 ± 4.8 | 15.2 ± 8.3 | <0.001       | 0.11          | 0.19               | 0.289               |
| Week 16                  | 11.8 ± 10.2| 9.0 ± 8.0  | 8.8 ± 3.4  | 7.2 ± 3.6  | <0.001       | 0.70          | 0.91               | 0.626               |
| Change                   | -4.1 ± 4.2 | -3.5 ± 2.8 | -3.4 ± 4.0 | -7.9 ± 8.1 |              |                |                     |                     |
| Triglycerides (mmol/l)   |            |            |            |            |              |                |                     |                     |
| Week 0                   | 2.3 ± 1.3  | 2.0 ± 1.1  | 1.6 ± 0.5  | 1.8 ± 0.7  | <0.001       | 0.01          | 0.01               | 0.71               |
| Week 16                  | 1.7 ± 1.5  | 1.6 ± 1.2  | 1.3 ± 0.5  | 1.2 ± 0.5  |              |                |                     |                     |
| Change                   | -0.6 ± 1.1 | -0.4 ± 1.0 | -0.3 ± 0.5 | -0.5 ± 0.6 |              |                |                     |                     |
| Total cholesterol (mmol/l)|            |            |            |            |              |                |                     |                     |
| Week 0                   | 4.8 ± 1.0  | 5.0 ± 1.1  | 4.3 ± 0.9  | 4.7 ± 0.9  | <0.001       | 0.89          | 0.54               | 0.628               |
| Week 16                  | 4.1 ± 1.1  | 4.4 ± 1.4  | 3.5 ± 0.9  | 4.0 ± 0.8  |              |                |                     |                     |
| Change                   | -0.7 ± 0.6 | -0.6 ± 0.8 | -0.8 ± 0.9 | -0.7 ± 0.6 |              |                |                     |                     |
| HDL cholesterol (mmol/l) |            |            |            |            |              |                |                     |                     |
| Week 0                   | 1.2 ± 0.3  | 1.2 ± 0.3  | 1.1 ± 0.3  | 1.1 ± 0.3  | 0.02         | 0.86          | 0.71               | 0.863               |
| Week 16                  | 1.1 ± 0.3  | 1.1 ± 0.3  | 1.0 ± 0.3  | 1.0 ± 0.2  |              |                |                     |                     |
| Change                   | -0.0 ± 0.2 | -0.1 ± 0.2 | -0.1 ± 0.2 | -0.1 ± 0.2 |              |                |                     |                     |
| LDL cholesterol (mmol/l) |            |            |            |            |              |                |                     |                     |
| Week 0                   | 2.7 ± 0.9  | 2.7 ± 0.9  | 2.4 ± 0.8  | 2.7 ± 0.6  | <0.001       | 0.37          | 0.27               | 0.208               |
| Week 16                  | 2.4 ± 1.0  | 2.5 ± 1.2  | 1.9 ± 0.9  | 2.4 ± 0.6  |              |                |                     |                     |
| Change                   | -0.3 ± 0.5 | -0.2 ± 0.6 | -0.5 ± 0.6 | -0.3 ± 0.4 |              |                |                     |                     |
| CRP (mg/l)               |            |            |            |            |              |                |                     |                     |
| Week 0                   | 3.3 ± 2.4  | 4.5 ± 2.4  | 3.0 ± 2.6  | 4.0 ± 2.5  | <0.001       | 0.55          | >0.99              | 0.183               |
| Week 16                  | 2.6 ± 1.9  | 3.5 ± 1.1  | 1.8 ± 1.1  | 3.0 ± 2.5  |              |                |                     |                     |
| Change                   | -0.7 ± 1.5 | -0.9 ± 1.9 | -1.2 ± 1.9 | -1.0 ± 1.9 |              |                |                     |                     |
| Creatinine clearance     |            |            |            |            |              |                |                     |                     |
| (ml/min per 1.73 m²)     |            |            |            |            |              |                |                     |                     |
| Week 0                   | 119.7 ± 22.2| 114.3 ± 46.9| 116.6 ± 24.4| 117.7 ± 24.9| <0.001       | 0.68          | 0.55               | 0.46                |
| Week 16                  | 113.1 ± 40.5| 96.6 ± 32.1| 108.7 ± 22.8| 114.2 ± 15.8|              |                |                     |                     |
| Change                   | -6.6 ± 32.0| -17.7 ± 37.6| -7.9 ± 22.6| -7.5 ± 16.4|              |                |                     |                     |

Data are means ± SD. *Changes over time in the groups from weeks 0 to 16 (repeated-measures ANOVA). †Comparison of the magnitude of change between diets (CON and CON+RT vs. HP and HP+RT) (planned contrast). ‡Comparison of the magnitude of change between exercise and nonexercise treatments (CON and HP vs. CON+RT and HP+RT) (planned contrast). |P| ≤ 0.05; |P| < 0.01; |P| < 0.01 significantly different from HP+RT.

The HP+RT group exhibited at least a 3.3-kg greater weight and fat loss and 21% greater reduction in WC compared with the other treatment groups. Previous studies in healthy, overweight/obese individuals without type 2 diabetes show greater reductions in weight and fat mass of similar magnitude when exercise training is combined with a hypocaloric HP diet compared with an isocaloric CON diet (6,7). The CON diet was designed to reflect standard dietary recommendations (15–20% of total energy as protein) (1). The HP diet was designed to achieve protein intake of >25%, corresponding to typically prescribed HP diets; it provided an average protein intake of 1.12 g·kg⁻¹·day⁻¹. Previous studies show that an HP diet compared with a CON diet is associated with greater reductions in fat mass (5,6). RT also reduces fat mass in obese individuals, independent of caloric restriction (14), suggesting that the separate interventional components of an HP diet and RT may have contributed to the greater weight and fat mass losses following the HP+RT treatment.

Although a significant main group effect was observed, post hoc analysis showed that greater weight, fat mass, and WC reductions in the HP+RT group only reached statistical significance compared with the CON and HP groups but not the CON+RT group (P ≥ 0.06), despite large absolute differences. Nevertheless, the additional weight and fat losses that occurred when RT was combined with an HP diet compared with a CON diet represent moderate to large effect sizes (0.67–0.85) and are considered clinically relevant and shown to produce important health outcomes (15). Furthermore, clin-
creased the data variability, subsequently effects were observed in our study, including previously observed (5). Although no sex effects were observed in our study, inclusion of men and women may have increased the data variability, subsequently lowering the statistical power.

Mechanisms underlying the greater weight and fat changes in HP + RT are not clear. Given that both diets were isocaloric and participants undertook the same RT program under controlled conditions, it suggests these changes reflect metabolic differences. The HP + RT group experienced approximately twofold greater reductions in fasting insulin compared with the other treatments, although, again, power was not sufficient to reveal significant differences. Nevertheless, there was a significant correlation between the changes in weight and fat mass and insulin levels. Insulin has fat-sparing effects and promotes adipose tissue accumulation (17). Hence, greater insulin reductions in the HP + RT group may explain the greater fat mass reductions; however, causation cannot be determined. Other evidence suggests that fat mass accumulation drives insulin resistance (17). Alternatively, fat has more positive effects on energy balance compared with other macronutrients (18). Therefore, although unlikely, the possibility that lower fat intakes in the HP diet contributed greater fat reductions in the HP + exercise group cannot be dismissed.

In the exercising groups, high compliance with the RT program achieved substantial strength gains, which is associated with metabolic disease reductions (19). Nevertheless, FFM reduced similarly across treatment groups. Although previous studies have observed protective effects of RT (20) and HP diets (3) on FFM during caloric restriction, these effects have not been consistently shown (5), and perhaps even higher relative protein intakes are required. Compared with this study, experiments demonstrating FFM preservation following a hypocaloric HP diet with RT (6,21) administered higher relative protein intakes (1.12 vs. 1.4 g · kg⁻¹ · day⁻¹). A meta-analysis showed that the degree of FFM retention during weight loss increases with increasing quartiles of protein intake (2), suggesting that relative protein intakes may be an important weight loss program design consideration.

Substantial reductions in CVD risk markers and glycemic control occurred during the intervention with no observable differences between the groups. Previous studies report that RT (14) and HP diets (22) improve A1C independent of weight loss in type 2 diabetic patients. The lack of any difference in glycemic control between the treatment groups in the present study may therefore be due to the hypoglycemic effects of energy restriction (23), masking any potential effects of exercise or diet composition. Under milder energy restriction, RT has been shown to provide additional reductions in A1C (9). Longer-term studies are required to separate out these effects. Nevertheless, the overall A1C reductions observed is clinically relevant and associated with a 21% reduction in diabetes-related mortality (24).

HP diets having potentially adverse effects on renal function remains a concern (25). However, no differences in creatinine clearance or presence of microalbuminuria between the diets groups were observed. Other short-term, interventional studies also report no differences in renal function in obese individuals with type 2 diabetes following either an HP or low-protein diet (5,22). This suggests that a hypocaloric HP diet does not adversely affect renal function, at least over the short term, in subjects without overt renal impairment. Nevertheless, diabetes is associated with impaired renal function, and the longer-term effects in this patient population warrants further investigation.

Although not statistically significant, higher participant withdrawals/exclusions in the HP diet groups are noteworthy. The exact reason/s are not entirely clear, but this is not consistent with previous studies comparing HP versus CON diets that report similar dropouts with both dietary treatments and in some studies lower dropouts following the HP diet (5,7).

In conclusion, participation in RT produced greater weight and fat loss and increases in muscular strength compared with energy restriction alone. Additionally, replacement of some carbohydrate for protein further magnified these effects, resulting in greatest reductions in weight, fat mass, WC, and insulin. All treatments had similar improvements in glycemic control and CVD risk. A lifestyle modification program combining an energy-restricted HP diet and RT appears to be a preferred treatment strategy in overweight/obese individuals with type 2 diabetes. Further studies should evaluate the longer-term effects.
of the study, and contributed to the manuscript. All authors agreed on the final version of the manuscript.

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