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The effect of 12 week-maximum fat oxidation (FATmax) intensity exercise on microvascular function in obese patients with nonalcoholic fatty liver disease and its mechanism

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Abstract. Fifty-four obese patients with non-alcoholic fatty liver disease (NAFLD) were selected for this study were randomly divided into an exercise group (16 men and 11 women, mean age 21.3 ± 1.0) and control group (16 men and 11 women, mean age 21.8 ± 0.8). The exercise group underwent a 12-week FATmax exercise intervention, while the control group did not engage in any type of systematic physical activity. The controlled diet was given to both groups. After the test, the microvascular reactivity of the exercise group was significantly higher than that of the control group ($p < 0.05$). After the experiment, the concentration of malondialdehyde (MDA), the activity of catalase (CAT) and the activity of exercise group were significantly lower than those of the control group ($p < 0.05$); and in contrast the activities of total superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX) were significantly higher than those of the control group ($p < 0.05$). The change in microcirculation function caused by 12-week FATmax intensity exercise may have an interaction mechanism with oxidative stress and antioxidant system function, and may improve the microvascular reactivity of obese NAFLD patients. In addition, also may improve of oxidative stress and antioxidant system functions.

Key words: FATmax — NAFLD — Microvascular reactivity — Exercise — Oxidative stress — Rehabilitation treatment

Introduction

At present, obesity has become a globally recognized health and safety problem. A series of metabolic diseases caused by obesity has become the killer of human health. During the period of COVID-19, the physical activity of the residents has dropped significantly, especially in the form of a network teaching and other home-based jobs, which leads to a serious lack of extracurricular physical activities and the incidence of obesity has increased significantly. Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease and one of the increasingly important public health problems in China (Fan et al. 2017). NAFLD is a kind of abnormal accumulation of lipid substances in liver tissue caused by multiple causes (except excessive drinking history, drugs, genetic diseases and clear liver injury and other factors). The clinical features of NAFLD are diffuse bubble like fatty degeneration of liver cells and accumulation of triacylglycerol (liver cell lipid exceeds 5% or more of liver wet weight) (Reimer et al. 2020; Ajmera et al. 2021). As the most common chronic liver disease in the world, NAFLD has a global prevalence of more than 25% (Williams et al. 2011), and in China it has reached more than 29% (Zhou et al. 2019; Wang et al. 2021). Among obese people, NAFLD incidence rate is as high as 60–90%, while that of non-obese people is 15% (Musso et al. 2016). So far, the reason and mechanism for the high prevalence of NAFLD in the obese population remain unclear, but it is commonly recognized in academic circles that obesity can significantly increase the prevalence of NAFLD and become an important risk factor in induc-

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ing its occurrence (Romero-Gomez et al. 2017; Polyzos et al. 2019). Obese NAFLD is the main disease type of NAFLD (Fabbrini et al. 2010). The study found that NAFLD can be well controlled through general exercise therapy at the early stage. Scientific exercise and reasonable diet can often reverse fatty liver without drug treatment (Lenasi et al. 2004).

Research suggests that after 4-week of aerobic exercise intervention with heart rate (HR) 60~65% gradually increased to HRmax 80~85% (Byrne et al. 2011; Ray et al. 2011; Piazzolla et al. 2020). Studies have confirmed that aerobic exercise, as an effective method for obese NAFLD patients to promote visceral fat distribution, could be improved, glucose metabolism could be promoted, and insulin resistance could also be reduced. It is also an effective way to treat non-alcoholic fatty liver disease in obese people (Houghton et al. 2017). However, the formulation of exercise intensity in relevant studies is not clear enough, and there is a lack of individualized exercise intensity formulation for different patients' physical function and exercise ability, which ultimately leads to restricted applicability of relevant research findings.

Although exercise can promote fat oxidation, only controlling the exercise intensity within a reasonable range can burn fat to the greatest extent. Maximum fat oxidation (FATmax) intensity refers to the exercise intensity corresponding to the peak of fat metabolism rate *per* unit time. This exercise intensity can promote fat decomposition to the greatest extent and attain the best fat reduction effect (Chavez-Guevara et al. 2020). However, few studies have explored the health-promoting effect of FATmax intensity on NAFLD patients in terms of microvascular function. Microvascular is the most important component in determining metabolic level since it is the only area for body material and energy metabolic exchange.

Microvascular dysfunction has been linked to metabolic dysfunction and abnormalities, which can lead to metabolic diseases like obesity and diabetes. Furthermore, with the increase in obesity, lipid factors may induce further damage to endothelial cells in microvascular, resulting in a reduction in vascular diastolic function (Machado et al. 2016).

Studies have reported that microvascular injury may be the primary location of endothelial cell injury in NAFLD patients, and microvascular dysfunction develops before arterial. In NAFLD patients, the diagnosis of microvascular function is an early indicator of endothelial cell impairment (Klonizakis et al. 2009). As a result, enhancing microvascular function can not only help to prevent metabolic diseases including obesity and hepatic adipose infiltration, but it can also help with patient rehabilitation. However, the impact of FATmax exercise on microvascular reactivity in NAFLD patients is yet unknown.

In addition, endogenous nitric oxide (NO) is one of the important vasoactive substances *in vivo*; it has the function of relaxing blood vessels and increasing tissue perfusion. A large amount of evidence shows that the increase of NO production is generally considered as the physiological mechanism of aerobic exercise to improve microvascular function (Lanting et al. 2022), but some studies believe that oxidative stress and antioxidant system function are also important physiological mechanisms affecting microvascular diastolic function (De Moraes et al. 2016; Stupin et al. 2018). It was found that 4-week treatment can reduce oxidative stress injury of the body, thereby reducing the degree of inflammatory reaction of the body and improving the endothelial function and microcirculation disorder of patients (Kar and Kavdia 2012). Other studies have pointed out that it can improve the renal function of elderly patients with diabetes nephropathy and reduce proteinuria. Its mechanism of action is related to reducing oxidative stress and then improving renal microcirculation disorder (Connes et al. 2022). It has also been pointed out that under the condition of critical illness, the body's antioxidant capacity is reduced, and oxidative stress is more likely to occur, with inflammatory disorder, phagocyte activation, excessive cytokine production and other internal environment disorders, which usually trigger systemic and local hypoperfusion, hypoxia, vascular endothelial cell damage and other pathological phenomena (Tham et al. 2015). Changes in blood flow in microvessels in response to various stimuli is a common method to evaluate the function of microvascular skin cells (Conti et al. 2015), particularly the local tissue heating approach, which has the best repeatability and can reliably assess the function of microvascular endothelial cells (Hodges et al. 2010).

Based on this, through exercise intervention of 12-week FATmax intensity in NAFLD patients, changes in microvascular reactivity were investigated, and their mechanism was also discussed through the perspective of body oxidation and antioxidant function, to provide exercise prescription reference for rehabilitation treatment of NAFLD patients.

Materials and Methods

Object of the study

The study was approved by the biomedical ethics committee of Hubei Minzu University (2020037). The diagnostic criteria referred to the guidelines for the diagnosis and treatment of nonalcoholic fatty liver disease in the Asia Pacific region (2017) (Chitturi et al. 2016; Wong et al. 2018).

The specific diagnosis process is as follows: (1) BMI ≥ 25 kg/m^2, the testing machine was In Body 770 High-end expert body composition analyzer, South Korea; (2) Male waist circumference ≥90 cm, female waist circumference ≥80 cm; (3) The diagnosis of NAFLD was based on chronically elevated alanine aminotransferase (ALT) levels (41 U/l for 6 months) in the presence of an echo bright liver on the abdominal ultrasonography. Similarly, hepatic steatosis was confirmed by the presence of ≥5.56% intrahepatocellular triglyceride content, and abdominal visceral fat was diagnosed as hepatic adipose infiltration by B-ultrasound; (4) Excluding patients with a history of alcoholism or heavy drinking in recent six months. (5) Patients with a fatty liver caused by viral hepatitis, drug-induced hepatitis and other diseases were excluded; (6) The examination of 14 items of liver function, 4 items of blood lipid, blood glucose and glycosylated haemoglobin confirmed that the pathogenesis of NAFLD was related to abnormal blood lipid metabolism; (7) It was also clear that there was no other type of liver disease except NAFLD.

Table 1. Basic information of the study subjects

Characteristic	Group		*p* value
	Control	Exercise	
Age (years)	21.8 ± 0.8	21.3 ± 1.0	0.061
Body mass index (kg/m^2)	27.9 ± 4.7	28.4 ± 3.7	0.762
Weight (kg)	77.7 ± 18.1	79.9 ± 14.8	0.746
Body fat (%)	31.2 ± 4.8	30.9 ± 5.7	0.389
Male waist circumference (cm)	95.2 ± 10.2	96.1 ± 11.3	0.662
Female waist circumference (cm)	86.1 ± 9.5	86.7 ± 10.1	0.621

NAFLD patients were randomly divided into control group (16 men and 11 women) and exercise group (16 men and 11 women).

A total of 54 subjects (all junior students without physical education courses) were recruited for this study. Consent was taken from the patients. The subjects were randomly divided into the exercise group and the control group, with 27 subjects in each group. They were divided into exercise group (16 men and 11 women, with an average age of 21.3 ± 1.0) and control group (16 men and 11 women, with an average age of 21.8 ± 0.8). Fifty four NAFLD patients completed the 12 week intervention expectation and then repeated baseline measurements during the visit (Fig. 1). The basic indicators of the two groups of students are shown in Table 1, and the overall experimental design is shown in Figure 2. The study was approved by the Biomedical Ethics Committee of Hubei Minzu University (2020037).

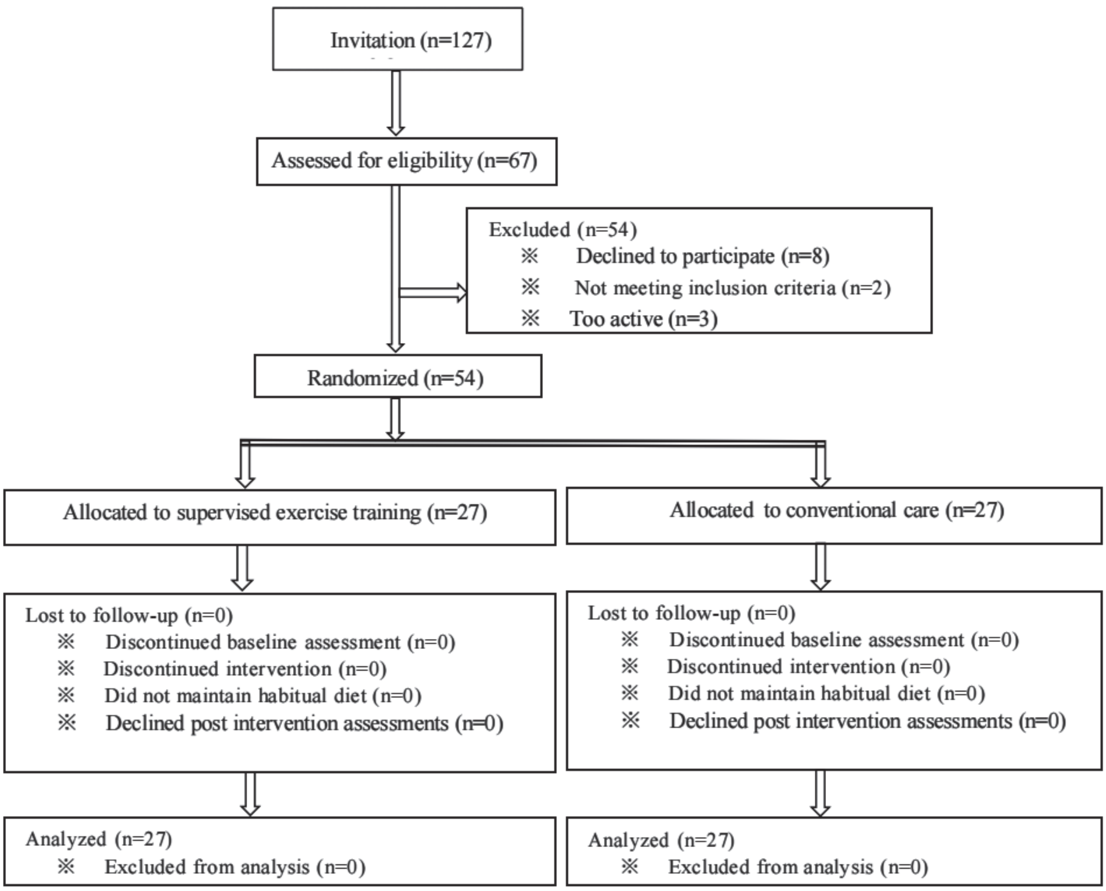

Figure 1. Participant flow diagram.

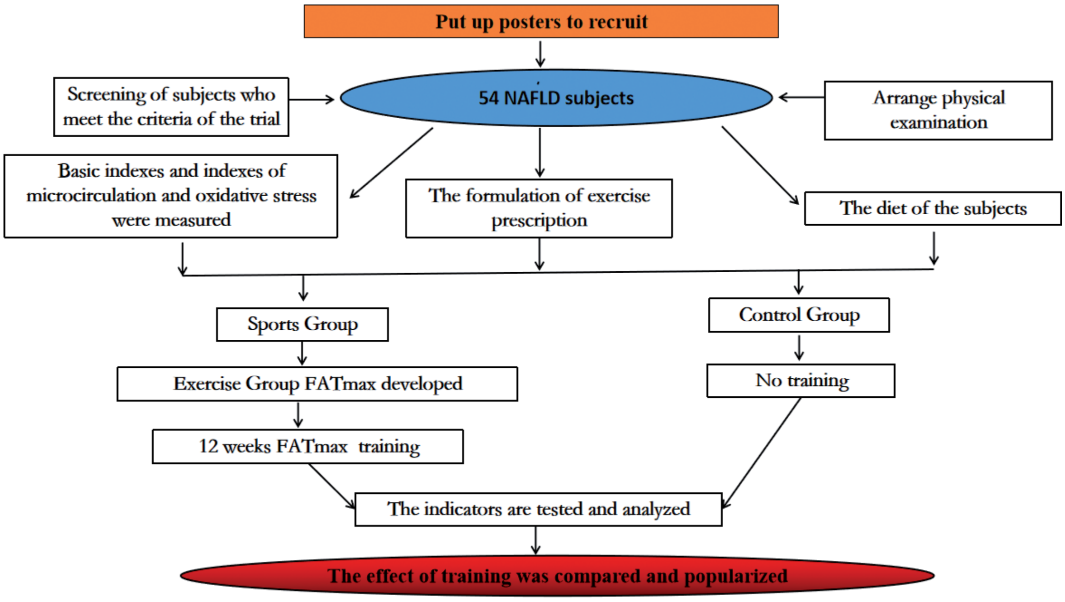

Figure 2. Design of this experiment.

Design of exercise prescription

Formulation of exercise intensity

The exercise intensity is determined by taking the heart rate corresponding to the individualized FATmax intensity as the exercise intensity of the exercise group. FATmax refers to the exercise intensity corresponding to the peak fat metabolism rate in unit time, which can achieve the best fat reduction effect. At present, FATmax exercise is widely used in weight loss and control, and shows good effect (Fiorenza et al. 2019). The FATmax intensity test was completed by PFT Ergo exercise cardiopulmonary function (Italy) and a supporting power bicycle. The specific test process is as follows: Warm-up without load for 2 min followed by a 15 W increase per minute for men and 10 W *per* minute for women, and the bicycle speed is 55–65 r/min → exercise to exhaustion → resume exercise without load for 3 min.

The standard of reaching exercise exhaustion was: (1) The heart rate reaches more than 90% of the maximum heart rate; (2) Oxygen uptake appeared to a plateau period and began to decline; (3) The speed of the bicycle is lower than 55 r/min; (4) Facial expression is painful, and subjective appealed to stop the test. If any 3 of the above requirements are met, it was judged as exhaustion. According to the FATmax judgment standard as proposed by AchtenJ: VO_2 and VCO_2 in the last 15 s of each level of load were brought into the formula: $1.67{*}VO_2 - 1.67{*}VCO_2$, the maximum fat oxidation rate (FATmax rate) of each subject was calculated, and the exercise intensity (heart rate) corresponding to FATmax rate was determined as the exercise intensity (Tan et al. 2016; Jiang et al. 2020). After testing and calculation, the FATmax intensity test is shown in Table 2.

Exercise frequency, time and cycle

The exercise group took aerobic jogging as the form of exercise. During the period from Sept. 28 to Dec. 21 in 2020 (12 weeks), they exercised once a week on Monday, Wednesday, Friday and Sunday, respectively. The duration of the exercise was 60 min, and the exercise intensity was the heart rate corresponding to the FATmax intensity. Before and after the exercise, they did a good job of warm-up and relaxation exercises to avoid sports

Table 2. FATmax intensity test

Group	FATmax rate (g/min)	Oxygen uptake corresponding to FATmax intensity		Power (W)	Heart rate (beat/min)
		Absolute value (ml/min)	Relative value (ml/kg/min)		
Control	0.33 ± 0.14	1406 ± 213	17 ± 4	70 ± 12	127 ± 19
Exercise	0.35 ± 0.12	1419 ± 240	18 ± 3	77 ± 11	124 ± 16

FATmax, maximum fat oxidation.

Table 3. Exercise intervention prescription of exercise group

Sports	Exercise intensity (heart rate)	Movement frequency	Exercise time	Movement cycle	Cautions
Running	124 ± 16 b/min	4 times/week	16:00–17:30 or 19:00–20:30	12 weeks	Heart rate monitoring, preparation and relaxation activities during exercise

injuries. Throughout the trial, the subjects were required to complete no less than 85% of the total exercise plan (Table 3). The control group did not take any form of physical exercise during the exercise intervention.

Dietary arrangement of subjects in both the groups

According to the type of food in the school canteen, the sports nutrition teachers would make a similar proportion of diet plan for the two groups of subjects, (Table 3), and the members of the research group would assist in completing the whole day's diet supervision from breakfast to dinner. The calorie setting was based on the World Health Organization (WHO) caloric and protein intakes and the nutrition standards issued by the FAO (Kummu et al. 2012), and the similar energy intakes were established according to the actual conditions of the subjects, include the type, amount, and total amount of your diet, and make sure there are no significant differences in your energy intake. In addition, during the three, the physical activity of subjects in the control group was monitored. If the intermittent physical activity of the control group subjects was more than 84 h (the average accumulated physical activity was more than 1 h every day) within 12 weeks (Table 4), the data after the test would be selected.

Test indicator

Microvascular reactivity testing

The microvascular relaxation response was measured by PF6000 dual channel laser Doppler blood flow. The test site was the skin at the midpoint of the connecting line between the cubital fossa of the right forearm and the distal process of the radius. The testing indexes included basal skin temperature (BKT), the average velocity of blood cells (AVBC), the concentration of moving blood cells (CMBC), and microcirculatory blood perfusion (MBP), MBP = AVBC*CMBC/100. The important indicator of MBP is microvascular reactivity. When the temperature of the local skin tissue was heated to 44°C, the microvessels reached the maximum relaxation state, and the blood flow in the blood vessels was the highest (Humeau-Heurtier et al. 2014; Yuan et al. 2018;). Microcirculation reactivity was tested twice before and after intervention.

Oxidation and antioxidation indexes testing

Malondialdehyde (MAD) concentration, catalase (CAT) activity, glutathione peroxidase (GSH-PX) activity, superoxide dismutase (SOD) activity, and total antioxidant capacity (T-AOC) were measured. Measurements were performed following an overnight fast, 12-h abstinence from caffeine, and 24-h abstinence from alcohol and strenuous exercise. Venous blood was drawn under fasting conditions. The blood volume of 5 ml was then centrifuged at room temperature (3500 rpm, centrifugation for 5 min), and the upper serum was taken for detection. The micro-plate method was used for MDA and T-AOC detection. Similarly, the visible light method was used for CAT detection, the colorimetric method was used for GSH-PX detection, and the enzyme-linked method was used for SOD determination.

Table 4. Diet plan for one week

Day	Breakfast	Lunch	Dinner
Monday	red bean curd with snow	chow mein, Goryeo	chicken slices with plum sauce, flower rolls
Tuesday	tomato egg noodle, wotou	rice, grilled mushrooms	steamed rolls, braised bean curd
Wednesday	millet congee with cucumber	layer cake, stewed crucian carp	pancakes, tofu stew
Thursday	milk, bread	rice, chicken fried green garlic	rolls, polenta
Friday	corn porridge, pie	millet porridge, vegetarian salad	rice, green pepper fried liver
Saturday	soya-bean milk, steamed stuffed bun	potato and carrot, rice	mixed kelp, braised bean curd
Sunday	millet congee, steamed bread	steamed rolls, chicken soup with assorted dishes	rice, mung bean porridge, mixed with three shreds

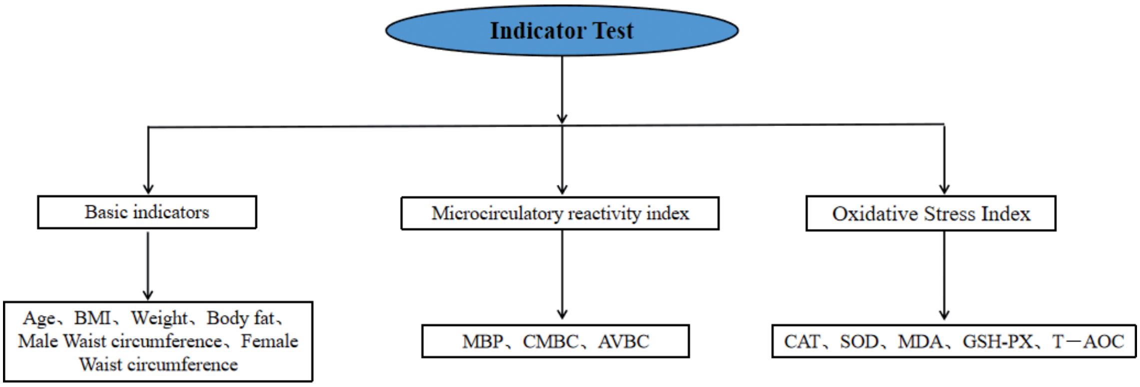

Figure 3. Test of basic indexes, microcirculation reactivity indexes and oxidative stress indexes. BMI, body mass index; MBP, microcirculatory blood perfusion; CMBC, concentration of moving blood cells; AVBC, average velocity of blood cells; BKT, basal skin temperature; CAT, catalase; SOD, superoxide dismutase; MDA, malondialdehyde; GSH-PX, glutathione peroxidase; T-AOC, total antioxidant capacity.

In summary, we tested subjects for basal, microcirculatory reactivity and oxidative stress indicators. (1) Basal indicators included age, BMI, weight, body fat, male waist circumference and female waist circumference. (2) Microcirculatory reactivity indicators included MBP, CMBC and AVBC. (3) Oxidative stress indicators included CAT, SOD, MDA, GSH-PX and T-AOC (Fig. 3).

The above indexes shall be tested once before and after the test.

Statistical methods

The data were statistically analyzed by SPSS (version 25.0) software. The normal distribution of the data was tested. Independent sample T test is used for comparison between groups, and paired sample T test is used for comparison before and after the test in the same group, and Bonferroni test was used for post comparison, and the significant difference was $p < 0.05$.

Table 5. Comparison of the changes in body composition before and after the experiment between the control and exercise groups

Indexes	Group	Before the test	After the test
Weight (kg)	control	77.7 ± 18.1	79.4 ± 14.2
	exercise	79.9 ± 14.8	72.1 ± 11.5*#
Body fat (%)	control	31.2 ± 3.1	32.0 ± 2.8
	exercise	30.9 ± 2.9	27.2 ± 2.8*#
BMI	control	27.9 ± 4.7	27.1 ± 5.7
	exercise	28.4 ± 3.7	25.2 ± 3.0*#

* $p < 0.05$ in comparison of within-group pre- and post-experimental variability; # $p < 0.05$ in comparison of post-experimental variability between groups.

Results

Changes in body composition of two groups before and after the test

It can be seen from Table 5 that the body weight, body fat rate and BMI of the exercise group after the test were significantly lower than those of the control group ($p < 0.05$). The body weight, body fat rate and BMI of the exercise group after the test were significantly lower than those before the test ($p < 0.05$).

Changes in microcirculatory blood perfusion in the two groups before and after the test

It can be seen from Table 6 that MBP, CMBC and AVBC in the exercise group were significantly higher than those in the control group after the test ($p < 0.05$). After the test, MBP and CMBC in the exercise group were significantly higher than those before the test ($p < 0.05$). The results showed that 12-week FATmax intensity training could effectively improve the microvascular reactivity of NAFLD.

Changes in oxidative stress and antioxidant defense indexes in the two groups before and after the test

It can be seen from Table 7 that after the test, MDA and CAT in the exercise group were significantly lower than those in the control group ($p < 0.05$); SOD and GSH-PX were significantly higher than those in the control group ($p < 0.05$). After the test, MDA and CAT in the exercise group were significantly lower than those before the test ($p < 0.05$); SOD was significantly higher than that before the test ($p < 0.05$).

Table 6. Comparison of microvascular blood flow (MBP), microvascular blood cell concentrations (CMBC) and microvascular blood flow velocity (AVBC) in control and exercise groups before and after the test

		MBP		CMBC		AVBC	
Indexes	Group	Before the test	After the test	Before the test	After the test	Before the test	After the test
Basic value	control	8.6 ± 2.6	7.8 ± 1.8	88.4 ± 35.1	85.7 ± 25.6	10.7 ± 2.6	9.9 ± 2.4
	exercise	8.0 ± 1.9	7.2 ± 2.2	81.0 ± 30.6	66.0 ± 21.5	11.2 ± 4.0	10.4 ± 2.2
Heating value	control	90.7 ± 28.7	91.3 ± 28.2	241.9 ± 50.6	252.8 ± 65.4	39.5 ± 10.4	38.7 ± 11.4
	exercise	89.9 ± 29.9	113.6 ± 31.6*#	240.5 ± 64.0	285.6 ± 50.7*#	39.6 ± 10.3	35.2 ± 8.8#
Difference	control	82.2 ± 26.6	83.5 ± 27.3	153.5 ± 49.2	167.2 ± 52.3	28.8 ± 10.6	26.4 ± 10.9
	exercise	81.9 ± 29.4	105.5 ± 31.2*#	159.4 ± 48.4	219.6 ± 47.5*#	28.4 ± 10.4	24.8 ± 9.6

* $p < 0.05$ in comparison of within-group pre- and post-experimental variability; # $p < 0.05$ in comparison of post-experimental variability between groups.

Discussion

The effect of FATmax exercise intensity on microvascular reactivity in college students with obese NAFLD

The change of lifestyle due to various reasons has made a relatively high incidence of NAFLD in the world, especially in China, and its morbidity is higher in the obese population than those in the non-obese population (Feng et al. 2014; Lu et al. 2016). Studies have found that the obese population is highly related to NAFLD morbidity (Eslam et al. 2020). With the further development of this disease, the fatty liver will develop in the direction of steatohepatitis, liver cirrhosis, and liver cancer, forming irreversible harm to the body (Meroni et al. 2020). Microvascular dysfunction plays an important role in this process. The microvascular function can decide the metabolic level of energy substances such as fat and sugar (Hu et al. 2018; Vita et al. 2019).

The decline of microvascular diastolic tube function leads to insufficient blood perfusion, material metabolism disorder and accumulation of metabolites (Padro et al. 2020; Koller et al. 2022). Studies have also suggested that the increase of hepatic advanced glycation end products and microcirculation disturbance may be the pathogenesis of NAFLD liver injury (Gimbrone et al. 2013; Pereira et al. 2017). Other studies suggested that once the disease is present, microvascular and endothelial function can be significantly impaired in patients with coronary artery (Chipperfield et al. 2019; Zuo et al. 2021). In conclusion, microvascular diastolic dysfunction is an important pathological feature in NAFLD patients and improving microvascular diastolic function and blood perfusion is helpful to the rehabilitation of patients.

In the treatment of NAFLD patients, lifestyle intervention is a scientific and effective method. Studies have shown that resistance exercise can improve liver metabolism in mice as well (Bae 2020). Some researchers believe that exercise intervention intensity is related to the degree of hepatic adipose infiltration and exercise ability (Kechagias et al. 2020), therefore, exercise intervention in patients with severe NAFLD should be carried out cautiously (Finelli et al. 2012; Zhang et al. 2019). Furthermore, a meta-analysis has suggested that exercise intervention can significantly reduce insulin resistance index, triglyceride, ALT, and body mass index in patients, while aerobic exercise has the best intervention effect (Chavez-Guevara et al. 2021).

In conclusion, it is believed that aerobic exercise is the best exercise choice to promote the rehabilitation of NAFLD patients, but the best exercise intensity should be formulated according to the physical function of the subjects. Therefore, this study has formulated individualized FATmax intensity for each subject's exercise ability. After 12 weeks of FATmax intensity intervention, the microvascular reactivity of the subjects was significantly improved. The microvascular reactivity in the exercise group was significantly higher than that in the control group ($p < 0.05$). In conclusion, 12 week FATmax intensity training can effectively improve the mi-

Table 7. Comparison of oxidative stress and antioxidant indexes between the control and exercise groups before and after the test

Parameter	Groups	Before the test	After the test
MDA (nmol/ml)	control	7.9 ± 1.7	8.1 ± 1.0
	exercise	8.0 ± 1.0	6.3 ± 0.8*#
CAT (U/ml)	control	7.3 ± 0.7	7.8 ± 0.4
	exercise	7.5 ± 1.4	6.4 ± 0.9*#
SOD (U/ml)	control	16.6 ± 2.2	16.2 ± 1.5
	exercise	17.0 ± 2.9	20.8 ± 3.2*#
GSH-PX (mmol/l)	control	18.4 ± 2.0	19.4 ± 2.6
	exercise	18.9 ± 2.1	20.9 ± 1.8#
T-AOC (mmol/l)	control	0.7 ± 0.2	0.7 ± 0.1
	exercise	0.7 ± 0.3	0.8 ± 0.5

* $p < 0.05$ in comparison of within-group pre- and post-experimental variability; # $p < 0.05$ in comparison of post-experimental variability between groups.

crovascular reactivity of NAFLD, and significantly improve the microvascular diastolic function of patients.

Donghui et al. (2019) have shown that 6 weeks of aerobic exercise combined with dietary intervention can effectively improve the microvascular reactive hyperemia of obese adolescents. 8-week aerobic training can significantly improve the skin microvascular reactivity and plasma adiponectin level of obese subjects (Pasqualini et al. 2010). Other studie has shown that 12 weeks of aerobic exercise can significantly improve the microvascular reactive congestion index of obese adolescents (Zhang et al. 2017). Through the analysis of the above scholars' research results, it is concluded that aerobic exercise is an effective way to improve the microvascular reactivity of obese people, and has a significant intervention effect on the microvascular reactivity of obese people, which is consistent with the results of this study. However, there are also some differences between these studies and ours: (1) The above studies mainly focus on ordinary subjects, while our research subjects are college students with non-alcoholic fatty liver disease. Compared with the general obese subjects, the microvascular function of our subjects decreased more significantly. (2) The above research has developed a unified intensity for the subjects, while our exercise program is to develop an accurate exercise prescription for the subjects, and our research has developed personalized maximum fat oxidation intensity for the exercise ability of the subjects, so our research is more accurate and effective in specifying exercise intensity.

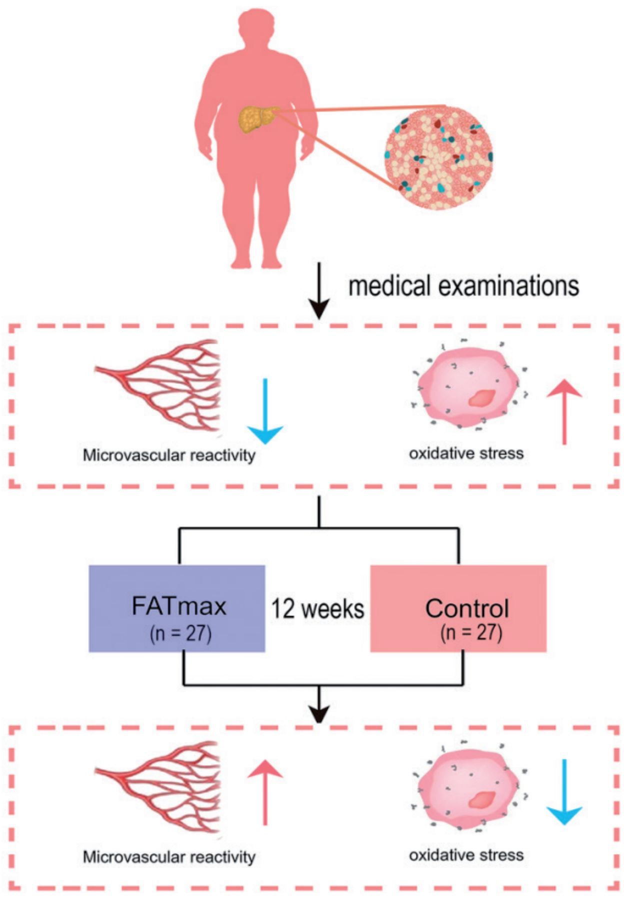

Figure 4. Exercise significantly promotes microvascular reactivity while reducing oxidative stress.

NAFLD is an independent risk factor for inducing hyperlipidemia, hypertension, diabetes and other diseases. The results showed that after 12 weeks of FATmax intervention, the body weight, body fat ratio and body index of the exercise group were significantly lower than those of the control group ($p < 0.05$). Therefore, 12-week FATmax intensity intervention may help reduce the probability of hyperlipidemia, hypertension, diabetes and other diseases. Moreover, research shows that improving microvascular diastolic function can improve the cardiopulmonary endurance level of NAFLD patients (Johnson et al. 2010). Microvascular function is one of the important factors that determine the level of cardiopulmonary endurance. After 12 weeks of FATmax intervention, oxidative stress indicators such as MDA, CAT and SOD have significant differences. After intervention, the antioxidant enzyme activities of MDA and CAT increase with the increase of exercise intervention time, and the antioxidant capacity of SOD gradually increases with the increase of exercise intervention time. This also shows a rapid antioxidant capacity to improve microvascular endothelial cells. Therefore, improving microvascular diastolic function is helpful to improve the cardiopulmonary endurance and overall health of NAFLD patients, and reduce the occurrence of adverse events.

The mechanism of FATmax exercise intensity on microvascular reactivity in college students with obese NAFLD

In the pathogenesis of NAFLD, the second strike theory proposed that the elevated levels of oxidative stress play a key role, which may be the starting point of liver and extrahepatic tissue damage (Rolo et al. 2012; Vergara et al. 2019). Meanwhile, the increased level of oxidative stress can also aggravate the damage and apoptosis of liver cells and accelerate the deterioration of the disease (Tilg et al. 2010). Therefore, the imbalance between oxidative stress and the antioxidant capacity of the body plays an important role in the occurrence and development of NAFLD (Diniz et al. 2019; Musso et al. 2010). Studies have also shown that aerobic exercise can improve the microvascular function in patients and can reduce the risk of cardiovascular disease by enhancing the bioavailability of the anti-atherosclerotic molecule (NO). However, body oxidative stress and antioxidant system also have an important influence on microvascular diastolic reactivity (Perry et al. 2015; Han et al. 2021).

The improvement of oxidative stress and antioxidant system function can repair damaged microvascular endothelial cells to a certain extent (Wu et al. 2020). Therefore, under the intervention of FATmax intensity for a certain period, the oxidative stress and antioxidant function of the subjects can decrease significantly. Furthermore, the improvement of the oxidative stress and antioxidant system functions of NAFLD patients was also conducive to the improvement of microvascular relaxation function, protection of microvascular endothelial cells, and the increase of endogenous NO production (Zoccali 2006). Studies have suggested that aerobic exercise can improve liver metabolism and oxidative stress levels and enhance the antioxidant capacity of NAFLD mice (Tilg et al. 2021). In addition, other studies have shown that aerobic exercise improves body weight and exercise capacity, and enhances liver metabolism and non-enzymatic antioxidant capacity in diseased mice (Ye et al. 2011; Fernandes et al. 2020).

In this study, after 12 weeks of FATmax intensive exercise intervention, the MDA and CAT of obese NAFLD patients decreased significantly. Although T-AOC activity was not significant in statistics, it had an increasing trend, which indicated that FATmax intensity exercise could reduce the level of oxidative stress and improve the ability of antioxidant system in obese NAFLD patients to some extent, reduce endothelium damage and increase microvascular reactivity, as shown in Figure 4 (exercise can significantly promote microvascular reactivity and reduce oxidative stress). Our study demonstrated that the improvement of oxidative stress and antioxidant defense system function may be one of the most important biological mechanisms in the microvascular reactivity in obese students with nonalcoholic fatty liver disease, which may be improved by the FATmax intensity exercise.

Conclusions and Recommendations

A 12 week-FATmax intensity exercise can improve the microvascular reactivity in obese students with nonalcoholic fatty liver disease. Furthermore, the improvement of oxidative stress and antioxidant defense system function may be the potential biological mechanism (Fig. 4). It is suggested that the obese students with NAFLD should take FATmax intensity aerobic exercise 4 times *per* week, and microvascular reactivity should be checked regularly, to evaluate the effect of exercise intervention.

Firstly, this paper uses FATmax intensity exercise to intervene NAFLD college students, discusses the mechanism of the interaction between the change of microcirculation function and the function of oxidative stress and antioxidant system, and discusses the improvement of NAFLD college students' physical function from the perspective of microcirculation, which is an innovation in the research program and perspective. Secondly, the study protocol developed individualized FATmax intensity exercises according to the subjects' exercise capacity in the exercise prescription, which fully considered the differences in physical functions of different subjects, so the design of the exercise prescription in this study was more scientific and reasonable.

In this paper, 12 week FATmax intensity exercise was used to intervene NAFLD college students. The results showed that the microcirculation function, oxidative stress and antioxidant system function of NAFLD college students were improved. However, FATmax exercise can change the mechanism of microvascular function in many ways. In the future, we will explore the biological mechanism of exercise changing microcirculation from the perspectives of nitric oxide, endothelin, VEGF, etc. These biological indicators are also important indicators that affect the function of microvascular contraction. In addition, this paper conducts 12 weeks of FATmax intensity aerobic exercise for NAFLD college students, but the intervention effect of single resistance exercise and resistance group combined with aerobic exercise on NAFLD college students is still uncertain, so whether different forms of exercise intervention have different effects on the intervention effect still needs to be further studied and determined.

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