# Comparing the Effects of Six-Month Aerobic Exercise and Resistance Training on Metabolic Control and Beta Cell Function in Chinese Patients with Prediabetes: A multicenter randomized controlled trial


## Abstract

### Aims

It is clear that aerobic training (AT) can delay pancreatic exhaustion and slow the progression from prediabetes to T2DM, but there is little information about the effects of resistance training (RT) on people with prediabetes. To compare the effectiveness of RT and AT in improvement of metabolic control and beta cell function protection among people with prediabetes.

### Methods

248 participants with prediabetes were randomized to three groups－AT (n=83), RT (n=82) and control (n=83). RT consisted of 13 different resistance exercises per session using elastic string. AT performed aerobic dance at 60~70% of maximum heart rate (HRmax). Both exercises were performed 6 months and 3 times/week. The improvement of metabolic control was the primary outcome and second outcomes were HOMA2-β and HOMA2-IR. Longitudinal changes between groups were tested with repeated-measures analysis.

### Results

217 out of 248 participants finished the study, but all participants were included in the intention-to-treat analyses. There was no statistical difference in demographic characteristic ($P > 0.05$). The average HbA1c in three groups was 5.98, 5.92 and 5.95,

respectively. Within-group analyses showed that fasting blood glucose (FBG), HOMA2-IR, HOMA2-β decreased in RT group, whereas FBG and HbA1c decreased significantly in AT group. Change in HbA1c was not significantly greater in RT cohort than in AT cohort ($P$ = 0.059), but the decrease in HbA1c in both exercise groups were higher than in control group ($P$<0.05).

**Conclusions**

Resistance training appears to improve metabolic control and preserve beta cell function comparable to aerobic training in participants with prediabetes.

**Highlights:** 1): Aerobic exercise and resistance exercise both improve glucose control.

2): Resistance training appears to preserve beta cell function to a degree comparable to that observed with aerobic exercise with prediabetes patients.

**Trial registration**

Clinicaltrials. gov Identifier: NCT 02561377.

**Key words**

Aerobic training; HbA1c; HOMA2-β; Prediabetes; Resistance training

## Introduction

Impaired glucose regulation (IGR) is characteristic of prediabetes. The prevalence of IGR has dramatically increased in China, half of the entire adult (50.1%) have had prediabetes in 2010[1]. According to the 20-year China Da Qing Diabetes Prevention Study[2], 92% of persons with impaired glucose tolerance (IGT) will progress to overt type 2 diabetes mellitus (T2DM) in 20 years, imposing a large health and economic burden on China. It has been showed that beta cell function decreased in patients with

prediabetes[3-4]. Studies used hyperglycemic clamp in IGT patients found 35-62% reduction in first-phase and 30-51% reduction in second-phase of insulin secretion compared with normal glucose tolerance (NGT)[5-6]. Autopsy data indicated that the beta cell volume of impaired fasting glucose (IFG) patients was decreased by 40% compared with non-diabetic controls[7]. In addition, diabetes-associated complications may affect patients with prediabetes as well as some individuals with insulin resistance and normal glucose tolerance[7-8]. To reverse the impending diabetes epidemic, it is clearly imperative to focus on prevention. Interventions for individuals with prediabetes should aim to improve insulin resistance, preserve islet beta cell mass, and prevent further loss of beta cell function.

Exercise and diet are the cornerstones of diabetes management[9]. It is generally accepted that regular physical activity provides substantial health benefits to individuals with T2DM and prediabetes[10-11]. The Diabetes Prevention Program (DPP) showed that lifestyle intervention among people with prediabetes can reduce T2DM incidence by 58%[11]. Aerobic training (AT) was used in DPP can improve insulin action, delay pancreatic exhaustion, and slow the progression from prediabetes to T2DM[11]. Another Resistance training (RT) improves insulin sensitivity[12] in a rodent model and glycaemia control in patients with prediabetes[13-14]. An updated research result showed that supervised resistance training can prevent diabetes incidence in people with prediabetes[15]. A study which was combined with AT and RT, resulted in significantly improved glycemic control, central adiposity, musculoskeletal and aerobic fitness in a

population of individuals with prediabetes[16]. Comparing to machine resistance training, elastic cord is a cheaper, safer, more convenient and effective sports equipment[17]. Therefore, in our study we used elastic cord. However, duration of these interventions was most relatively brief (10-12 weeks). Moreover, studies did not distinguish effects on beta cell function from effects on insulin sensitivity or allow for comparisons between RT and AT. Both need to be understood if we are to implement optimal methods to delay or prevent the onset of T2DM. Accordingly, this study aimed to analyze improvement in metabolic control, beta cell function during a six-month intervention in prediabetes undergoing either resistance training or aerobic exercise. We hypothesized that six-month resistance exercise would have effects on decreasing HbA1c and improving HOMA2-β, HOMA2-IR.

## METHODS

### Study Participants

Participants were enrolled at Center 1 (The Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing, China) between January, 2014 and April, 2014. Participants were recruited at two other centers between May, 2014 and December, 2014 (Center 2, Danyang People's Hospital of Jiangsu Province, Danyang, China; Center 3, The First Affiliated Hospital of Guangxi Medical University, Guangxi, China). Those who had a history of prediabetes (already diagnosed by OGTT) were administered a confirmatory OGTT. Those without a history of prediabetes were pre-screened to confirm eligibility. Inclusion criteria specified

individuals of either sex <75 years old with prediabetes defined by any of the following three standards: 1) FBG between 100 mg/dL (5.6 mmol/L) and 125 mg/dL (6.9 mmol/L) (IFG) on two separate occasions. 2) Blood glucose concentration of 140 mg/dL (7.8mmol/L) to 199 mg/dL (11.0 mmol/L) two hours after ingestion of 75g oral glucose (IGT). 3) HbA1c between 5.7% and 6.4%[18] on two occasions. Participants were excluded if they had been diagnosed with diabetes, cardiovascular or cerebrovascular disease, were pregnant or breastfeeding, had severe physical disability, or lacked the intellectual or emotional capability to adhere to the study protocol.

**Trial Design and Randomization**

A total of 248 participants met inclusion criteria and were invited to participate in the study. The flow diagram of this study was shown in Fig. 1. Participants were assigned to one of three groups using numbers generated randomly by computer: (1) a control group (C group, n=83); (2) an aerobic training group (AT group, n=83); (3) a resistance training group (RT group, n=82). The study was approved by the ethics committee of the Affiliated Hospital of Integrated Traditional Chinese and Western Medicine. Participants provided written informed consent prior to enrollment.

**Screening maximal oxygen consumption ($VO_{2max}$)**

For safety purposes, a modified Bruce protocol treadmill test (ERS.2, Ergoline, German) was used to determine maximum heart rate (HRmax) and $VO_2$max before starting the exercise program. Throughout the treadmill test we monitored participant blood pressure and heart rate according to standard procedures and terminated the test when

the participant reached volitional fatigue. During the test, the heart rate of patients was monitored by a heart rate watch (Polar® A370, Polar, Finland), and each individual's HRmax was defined when they rate their dyspnea and fatigue. All participants were performed continuous monitoring of electrocardiogram during these maximal exercise tests. Those found to have typical angina pectoris, syncope, systolic blood pressure drop ≥10mmHg, sustained ventricular tachycardia and ST elevation of ≥1.0 mm were excluded from the this study.

**Exercise Programs**

**Aerobic training program**

Participants participated in the AT sessions 3 times/week for 60 minutes/session under the supervision of a qualified research nurse (including 5 minutes of warm-up, aerobic dancing for 50 minutes and 5 minutes of stretching exercises). Participants performed aerobic dancing at 60~70% of their HRmax as determined by their treadmill test result. Heart rate was monitored by Polar during training, which was connected to the computer. When the heart rate exceeded 60~70% of their HRmax, we would adjust the scheme. The target heart rate range was progressively increased as described. The exercise component was aerobic dancing derived from a previously published diabetes quantitative exercise research project in one of our study centers, the First Affiliated Hospital of Guangxi Medical University, Guangxi, China.

**Resistance training program**

Participants were involved in RT sessions 3 times/week supervised by our research assistants in the gardens of 2 hospitals (Nanjing and Danyang), and the community squares (Guangxi Guilin). There were 13 exercise pieces in the protocol: leg presses, leg extensions, chest presses, pull downs, rowing motions, calf raise, seated leg curl,

shoulder presses, straight-arm forwards, straight-arm backwards, leg rotation left, leg rotation right and abdominal crunch movements. The protocol took approximately 50 minutes to complete.

Strength was assessed at baseline by performing a one repetition maximum (1RM) test (NitroPlus, Nautilus, Inc., Vancouver, WA, USA) on the press and extension of arms and legs, and we accurately corrected the resistance by measuring 1RM throughout the RT intervention. The resistance for each bungee cord during the first 1-2 weeks was set by the trainers at 50% of 1RM, with frequency of 1-2/week, and 6-8 repetitions of 13 different activities. And then gradually increased to 3/week, 10-15 repetitions at 60% of 1RM until completing the intervention[15].

**Oral glucose tolerance test (OGTT)**

Before and after the experimental period, blood was drawn after an overnight fasting and 2-hour after 75g glucose intake. Post-tests were conducted within 7 days after the end of the intervention period. For personal issues, 6 subjects had their blood drawn 14 days after the end of the intervention period.

OGTT was performed by administering a 75 g glucose solution after a 10-h fast with plasma glucose sampling before and 120 min after glucose administration. The OGTT was performed both before and after the completion of the six-month exercise program. Plasma glucose was analyzed by a YSI 2700 Select Biochemistry Analyzer (YSI, Inc, Yellow Springs, OH). Serum insulin was measured by solid-phase, enzyme-labelled chemiluminescent immunometric assay (Immulite 2000; Diagnostic Products, Los

Angeles, CA). $HbA_1c$ was determined by high performance liquid chromatography (Bio-Rad Diamat, Munich, Germany).

**Blood lipid assays**

The fasting serum concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and plasma triacylglycerol were determined by colorimetric methods using commercial kits (Abbott, Abbott Park, IL) with an Architect c8000 analyzer (Abbott) according to the instructions of the manufacturer.

**Anthropometric measures**

Body weight and height were measured in all participants wearing light clothing and standing barefoot. Body mass index (BMI) was calculated from weight and height ($kg/m^2$). Waist circumference was measured at the midpoint between the lower ribs and the iliac crest at the end of normal expiration. The method of measuring abdominal adipose tissue was reported elsewhere[19].

**Diet and physical activity**

All participants were asked to follow a healthy diet (55-60% carbohydrate, 15-20% protein, and 25-30% fat) throughout the study. Individualized meal plans were made by the dietitian and they were asked to record their 24-hour food intake during the enrollment period and throughout the six-month study.

Participants completed a questionnaire to quantify their routine physical activity before entry into the study. Participants were asked to record the frequency (days/week) and

duration (h and min/day) of daily physical activity. All participants were requested to maintain habitual physical activity throughout the intervention.

**Statistical analyses**

Power and sample size calculations were based on a predicted HbA1c difference of 0.66 HbA1c units with an SD of effect of 1.2 HbA1c units[20]. The required sample size for 80% power using a 2-tailed test at alpha=0.05 is 70 each group and an expected dropout rate of 15%. Thus, we aimed to recruit 242 subjects in total. Finally, 248 subjects were enrolled in this study. Analysis used the intention-to-treat principle and included all randomly allocated participants. The normality of distribution was assessed by skewness and kurtosis analysis. Baseline data were compared with the use of one-way analysis of variance (ANOVA) or Kruskal-Wallis analysis. A Chi quadrate test for categorical variables. Within-group comparisons (baseline and six months) used paired t-tests. Longitudinal changes between groups were tested with the use of repeated-measures analysis of variance. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using SPSS 24.0 (SPSS Inc, Chicago, IL, USA).

**RESULTS**

248 patients were included, and 217 patients completed the 6-month study, so the adhesion rate is 87.5%. Throughout the study period, no exercise-related adverse events were found. The dropouts in AT, RT and control group were 10, 11, and 10, respectively. As shown in Table 1, there were no differences in baseline variables across groups. The

mean age in AT group was 60.93, RT group was 59.91 and control group was 60.73. The average HbA1c in three group was 5.98, 5.92 and 5.95, respectively.

As shown in Table 2, there were several statistically significant differences in metabolic outcomes among three groups and between the aerobic and resistance exercise groups. After training, no significant difference was found in the change of HbA1c between AT and RT (*P*=0.059). But both were significantly better than the control group (Group-by-time interaction *P* <0.001). With respect to FBG, the change of FBG was (-0.04 ([-0.07, -0.01]) in the AT group, (-0.07 ([-0.10, -0.04]) in the RT group and (0.06 ([0.03, 0.09], [square root mean, 95% CI]) in the control group (Group-by-time *P*< 0.001). However, there was no significant difference between the AT and RT groups. At six months, both the AT and RT groups experienced significant improvement in HOMA2-β vs. the control group (Group-by-time interaction *P*<0.001). The improvement in HOMA2-β was no significantly greater in the resistance exercise group (0.36 [0.04, 0.69]) than in the aerobic exercise group (0.15 [-0.19, 0.49] [square root mean, 95% CI], *P* = 0.7). Body weight, BMI, 2hPG and SBP improved in both exercise groups compared to controls (*P* <0.05); although body weight, BMI, 2hPG and SBP decreased more in the AT group than among those in the RT group, the differences were not statistically significant.

Figures 2, 3 and 4 depicts the range of individual subjects' responses among three groups. After aerobic exercise, 45.8% of the participants showed reduction in $HbA_1c$, 54.2%, 57.8%, and 51.8% of participants showed a decrease in 2hPG, FBG, HOMA2-IR,

and HOMA2-β was improved in 53% of participants, respectively (Fig. 2). Resistance exercise decreased $HbA_1c$ in 37.8% of participants, 40.2%, 58.5%, and 57.3% of the participants had reductions in 2hPG, FBG and HOMA2-IR, and HOMA2-β was improved in 50.0% of participants, respectively (Fig. 3). In the controls, 22.9% of the participants had a decrease in $HbA_1c$, and the percent decreases in 2hPG, FBG and HOMA2-IR were 28.9%, 16.9%, 38.6%, 28.9% of participants had an increase in HOMA2-β, respectively (Fig. 4).

Fig. 5 depicts results for HbA1c, 2hPG, FBG, HOMA2-IR, HOMR2-β and insulin before and after six-month intervention. AT but not RT caused a reduction in HbA1c ($P$=0.041, $P$=0.361). Participants in the RT and AT group showed no significant decrease in 2hPG ($P$ =0.079, $P$ =0.691). FBG decreased significantly in both exercise groups ($P<0.01$). Both HOMA2-IR and HOMA2-β were improved significantly in RT group ($P$=0.005, $P$=0.049). But in the control group, HOMA2-β was significantly decreased compared with baseline ($P<0.001$). Among control participants, HbA1c, 2hPG and FBG significantly increased after six months ($P<0.01$).

We also tried some correlations between variables. The Spearman results showed that there was no correlation between Statins use and $A1_c$ ($P$=0.313), or hypotensive drugs and $A1_c$ ($P$=0.292).

**Discussion**

In this study of the effects of exercise in participants with prediabetes, we have both confirmed the well-recognized efficacy of aerobic training in preventing T2DM and in

addition, demonstrated for the first time a set of comparable benefits of resistance training. These include the demonstration that RT improves metabolic control and beta cell function to a degree comparable to that observed with AT.

A novel finding of this study was that, compared to controls, both AT and RT showed significant improvement in $HbA_{1c}$, but no significant improvement in RT was observed in $HbA_{1c}$ relative to baseline. Previous studies did not measure or failed to prove that the improvement in A1c with RT[21-25]. Most of them did not measure $A_{1c}$[21-22,24-25], and one study that did check A1c was only 12-week in duration[23], with 36 prediabetes patients in RT group, 39 in Nordic Walking group, and 40 in control group, and they did not reach statistical significance, because $A_{1c}$ requires a relatively long trial to observe its improvement, especially for patients with predaibetes, whose $A1_c$ was 5.4%-5.5%. On the other hand, even though the participants were randomized into 3 groups in previous study, the UKK fitness index in the RT group were much lower than those in the control and Nordic Walking group, which could partially cause insignificant difference in $A1_c$ between RT and control group. A larger sample size in our study may have given us the statistical power to detect improvement in $A_{1c}$. A meta-analysis showed that RT had a clinically and statistically significant effect on $A1_c$ for patients with “abnormal glucose metabolism”, but inspection of the 13 studies included in that analysis revealed that in 11 studies $A_{1c}$ was measured in patients with T2DM, and only two studies targeted prediabetes. The latter two studies did not report $A_{1c}$[14]. The Health Professionals Follow-up Study observed men engaged in RT over a period of 18 years

and showed a 34% reduction in risk of T2DM[26], but unfortunately, $A_{1c}$ was not reported either. Our data suggest that six-month of moderate RT with 150min /week can improve $A_{1c}$ in patients with prediabetes.

It has been well established that aerobic exercise can increase insulin sensitivity and protect beta cell function in patients with prediabetes[27-28]. Our study reveals that six-month of moderate resistance training was as effective as aerobic training in decreasing HOMA2-IR and increasing HOMA2-β in patients with prediabetes. It has also been reported that moderate short-term resistance training (≤12-week) can improve blood glucose control[13-14] and that intense RT can enhance insulin sensitivity during RT in patients with prediabetes[29] and in obese adolescents[30]. Our results demonstrate that six-month of RT not only improved insulin resistance, but also importantly protected beta cell function in patients with prediabetes, a finding previously absent in the literature[21-26].

Several possible mechanisms could explain the efficacy of RT in preserving beta cell function. Firstly RT may up-regulate HK2 and GLUT4, two key regulators of insulin mediated glucose transport in contracting skeletal muscle. This could in turn enable greater glucose flux across the plasma membrane[31]. Secondly, RT increases energy expenditure, decreasing blood glucose concentration, thereby reducing insulin requirements. Thirdly, RT may increase lean body mass for patients with type 2 diabetes[32], decrease fat mass[33], decrease visceral fat and its associated inflammatory markers[34], decrease oxidative stress, and increase mitochondrial oxidative capacity[35]. In

aggregate, these effects could contribute to the preservation of beta cell function.

Beta cell function is a stronger predictor of change in glycaemia control after an exercise intervention than is change in insulin sensitivity[36]. Decrease in beta cell function is a key to developing diabetes[37]. In addition, as with AT, RT can improve beta cell function. For all of these reasons, RT appears to have the potential to be an effective way to prevent T2DM in at-risk in patients.

Insulin resistance is commonly associated with prediabetes. After six months of exercise, we found that HOMA2-IR decreased in both RT and AT groups compared with the control group, but there were no significant differences between the two intervention groups. Previous studies have failed to measure or document an improvement in HOMA-IR[21-25]. Many studies did not measure changes of HOMA-IR with resistance exercise in persons with prediabetes[21-22,25]. Two other studies examining insulin resistance did not find a statistical significant improvement in insulin resistance[23-24]. Laurie et. al observed an acute enhancement to insulin sensitivity during brief but intensive RT in patients with impaired fasting glucose[29], but this acute increase of insulin sensitivity was diminished after stopping RT. Our study showed that longer (six months) regular (3 times 150 min total/week) moderate RT can significantly maintain the improvement in insulin sensitivity.

We recognize that failure to observe changes in HOMA2-IR with resistance exercise in persons with prediabetes has been reported[21,23]. We would argue that the discrepancy can be explained by differences in duration (six months vs.12 weeks), statistical power

(sample sizes of 248 vs. 144 and 159), the frequency of exercise (3 times/week vs. 2 times/week[21] vs. not specified[23]), and the different measures of HOMA-IR (HOMA2-IR vs HOMA-IR).

**Limitations:** We didn't have any follow-up measures of $VO_2$max, strength mainly due to a safety reason, for the subjects were old people with an average age of 60 years old and they were exhausted during the first time measuring $VO_2$max. In addition, for male patients with prediabetes were reluctant to participate the program, we recruited more female participants in this study, this may cause bias to the results. In conclusion, our study indicates that six-month of RT can achieve comparable improvements in beta cell function to that achieved by aerobic exercise to prevent the development of type 2 diabetes.

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**Disclosure**

None declared.

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**Figure legends**

Fig. 1. Study flow diagram.

Fig. 2. Subjects with pre-diabetes underwent six months of aerobic exercise. HbA1c, 2hPG, FBG, HOMA2-IR, HOMA2-β and insulin in response to exercise were measured as the post-exercise minus pre-exercise (Δ) values. The X-axis represents each individual subject's data point. Y-axis data above and below the origin indicate increases and decreases, respectively in each variable in response to aerobic exercise.

Fig. 3. Subjects with pre-diabetes underwent six months of resistance exercise. HbA1c, 2hPG, FBG, HOMA2-IR, HOMA2-β and insulin in response to exercise were measured as the post-exercise minus pre-exercise (Δ) values. The X-axis represents each individual subject's data point. Y-axis data above and below the origin indicate increases and decreases, respectively in each variable in response to resistance exercise.

Fig. 4. Subjects with pre-diabetes underwent six months of non-exercise. The responsiveness of HbA1c, 2hPG, FBG, HOMA2-IR, HOMA2-β and insulin were measured as the post-values minus (Δ) pre-values. The X-axis is the individual subject data points. The X-axis represents each individual subject's data point. Y-axis data above and below the origin indicate increases and decreases, respectively in each variable in controls who did not exercise.

Fig. 5. HbA1c, 2hPG, FBG, HOMA2-IR, HOMA2-β and insulin in the three group before and after exercise. *$P$<0.05, **$P$<0.01 between baseline and after six months of intensive physical training.