Sequences of Aerobic and Resistance Exercise and Cardio-metabolic Functions in T2D (ARRA)
NCT06145542
January 25, 2025
Study Protocol and Statistical Analysis Plan

Participants

Fifty-six T2D patients aged 50 years to 70 years, with a duration of T2D of at least one year. T2D is diagnosed by physicians according to the following criteria: random blood glucose ≥11.1 mmol·L-1 (200 mg·dL-1), fasting plasma glucose ≥7.0 mmol·L-1 (126 mg·L-1), oral glucose tolerance test ≥11.1 mmol·L-1 (200 mg·dL-1), or HbA1c ≥6.5% (48 mmol/mol).

Exclusion criteria are patients with T1D, diseases diagnosed by physicians that are unsuitable for exercise intervention, patients who have regular physical activity habits (90min moderate intensity exercise or 75min high intensity exercise), and currently under dietary program for weight loss.

Randomization

Participants are randomized in a 1:1 ratio into aerobic-then-resistance exercise group (AR, n=28) and resistance-then-aerobic exercise group (RA, n=28). Randomization is stratified by age and HbA1c (≤ or >medians) with a block size of 4.

Continuous glucose monitoring

Participants undergo a 14-day continuous glucose monitoring (CGM, FreeStyle libre Pro, Abbott Diabetes Care Ltd, Witney, UK) started at two time points: one week before initializing the exercise intervention and at the 8th week of the intervention. An ambulatory glucose monitoring sensor is attached to the posterior aspect of the participants' non-dominant arm, with a guide needle implanted into the subcutaneous tissues. Sensor attachment is manipulated by a research assistant at the study site, between 8:00 to 10:30 on the same day of blood sample collection. Participants do not have access to their own CGM data during the monitoring periods. Following the monitoring period, data are exported and saved from the sensor using scanner of the CGM system by a research assistant at the study site. CGM data collected starting from 00:00 on the second day following the sensor attachment until 00:00 on the day of sensor detachment are included in the analyses.

Assessments of regular glycemic outcomes and covariates

Baseline information included age, sex, duration of T2D, and medication are obtained by the specialist physician during the recruitment procedure. Prior to the exercise intervention, participants’ body mass index (BMI) and blood pressure were measured at the study site. Measurements of participants' fasting plasma glucose, fasting insulin, and hemoglobin A1c (HbA1c) are taken within the week before and after an 8-week exercise intervention. Following an overnight fasting period of ≥8 hours, 10 ml of venous blood is collected before breakfast (7:00-8:00), and tested by the Laboratory Department of the Community Health Service Center.

Exercises intervention program

Exercise intervention is implemented in the gym room at the Community Health Service Center. The room was equipped with multiple devices for both aerobic and resistance training, which allowed a maximum of six participants to perform exercise at the same time. Room temperature is between 18-22 °C, controlled

by air conditioning. The training program is designed to take place three times a week for a total of eight weeks. Exercise intervention is scheduled for approximately 70 minutes per session (30 minutes of aerobic and 30 minutes of resistance, no break between two types, 5-min of preparation and 5-min relaxation stretching movements before and after each intervention), performed between 8:00 to 11:00 or between 14:00 to 16:30, Monday through Saturday. Exercise sessions starts at least 30 minutes after meals.

The target heart rate during aerobic exercise is set as resting heart rate (HR) + 40%-70% of heart rate reserve (HRR). Participants' HRR was calculated based on their resting HR and maximum heart rate (HRmax=208-0.7×age) as HRmax - HR. Heart rate monitors (OH1, Polar Oy, Oulu, Finland) are used during all exercise sessions to track exercise intensity and ensure that it remained within the specified range. Aerobic exercise is performed on bicycle ergometers (Ergoselect 100K, Ergoline GmbH, Bitz, Germany) for a continuous 30 minutes with a progressive intensity of 40%-70% HRR. Resistance level is set according to an adaptive training prior to the first intervention, pedal cadences are 50-60r/min.

Resistance exercise is conducted using a set of equipment (Nanjing Kuanyue Health Technology Co., Ltd, Nanjing, China) including chest press/ row, leg extension/ curl, abdominal/ back, biceps/ triceps, inner/ outer thigh, and push/ pull machines. Prior to conducting the 1 repetition maximum (RM) testing for the major muscles of the upper and lower limbs, all participants receive proper instructions on how to use the equipment. The Brzycki 1-RM prediction equation is used to estimate the 1RM based on the recorded resistance and repetitions. All participants performed resistance exercise with a weight of 60%-80% 1RM. Movements on each machine are repeated 10-12 times per unit for a total of 4 units, with a-30 second break between units. Resistance training involves progressive overload over an 8-week period.

In all intervention sessions, participants in AR group complete aerobic exercise before starting resistance exercise, while participants in RA group performe two types of exercise in a reversed order. Participants are instructed to maintain their usual lifestyle but refrain from engaging in other forms of regular exercise throughout the intervention period. Prior to enrollment and during the intervention period, weekly dietary guidance on diabetes management is delivered by a dietitian from the Community Health Service Center to minimize the possibility of dietary changes during the intervention.

Statistical analysis plan

A sample size of 54 participants is considered adequate to achieve 95% power for detecting within-between interactions, using measures taken at pre- and post-intervention time points, based on a medium effect size (f = 0.25, G*Power, version 3.0.10). Analyses are carried out following the intention-to-treat principle. The personnel who conduct the analyses are blinded about participants' randomization group. Data are checked for normality by using the Shapiro-Wilk test. Between group comparisons of the outcome variables are

conducted using analysis of covariance (ANCOVA), controlling for the baseline value of the variable of interest, while within-group pre-post-intervention comparisons are performed using paired samples t-tests. Between-group comparisons of non-normally distributed outcome variables are conducted using the Mann-Whitney U test, and within-group comparisons are conducted using the Wilcoxon signed-rank test. Repeated measures analysis of variance (ANOVA) is used to analyze blood glucose levels at various time points during exercise and recovery periods (90 minutes post-exercise), including the main effects of time and group, as well as interaction between time × group. Additionally, the change rates of overnight blood glucose levels recorded by CGM on non-exercise days are analyzed for the main effect of group. Between group comparisons of baseline values are analyzed using independent samples t-tests, Mann-Whitney U test, or chi-square test. All tests are two-tailed, P values < 0.05 are considered statistically significant. All analyses are performed using SPSS statistical software version 26 (IBM Corp., Armonk, NY, USA).