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The effects of aerobic exercise combined with resistance training on inflammatory factors and heart rate variability in middle-aged and elderly women with type 2 diabetes mellitus

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Abstract

Objective: This study investigated the effects of aerobic exercise combined with resistance training on serum inflammatory factors and heart rate variability (HRV) in women with type 2 diabetes mellitus (T2DM).

Methods: A total of 30 patients with diabetic cardiovascular autonomic neuropathy (DCAN) were randomly divided into a control group ($n = 15$) and an exercise group ($n = 15$). The control group was treated with routine hypoglycemic drugs, while the exercise group was treated with routine hypoglycemic drugs + resistance training (AE+RT). The levels of fasting plasma glucose (FBG), two-hour plasma glucose (2hPG), serum inflammatory factors C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) were measured before and after the intervention. The HRV was evaluated by 24-h ambulatory electrocardiogram.

Results: After the intervention, the levels of FBG, 2hPG, serum inflammatory factors, IL-6 and TNF-α in the exercise group were significantly lower than those in the control group ($p < .05$) with no significant differences in serum CRP ($p > .05$). After the intervention, the HRV time domain and frequency domain indexes in the two groups were significantly improved compared with those before the exercise experiment ($p < .01$) and with no significant difference in (lnlf) ($p > .05$). The time-domain indexes, i.e., SDNN and RMSSD, as well as the frequency domain index, i.e., (lnhf), were significantly higher in the exercise group than in the control group, whereas lnlf/lnhf were significantly lower than those in the control group ($p < .05$).

Conclusions: Compared with routine hypoglycemic drug therapy, combining aerobic exercise and resistance training helped to reduce the level of blood glucose and serum inflammatory factors in T2DM patients with DCAN, and improved autonomic nerve function.

Xiaoyun Su and Jiping He contributed equally to this study.

KEYWORDS
aerobic exercise and resistance exercise, blood glucose, heart rate variability, inflammatory cytokines, type 2 diabetes

1 | INTRODUCTION

Diabetic cardiovascular autonomic neuropathy (DCAN) is one of the common chronic complications of type 2 diabetes mellitus (Henning, 2018). Its incidence is between 20% and 73%. Clinical manifestations include decreased heart rate variability (HRV), postural hypotension and resting tachycardia (Xu et al., 2019). The condition can also easily lead to myocardial infarction, sudden cardiac death and painless myocardial ischemia. Additionally, DCAN is an important factor in the death of patients with cardiovascular and cerebrovascular diseases (Pop-BusuiR et al., 2017; Cha et al., 2016). As a mature and noninvasive method for detecting cardiac autonomic nerve function (sympathetic and vagus nerve activity), HRV analysis is considered an early index for predicting and diagnosing DCAN (Picard et al., 2021).

Studies have shown that inflammation is involved in the occurrence and development of type 2 diabetes mellitus (T2DM). Inflammatory factors destroy islets through multiple links β Cells, which can lead to decreased insulin secretion and insulin resistance and contribute to the occurrence of diabetes-related complications (Chen et al., 2020). Lu Bingyan, a domestic scholar, found that serum inflammatory factors, such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) were closely related to the pathogenesis of DCAN (Lu, 2017). The central nervous system can reduce the production of cytokines by balancing the activities of the sympathetic nerve or vagus nerve, and myocardial ischemic experimental animal models confirmed that stimulating the vagus nerve could significantly inhibit the release of TNF-a and IL-6 (Bakkar et al., 2020). Therefore, HRV and inflammatory factors may play an important role in autonomic nerve injury caused by T2DM.

Physical exercise is considered to help prevent the progression and complications of T2DM by reducing the level of plasma inflammatory markers. In addition, a study indicated that the anti-inflammatory effect of exercise was related to the type, dose and intensity of exercise (Pan et al., 2018). Balducci et al. (2010) found that, compared with patients with aerobic training only, the reduction of inflammatory markers in T2DM patients who engaged in aerobic exercise combined with resistance training (AE + RT) was greater. It is thus suggested that AE + RT has a better effect on countering the risk factors of diabetic complications than aerobic exercise alone.

Based on the above research, the assumption can be made that AE + RT may improve cardiac autonomic regulation function in patients with diabetic autonomic neuropathy by reducing serum inflammatory levels. To test this hypothesis, the present study measured the effect of 12-week AE + RT on serum inflammatory factors (IL-6 and TNF-α), CRP level and HRV (time domain and frequency domain indexes) in patients with T2DM to provide a theoretical basis for improving the autonomic nerve function of AE + RT patients with autonomic neuropathy.

2 | DATAS AND METHODS

2.1 | General information

Female patients with T2DM complicated with DCAN from January 2021 to January 2022 were selected as the research participants. A total of 30 cases were selected by random sampling. The inclusion criteria were as follows: (1) participants met the diagnostic criteria of diabetes and DCAN as per China's guidelines for prevention and treatment of type 2 diabetes mellitus (Clinical Guidelines for Prevention and Treatment of Geriatric Diabetes in China, 2022); (2) based on a standard diagnosis, patients met the diabetes mellitus and autonomic nerve dysfunction criteria (Zhao & Wu, 2013); (3) the patient was female and older than 56 years; (4) the patient was not taking any drugs that would affect the study outcomes.

The exclusion criteria were as follows: (1) patients with coronary heart disease, dilated cardiomyopathy, heart failure, hypertension and hyperthyroidism; (2) patients with a history of myocardial infarction and autonomic neuropathy caused by other factors; (3) the patient had a serious liver and/or kidney disorder, abnormal thyroid function, an acid-based disorder concerning water and electrolyte balance and other diseases; (4) an allergic constitution or a possible allergy to the drugs that were used in this study.

According to the admission number, the patients were randomly divided into the exercise (15 cases) and the control (15 cases) group, respectively. All participants provided signed informed consent for inclusion in the study prior to conducting the trial. Three participants withdrew from the study for personal reasons. Finally, there were 14 participants in the exercise group and 13 in the control group. There was no significant difference in general clinical data (age, height, weight, body mass index and course of the disease) between the two groups ($p > .05$) as shown in Table 1.

2.2 | Intervention method

The intervention method was conducted as follows.

The control group received regular treatment for diabetes, including amendments to their diet, regular and balanced exercise, abstinence from smoking and alcohol and according to their individual condition, metformin tablets or subcutaneous injection of insulin aspartate was delivered to control blood sugar in the required range. For participants with hypertension and hyperlipidemia, this

TABLE 1 Basic information of the subjects

Group	n	Age (year)	Height (m)	Body weight (kg)	BMI (kg/m^2)	Course of disease (year)
Control	13	63.61 ± 2.56	1.61 ± 0.02	65.68 ± 2.34	25.67 ± 0.96	7.89 ± 2.46
Exercise	14	64.01 ± 1.98	1.60 ± 0.03	63.82 ± 1.92	24.90 ± 0.67	8.14 ± 1.84
t/χ^2		1.671	0.764	1.181	1.003	1.332
p		.061	.516	.093	.076	.068

was combined with valsartan, atorvastatin and other drugs to control blood pressure and blood lipid levels in normal ranges. Oral mecobalamin tablets (0.5 mg, batch no. 20151219), were also given (0.5 mg at a time, 3 times a day).

In the exercise group, patients were treated with routine hypoglycemic drugs combined with AE + RT, three times a week, for 60 min each time. The AE + RT (Ma, 2014) conditions were as follows: aerobic exercise combined with resistance training, 60 min each time (a warm-up session for 10 min, formal training for 40 min, finishing exercises for 10 min). The aerobic exercise included walking on a treadmill at a medium intensity (65%–70%, [HRmax]) for 20 min. Participants wore a Polar watch to monitor their exercise intensity and to accurately judge whether aerobic exercise had been carried out within the target heart-rate range. The resistance strength-training mainly comprised a dumbbell (used alongside body side flexion, scissors deep squat, arm flexion and extension, bending lift, side flat lift), an elastic belt and other strength-training tools and unarmed training techniques (e.g., knee-bending sit-up, supine leg-lift, supine two head up, seated thigh adduction and small leg-lift). Resistance training was carried out for 20 min at an exercise intensity of 70%–85% per one-repetition maximum. Three groups of resistance training exercises were completed each time, with resting periods between each group ranging from 3–5 min. Training intensity (the number of groups, exercise intensity and repetition times) was adjusted according to the performance of each participant during training.

The following points were strictly followed when implementing the exercise instructions.

1. The safety principle. Before implementing the exercise tests, an incremental load exercise test was carried out using a power bicycle to determine whether the participants experienced any discomfort, based on the American Sports Medical Association standards (Hill, 2008).
2. The personalization principle. The specific exercise type was selected, based on the patient's hobbies.
3. Exercise intensity measurement and monitoring. The first 2 weeks focused on adaptation training and learning. Once adaptation and mastery had been achieved, steps were taken to ensure that exercises were conducted at the correct intensity. Heart rate was adopted as the standard for formulating personalized exercise intensity as follows: the upper limit of exercise heart rate = 170 age, 5–7 times/week, approximately 20 min/time, or 60 min in total, and the exercise routines were completed three times a day. For patients with physical permission, exercise twice a day. These parameters were combined with subjective exercise intensity scoring and individual self-perception as a means to monitor exercise intensity.

2.3 | Observation index

2.3.1 | Serum inflammatory factors

All the participants took 5 ml of elbow vein blood from the abdomen before the exercise intervention, as well as on the second day after the intervention. The blood samples were centrifuged at a low temperature (4°C) for 10 min (4,000 R/min) and the serum was separated. The serum inflammatory factors, i.e., IL-6 and TNF-α, were measured using an enzyme-linked immunosorbent assay (Abcam) according to the manufacturer's instructions. The fasting blood glucose and 2-h postprandial blood glucose were measured by a fully automated biochemical analyzer (Hitachi 7600).

2.3.2 | Heart rate variability measurement

Before and after conducting the experiment, the subjects rested on their backs for 15 min and then used the 12-channel recorder (DMS, USA) to record a 24-h ambulatory electrocardiogram. The HRV indexes recorded in a 24-h ambulatory electrocardiogram were subsequently analyzed. The time-domain indexes included the following: standard deviation of normal sinus R-R interval (SDNN); (MS), reflecting the overall change in autonomic nerve function; the root mean square of the difference between adjacent normal R-R intervals (RMSSD) MS, reflecting vagus nerve function.

The frequency-domain indexes included the following: low-frequency power (LF) (0.04–0.15 Hz, reflecting cardiac sympathetic nerve activity), high-frequency power (HF) (0.15–0.40 Hz, reflecting cardiac vagus nerve activity) and an lnlf/lnhf ratio reflecting the balance of sympathetic and vagus nerve activity.

2.4 | Statistical treatment

The SPSS Statistics 21.0 software program was used to analyze the data. The measurement data were expressed as mean ± standard deviation using a t-test, and the counting data were expressed as percentage (%) counts using a chi-square test. The LF and HF were first transformed by a natural logarithm to ensure that they conformed to a normal distribution. A paired *t*-test was applied to compare the experimental data before and after applying AE + RT in the two groups (control and exercise). An independent sample *t*-test was conducted to compare the differences in serum inflammatory factors, blood glucose and HRV indexes between the groups before and after the exercise intervention. The difference was statistically significant ($p < .05$).

3 | RESULTS

3.1 | The effect of aerobic exercise and resistance training on blood glucose level in elderly type 2 diabetes mellitus patients

Before conducting the experiment, there was no significant difference in FBG and 2hPG values between the two groups ($p > .05$); Following the intervention, the FBG and 2hPG values in the control and exercise groups decreased significantly compared with those before the experiment ($p < .01$). The FBG and 2hPG values in the exercise group were significantly lower than those in the control group ($t = 2.380$, $p = .027$; $t = 2.256$, $p = 0.033$; see Table 2).

3.2 | The effect of aerobic exercise and resistance training on heart rate variability in elderly type 2 diabetes mellitus patients

Before conducting the experiment, there was no significant difference in the HRV time-domain (SDNN and RMSSD) and frequency domain indexes (lnlf, lnhf and lnlf/lnhf) between the two groups ($p > .05$). After the intervention, the above indexes in the control and exercise groups decreased significantly compared with those before the exercise ($p < .01$). There was no significant difference in the lnlf index between the exercise and the control group ($t = 0.605$, $p = 0.551$); the time domain indexes (SDNN and RMSSD) and the frequency domain index (lnhf) in the exercise group were significantly higher than those in the control group ($t = -4.409$, $p = 0.000$; $t = -2.252$, $p = 0.033$; $t = -2.185$, $p = 0.039$). The Lnlf/lnhf was significantly lower in the exercise group than in the control group ($t = 2.093$, $p = 0.047$; see Table 3).

3.3 | The effect of aerobic exercise and resistance training on serum inflammatory factors in elderly type 2 diabetes mellitus patients

Before conducting the experiment, there was no significant difference in the levels of serum inflammatory factors (IL-6, CRP and TNF-α) between the two groups ($p > .05$). After the intervention, the levels of IL-6, CRP and TNF-α in the exercise group were significantly lower compared with before the exercise ($p < .01$). The levels of serum IL-6 and TNF-α in the exercise group were significantly lower than those in the control group ($t = 3.685$, $p = 0.001$; $t = 2.312$, $p = 0.029$). There was no significant difference in serum CRP between the two groups ($t = 1.038$, $p = 0.309$). See Table 4.

4 | DISCUSSION

The current study examined the combined effect of aerobic exercise and resistance training on serum inflammatory factors and HRV in a cohort of female T2DM patients with DCAN. The primary findings can be summarized as follows: (1) Compared with the conventional treatment of T2DM, the combined exercise strategy can significantly reduce FBG and 2hPG. (2) Compared with before the intervention, the HRV indexes were reduced in both the groups; however, the combined strategy had a more prominent effect. (3) There was a significant reduction in inflammatory markers (IL-6, CRP and TNF-α) following the implementation of the combined strategy. The present study further emphasized the fact that a combined strategy that included hypoglycemic drugs, lifestyle changes and exercise was essential for the treatment of T2DM patients. This strategy may help to reduce complications and improve patient prognosis.

4.1 | The effect of aerobic exercise and resistance training on blood glucose in elderly type 2 diabetes mellitus patients

Diabetes is a global health concern. The disease is expected to affect 439 million people by 2030, of which approximately 85%–90% will be T2DM (Yang et al., 2017). Reportedly, the combination of aerobic exercise and resistance training is more beneficial for stabilizing

TABLE 2 Comparison of FBG and 2H PG levels between the two groups before and after intervention

Indicators	Group	Before intervention	After intervention	*t*	*p*
FBG (mmol/L)	Control	9.63 ± 1.19	7.36 ± 1.07	11.315	.004
	exercise	9.74 ± 1.36	6.92 ± 0.76	9.761	.009
t		1.007	2.380		
p		.281	.027		
2 h PG (mmol/L)	Control	14.66 ± 2.09	9.834 ± 1.75	12.978	.000
	exercise	15.03 ± 1.48	8.78 ± 1.27	7.480	.003
t		1.711	2.256		
p		.094	.033		

TABLE 3 Comparison of HRV test results of patients in each group before and after treatment

HRV	Group:	Before intervention	After intervention	t	*p*
SDNN (ms)	Control	110.54 ± 6.31	120.31 ± 5.13	−9.934	.000
	exercise	108.93 ± 6.66	127.71 ± 3.36	−11.612	.000
t		1.639	4.409		
p		.071	.000		
RMSSD (ms)	Control	39.71 ± 2.67	46.07 ± 3.56	−8.610	.002
	exercise	38.54 ± 4.31	48.14 ± 3.30	−16.914	.000
t		1.366	−2.252		
p		.073	.033		
LnLF (ms^2)	Control	4.11 ± 0.45	4.01 ± 0.48	2.11	.061
	exercise	4.12 ± 0.47	3.89 ± 0.56	3.200	.007
t		0.763	0.605		
p		.542	.551		
LnHF (ms^2)	Control	4.27 ± 0.48	4.49 ± 0.39	1.970	.011
	exercise	4.26 ± 0.52	4.81 ± 0.35	−7.198	.000
t		0.041	2.185		
p		.918	.039		
LnLF/LnHF	Control	0.97 ± 0.13	0.92 ± 0.12	2.482	.029
	exercise	0.98 ± 0.16	0.81 ± 0.13	9.869	.000
t		0.163	2.093		
p		.781	.047		
HR (Time / minute)	Control	74.31 ± 3.66	73.32 ± 4.07	2.793	.016
	exercise	75.14 ± 4.77	72.00 ± 4.45	9.549	.000
t		3.211	2.984		
p		.022	.035		

TABLE 4 Comparison of serum inflammatory factors between the two groups

HRV	Group	Before intervention	After intervention	*t*	*p*
IL-6 (pg/ml)	Control	2.67 ± 0.29	2.50 ± 0.32	3.854	.012
	exercise	2.71 ± 0.32	2.14 ± 0.17	6.596	.078
t		1.004	3.685		
p		.185	.001		
CR (mg/L)	Control	2.97 ± 0.28	2.85 ± 0.30	2.121	.075
	exercise	3.02 ± 0.29	2.75 ± 0.21	6.592	.019
t		0.903	2.312		
p		.565	.029		
TNF-α (pg/ml)	Control	3.73 ± 0.26	3.63 ± 0.23	3.950	.046
	exercise	3.76 ± 0.17	3.44 ± 0.20	7.980	.000
t		0.677	1.038		
p		.782	.309		

blood glucose levels and the overall rehabilitation of T2DM patients (Mangiamarchi et al., 2017). Domestic scholar, Zhao Xiujun (Yang et al., 2017), found that compared with T2DM patients who only participated in aerobic exercise, aerobic exercise combined with resistance training could better control blood glucose levels and glycosylated hemoglobin in T2DM patients. In the present study, after 12 weeks of aerobic exercise combined with resistance training, the fasting blood glucose and 2hPG of the middle-aged and elderly T2DM patients in the exercise group had decreased significantly. This result was consistent with the research results of the studies denoted above.

Research indicated that aerobic training involved the continuous activity of multiple large muscle groups, and that resistance training could increase muscle strength. An increase in large muscle group activity and muscle strength can make the body more sensitive to insulin, promote expression of the glucose transporter gene and stimulate the intake of glucose by cells, resulting in the reduction of glucose (Wormgoor et al., 2017). Accordingly, aerobic exercise combined with resistance training may be a safe and effective auxiliary rehabilitation scheme for T2DM patients.

4.2 | The effect of aerobic exercise and resistance training on heart rate variability in elderly type 2 diabetes mellitus patients

Research has shown that physical exercise is a low-cost and efficient intervention method for autonomic nerve dysfunction in cases of T2DM (Bhati et al., 2018). Compared with a single exercise, aerobic exercise, combined with resistance training, has a better effect on the improvement of cardiovascular autonomic nerve function (Sanches et al., 2015). Pagkalos et al. (2008) found that after 6 months of aerobic exercise (exercise intensity 70%–85% HRmax, 3 times/week), the SDNN, RMSSD and pNN50 of T2DM patients with and without DCAN had increased significantly. However, HF and LF increased significantly in T2DM patients with DCAN, suggesting that exercise had a better effect on T2DM patients with cardiac autonomic neuropathy. The results of the current study are consistent with those presented in (Pagkalos et al., 2008). After 12 weeks of aerobic exercise combined with resistance training, the HRV indexes in the time and frequency domains in the control and exercise groups decreased significantly compared with those before exercise. Compared with the control group, the combined exercise types significantly increased the time domain indexes (SDNN, RMSSD), as well as the frequency domain indexes (HF/LF) in T2DM patients with DCAN, but there was no significant difference in LF values.

It is suggested that aerobic exercise combined with resistance training can help prevent and control cardiovascular autonomic neuropathy in T2DM patients. The different research results obtained for a variety of studies may be related to the selection of participants (those with/without DCAN). In addition, (Weng et al., 2018) found that FBG and 2hPG were the main risk factors for abnormal HRV. Therefore, the improvement of cardiac autonomic nerve function in T2DM patients with DCAN may be related to the reduction of FBG and 2hPG levels in T2DM patients.

4.3 | The effect of aerobic exercise and resistance training on serum inflammatory factors in elderly type 2 diabetes mellitus patients

Inflammation theory suggests that a chronic low-grade inflammatory response is related to the pathogenesis and related complications of T2DM, and serum IL-1, IL-6 and TNF increase with the age and disease course of T2DM patients. The level showed an upward trend. Recent studies found that physical activity and exercise training could help to prevent the development and complications of T2DM by reducing the level of plasma inflammatory markers (Bellavere et al., 2018). However, there are different conclusions on the effect of exercise on inflammatory factors, which may be related to different training programs. Studies showed that compared with aerobic exercise, aerobic exercise combined with resistance training and high-intensity exercise significantly reduced serum CRP and IL-6 levels in T2DM patients with metabolic syndrome, which was not related to weight loss (Seyedizadeh et al., 2020). It is suggested that long-term high-intensity exercise, particularly mixed training, will have a better anti-inflammatory effect. Some scholars believe that aerobic exercise combined with resistance training can reduce serum inflammatory factors IL-6 and TNF- α levels and improve metabolic abnormalities in T2DM patients, thereby reducing the harmful effects of diabetes-related inflammation on health (Cassidy et al., 2019). The results obtained in this study indicated similar outcomes. After 12 weeks of aerobic exercise combined with resistance training, compared with the control group, the group that participated in combined exercise types had significantly reduced serum IL-6 and TNF in patients with T2DM- α and CRP levels. Studies suggested that in healthy individuals and patients with cardiovascular disease, HRV was related to inflammatory markers IL-6, TNF-α and CRP (Williams et al., 2019). Shen et al. (2018) noted that effective blood glucose control may reduce the level of serum inflammation in T2DM patients for controlling DCAN.

In conclusion, the improvement of HRV in T2DM patients by 12-week aerobic exercise combined with resistance training may be related to the reduction of blood glucose levels and inflammatory state. However, the specific mechanism in this regard requires further investigation.

The limitations of the current study are as follows: (1) a small sample size; (2) due to the limitation of single disease medical insurance amount, the short intervention time and no subsequent follow-up data, it was impossible to obtain the long-term effect of AE + RT exercise intervention in T2DM patients with DCAN. Therefore, in the future, the researchers will have to conduct longer-term follow-ups with larger sample sizes, as well as additional prospective studies to further confirm the results presented herein.

5 | CONCLUSION

Compared with the use of hypoglycemic drugs only, routine hypoglycemic drug therapy combined with AE + RT exercise reduced the level of blood glucose and serum inflammatory factors and improved autonomic nerve function in patients with T2DM complicated with DCAN. Therefore, the experiment herein can help to control cardiovascular autonomic neuropathy in T2DM patients with DCAN. However, in the future, longer-term follow-up is needed to verify the long-term effect of AE + RT exercise intervention in T2DM patients with DCAN.

AUTHOR CONTRIBUTIONS

Conceptualization: Su XY, He JP. Investigation: Li HM. Supervision: Cui JM, Men J. Writing–original draft: Su XY, He JP. Writing–review and editing: Su XY, He JP. Approval of the final manuscript: all authors.

CONFLICT OF INTEREST

None of the authors had any personal, financial, commercial, or academic conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

ETHICAL APPROVAL

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Fenyang College Shanxi Medical University.

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