BMJ Open Diabetes Research & Care

Effect of progressive resistance training with weight loss compared with weight loss alone on the fatty liver index in older adults with type 2 diabetes: secondary analysis of a 12-month randomized controlled trial

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To cite: Freer CL, George ES, Tan S-Y, *et al*. Effect of progressive resistance training with weight loss compared with weight loss alone on the fatty liver index in older adults with type 2 diabetes: secondary analysis of a 12-month randomized controlled trial. *BMJ Open Diab Res Care* 2022;**10**:e002950. doi:10.1136/bmjdrc-2022-002950

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2022-002950).

Received 19 May 2022
Accepted 31 August 2022

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ABSTRACT

Introduction Non-alcoholic fatty liver disease (NAFLD) is highly prevalent (~75%) in people with type 2 diabetes (T2D). Since exercise and weight loss (WL) are recommended for the management of both NAFLD and T2D, this study examined whether progressive resistance training (PRT) plus WL could lead to greater improvements in the fatty liver index (FLI), an indicator of NAFLD, compared with WL alone in older adults with T2D.

Research design and methods This study represents a secondary analysis of a 12-month, two-arm randomised controlled trial including 36 overweight and obese adults (60–80 years) with T2D randomly allocated to supervised PRT plus WL (hypocaloric diet) (n=19) or WL plus sham (stretching) (n=17) for 6 months (phase I), followed by 6-months home-based training with ad libitum diet (phase II). FLI, which is an algorithm based on waist circumference, body mass index, triglycerides and gamma-glutamyl transferase, was assessed at baseline and every 3 months. Linear mixed models were used to analyse between-group differences over time, adjusting for baseline values.

Results At baseline, the mean±SD FLI was 76.6±18.5 and the likelihood of NAFLD (FLI >60) in all participants was 86%. Following phase I, both groups had similar statistically significant improvements in FLI (mean change (95% CI): PRT+WL, −12 (−20 to −4); WL, −9 (−15 to −4)), with no significant between-group difference. After the subsequent 6-month home-based phase, the improvements in FLI tended to persist in both groups (PRT+WL, −7 (−11 to −2); WL, −4 (−10 to 1)), with no between-group differences.

Conclusions In older overweight adults with T2D, PRT did not enhance the benefits of WL on FLI, a predictor of NAFLD.

Trial registration number ACTRN12622000640707.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Lifestyle strategies such as weight loss through hypocaloric diets and exercise, including progressive resistance training (PRT), are cornerstone to prevention and management of both type 2 diabetes (T2D) and non-alcoholic liver disease (NAFLD).

⇒ However, whether PRT plus weight loss is more effective for improving NAFLD than weight loss alone is not known.

WHAT THIS STUDY ADDS

⇒ In this 12-month randomized controlled clinical trial including 36 older overweight and obese sedentary adults with T2D, weight loss with or without PRT was associated with similar significant reductions in the fatty liver index (FLI), an indicator of NAFLD.

⇒ This was likely due to the favourable changes (losses) in both weight and adiposity which were similar between the groups, despite PRT providing some additional benefits to muscle (lean) mass.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ While this study indicates that weight loss is the key factor driving improvements in the FLI in older adults with T2D, further research is needed to explore the potential synergistic effects of exercise combined weight loss on other liver outcomes (eg, hepatic fat) in a large sample of older adults with T2D and NAFLD to help shape future clinical guidelines.

INTRODUCTION

Type 2 diabetes (T2D) is a serious global public health issue, estimated to affect 462 million people globally.[1] Individuals with T2D are also at significantly higher risk of multiple other chronic diseases, including non-alcoholic fatty liver disease (NAFLD).[2] In fact, the prevalence of NAFLD in people with T2D has been identified as high as 60%–75%,[3] with the rapidly rising burden of both diseases heightened by poor dietary habits, physical inactivity and sedentary behaviours.[4 5] Both

conditions also share several common metabolic risk factors and pathophysiological and inflammatory pathways,[6] with a growing body of evidence indicating a bidirectional relationship between T2D and NAFLD.[4 7]

For both T2D and NAFLD, lifestyle strategies including weight loss (WL) through dietary modification and exercise are the cornerstone for prevention and management.[8 9] Available evidence indicates calorie restriction used to induce WL (7%–10% total body weight) is effective for improving glycemic control and reducing liver fat in those with T2D and NAFLD.[10 11] However, WL is often associated with a concurrent loss in muscle (lean) mass,[12] which is important as there is growing evidence that low muscle mass is independently associated with poor glycemic control[13] and increased risk of T2D,[14] including in those with NAFLD.[15 16] A meta-analysis of 18 cross-sectional studies involving 48 709 adults also found that low muscle mass was associated with a 1.3-fold and 2.4-fold increased risk and severity of NAFLD, respectively.[17] This suggest that optimising muscle (lean) mass may represent an important approach to prevention and management of both T2D and NAFLD.

Progressive resistance training (PRT) is one method that has been shown to improve body composition, particularly muscle (lean) mass, as well as glycemic control and blood lipids in people with T2D.[18] Resistance training has also been shown to reduce liver fat (10%–25%), liver enzymes and the FLI, as well as improve muscle (lean) mass in people with NAFLD.[19 20] In older adults with obesity and those with T2D, we and others have shown that PRT can prevent the concurrent loss of muscle (lean) mass associated with WL while resulting in similar reductions in fat mass and total body weight, as achieved by WL alone.[21–23] Furthermore, in older overweight adults with T2D we have shown that high-intensity PRT (75%–85% of one repetition maximum strength) in combination with moderate WL (−2.5 to −3.1 kg) was more effective at improving glycemic control (glycated hemoglobin (HbA1c)) and lean mass compared with WL alone, despite similar losses in fat mass.[22 23] However, whether PRT combined with WL is more effective at improving NAFLD outcomes, compared with WL, has not been examined. Therefore, the aim of this study, which is a secondary analysis of our previous 12-month RCT,[22 23] was to investigate whether 6 months of high-intensity PRT combined with WL can reduce the risk of NAFLD (improve FLI) in older overweight and obese adults with T2D compared with WL alone. A secondary aim was to evaluate whether any improvement in FLI following the supervised and structured training can be maintained following 6 months of home-based exercise training without any further instruction to lose weight.

METHODS

Study design

This is a secondary analysis of a prior two-arm, 12-month RCT consisting of two phases involving 36 older overweight and obese adults with T2D.[22 23] Phase I incorporated 6 months of supervised and structured gym-based PRT with WL and phase II involved a further 6 months of home-based PRT with ad libitum diet. Participants were randomly assigned (via a computer-generated random number table in Excel) to either of the two groups by an independent researcher. Recruitment to the intervention occurred over a 2-year period (February 1999 to January 2001). Repeated measures were conducted at 3, 6, 9 and 12 months for all outcomes, other than body composition (6 and 12 months). As previously reported,[22 23] participants were initially randomized to either PRT+WL (n=19) or sham (flexibility) training+WL (n=17) for the first 6 months. All assessments and training were performed at Deakin University, Melbourne, Australia. The study was retrospectively registered with the Australian and New Zealand Clinical Trial Registry (ACTRN12622000640707).

Participants

As previously reported,[22 23] 36 overweight and obese adults aged 60–80 years with T2D were recruited from the International Diabetes Institute Clinics. Participants were initially screened by telephone, with eligible participants (n=110) required to undertake further assessments to determine eligibility (HbA1c, resting blood pressure, ECG, medical history). Participants were included based on the following criteria: established T2D (>6 months), being treated with diet or a oral hypoglycemic agent (excluding insulin), HbA1c range 7%–10%, overweight or obese (body mass index (BMI) >27 kg/m^2 and ≤40 kg/m^2), not participating in regular PRT and engaging in <150 min moderate or <60 min vigorous exercise/week (preceding 6 months), non-smoker and consuming <2 alcoholic drinks/day. Exclusion criteria were: history/evidence of ischemic heart disease, systemic diseases, hypertension (>160/90 mm Hg), advanced diabetic neuropathy and/or retinopathy and conditions (severe orthopedic, cardiovascular or respiratory) that prevent participation and those with absolute exercise contraindications according to the American College of Sports Medicine guidelines.[24] A total of 47 participants (24 men, 23 women) were deemed eligible, of which 36 agreed to participate. As reported previously,[22 23] in the first 8 weeks six participants (PRT+WL group, n=2, sham+WL group, n=4) withdrew due to non-related health problems or commitments and one participant was excluded due to starting insulin. In total, 81% of participants (PRT+WL, n=16, 84%; sham+WL, n=13, 76%) completed phase I. An additional three participants (PRT+WL, n=2; sham+WL, n=1) withdrew during the first 2 weeks of phase II (home-based training) due to travel, osteoarthritis knee pain and unrelated personal issues. Thus, 26 participants (PRT+WL, n=14, 74%; sham+WL, n=12, 71%) completed the 12-month intervention (figure 1).

Intervention

Phase I: supervised gym-based intervention

A detailed description of the exercise intervention has been previously reported.[22 23] Briefly, for the first 6-month

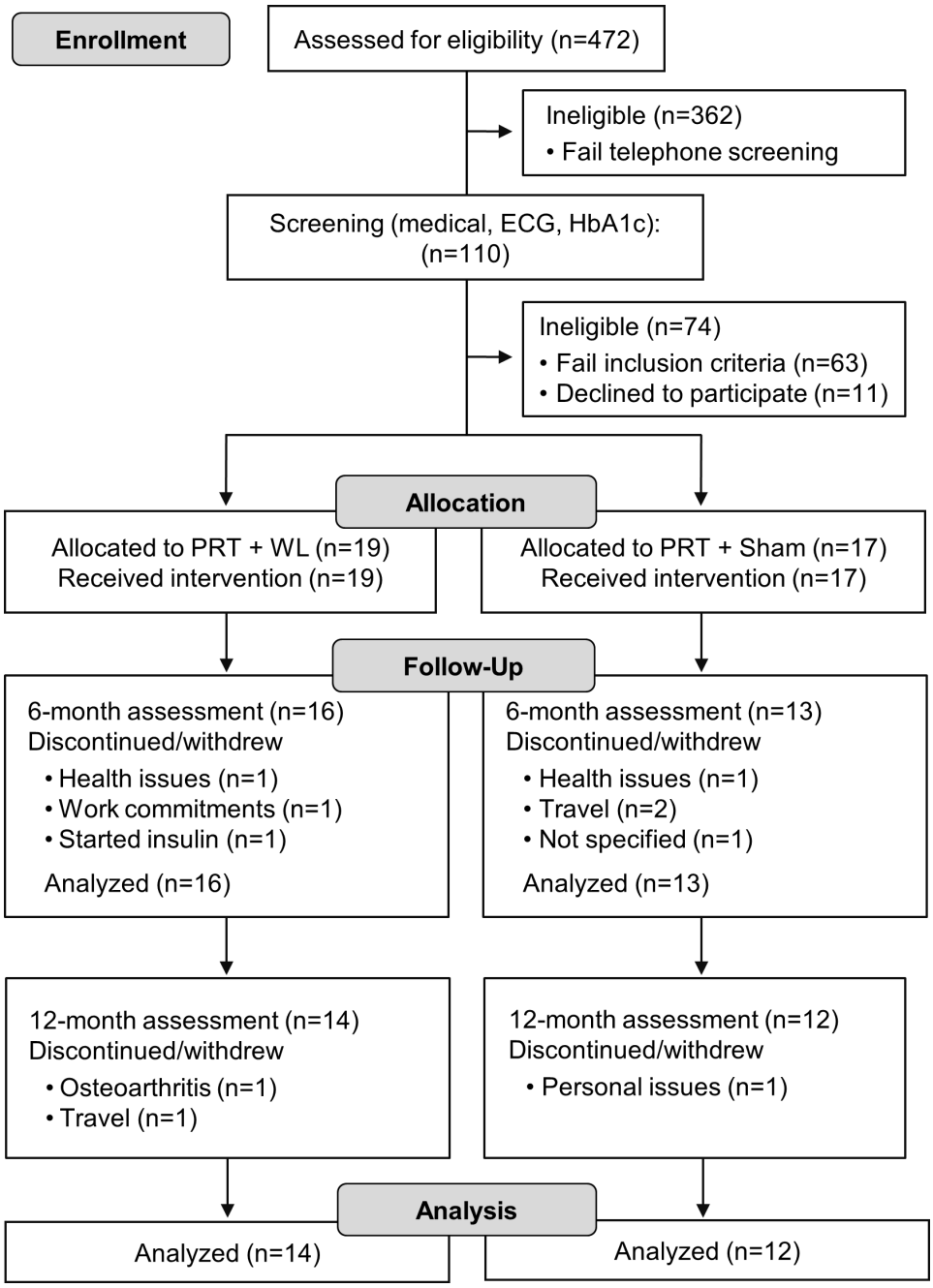

Figure 1 Study flow chart. HbA1c, glycated hemoglobin; PRT, progressive resistance training; WL, weight loss.

gym-based intervention, all participants attended the exercise laboratory at Deakin University three non-consecutive days per week. Those randomized to PRT performed an individually prescribed 45–60 min, high-intensity (75%–85% of their one repetition maximum strength) program consisting of free weights and weights machines (three sets of 8–10 repetitions, nine exercises). To ensure correct technique and progression, all sessions were fully supervised. The sham flexibility group sessions consisted of 5 min of stationary cycling (no workload) followed by a sequence of static stretching exercises (~30 min) designed to provide participation and improve flexibility but not to elicit changes in muscle strength or fitness.

Phase II: home-based training

Following the 6-month supervised gym-based intervention, participants were prescribed a home-based exercise program in which they were provided with individualised instructions and equipment (dumbbells and ankle weights for PRT group and flexibility chart for flexibility group). Participants were asked to train 3 days/week at home and/or at a community or commercial leisure centre. To facilitate transition, participants in the PRT+WL group performed the home-based PRT program within the structured and supervised gym setting for the final month of phase I. The home-based exercises replaced weight machines with dumbbells and ankle weights and

participants were requested to complete nine exercises (three sets of 8–10 repetitions) with the aim to exercise at a moderate intensity (at least 60% of maximum). Participants attended the gymnasium monthly to monitor technique and progression and completed weekly exercise diaries to monitor adherence. In addition, weekly phone calls (first month) and subsequent fortnightly calls monitored adherence and enabled participants to ask questions and receive feedback. A single home visit was conducted early during the home program to ensure safety and provide additional weights to facilitate progression. Participants in the control flexibility group were requested to maintain the flexibility program at home.

Weight loss intervention

Four weeks prior to the commencement of phase I, all participants were placed on a healthy eating plan supplying ≤30% total energy from total fat (≤10% saturated fat) with protein and carbohydrate being distributed for remaining energy. Individually prescribed by a dietitian, the plan was designed to induce moderate WL (~0.25 kg/week) throughout phase I. Interviews every 2 weeks by the dietitian and completion of a weekly checklist were used to assess adherence. Changes in nutrient intake were assessed via a 3-day food record conducted at 3 and 6 months. Nutrition information was analyzed using Foodworks nutrient analysis software (Xyris, Brisbane, Queensland, Australia). Following the gym-based intervention (phase I), participants were not required to adhere to the healthy eating (WL) plan and did not receive further dietary recommendations.

Measurements

Health and medical history

Information on participants health and medical history were assessed via an interviewer questionnaire conducted at baseline. Information collected included: duration of diabetes (years), age of diabetes onset, oral hypoglycemic medication use, lipid-lowering medication use, history of several diseases (eg, hypertension, retinopathy, neuropathy and arthritis/osteoarthritis) and supplement usage.

Anthropometry

Height (cm) was measured using a Holtain stadiometer (Holtain, Croswell, Wales) and weight (kg) using SECA electronic scales, assessed to the nearest 0.1 kg. Waist circumference (WC) was measured at the midpoint between the iliac crest and lower edge of rib cage using a non-elastic measuring tape.

Biochemical measures and the fatty liver index

Morning venous blood samples were collected at baseline, 3, 6, 9 and 12 months with all samples obtained after an overnight fast and at least 48 hours post exercise. The biomarkers (gamma-glutamyl transferase (GGT) and triglycerides (TG)) were analyzed using standard laboratory procedures. The FLI, a well-validated and simple algorithm, was defined by the following formula[25]:

$$FLI=(e^{0.953\times LN\ (TG)+0.139\times BMI+0.718\times LN\ (GGT)+0.053\times WC-15.745})/(1+e^{0.953\times LN\ (TG)+0.139\times BMI+0.718\times LN\ (GGT)+0.053\times WC-15.745})\times 100$$

Scores for the FLI range from 0 to 100, with a score ≥60 being used to consider the likely presence of NAFLD and <30 to rule out the presence of liver steatosis.[25] Blood measures were available for the following number of participants: baseline, 3 and 6 months (PRT+WL, n=16; sham+WL, n=13), 9 and 12 months (PRT+WL, n=14; sham+WL, n=12).

Habitual physical activity

An interview-administered validated 7-day physical activity recall questionnaire was used to estimate habitual physical activity (energy expenditure, kcal/day), excluding the exercise intervention.[26]

Statistical analysis

Statistical analysis was conducted using Stata SE Statistical software. The data were analyzed using a modified intention-to-treat approach, including all randomized participants with at least one follow-up measurement. A linear mixed model was used to analyze the data, with random intercepts for participants, time as a repeated measure and an interaction between group and time. For all models, normality and homogeneity of variance of the residuals were checked using quantile-quantile plots and scatter plots, respectively. No data imputation was undertaken. The results were analyzed adjusted for baseline values (model 1), and model 1 plus baseline total lean body mass (model 2), and model 1 plus baseline physical activity (model 3). A mixed effects logistic regression model was used to analyze group differences for the changes in proportion of participants with an FLI ≥60. Statistical significance was set at $p<0.05$.

RESULTS

Participant characteristics

Baseline characteristics are shown in table 1. The mean±SD age and BMI of the participants was 67.3±5.1 years and 31.9±3.5 kg/m^2, respectively, with 69% of the participants classified as obese (BMI >30). The mean duration of diabetes was 8.1±6.5 years and 86.2% of participants were taking oral hypoglycemic medication (other than insulin) and 34.5% of participants were taking lipid-lowering medications. During phase I, four participants (PRT+WL n=3, sham+WL n=1) decreased their oral hypoglycemic medication dosage while four participants (PRT+WL n=2, sham+WL n=2) increased medication. During phase II, one participant increased and one decreased hypoglycemic medication dosage (both PRT+WL). Regarding lipid-lowering medication, one participant commenced lipid-lowering medication (sham+WL) during phase I, while during phase II, one participant (PRT+WL) commenced and one ceased (sham+WL) medication. At baseline, 86.2% of participants had a likely presence of NAFLD (FLI >60), while 3.5% indicated an absence of NAFLD (FLI <30) (table 1).

Table 1 Baseline characteristics of participants in the progressive resistance training plus moderate weight loss (PRT+WL) and moderate weight loss group (sham+WL)

Characteristic	PRT+WL (n=16)	Sham+WL (n=13)
Male/Female, n	10/6	6/7
Age (years)	67.6±5.2	66.9±5.3
Height (cm)	167.8±8.7	166.0±9.2
Weight, kg	88.7±10.9	89.5±12.1
BMI, kg/m^2	31.5±10.9	32.5±3.8
Waist circumference (cm)	105.3±7.5	103.3±11.4
Age at diagnosis (years)	60.1±5.0	58.1±8.6
Duration diabetes (years)	7.6±5.4	8.8±7.9
Oral hypoglycemic medication use, n (%)	15 (94%)	10 (78%)
Lipid-lowering medication use, n (%)	5 (31%)	5 (38%)
Estimated physical activity (kJ/day)	3022±413	3110±428
FLI <30, n (%)	0 (0%)	1 (8%)
30–59, n (%)	2 (13%)	1 (8%)
>60, n (%)	14 (87%)	11 (85%)

Values presented are mean±SDs unless otherwise indicated.
BMI, body mass index; FLI, fatty liver index.

Adherence to intervention

As reported previously,[22 23] average adherence to the exercise program was 88% and 85% (PRT+WL and sham+WL, respectively) during phase I. During the home-based training (phase II), mean adherence was 73% in PRT+WL and 78% in sham+WL.

Anthropometry and biochemical measures

There was a comparable statistically significant reduction in body weight in both the PRT+WL and sham+WL groups after 3 months (mean±SD change: −1.8±2.0 kg vs −2.0±1.5 kg, both p<0.01) and 6 months (−2.5±2.9 kg vs −3.1±2.1 kg, both p<0.01) relative to baseline. At completion of 12 months, both groups experienced similar increases in weight (mean change relative to baseline: PRT+WL, -1.7±1.9 kg; sham+WL, -1.6±2.0 kg, both p<0.05), however weight did remain significantly lower than baseline values for both groups.

The absolute within-group changes and net between-group differences for the change in BMI, WC, GGT, TG and FLI relative to baseline are shown in table 2. After phase I, comparable statistically significant reductions in BMI and WC were observed within each group. Neither group experienced a significant change in TG levels after the initial 6 months. PRT+WL had a significant 7.4 and 9.1 U/L (both p<0.05) decrease in GGT after 3 and 6 months, respectively, but these changes did not differ significantly from sham+WL after 3 months (p=0.06) or 6 months (p=0.09). At completion of phase II, BMI and WC remained significantly lower than baseline values for both groups with no significant between-group differences (table 2). TG levels remained relatively unchanged (both groups) and there were no significant within-group changes relative to baseline nor group differences in GGT after 9 or 12 months.

Fatty liver index

At completion of 6 months, both groups experienced a statistically significant reduction in FLI, with no significant between-group differences for the change after 3 months (interaction, p=0.50) or 6 months (interaction, p=0.56) (table 2 and figure 2). All results for FLI remained unchanged after further adjusting for baseline total lean body mass and baseline physical activity. After 12 months (phase II), the significant improvement in FLI persisted in PRT+WL relative to baseline but not sham+WL, however between-group differences for the change over time were not significant (interaction, p=0.75). Regarding NAFLD risk, the proportion of participants with an FLI score ≥60 after 3 months and 6 months decreased from baseline by 26% and 25% in the PRT+WL and 16% and 8% in the sham+WL, respectively (figure 3). At completion of 12 months, there was a 9% and 10% reduction from baseline in the PRT+WL and sham+WL for the proportion of participants with a FLI ≥60. There was no statistically significant difference between groups for the change in proportion of participants with a FLI ≥60 at 3 months (p=0.93), 6 months (p=0.37), 9 months (p=0.48) or 12 months (p=0.73).

DISCUSSION

The main finding from this RCT in older overweight and obese adults with T2D was that 6 months of moderate WL, with or without supervised high-intensity PRT, was associated with similar significant improvements (reductions) in FLI. A second key finding was that FLI tended to increase in both groups in parallel with weight regain during the second 6 months following the ad libitum diet, but remained below baseline levels in those undertaking the home-based PRT. While this indicates that home-based PRT may help to attenuate some of the weight-related regains in FLI, collectively, findings from this study suggest that the primary factors driving changes in FLI are alterations in body weight and adiposity and that PRT provided no or little additional benefits in older overweight and obese adults with T2D. However, the findings related to PRT should be interpreted with caution considering the modest sample size which likely limited our ability to detect any additive benefits of PRT over WL on FLI in this study involving secondary data analysis.

Since we have previously reported significantly greater improvements in glycemic control (HbA1c −1.2±1.0% vs −0.4±0.8%) and total body lean mass (0.5±1.1 kg vs −0.4±1.0 kg), and greater reductions in inflammatory markers interleukin-10 and tumor necrosis factor-α, compared with sham+WL group,[22 23] we hypothesized that there would be a greater improvement in FLI in those

Table 2 Baseline values and absolute within-group changes after the supervised, gym-based training (phase I, 3 and 6 months) and the home-based training (phase II, 9 and 12 months) in PRT+WL and sham+WL for BMI, waist circumference, triglycerides, gamma-glutamyl transferase and FLI and the net between-group differences for change relative to baseline

	Mean (95% CI) absolute change from baseline				
	Baseline	**Δ 3 months**	**Δ 6 months**	**Δ 9 months**	**Δ 12 months**
BMI, kg/m^2					
PRT+WL	31.5±3.4	−0.6 (−1.0 to −0.3)**	−0.9 (−1.4 to −0.3)**	−0.8 (−1.3 to −0.3)**	−0.6 (−1.0 to −0.2)**
Sham+WL	32.5±3.8	−0.7 (−1.0 to −0.4)***	−1.1 (−1.5 to −0.7)***	−1.1 (−1.7 to −0.6)**	−0.6 (−1.0 to −0.1)*
Net difference (95% CI)		0.1 (−0.4 to 0.6)	0.2 (−0.5 to 0.9)	0.3 (−0.4 to 1.0)	0.0 (−0.5 to 0.5)
P value†		0.76	0.62	0.32	0.79
Waist circumference, cm					
PRT+WL	105.3±7.5	−3.8 (−5.6 to −1.9)***	−6.9 (−10.0 to −3.9)***	−6.8 (−10.5 to −3.0)**	−3.7 (−6.5 to −1.0)*
Sham+WL	103.3±11.4	−3.1 (−5.2 to −1.0)**	−6.7 (−10.4 to −3.0)**	−6.4 (−10.0 to −2.7)**	−2.3 (−4.3 to −0.2)*
Net difference (95% CI)		−0.7 (−3.3 to 2.0)	−0.3 (−4.8 to 4.2)	−0.4 (−5.4 to 4.6)	−1.4 (−4.8 to 1.9)
P value†		0.74	0.88	0.75	0.32
Triglycerides, mmol/L					
PRT+WL	1.83±0.75	−0.23 (−0.60 to 0.15)	−0.24 (−0.63 to 0.15)	−0.39 (−0.80 to 0.01)	−0.09 (−0.44 to 0.26)
Sham+WL	1.85±0.78	−0.05 (−0.58 to 0.47)	−0.08 (−0.45 to 0.28)	0.12 (−0.56 to 0.79)	0.28 (−0.49 to 1.04)
Net difference (95% CI)		−0.17 (−0.77 to 0.43)	−0.16 (−0.68 to 0.36)	−0.51 (−1.23 to 0.21)	−0.37 (−1.13 to 0.39)
P value†		0.52	0.48	0.39	0.60
Gamma-glutamyl transferase, U/L					
PRT+WL	45.9±47.6	−7.4 (−13.7 to −1.0)*	−9.1 (−16.1 to −2.1)*	−4.8 (−14.4 to 4.8)	−2.1 (−11.5 to 7.3)
Sham+WL	34.2±28.5	3.2 (−6.9 to 13.4)	7.0 (−15.3 to 29.3)	5.2 (−9.0 to 8.6)	0.9 (−6.0 to 7.8)
Net difference (95% CI)		−10.6 (−21.5 to 0.3)	−16.1 (−36.4 to 4.2)	−10.0 (−27.5 to 7.6)	−3.0 (−14.4 to 8.4)
P value†		0.06	0.09	0.07	0.10
FLI					
PRT+WL	77.2±20.0	−7.0 (−12.0 to −2.0)**	−12.3 (−20.3 to −4.2)**	−11.7 (−17.6 to -5.9)***	−6.5 (−10.8 to −2.2)**
Sham+WL	75.9±19.8	−10.8 (−23.6 to 2.1)	−9.3 (−14.8 to −3.8)**	−10.1 (−19.1 to −1.0)*	−4.3 (−9.9 to 1.4)
Net difference (95% CI)		3.8 (−8.3 to 15.9)	−2.9 (−12.7 to 6.9)	−1.6 (−11.5 to 8.2)	−2.3 (−8.9 to 4.3)
P value†		0.50	0.56	0.95	0.75

All baseline values are unadjusted means±SDs. All change values are unadjusted means (95% CI) and expressed as absolute changes from baseline. Mean net differences (95% CI) were calculated by subtracting within-group changes for PRT+WL from within-group changes from WL.
*P<0.05, **p<0.01, ***p<0.001 within-group change from baseline.
†P values represent group-by-time interaction from linear mixed models adjusted for baseline values.
BMI, body mass index; FLI, fatty liver index; PRT, progressive resistance training; WL, weight loss.

undertaking PRT. This hypothesis was also informed by previous research demonstrating PRT may benefit NAFLD through enhanced insulin sensitivity,[27] reduced inflammation[28] and/or increased muscle mass.[29 30] However, few studies have assessed the effect of PRT on FLI directly, and studies assessing other liver outcomes (eg, liver fat, liver enzymes), are limited and have reported mixed findings.[19 27 31] For example, previous research has indicated 8–12 weeks of PRT at moderate intensity (50%–70% of one repetition maximum strength), independent of WL, can achieve modest reductions in liver fat (10%–13%) in those with NAFLD.[30 32] More notable decreases in liver fat (26%) and improvements in the liver enzyme ALT have been demonstrated after 4 months of high-intensity PRT (70%–80% of one repetition maximum strength) combined with dietary advice in T2D participants with NAFLD.[19] Together, these findings suggest that high-intensity PRT may result in more favorable NAFLD outcomes. Therefore, the lack of any additional benefits of PRT in our study were somewhat unexpected as participants were prescribed a high-intensity (75%–85% of one repetition maximum strength) PRT program (phase I) in which adherence was excellent (mean 88%) and the program resulted in multiple other benefits over WL alone as indicated above. Furthermore, in our cohort of older overweight and obese adults with T2D, 86% of participants were identified to be at high risk of NAFLD (FLI >60). One possible explanation is that the FLI includes only selected measurements of body fat (WC) and liver function (eg, GGT), and thus may not be sensitive to changes in liver fat in response to the PRT above WL alone, or the difference was not substantial enough to be detected by the small sample size of our trial. Although FLI is well validated in population studies,[25] it is conceivable there may have been benefits to other key liver outcomes (eg, liver fat, liver enzymes) that we did not assess and are not reflected in the FLI or conversely a longer duration of

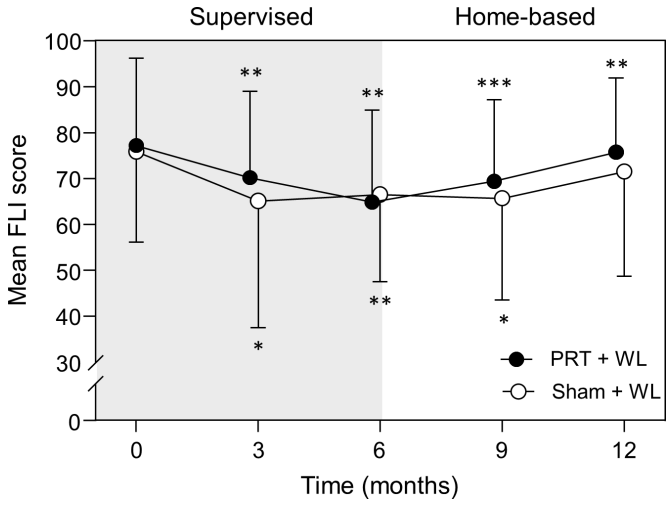

Figure 2 Mean (±SD) fatty liver index (FLI) scores in the progressive resistance training plus weight loss (● PRT+WL) and weight loss (○ sham+WL) group at baseline, 3, 6, 9 and 12 months. *P<0.05, **p<0.01, ***p<0.001 vs baseline. The grey shaded region represents the supervised, gym-based training phase and when both groups were prescribed a moderate weight loss diet and the white region represents the home-based training phase with the ad libitum diet.

high-intensity PRT may be required to elicit improvements in FLI. However, there is some evidence supporting the benefits of 10–24 weeks of PRT for improving FLI (13%–18%) in older menopausal women with obesity[33] and those with T2D,[34] but these studies included PRT in conjunction with aerobic training (AT). Aerobic training is often associated with greater reductions in visceral fat relative to PRT and changes in adipocytokines,[35] which may explain the observed improvements in FLI in these studies.

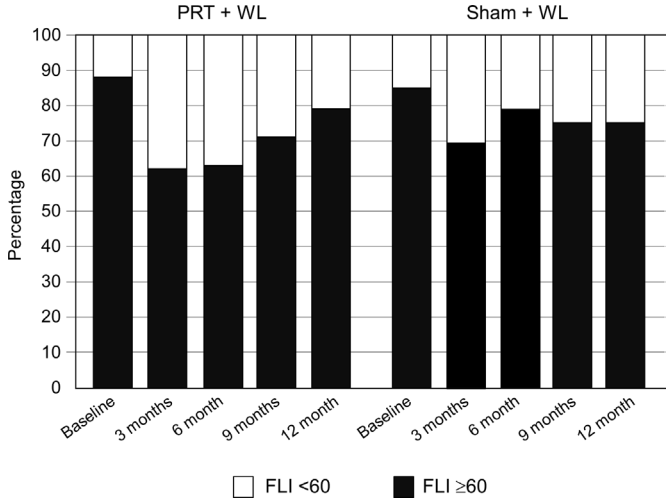

Figure 3 Proportion of participants in the progressive resistance training plus weight loss (PRT+WL) and weight loss (sham+WL) groups that were classified as likely to have non-alcoholic fatty liver disease (fatty liver index (FLI) ≥60) at baseline, 3, 6, 9 and 12 months. The first 6 months represent the supervised, gym-based training and the second 6 months the home-based training.

There is emerging evidence indicating that lean (muscle) mass may play an important role in NAFLD,[36] with research highlighting an inverse association between measures of muscle mass and NAFLD risk and severity.[17] For instance, a population-based study involving 10 534 community-dwelling adults (2631 with NAFLD) aged 51.4 (SD 8.3) years found those in the highest tertile for body weight-adjusted appendicular skeletal muscle mass gain after 1 year, exhibited a significant reduction in liver fat, and resolution of baseline NAFLD after 7 years.[37] Therefore, it is possible that PRT-related improvement in muscle mass may play a role in improving NAFLD outcomes. This is likely mediated by improved insulin resistance and muscle-liver crosstalk via modification in myokines.[38] There is consistent evidence from clinical trials highlighting the effectiveness of PRT in healthy people and those with chronic conditions as a strategy to improve lean (muscle) mass,[39 40] including people with NAFLD.[29 30] However, whether PRT-related changes in muscle (lean) mass are associated with improvements in liver outcomes in people with NAFLD remains uncertain. A 12-week RCT in sedentary obese men with NAFLD reported a ~14% reduction in liver fat following a high-intensity PRT program, without any accompanying WL,[30] in which the men experienced a mean 1.2 kg gain in muscle mass. As we have reported elsewhere,[22 23] the PRT+WL group in our study experienced a significant mean 0.5 kg increase in total body lean mass after 6 months while the WL group had a mean 0.4 kg reduction, with both groups experiencing similar losses in fat mass. It is plausible that the lean mass gain of 0.5 kg in our study was not substantial enough to translate into any benefits to FLI. Whether there is an optimal gain in muscle (lean) mass that may elicit improvements in FLI is not known, but further prospective studies and intervention trials are needed to evaluate whether a given exercise-induced change in lean (muscle) mass may be associated with improvements in liver-specific outcomes in people with NAFLD, independent of changes in weight or fat mass.

The finding that there were similar significant reductions in FLI in both the PRT+WL and sham+WL groups in our study is likely attributed to the modest WL experienced by both groups. Furthermore, both groups achieved comparable improvements in measures of adiposity, including BMI, WC and fat mass (mean change after 6 months: −2.1 to −2.4 kg).[22 23] Given that WL is recommended as one of the key strategies to reduce liver fat, it is possible the effects of PRT in our study were masked by the effects of changes in body weight and fat mass. There is compelling evidence that hypocaloric diets resulting in WL of 7%–10% of total body weight are associated with reductions in liver fat (~40%–50%) and liver markers in those with NAFLD.[41–45] In terms of FLI, a 32%–38% reduction was reported following WL of ~9%–11% via hypocaloric diets in 98 overweight and obese adults with NAFLD.[46] In our study of older overweight and obese adults with T2D, a significant although more modest (~13%–16%) reduction in FLI was observed after 6 months. The smaller changes in FLI observed in our study are likely related to the smaller

reductions in body weight (mean change 2.8% PRT+WL and 3.5% sham+WL). In agreement with our findings, another study conducted in 716 participants with NAFLD reported that a 3.4% reduction in total body weight was associated with a 12% reduction in FLI, after 6 months of a lifestyle intervention (diet and habitual physical activity).[47] Collectively, these findings support previous research highlighting a strong relationship between the magnitude of change (loss) in weight (adiposity) and subsequent changes in FLI.[48]

Another key outcome from our study was that the WL-related improvements in FLI during phase I in both groups tended to increase (return to baseline values) during phase II with the ad libitum diet and concomitant gains in weight and fat mass. In agreement with these findings, previous research conducted in 98 overweight and obese adults with NAFLD demonstrated that WL (diet induced) reductions in FLI were reversed ensuing subsequent weight regain.[48] However, it is worth noting that FLI did remain significantly below baseline values in the PRT+WL group after phase II in our study. Nevertheless, this was not significantly different from the sham+WL group which limits our ability to make claims about the potential benefits of PRT alone as a modality to maintain WL-induced improvements in FLI. A potential reason for why the home-based PRT training did not result in greater benefits to FLI relative to the sham exercise may relate in part to a reduction in training adherence (88%–73%) and total training volume (~52%) in phase II, as machine weights were replaced by free weights (dumbbells, ankle weights) which limited (and reduced related to phase I) the total training load prescribed.[23]

The strengths of this study are that it is the first to examine the effect of PRT+WL versus WL alone in NAFLD using FLI in older overweight and obese adults with T2D. The RCT design with a long-term follow-up (12 months), and high adherence to the high-intensity PRT are also noteworthy strengths. However, there are several limitations. First, this study represents a secondary analysis of a previous RCT with a small sample size that was not designed to detect any potential between-group differences in FLI. Second, liver enzymes and direct measures of liver fat were not available, and FLI was used as a surrogate determinant of NAFLD risk. Third, both BMI and WC are parameters in the FLI equation, and therefore changes in FLI are primarily mediated by reductions in body weight, and thus does not capture the potential beneficial effects of changes in lean mass on liver fat. Therefore, it is possible that PRT may have induced additive improvements in liver outcomes unable to be captured in the present study. Given most previous studies report liver fat as the primary outcome, capacity for more meaningful comparison between other PRT-related studies was also limited. Future studies may also consider a more comprehensive assessment of body composition, including muscle adiposity, as there is evidence that individuals with high muscle fat are more likely to have higher liver fat.[49]

CONCLUSION

In sedentary, older overweight and obese adults with T2D, 6 months of moderate WL was associated with improvements in FLI, but high-intensity PRT did not provide any added benefits. While these findings support the role for improving (reducing) weight and adiposity as a key strategy for the management of NAFLD in overweight and obese adults with T2D, the lack of any significant added benefits of PRT must be considered given the modest sample size. This likely limited our ability to detect any additive effects from this trial which represents secondary data analysis. Further large-scale and appropriately powered RCTs assessing liver-specific outcomes and other forms of exercise (eg, PRT combined with AT) are required to provide greater insight into the potential synergistic effects of exercise with WL in this cohort.

Contributors DWD: study design. RMD, ESG and S-YT: research concept. RMD and DWD conducted the research. CLF, GA and RMD: analyzed the data. CLF wrote the manuscript. ESG, S-YT, GA, DWD and RMD: reviewed and edited the manuscript. RMD is the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of data analysis.

Funding This study was financially supported by a grant (grant number: 98-0146) from the Victorian Health Promotion Foundation (VicHealth). The Rotary Club of Kew, Victoria, Australia and Soroptimist International, Brighton Division provided funds for the purchase of exercise equipment.

Competing interests All authors have completed the ICMJE uniform disclosure form and declare: no support from any organization for the submitted work, DWD has received research grants from the National Health and Medical Research Council, no other relationships or activities that could appear to have influenced the submitted work.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the International Diabetes Institute and Deakin University Human Research Ethics Committees (EC 26-99). All participants provided written informed consent prior to participation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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Study Protocol

The Long-Term Effects of Resistance Training and Diet in Elderly Type 2 Diabetics

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1.1 Objectives

The present study plans to assess the efficacy and feasibility of dynamic resistance training involving circuit weight training (CWT) in 60 overweight elderly persons with type 2 diabetes. More specifically, in a parallel study design with 3 phases, including an initial dietary run-in phase, this study will assess (Figure 1):

1. the feasibility of 24 weeks supervised dynamic resistance training within a laboratory-based setting combined with moderate energy-restriction and its effects on strength, glycaemic control, body composition, bone mineral density, lipid profile, blood pressure and general well-being, compared to moderate energy restriction alone (phase 2).
2. the feasibility of an additional 24-week home-based resistance training or resistance training within community/commercial facilities and its impact on muscular strength, glycaemic control, body composition, bone mineral density, lipid profile, blood pressure, general well-being and exercise behaviour (phase 3).

1.2 Background Information

Type 2 diabetes is frequently associated with adverse health outcomes, including hypertension, cardiovascular disease, stroke, and peripheral vascular disease. It is also well documented that poor glycaemic control is associated with the presence or progression of long-term complications such as neuropathy, nephropathy and renal failure, foot ulcers, lower limb amputations and visual disorders.

The importance of regular physical activity in type 2 diabetes is adequately described in several epidemiological studies such as the Da-Qing study in China [1], showing improved glycaemic control in people with diabetes and reduced diabetes risk in physically active individuals with impaired glucose tolerance. Furthermore, its favourable effects on glycaemic control support the role of increased physical activity for the prevention of diabetes complications, since data from the Diabetes Control and Complications Trial (DCCT) [2] have convincingly shown that improving glycaemic control in people with type 1 diabetes can prevent or delay the progression of long-term complications of diabetes. Similar data are accumulating for people with type 2 diabetes [3].

Nevertheless, the promotion of physical activity in type 2 diabetics, particularly older individuals, still remains a challenge. Studies documenting poor patient compliance have led to suggestions that increasing physical activity may not be a feasible means of improving diabetic control in older people with type 2 diabetes [4]. It is probable that aging itself contributes to exercise non-compliance, since it is associated with a host of metabolic and physiological changes that can affect functional capacity and impinge on an individual's ability to perform physical activity. Together these factors result in age-related decreases in muscle strength and aerobic capacity, which contribute to decreases in functional independence and lead to increased frailty and injury risk in the elderly [5, 6]. Furthermore, diabetes and its complications can accentuate the 'normal' age-related deterioration in physical function. Hence, many older type 2 diabetics may miss the benefits of regular physical activity on glycaemic control, cardiovascular disease, weight and psychological health.

Physical activity involving resistance (weight) training may be a logical approach in older individuals because of its positive effects on many of the physiological alterations that accompany aging. Current research indicates that age does not decrease the capacity of the muscle to adapt to resistance training. Indeed, in older individuals, resistance training

interventions employing moderate to high intensities (60 to 90% of maximum strength) have been shown to increase muscle strength and function as well as increase skeletal muscle mass [7, 8]. Favourable alterations in energy expenditure and body composition, including increased fat-free mass and decreased fat mass or body fat, with preferential decreases in the trunk region, have also been observed in some [7, 8], but not all [9], studies following resistance training. Other studies have also shown that resistance training can favourably influence serum lipids and blood pressure [10] and can improve insulin action in middle-aged/older men [11] and post-menopausal women [9]. There is also evidence that resistance training may increase or preserve bone mineral density in post-menopausal women [5, 22] and middle-aged/elderly men [23].

Clearly there is a deficiency in knowledge concerning the efficacy of resistance training in patients with type 2 diabetes. It is believed that previous discouragement for this form of exercise in individuals at risk of heart disease due to the fear of precipitating cardiac or vascular complications, together with its poor impact on aerobic fitness have contributed to this situation. Nevertheless, there is now a considerable body of evidence to indicate that moderate intensity, dynamic, high-volume (moderate to high number of repetitions) resistance training, such as circuit weight training (CWT), can be used effectively and safely in such individuals [12]. Indeed, mild to moderate dynamic resistance training has become an integral component in the physical rehabilitation of patients with cardiac disease [13]. Furthermore, because body weight is supported throughout, dynamic resistance training has the unique potential to overcome the orthopaedic stress commonly associated with endurance exercise involving prolonged periods of weight bearing.

While studies have shown that dynamic resistance training programs can be performed safely in type 2 diabetes patients, the efficacy and feasibility of this type of exercise in older (> 60 years) is not known. Furthermore, the impact of resistance training in combination with moderate energy restriction in type 2 diabetes patients has not been investigated. These issues will be addressed in a three-phase study, whereby the efficacy of dynamic resistance training within a supervised setting for 6 months in elderly type 2 diabetics will be assessed in combination with moderate energy restriction, followed by a 6-month period of non-laboratory-based resistance training performed at home and/or within community facilities.

It is postulated that the combination of resistance exercise training with moderate energy restriction will counterbalance fat-free mass loss often seen with energy restriction alone and may have additive or synergistic benefits in the non-pharmaceutical management of glycaemic control, cardiovascular risk factors and general well-being of elderly type 2 diabetics.

1.3 Description of Project

Eligibility Criteria

60 overweight male and females with type 2 diabetes, age range 60-80 years, will be recruited both from the clinics of the International Diabetes Institute (IDI) and in response to a local media campaign. Inclusion criteria will comprise established (> 6 months) but controlled (diet and/or medication) type 2 diabetes (Hb_{A1c} < 9.0 %), sedentary lifestyle (less than two 30 min sessions of vigorous exercise per week for the preceding 6 months) and a body mass index (BMI) > 29 kg/m^2 but < 40 kg/m^2. All volunteers will undergo further medical examination including medical history, physical examination, and a resting 12-lead ECG to determine suitability for participation.

Exclusion Criteria
Volunteers will be non-smokers or ex-smokers for at least 6 months. Volunteers with a severe orthopaedic, cardiovascular, or respiratory condition that precludes participation in an exercise program will be excluded. Those taking insulin or lipid-lowering medication will not be included. Poorly treated hypertensives (anti-hypertensive medication and BP > 160/90 on at least two occasions) will be excluded.

Withdrawal Criteria
Volunteers who have successfully completed 12 weeks or more of the laboratory-based intervention or who for medical or personal reasons wish to withdraw from the study, will have all endpoints measured and will be considered in the final analysis. Withdrawals prior to this time will whenever possible be replaced.

Sample Size
Based on the experience of an Australian study involving exercise training in older type 2 diabetic patients over a 6-month period [4], 30 participants in each study group will provide at least 80% power to demonstrate a 0.6% decrease in glycated haemoglobin or a 0.1 mmol/l increase in HDL-C. Assuming that a retention rate of at least 80% is achieved, this will require the recruitment of 75 participants. The proposed 24-week duration of resistance training or energy restriction in phase 2 should be sufficient for changes in glycated haemoglobin and body composition.

Study Location
The study will be predominately conducted at Deakin University (Toorak). Existing facilities and resources will be used for the collection of laboratory and clinical measurements and administration of the strength testing and training protocols.

Recruitment
Patients attending the diabetes clinics at the International Diabetes Institute (IDI) will be formally invited to participate in the research project in a document distributed by their supervising physician. This document will outline the aims of the project and the procedures involved and will be similar to the subject information sheet. Subjects will be in a dependent relationship with their supervising physician, however, there shall be no prejudice to further medical care should the individual choose not to participate in the study and may withdraw at any stage. In addition, advertisements for the study will placed on notice boards throughout the clinic. A local media advertising campaign (newspapers, radio) will also be initiated to seek appropriate volunteers.

Screening
The research nurse, in conjunction with the supervising physician, using previous medical records held at IDI initially will identify the suitability of volunteers who wish to participate according to the inclusion and exclusion criteria outlined above. A telephone screening questionnaire will also be used to identify potential volunteers (Appendix A). Those who appear suitable will attend a screening visit at Deakin Toorak. During this visit, $HbA1_c$ and BMI will be determined, and a physician will decide on the suitability of volunteers who wish to participate according to the inclusion and exclusion criteria outlined above. Suitable volunteers will be asked to a complete screening questionnaire to obtain lifestyle information including medical history, medication use, alcohol consumption, past tobacco use and physical activity levels during work, domestic and leisure activities (Appendix A). A resting 12 lead ECG will also be performed. Participants will be required to give informed consent before commencing the study. Eligible participants will be required to provide contact details of their supervising physician who

will be given a description of the study and its requirements and utilised as a point of reference in the event of adverse effects arising during the study.

1.4 Study Design

The study will be completed over 3 phases:

Phase 1: All participants will be instructed and guided by a dietitian for 4 weeks on achieving a standard diabetic diet according to current diabetic dietary guidelines [14]. During this 4-week period all participants will be familiarised with the resistance exercise equipment and their strength determined by measurement of one-repetition maximum (1RM).

Phase 2: After the initial clinical and laboratory measurements, participants will continue with the diet and will be randomly assigned (age/sex/BMI matched) to either:

1. Progressive resistance training (supervised 3 times per week) + Moderate Energy Restriction
2. Placebo exercise (supervised stretching/flexibility exercises 3 times per week) + Moderate Energy Restriction

Supervised training will be performed in a group setting for a period of 24 weeks, during which time participants will be instructed to follow the dietary recommendations. Alterations in medication will be documented. Maximum strength (1RM), clinical and laboratory measurements will be assessed before the intervention, at 12 weeks, and after the 24-week intervention. Participants randomised to resistance training will have strength reassessed monthly to account for strength gains.

Phase 3: At the completion of phase 2, participants will be provided with individualised instruction on how to perform resistance training or flexibility training at home and/or within commercial/community facilities. Questionnaires completed at the end of phase 2 will be utilised to initiate appropriate behavioural strategies based on the Transtheoretical Model (TTM) and social-cognitive theory (SCT) (Questionnaires to be developed). Regular telephone contact will be made during this period. Participants will return to the IDI for the assessment of strength, blood measurements, blood pressure and body composition after 12 weeks and again 12 weeks later during this phase.

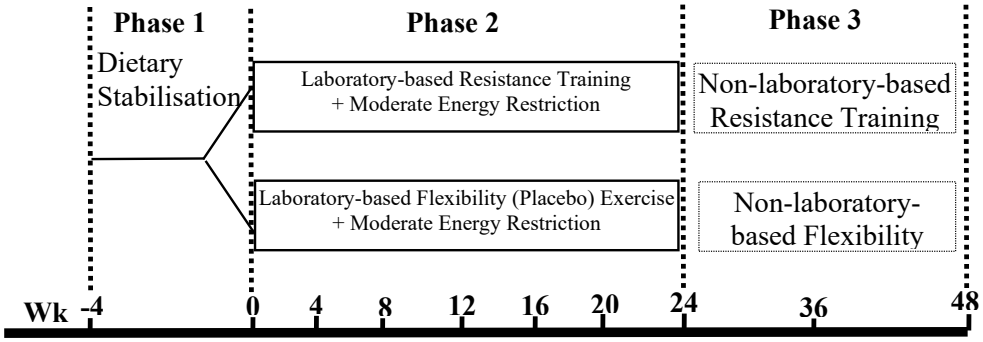

Figure 1: The proposed study design

Diet

During phases 1 and 2, all participants will be guided by a dietitian to follow standard diabetic dietary guidelines [14]. This includes Carbohydrate 55-60%, Protein 0.8 g/kg, Fat < 30%, Cholesterol < 300 mg/day, Fibre 40 g/day and P/S ratio > 1.

Volunteers will be asked to complete 2 weighed, 3-day (two working days, one weekend day) food records during Phase 1 to estimate energy requirements. At the completion of the dietary run-in period, all volunteers will receive dietary counselling about the diet plan at the appropriate energy level to be followed throughout the duration of the study. During phase 2 (intervention), each volunteer will complete four 3-day food records, each representing two weekdays and 1 non-weekday of each week. All analyses of nutritional data will be performed by a dietitian using the Diet 1 V4.22 nutrition analysis computer program.

Moderate Energy Restriction
In addition to the above-mentioned diet, during phase 2 participants will undergo further individualised dietary counselling fortnightly or whenever required to achieve moderate energy restriction. This diet will be tailored on an individual basis to induce approximately 0.25 kg weight loss per week. It is acknowledged that participants involved in CWT may require less energy restriction than controls due the increased energy expenditure of the program. Body mass will be measured for all participants weekly during the intervention. During the final 4 weeks of the 6-month program, all individuals will be instructed to maintain a constant weight on diets similar in composition to the diet advised during phase 1.

Self-Blood Glucose Monitoring (SBGM)
During phase 2, participants will be required to perform self-monitoring of blood glucose using portable monitors on 4 days of the week (2 exercising days, 2 non-exercising days). On these days, they will be required to perform SMBG in the morning prior to breakfast (fasted) and immediately following the exercise session or at the same time on the non-exercising day. The correct procedures required for the use of the blood glucose monitor will be provided by IDI diabetes educators. The participants will be required to document their blood glucose level on a standardised record form and return it at the completion of each week. Dr Dunstan's previous experience with this protocol but with additional measurements performed 2 hours after lunch and the evening meal, shows that persons with type 2 diabetes can successfully achieve the required measurements with adequate instruction and encouragement and are able to comply with the requirements for at least 8 weeks [15, 16].

Maximum Strength Testing
Following initial familiarisation sessions, one-repetition maximum (1RM) strength will be determined for each exercise used in the circuit for all participants under the supervision of a trained instructor. Participants will be given a brief warm-up using a light workload prior to each exercise. Following the successful completion of 3-5 repetitions and after a brief rest (1 min), the workload will be increased incrementally until the participant can perform only one complete repetition (1RM). This weight will be used to determine the appropriate training intensity (60-80% 1RM). Strength testing will be repeated after 3 months and at the end of the laboratory-based intervention for all participants and monthly during the intervention for participants involved in ST program to account for strength improvements. During phase 3, all participants will return to the exercise laboratory after 3 months and at the end of 6 months for strength testing.

Progressive Resistance Training (PRT) Program
Supervised PRT will be performed in an exercise laboratory on 3 non-consecutive days of the week for 24 weeks. Pin-loaded weight machines and free-weights will be used. A warmup and cool down will be performed before and after the exercise session. Participants will perform 8-10 repetitions at the appropriate intensity (60-80% 1RM) in a slow, controlled manner within 30 seconds. They will then rest for 30-60 seconds before proceeding to the next exercise station. Three sets of between 8 and 10 repetitions will be completed during each session. Each exercise session (approximately 45 mins) will be supervised by an experienced instructor to

ensure correct, safe techniques are performed and to monitor the appropriate amount of exercise and rest intervals.

Stretching/Flexibility (Placebo) Program
This program will serve as a control exercise program and is intended to provide participative involvement and to minimise co-intervention bias. Participants will attend the exercise laboratory 3 times per week, during which a series of stretching/flexibility exercises will be performed for 30 minutes. Dr Dunstan's previous experience with this exercise regimen indicates that this program usually does not increase the pulse rate above 100 bpm and does not induce changes in cardiovascular fitness or glycaemic control in middle-aged type 2 diabetic patients [15]. His PhD research experience demonstrated excellent compliance with this placebo exercise regimen performed 3 times per week for 8 weeks in a supervised setting, as shown by having 20 out of 24 participants complete all sessions during this period [15].

Non-Laboratory-Based Training
This encompasses a 24-week period where participants will be required to follow an individualised resistance training or flexibility training program at home and/or within community/commercial facilities. Participants will be individually guided and provided with written information on the selection of exercise equipment and training facilities at the end of the laboratory-based intervention. Provisions will be made for the use of IDI weight equipment during this period for participants who do not wish to purchase their own equipment. Questionnaires based on TTM and SCT described earlier will be utilised to implement and analyse exercise behavioural change (To be developed). Initially, participants will be telephoned by a staff member every week for the first 4 weeks to check his or her progress. Thereafter, telephone contact will be made fortnightly. This will be used to administer questionnaires, monitor progress, answer questions, and provide individualised feedback. Participants will also be required to complete weekly activity logs.

Non-Intervention Controls
Volunteers fulfilling the eligibility criteria but excluded on the basis of having a previous history or physical signs suggestive of ischaemic heart disease only will be invited to serve as comparison group of participants (non-intervention controls) for bone mineral density and body composition measurements. This group will not receive diet or exercise intervention and will undergo body composition assessment (anthropometry, BIA & DEXA) and have glycated haemoglobin, 24-hour urine and questionnaires measured once at baseline (end of phase 1) and again after 6 months (end of phase 2) and 12 months (end of phase 3). This group will be instructed to maintain their usual dietary and physical activity patterns throughout the 12-month period. Participants in this group will be required to give informed consent to participate.

Compliance with Study Requirements
Compliance with the diets will be assessed by weekly food checklists and monthly 3-day food records. A seven-day physical activity recall questionnaire [17] will be administered fortnightly during phases 2 and 3 to monitor habitual activity levels (Appendix A). This questionnaire takes approximately 10 minutes to complete. Compliance with the exercise training regimens during phase 2 will be assessed by attendance to the supervised exercise sessions. Dr Dunstan's previous experience with exercise training shows that excellent exercise compliance can be achieved in type 2 diabetic patients in such studies. In the previously mentioned study involving CWT, participants were required to attend exercise sessions held on campus at UWA 3 times per week for a period of 8 weeks. As already indicated, all participants completed at least 22 of the 24 exercise sessions required, with 9 of the 11 participants completing all 24 sessions over this period. His other PhD research study required all participants to attend 3 exercise sessions per week for 8 weeks at Royal Perth Hospital, located in the CBD of Perth. In this study, half

were assigned to moderate aerobic exercise training involving stationary cycling for 30 mins, while the remainder performed light exercise involving stretching/flexibility exercises for 30 minutes. Briefly, of the 52 participants who commenced the intervention, only 3 were excluded from the final analysis. Despite the intensive nature of the study, all participants were able to successfully complete at least 21 of a possible 24 exercise sessions during this period (88% adherence), with 45 participants (92%) completing all sessions. Dr Dunstan has identified several helpful initiatives to improve compliance with study requirements. In particular, conducting group exercise sessions proved to be highly beneficial because it enabled social interaction among participants with similar medical concerns within a friendly atmosphere. Also, in recognition of work and family commitments, he gave participants the choice of early morning or evening exercise times. In the event of a missed session, participants were telephoned and a supplementary catch-up session (usually a Saturday morning) was organised. It is envisaged that the recruitment of elderly participants, many of whom will be retired, will enable even greater flexibility in exercise session scheduling in the proposed study. Questionnaires administered at the completion of laboratory-based intervention will be used to identify each individual's stage of readiness for change and the appropriate intervention strategy based on TTM and SCT administered to enhance exercise compliance during phase 3. In addition, participants will be telephoned fortnightly and will be instructed to complete logs describing the exercise frequency, duration and rating of perceived exercise for each training session. These will be returned monthly via mail.

1.5 Data Collection

Blood and Urine Measurements

A small blood sample (2.5 ml) will be collected during screening for the measurement of glycated haemoglobin levels. A 25 ml fasting blood sample will be collected before, during (12 weeks) and after the laboratory-based intervention. Samples will be assayed for: routine biochemical and haematological profile, glucose, insulin, C-peptide, serum lipids (triglycerides, total cholesterol, HDL-C and LDL-C), glycated haemoglobin, testosterone, estrogen, insulin-like growth factor (IGF-I), intact parathyroid hormone and markers of bone formation (procollagen type I propeptide, osteocalcin). A 24hr urine collection will be performed at these time points for measurement of urinary sodium, potassium, calcium, creatinine and albumin excretion and markers of bone resorption (pyridinoline cross-links). Measurements will be assessed again following 12 weeks and 24 weeks of non-laboratory-based training.

Laboratory Measurements

All blood samples will be centrifuged immediately at IDI and then sent by courier to an off-site testing laboratory for analysis. Serum for insulin assays will be frozen at - 70 degrees and measured in a single assay to minimise inter assay variability.

Body Composition and Bone Mineral Density

Anthropometric measurements, including body mass, height, skinfold and circumference measurements will be assessed using standardised protocols by the International Society of the Advancement of Kinanthropometry and administered by a Anthropometry-certified graduate officer. Dual energy X-ray absorptiometry (DEXA) will be performed under the guidance of a trained technician once at baseline and once at the end of the respective six-month interventions to assess total body, lumbar spine and proximal femur bone mineral density, fat-free mass and lean mass. In addition, Bioelectrical Impedence Analysis (BIA) will be performed once during baseline and once at the end of the end of the respective interventions. Fat mass, fat-free mass and total body water will be estimated, based on BIA. This technique of body composition measurement was recently assessed by a panel of experts in the US [18], who concluded that BIA provides a reliable estimate of total body water under most conditions and is a useful technique for body composition in healthy individuals and those with mild-to-moderate

obesity, including diabetes mellitus. These procedures will be used collectively to assess body composition changes resulting from the respective interventions.

Blood Pressure
Resting blood pressure will be measured at the beginning, mid-way (3 months) and at the end of each respective intervention period. Systolic and diastolic blood pressure will be determined manually by a trained assessor using a conventional mercury sphygmomanometer with participants having rested (5 mins) in a seated position. The mean of 3 separate readings (30 secs apart) will be recorded.

Physical Function Tests
A collection of simple tests will be used to measure changes in physical function. These include: a timed backward tandem walk test over a 6-metre course (dynamic balance); standing balance, measured with semi-tandem, tandem, and one leg stands in sequence and timed; chair stand (no. of stands in 60 seconds); reaching down and returning to standing position (seconds); 3 metre walk (lengths in 60 seconds); 360° turn (steps to complete); and manual dexterity (seconds required to turn a coin five times).

General Health and Well-Being
A self-reported, generic measure of health status that has been validated for adult age groups in Australia, the US and the UK called the SF36 questionnaire will be used to assess general health and well being at baseline and after 24 weeks of both laboratory-based and non-laboratory-based training (Appendix A). This questionnaire measures 8 important health concepts including, physical function, the impact of both physical health and emotional health on role performance, bodily pain, social functioning, general mental health, vitality and general health perceptions. This questionnaire was recently used in the 1995 ABS National Health Survey.

Exercise Behaviour
As indicated, questionnaires administered at baseline and at the end of each respective intervention period will be utilised for the initiation of individualised intervention strategies based on the Trans-Theoretical (stages of change) model [19] and social-cognitive theory [20]. These questionnaires will be used to analyse the implementation and maintenance of exercise behaviour change. Pre-testing on specific measures and items will be used to determine whether paper and pencil or personal interview formats, or a combination of these, are most appropriate. Self-efficacy and stage of change items have been developed through earlier studies and can be adapted and expanded for elderly type 2 diabetic patients.

1.6 Statistical Analysis
Data will be analysed using the Statistical Package for the Social Sciences (SPSS Inc., USA) for Windows. Independent t-tests will be used to assess between-group comparisons for the changes during the respective interventions. A pooled time-series regression analysis using a random effects model [21] will be used to evaluate changes in self-monitored blood glucose readings during the laboratory-based intervention period.

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