Aerobic Training Increases Hippocampal Volume and Protects Cognitive Function for Type 2 Diabetes Patients with Normal Cognition

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ABSTRACT

Aim To evaluate the effects of aerobic training on hippocampal volume and cognitive function in patients with type 2 diabetes mellitus (T2DM) with normal cognition.

Materials and methods One hundred patients with T2DM aged 60–75 years who met inclusion criteria were randomized into the aerobic training group (n = 50) and control group (n = 50). The aerobic training group received 1 year of aerobic training, while the control group maintained their lifestyle without additional exercise intervention. The primary outcomes were hippocampal volume measured by MRI and Minimental State Examination (MMSE) score or Montreal Cognitive Assessment scale (MoCA) scores.

Results Eighty-two participants completed the study (aerobic training group, n = 40; control group, n = 42). There was no significant difference between the two groups at baseline (P > 0.05). After one year of moderate aerobic training, increase in total and right hippocampal volume in the aerobic training group were significantly higher than in the control group (P = 0.027, P = 0.043, respectively). In the aerobic group, total hippocampal volume significantly increased after the intervention compared with baseline (P = 0.034). The between-group difference in the change of MMSE and MoCA scores was statistically significant (P = 0.015, P = 0.027, respectively). Logistic regression showed strong correlations between aerobic training and increase in total hippocampal volume (OR:1.091, [95 %CI 0.969, 1.228], P = 0.002), improvement of MMSE scores (OR:1.127, [95 %CI 1.005, 1.263], P = 0.041) or MoCA scores (OR:2.564, [95 %CI 2.098.2.973], P = 0.045).

Conclusions One-year moderate aerobic training increased total and right hippocampal volume and protected cognitive function for T2DM patients with normal cognition. Early intervention focusing on cognition protection should be considered for T2DM patients in clinical settings.

Introduction

Cognitive impairment, which includes mild cognitive impairment (MCI) and dementia, is now one of the most common and serious diseases for older adults. Studies have shown that diabetes is an independent risk factor for cognitive impairment [1]. People with type 2 diabetes mellitus (T2DM) are more likely to have cognitive dysfunction than normal people, and the incidence of MCI in patients with T2DM is 1.5 times that of patients without diabetes [2]. Once cognitive impairment occurs in T2DM patients, more than one-third of the patients may progress to dementia in the future [3]. Therefore, the prevention of MCI is particularly important before cognitive impairment occurs in T2DM patients.

The hippocampus is a crucial structure for memory and study in the brain [4]. The decrease and atrophy of the hippocampus is a sign of MCI [5]; therefore, it is very important to explore the increase or decrease of hippocampal volume for the change of cognitive function. At the same time, the hippocampus is rich in insulin and insulin receptor, which is easily affected by blood glucose level [6]. MRI studies have confirmed that the hippocampal volume of T2DM patients tends to atrophy [7], so it is very important to carry out the preventive intervention in advance.

Exercise training can cause adaptive changes in brain structure to maintain or improve cognitive function for the elderly with normal cognitive function [8]. An experimental study reported that aerobic training significantly improved cognitive function for T2DM patients with MCI [9]. At the same time, a study has confirmed that a year of moderate-intensity aerobic training can increase hippocampal volume in healthy elderly [10].

To our knowledge, no intervention study has examined the impact of aerobic training on T2DM patients with normal cognitive function to prevent MCI. This study explored the effect of one-year aerobic training on cognitive function and hippocampal volume in T2DM patients with normal cognitive function. We hypothesized that aerobic training would increase hippocampal volume and improve cognitive function after one year of training.

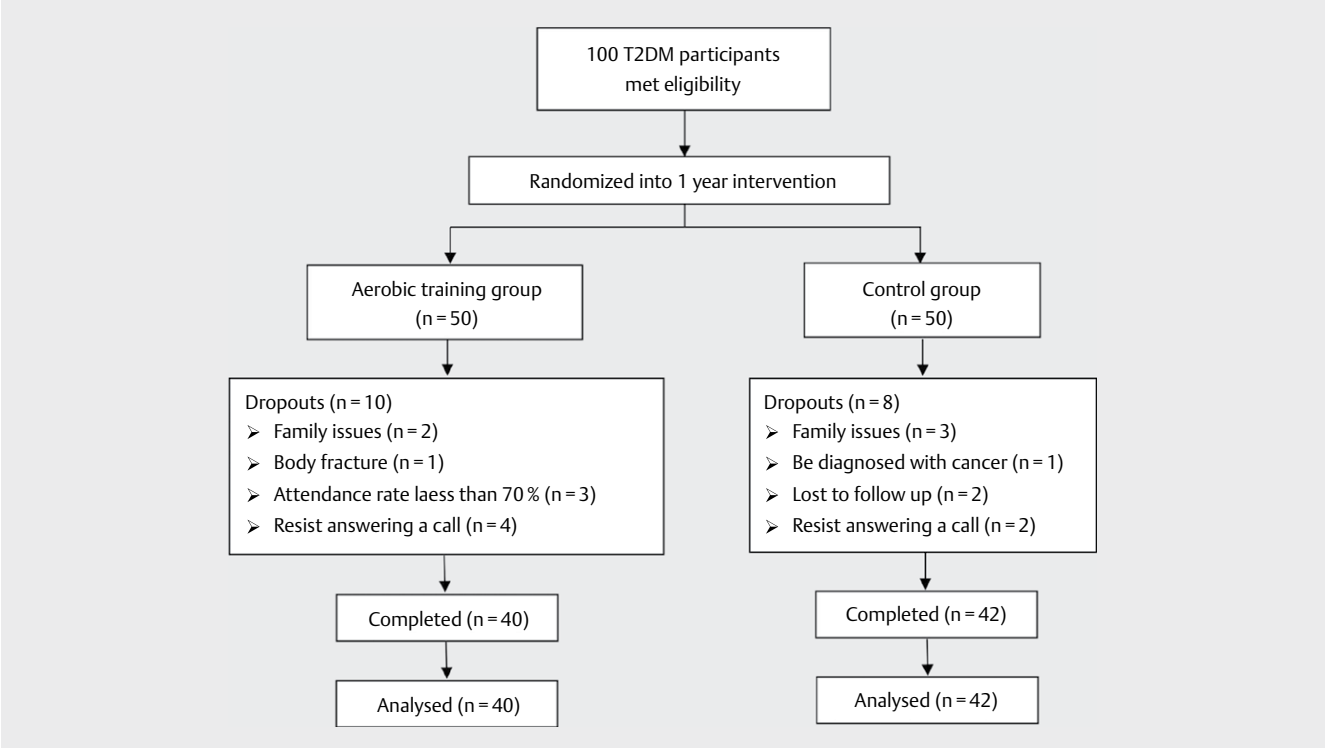
Materials and Methods

Study participants

Participants were recruited between December 2018 and January 2019 at the Integrated Traditional Chinese and Western Medicine Hospital Affiliated to the Nanjing University of Chinese Medicine (Nanjing, China). The inclusion criteria included: ① participants with T2DM [11]; ② $18.5 \leq BMI \leq 35\ kg/m^2$; ③ had normal cognitive function (mini mental state examination [MMSE] ≥ 27 points, Montreal Cognitive Assessment scale [MoCA] ≥ 26 points); ④ primary school education or above; ⑤ duration of T2DM was > 5 years. Patients with malignant tumors, mental disorders, severe heart, liver, and kidney disease, patients with contraindications to MRI, severe loss of vision and hearing, and pregnant or lactating women were excluded.

Trial design and randomization

This study was a 12-month, randomized controlled trial. No blinding was performed to assign the participants and trainers after randomization, but the study results were measured by evaluators who were blinded for the study. Eventually, 100 patients who met inclusion criteria were enrolled in the study. The flow chart of the study is shown in ▶ **Fig. 1**. Patients were randomly assigned to the control group (n = 50) and aerobic training group (AT group, n = 50)



▶ **Fig. 1** Study flow diagram.

based on numbers and assignments placed in a sealed envelope, which were randomly numbered lists made by an independent researcher using Excel. The protocol (NCT04489966, registered at www.clinicaltrial.gov) was approved by the Ethical Committee of Jiangsu Province Hospital for the Integration of Chinese and Western Medicine. All participants were verbally introduced to the study and signed the informed consent.

Intervention

All participants received diabetes self-management education once a month; the course focused on basic knowledge of diabetes, diet management, and blood glucose monitoring). Participants in the control group were asked to maintain their usual physical activity and received no organized exercise intervention. The AT group was supervised by the trainers who had received professional training and participated in outdoor aerobic training accompanied by music three times per week for 60 min/session. Each aerobic training was led by 1–2 professionals. The content of the exercise mainly included: 5 min of warm-up, 50 min of aerobic dancing, and 5 min of relaxation training. In the first 2 weeks, participants would learn the moves, and the exercise intensity would be calculated step by step. Heart rate measurements are commonly used to assess the heart's response or recovery from exercise and to prescribe exercise intensity [12]. We referred to the study by Dr. Karvonen, in which 220-age was used as the maximum heart rate [13]. A more extensive review of the literature revealed that there is no accurate method to estimate the maximum heart rate. This formula was not developed from original research but resulted from observation based on data from approximately 11 references consisting of published research or unpublished scientific compilations [14]. Consequently, the formula %HRmax = 220-age has no scientific merit for use in exercise physiology and related fields and should not be used in future studies.

The estimation of maximum heart rate needs to take into account population factors and specific exercise, so more studies are needed to obtain multivariate regression equations. If the participant was unable to attend the regular exercise three times a week (for example, weather and temporary events.), a complementary workout could be performed on Saturday morning to achieve the effect of three times a week.

Measurements

Body composition and metabolic variables

General information of all patients before the intervention was collected as follows: age, sex, height, weight, body mass index (BMI), waist circumference (WC), hip circumference (HC), systolic blood press (SBP), diastolic blood press (DBP), diabetes course, education, payment method, marital status, smoking and drinking, drug use and International Physical Activity Questionnaire (IPAQ). The control group followed their regular lifestyle without aerobic training and recorded daily physical activity.

Height, weight, and muscle mass were measured using a body composition analyzer (SK-X80, Yuwell). BMI (kg/m^2) was calculated based on weight and height measured in light clothing and without shoes. The waist-hip ratio was calculated as the ratio of waist circumference to hip circumference. Waist circumference is measured at the midpoint between the rib and the iliac crest. Hip circumference was measured horizontally at the pubic symphysis, and the posterior gluteus maximus was measured as the subject stood upright.

Serum routine biochemical parameters were measured using the commercial assay on a Roche Cobas 6000 Automated Analyzer. Bole D-10 was used to measure HbA1c. All patients fasted for more than 8 hours for blood tests. HOMA2-IR and HOMA2- were calculated using HOMA2 software (HOMA Calculator V2.2.3). The early insulin secretion function was estimated using the following index equation to evaluate: (ΔI30 /ΔG30) = (30minINS − FINS) / (30minPG − FPG).

The professional used an electronic sphygmomanometer (SK-X80, Yuwell) to measure the blood pressure of the right arm in the sitting position of the patient, with the palm up to ensure that the brachial artery of the right upper arm is at the same level as the heart.

Hippocampal volume

MRI experiments were conducted using a 3.0 T MRI system (MR750, GE Healthcare, Milwaukee, WI, USA) with an 8-channel head coil array. A three-dimensional brain volume imaging (3D-BRAVO) sequence covering the whole brain was used for all patients to acquire high-resolution brain structural imaging data (TR = 9.5 ms, TE = 3.9 ms, flip angle = 12 °, FOV = 22 cm × 22 cm, matrix = 320 × 320, slice thickness = 1.5 mm, interlayer spacing = 1.5 mm). During the examination, the patient was told to relax and close their eyes and stay awake, keep their head and body as still as possible, plug their ears with cotton balls to reduce the noise, fix their heads with soft sponge pads to avoid movement, and ensure the image quality. All the scans were performed by the same imaging doctor.

In this study, voxel-based morphometry (VBM) was used for the segmentation and volumetric analysis of the left and right hippocampus. The advantage of VBM is that it does not favor one particular structure [15] but can uniformly and comprehensively evaluate the anatomical differences of the whole brain [16].

The segmentation mainly combines the coronal, sagittal, and horizontal view angles of the brain. According to the definition of Malykhin [17], Agarwal [18], and Frisoni [19], the hippocampus is classified as hippocampal head, hippocampus body, and hippocampus tail.

After each coronal plane area of each segment of the hippocampus was measured by MRI, the total area of each segment of the hippocampus multiplied by layer thickness was obtained by adding the area of each level of the hippocampus head, body, and tail. Finally, the volumes of the hippocampus head, body and tail were obtained.

The intracranial volume (ICV) was measured by anteroposterior diameter, transverse diameter, and upper and lower diameter. The standardized volume of the hippocampal head, body, and tail = (the actual volume of hippocampal subregion/the actual volume of the individual cranial cavity) × the average volume of the cranial cavity in all the included population.

Mini-mental State Examination (MMSE)

The MMSE [20] is a widely used cognitive screening scale with a Cronbach's alpha of 0.91. It includes five aspects: orientation, memory, concentration and calculation, recall, and language ability,

with a total score of 30. In each dimension, the lower the score, the worse the cognitive function. Low MMSE scores indicate poor cognitive function.

The Montreal Cognitive Assessment scale (MoCA)

The Montreal Cognitive Assessment[21] (MoCA) was performed to test for cognitive impairment. Chronbach's alpha of the scale was 0.87, which included eight aspects: visuospatial and executive function, naming, memory, attention, language, abstraction, delayed recall, and directivity, with a total score of 30. In each dimension, the lower the score, the worse the cognitive function. Low MoCA scores indicate poor cognitive function.

Statistical analysis

The sample size was calculated based on the PASS15, MMSE, and the MoCA score of the study object was taken as the outcome indicator. An analysis was conducted to determine the sample size based on the MMSE increased value of 0.8 and an SD of 2.4. The required sample size for 80 % power using a 2-tailed test at alpha = 0.05 is 45 in each group. We calculated that a sample of 90 patients would be required in the analysis, and we increased the sample to 100 to allow for a dropout rate of 10 %.

All analyses were performed using IBM SPSS 25 version (IBM-Corp, Armonk, NY, USA). Normally distributed data were expressed as mean ± SD. A Chi-square test was used for the comparison of categorical variables between the two groups, and an unpaired t-test was used for the comparison of continuous variables between the two groups. When the data were not normally distributed, a nonparametric test of two independent samples was used. Within-group differences were tested by the Wilcoxon signed-rank or paired t-test. The chi-square test was used for categorical variables. Binary logistic regression was used to explore whether aerobic training impacted an increase in total hippocampal volume, improvement in MMSE scores, or MoCA scores. The strengths of associations were expressed as odds ratios along with 95 % confidence intervals. The results of the chi-square test expressed in the form of bar graphs were used to show whether there was a statistically significant difference in the proportion of people grouped according to changes in total hippocampal volume, MMSE, and MoCA scales. Within-group differences displayed in radar diagrams of MMSE and MoCA scores before and after aerobic training. *P*-values < 0.05 were considered to indicate statistical significance.

Results

Adherence

A total of 100 eligible T2DM patients were included in this study. After 1 year of intervention, 82 patients finally completed the study. Ten patients in the AT group and eight patients in the control group dropped out, with a dropout rate of 18 %. The reasons for dropping out were family issues (n = 5), the attendance rate of less than 70 % in the AT group (n = 3), loss to follow-up (n = 2), resist answering a call (n = 6), and one of the participants was diagnosed with cancer (n = 1). Furthermore, one participant suffered a body fracture from the accident and failed to continue (▶ **Fig. 1**).

Between-group differences in demographic and clinical characteristics

The demographic and clinical characteristics of the two groups are shown in ▶ **Table 1**. No statistically significant differences were detected between them in hippocampal volume (total, left and right, p > 0.05), MMSE or MoCA scores (p > 0.05). Baseline clinical characteristics of the 82 eligible subjects were well balanced between AT and control group with overall (mean ± SD) age (66.93 ± 4.9) years, BMI (24.43 ± 3.1) kg/m², and HbA1c (6.96 ± 1.1) %. The duration of T2DM was (11.90 ± 6.3) years (data not shown).

Between-group differences in primary outcomes

Statistical analysis showed a significant difference in the total and right hippocampal volume of the participants between the two groups ($p = 0.027$, $p = 0.043$) (▶ **Table 2**). The AT group had significantly increased MMSE and MoCA scores compared with the control group ($p = 0.015$, $p = 0.027$). A significant decrease in WC (Δ-0.88 ± 7.10 cm) was observed in the AT group compared with the control group (p = 0.029). A reduction in FPG and 30minPG (Δ-0.17 ± 0.83 mmol/L, Δ-0.14 ± 2.57 mmol/L) in the AT group is apparent after 1 year of aerobic training, and the differences were statistically significant between the two groups ($p = 0.021$, $p = 0.036$). HOMA2 -β and Δ I30/Δ G30 have improved, and there were significant differences between the two groups ($p = 0.003$, $p = 0.046$) (▶ **Table 2**).

The results of binary logistic regression

Binary logistic regression was used to explore whether aerobic training had an impact on an increase in total hippocampal volume, improvement of MMSE scores, or MoCA scores. Model 1 only analyzed the relationship between aerobic training and total hippocampal volume, and the results showed that aerobic training improved total hippocampal volume compared to the control group (OR 2.726, [95 %CI: 1.105–6.728], $p = 0.030$). Similarly, binary logistic regression revealed that the aerobic training group had significantly increased values in MMSE and MoCA scores compared to the control group. (OR 2.848, [95 %CI: 1.050–7.720], $p = 0.040$), (OR 2.703, [95 %CI: 2.151–2.906], $p = 0.030$).

In the partially adjusted model (model 2) and adjusted model of general data and biochemical indices (model 3), aerobic training was strongly associated with the increase in total hippocampal volume and improvement in MMSE, or MOCA scores (▶ **Table 3**).

Within-group comparison in MMSE, MoCA scores, and hippocampal volume

Total MMSE scores were compared between the aerobic group and the control group after one year, and at baseline, there were no significant differences between the two groups ($p = 0.103$, $p = 0.05$, respectively).

Within the control group, recall ability decreased after one year compared to the baseline. ($p = 0.010$) (▶ **Fig. 2b**). Compared with the baseline, there was an improvement in total MoCA scores in the AT group only after the one-year aerobic training ($p = 0.001$). Within the AT group only, delayed recall ability was increased after the one-year aerobic training compared to the baseline ($p = 0.025$) (▶ **Fig. 2c**). Data were analyzed using the paired t-tests (▶ **Fig. 2**).

▶ **Table 1** Baseline characteristics of participants

Variables	Aerobic training group (n = 40)	Control group (n = 42)	F/x²	*p*-value
Age (years)	65.73 ± 3.99	68.07 ± 5.47	−1.949	0.051
Sex, n (%, male)	19 (47.5%)	22 (52.4%)	0.195	0.659
Duration of diabetes (years)	11.80 ± 6.17	12.00 ± 6.55	−0.037	0.970
BMI (kg/m²)	24.03 ± 2.94	24.80 ± 3.21	−1.135	0.260
WC (cm)	82.30 ± 9.94	84.24 ± 9.71	−0.893	0.375
HC (cm)	94.13 ± 6.24	94.40 ± 7.19	−0.188	0.851
Muscle mass (kg)	38.20 (36.38, 47.50)	43.75 (35.65, 50.80)	−0.385	0.700
SBP (mmHg)	134.60 ± 16.39	137.29 ± 13.55	−0.810	0.420
DBP (mmHg)	78.25 ± 10.35	78.26 ± 8.29	−0.006	0.995
HbA1c (%)	6.79 ± 0.97	7.12 ± 1.19	−1.203	0.229
FINS (mmol/L)	6.15 (4.25, 9.30)	7.94 (4.99, 10.76)	−1.266	0.205
30 minINS (μU/mL)	20.43 (10.90, 39.19)	22.85 (16.16, 37.35)	−0.988	0.323
FPG (mmol/L)	6.63 ± 1.67	6.88 ± 1.81	−0.584	0.559
30minPG (mm ol/L)	12.37 ± 2.71	12.90 ± 3.13	−0.813	0.419
2 hPG (mmol/L)	10.52 (8.31, 13.06)	10.43 (8.25, 14.52)	−0.353	0.724
HOMA2-IR	0.88 (0.62, 1.31)	1.03 (0.69, 1.54)	−1.257	0.209
HOMA2-β	54.45 (32.78, 70.20)	54.30 (39.68, 89.10)	−0.622	0.534
ΔI30/ΔG30	3.72 ± 3.89	4.13 ± 3.65	−0.779	0.436
TC (mmol/L)	4.63 ± 0.97	4.21 ± 1.04	1.916	0.059
TG (mmol/L)	1.21 (0.96, 1.72)	1.29 (1.04, 1.72)	−0.343	0.731
HDL-C (mmol/L)	1.30 (1.05, 1.53)	1.24 (1.00, 1.42)	−1.044	0.297
LDL-C (mmol/L)	2.87 ± 0.71	2.55 ± 0.78	1.976	0.073
Smoker, n(%)	3 (7.5%)	7 (16.7%)	0.866	0.352
Alcohol drinker, n(%)	9 (22.5%)	11 (26.2%)	0.151	0.697
Dyslipidemia , n(%)	13 (32.5%)	22 (52.4%)	3.310	0.069
Hypertension, n(%)	16 (40.0%)	25 (59.5%)	3.124	0.077
Family history of diabetes, n(%)	19 (47.5)	23 (54.8)	0.432	0.511
Hypoglycemic drugs, n(%)	34 (85.0%)	37 (88.1%)	0.169	0.681
Total hippocampal volume (cm³)	7.45 ± 0.42	7.29 ± 0.46	−1.540	0.124
Right hippocampal volume (cm³)	3.71 ± 0.23	3.65 ± 0.27	−1.160	0.246
Left hippocampal volume (cm³)	3.74 ± 0.22	3.64 ± 0.22	−1.883	0.060
MMSE	29.03 ± 1.14	29.10 ± 0.96	5.762	0.763
MoCA	27.60 ± 1.11	27.90 ± 1.17	0.026	0.873

Abbreviations: BMI = body mass index; WC = waist circumference; HC = hip circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure; HbA1c = hemoglobin A1c; FINS = Fasting Insulin; 30 minINS = 30 Minutes Insulin; FPG = fasting plasma glucose; 30 minPG = 30 Minutes Plasma Glucose; 2hPG = 2 h postprandial glucose; HOMA2-IR = Homeostasis model assessment of insulin resistance; HOMA2-β = Homeostasis model assessment of Beta Cell Function;ΔI30/ΔG30 = early insulin secretion index; TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MMSE = Mini-mental State Examination; MoCA = Montreal Cognitive Assessment scale; Data expressed as mean ± SD for continuous characteristics; n (%) for categorical characteristics; Median [interquartile range] for variables with abnormal distributions. *p*-value significance in < 0.05.

Within the aerobic group, total hippocampal volume significantly increased after the intervention compared with baseline (P = 0.034). However, hippocampal volumes (left, right, and total) decreased in the control group, and the differences were not statistically significant (▶ **Fig. 3**).

Discussion

Main findings

To our knowledge, this is the first randomized controlled trial of up to one year to evaluate the effects of aerobic training on hippocampal volume and cognitive function in T2DM patients with normal cognition. This study found that even in the T2DM patients with a normal cognitive state, one-year moderate aerobic training provided significant benefits in total and right hippocampal volume and cognitive function.

Effects on hippocampal volume

In our study, total and right hippocampal volume increased, and the proportion of patients with increased volume of the right hippocampus in the AT group was higher than that in the control group.

▶ **Table 2** Comparison of hippocampal volume and lab values between two groups

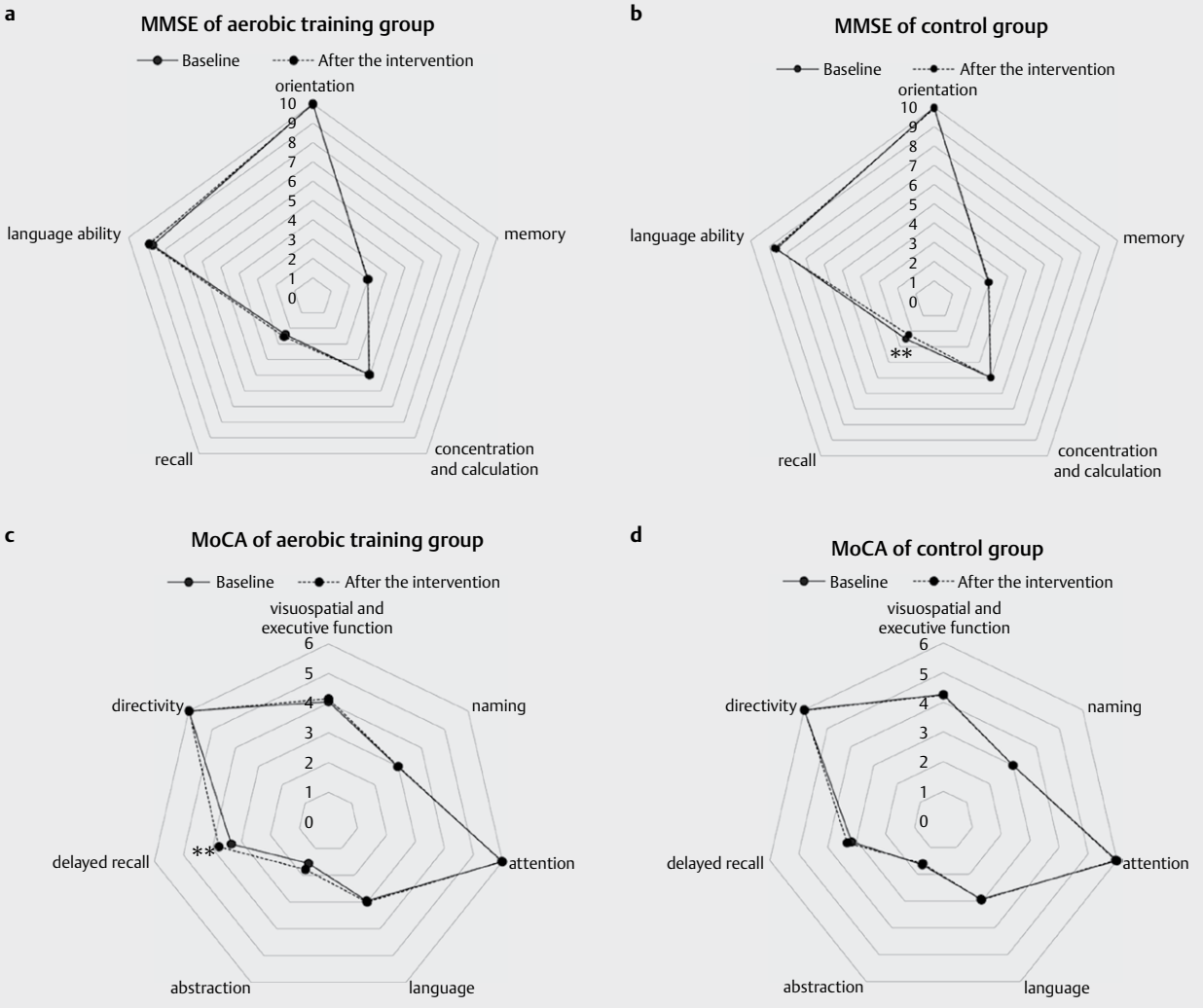
Variables		Aerobic training group (n = 40)	Control group (n = 42)	T/Z	*p*-value
Total hippocampal volume (cm^3)	After Δ	7.56 ± 0.57 0.11 ± 0.65	7.05 ± 0.78 −0.24 ± 0.77	2.247	0.027
Right hippocampal volume (cm^3)	After Δ	3.80 ± 0.41 0.09 ± 0.46	3.53 ± 0.45 −0.12 ± 0.48	2.058	0.043
Left hippocampal volume (cm^3)	After Δ	3.76 ± 0.34 0.02 ± 0.36	3.52 ± 0.41 −0.12 ± 0.40	−1.753	0.080
MMSE	After Δ	29.33 ± 0.69 0.30 ± 1.14	28.86 ± 1.03 −0.24 ± 1.30	5.090	0.015
MoCA	After Δ	28.33 ± 1.23 0.73 ± 1.30	27.95 ± 1.71 0.05 ± 1.41	0.065	0.027
BMI (kg/m^2)	After Δ	23.74 ± 2.79 −0.29 ± 0.79	24.81 ± 3.12 0.01 ± 0.84	−1.948	0.051
WC (cm)	After Δ	81.43 ± 9.47 −0.88 ± 7.10	85.26 ± 9.73 1.02 ± 3.82	−2.187	0.029
HC (cm)	After Δ	93.05 ± 6.25 −1.08 ± 5.31	95.19 ± 7.36 0.79 ± 3.89	−1.657	0.097
SBP (mmHg)	After Δ	123.93 ± 16.18 −10.68 ± 13.78	133.26 ± 13.91 −4.02 ± 11.79	−1.843	0.065
DBP (mmHg)	After Δ	72.30 ± 8.79 −5.95 ± 9.09	76.60 ± 8.26 −1.67 ± 6.48	−1.677	0.094
HbA1c (%)	After Δ	6.70 ± 0.79 −0.88 ± 0.40	7.23 ± 1.21 0.11 ± 0.53	−1.926	0.058
FINS (μU/mL)	After Δ	6.92 (4.28,11.23) 0.10 ± 4.87	7.51 (5.50,1.23) 0.06 ± 2.54	−1.545	0.122
30minINS (μU/mL)	After Δ	26.40 (16.80,43.06) 4.22 ± 18.08	28.16 (17.42,37.22) −0.42 ± 10.01	−1.888	0.059
FPG (mmol/L)	After Δ	6.46 ± 1.45 −0.17 ± 0.83	7.20 ± 1.73 0.32 ± 1.06	−2.353	0.021
30 minPG (mmol/L)	After Δ	12.24 ± 2.25 –0.14 ± 2.57	13.95 ± 2.39 1.05 ± 2.91	−2.101	0.036
2 hPG (mmol/L)	After Δ	9.24 (7.38,11.93) −1.12 ± 2.42	10.56 (9.45,14.84) −0.05 ± 2.54	−1.953	0.054
HOMA2-IR	After Δ	0.94 (0.61,1.62) −0.003 ± 0.69	1.07 (0.76,1.62) 0.02 ± 0.38	−0.761	0.446
HOMA2-β	After Δ	58.80 (41.33,80.33) 6.13 ± 24.27	48.55 (31.05,73.90) −7.46 ± 20.49	−3.010	0.003
ΔI30/ΔG30	After Δ	4.92 ± 5.44 1.20 ± 3.24	3.39 ± 2.90 −0.74 ± 2.81	−1.995	0.046
TC (mmol/L)	After Δ	4.60 ± 0.89 −0.03 ± 0.83	4.03 ± 0.85 −0.18 ± 0.85	−0.687	0.492
TG (mmol/L)	After Δ	1.20 (0.83,1.53) −0.12 ± 0.36	1.26 (0.90,1.63) −0.12 ± 0.50	−0.608	0.543
HDL-c (mmol/L)	After Δ	1.38 (1.15,1.67) 0.08 ± 0.17	1.30 (1.04,1.55) 0.09 ± 0.22	−0.116	0.908
LDL-c (mmol/L)	After Δ	2.75 ± 0.72 −0.12 ± 0.58	2.64 ± 0.95 0.10 ± 0.70	−1.832	0.067

Abbreviations: BMI = body mass index; WC = waist circumference; HC = hip circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure; HbA1c = hemoglobin A1c; FINS = Fasting Insulin; 30 minINS = 30 Minutes Insulin; FPG = fasting plasma glucose; 30 minPG = 30 Minutes Plasma Glucose; 2 hPG = 2 h postprandial glucose; HOMA2-IR = Homeostasis model assessment of insulin resistance; HOMA2-β = Homeostasis model assessment of Beta Cell Function;ΔI30/ΔG30 = early insulin secretion index; TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Data expressed as mean ± SD for continuous characteristics; Median [interquartile range] for variables with abnormal distributions; MMSE = Mini-mental State Examination; MoCA = Montreal Cognitive Assessment scale; Δ Calculated as post-training value minus pre-training value. *p*-value significance in < 0.05.

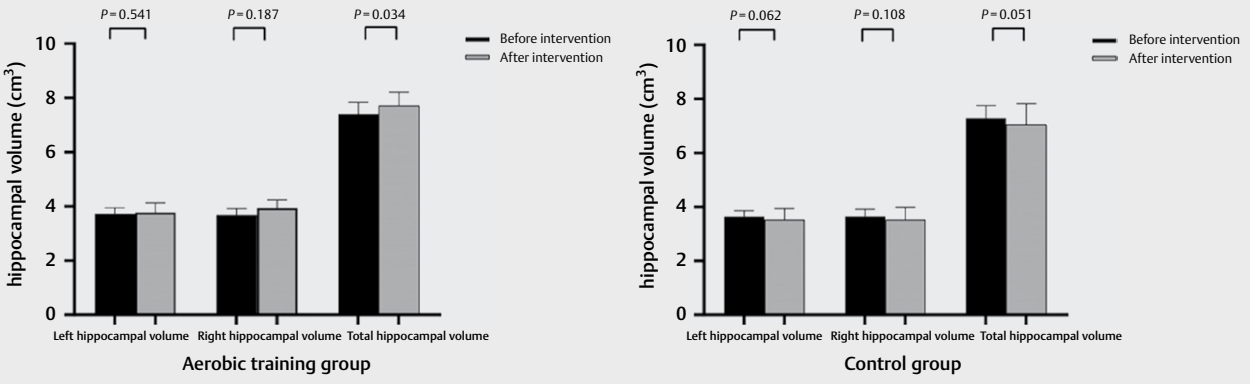
▶ **Table 3** Binary logistic regression analysis of aerobic training to the increase of total hippocampal volume, improvement of MMSE and MoCA scores

Model	Increase of total hippocampal volume			Improvement of MMSE scores			Improvement of MoCA scores		
	β	OR (95%CI)	*p*	β	OR (95%CI)	*p*	β	OR (95%CI)	*p*
1	1.003	2.726 (1.105,6.728)	0.030	1.046	2.848 (1.050,7.720)	0.040	0.995	2.703 (2.151,2.906)	0.030
2	0.109	1.897 (1.827,2.972)	0.008	0.219	1.244 (1.026,1.509)	0.026	1.099	3.003 (3.001,3.113)	0.033
3	1.145	1.091 (0.969,1.228)	0.002	0.119	1.127 (1.005,1.263)	0.041	1.176	2.564 (2.098.2.973)	0.045

Model 1: Regression analysis without adjusted variables. Model 2: Adjusted for sex, age, height, weight, hip circumference. Model 3: Adjusted for sex, age, height, weight, hip circumference, SBP, DBP, duration of T2DM, smoking, alcohol consumption, HbA1c, HOMA2-IR, HOMA2-β, HDL-C, LDL-C.
MMSE = Mini-mental State Examination; MoCA = Montreal Cognitive Assessment scale; OR = odds ratio; CI: confidence interval



▶ **Fig. 2** Changes in the Summary of MMSE and MoCA scores after one-year intervention within the AT and control group. Radar diagram of MMSE within the aerobic training (AT) group (**a**) and radar diagram of Mini-mental State Examination (MMSE) within the control group (**b**), radar diagram of MoCA within the AT group (**c**), and radar diagram of MoCA within the control group (**d**). (B) In the control group, recall ability was improved over one-year compared to baseline (** p = 0.05, p = 0.010), (C) In the AT group, delayed recall ability was increased after the one-year aerobic training compared to baseline (** p = 0.05, p = 0.025); The data were analyzed using the paired t-test.



▶ **Fig. 3** Within-group comparison of hippocampal volume before and after one-year intervention.

So far, many clinical studies in non-T2DM patients have shown that hippocampal volume benefits from aerobic training [22], similar to that observed in our study. However, another clinical study for non-T2DM patients [23] found that both the paleolithic diet and the diet combined with the aerobic training group improved right hippocampal volume, but no additional benefits on hippocampal volume have been reported when aerobic training was added to the paleolithic diet. This inconsistency might be related to their small sample size (n = 24), short-term intervention (12 weeks), and the difference of subjects (diabetes VS non-T2DM).

It is worth noting that in our study, left hippocampal volume increased by 0.5 %, 2.4 % in right hippocampal volume, and 1.5 % in total hippocampal volume. These changes in volume were less than those reported by Ten et al. [24], who showed that after six months of mild twice-weekly aerobic training (outdoor walking program), the volume of the left, right, and total hippocampus increased by 5.6 %, 2.5 %, and 4 %, respectively. The differences might be explained by the following reasons. First, their subjects were patients with mild cognitive impairment, which aggravated the damage to hippocampal volume, so there is great space for improvement. Second, the subjects of their study were female patients, and women were more likely to benefit from aerobic training than men [25].

Our study found that the participants' total and right hippocampal volume increased after 1 year of aerobic training. Diabetes can cause cognitive impairment, neurophysiological and structural changes in the brain, such as hippocampal atrophy, memory impairment, and decreased learning ability [26]. Hippocampal atrophy is a major pathway for cognitive impairment in patients with T2DM [27]. Brain-derived neurotrophic factor (BDNF) is a protein that has been proven to be related to the growth and survival of neurons [28]. Studies have shown that reduced levels of BDNF may be responsible for impairing synaptic plasticity and neurogenesis in the hippocampus [29]. Adlard et al. studied the effects of exercise on BDNF levels in rats and observed a positive dose response between this physical activity and BDNF levels in the brain [30]. Exercise enhances the health and function of neurons by releasing BDNF [31].

Besides, evidence suggests that insulin-like growth factor-1(IGF-1) is considered to mediate the relationship between exercise and neurocognition [32]. Exercise may improve neurocognitive function by increasing IGF-1 [33]. Clinical experiments have confirmed that IGF-1 can inhibit neuronal apoptosis caused by many factors [34]. Exercise training can increase the number of new neurons in the hippocampus through the increase of IGF-1, which mediates the proliferation of hippocampal neurons and improve cognitive function [35]. The current clinical studies can only partially explain the intervention mechanism [33–35], but our one-year randomized controlled study could provide great evidence that aerobic training increased total and right hippocampal volume and had a protective effect on cognitive function in T2DM patients with normal cognition. Therefore, we need to intervene early to have a better clinical effect in such patients; otherwise, by the time patients have progressed to Alzheimer's disease, the exercise would not affect the improvement of hippocampal volume [36].

Effects on cognitive function

Our study confirmed that aerobic training could improve MMSE and MOCA scores of T2DM patients even with normal cognition and protect cognitive function. The result was consistent with an earlier study conducted for 6 months which demonstrated that aerobic training may have cognitive benefits for T2DM adults with normal cognition [37]. However, they only took the mean and 95 % confidence interval before and after intervention which may lead to a lack of credibility in their study. Remarkably, not only tests of efficacy or statistical significance were provided for the difference between groups but also the chi-square test results in cognitive measures were shown in our study, which increased the credibility.

A study conducted in Canada found that after 24 weeks of exercise and lifestyle intervention, the cognitive score of T2DM patients with normal cognition decreased [38]. The small sample size (n = 17) and short study time (24 weeks vs 12 months) may lead to the contingency of the results. One of the research tools they used was the California Verbal Learning Test (CVLT-II) [39], which is mostly used to measure both verbal and episodic memory, while MMSE and MoCA scales were used in our study, which can show cognitive levels more sensitively [40]. This may be the reason for the different results. Similarly, one study showed that different types of physical exercise do not always improve the cognitive function of T2DM

patients. The molecular mechanisms underlying exercise prevention and treatment of cognitive decline in T2DM patients deserve further and in-depth investigation [41].

Strengths and limitations

This is the first known randomized controlled trial to explore the single effect of moderate aerobic training on hippocampal volume for one year, and it verifies that aerobic training is effective in improving the hippocampal volume and protecting cognition in T2DM patients without cognitive impairment. Our aerobic training was led and supervised by professionals, which ensured the quality of our interventions. The one-year randomized controlled trial provided new insights into the clinical evidence that aerobic training provides for the prevention of cognitive impairment.

Limitations of our study should motivate further research. One is that we examined changes only in hippocampal volume, not other brain regions. Meanwhile, the regional brain volumes were not normalized by intracranial volume (ICV) to control for sex and height. Second, the sample size is worth further expanding. Third, both groups of intervention and control subjects received diabetes self-management education. While they were encouraged to pursue usual lifestyle choices, controls in receipt of comprehensive diabetes education may have made substantive changes to their diabetes self-management practices. However, this would only attenuate the already significant difference in the change of hippocampal volume, MMSE, and MoCA scores between the two groups.

Future research

With the increasing burden of T2DM and cognitive impairment on individuals and society, further research on the preventive measures in the cognition of T2DM patients is needed. This requires a longer follow-up to verify whether aerobic training can prevent mild cognitive impairment. Although our results showed that one year of moderate aerobic training can increase hippocampal volume and protect the cognition of patients without cognitive impairment, further evaluation also needs to be proved by experiments on the molecular mechanism of amyloid deposition and structural changes in other parts of the brain.

To sum up, this one-year randomized controlled study provides strong evidence that one-year moderate aerobic training had a positive impact on increasing total and right hippocampal volume and cognitive function in T2DM patients with normal cognition. This suggests that early intervention in the cognitive function of T2DM patients can maximize the potential benefits.

Trial registration

ClinicalTrials.gov NCT04489966

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Authors' contributions: QL conceived and designed the study. YW, LW, JY, and XY collected the epidemiological and clinical data. JY and XY assisted with patient recruitment and training supervision. YW, LW, and JY drafted the manuscript. YW, LW, JY, XY, and QL contributed to the acquisition, analysis, and interpretation of data. QL and TC contributed to the critical revision of the manuscript for important intellectual content. All authors read, revised, and approved the final draft. QL and TC are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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