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ФЕРМЕНТЫ ПЕЧЕНИ ПРИ НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ: ОТВЕТ НА ПИРАМИДАЛЬНУЮ АЭРОБНУЮ ТРЕНИРОВКУ В СРАВНЕНИИ С НЕПРЕРЫВНОЙ АЭРОБНОЙ ТРЕНИРОВКОЙ

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Liver Enzymes in Non-Alcoholic Fatty Liver Diseases: Response to Pyramidal Versus Continuous Aerobic Training

Аннотация

Цель. Исследовалось влияние выбора типа тренировки (консервативная нефармакологическая терапия первой линии при неалкогольной жировой болезни печени (НАЖБП)) на улучшение показателей ферментов печени. Проведено сравнительное исследование, направленное на оценку ответа ферментов печени на пирамидальные упражнения с повышающейся интенсивностью (интервальные) в сравнении с непрерывными аэробными упражнениями у пациенток женского пола с НАЖБП. **Материалы и методы.** 38 участниц с НАЖБП рандомизировали в группу пирамидальных тренировок (n=19) и группу непрерывных тренировок средней интенсивности (n=19). Участницы обеих групп соблюдали рассчитанную на 12 недель диету с низким потреблением калорий и выполняли упражнения три раза в неделю. В дополнение к измерению индекса массы тела (ИМТ) и окружности талии (ОТ) у пациенток с НАЖБП определяли уровни сывороточной аланинтрансаминазы (АЛТ), щелочной фосфатазы (ЩФ), липопротеинов высокой плотности (ЛПВП), аспартатаминотрансферазы (АСТ), триглицеридов (ТГ) и гаммаглутаминтрансферазы (ГГТ) на исходном уровне и через 12 недель. **Результаты.** По завершении обеих программ тренировок наблюдались заметные улучшения. Пирамидальные аэробные упражнения привели к более существенным и заметным улучшениям показателей по сравнению со вторым типом тренировок (аэробные тренировки умеренной интенсивности). **Заключение.** Оба типа тренировок (аэробные тренировки умеренной интенсивности или пирамидальные упражнения) существенно улучшили показатели АЛТ, ИМТ, АСТ, ЛПВП, ГГТ, ЩФ, ОТ и ТГ у пациенток с НАЖБП, при этом пирамидальные тренировки оказались более эффективными по сравнению с непрерывными упражнениями умеренной интенсивности.

Ключевые слова: Пирамидальные упражнения, аэробные упражнения, ферменты печени, липидный профиль, неалкогольная жировая болезнь печени

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Было получено согласие пациенток с НАЖБП на участие в исследовании, медицинское/клиническое исследование одобрено этическим комитетом (P.T.R.E.C/012/004669), также применялись универсальные рекомендации Хельсинской декларации. В этом исследовании НАЖБП период, рассчитанный для программы тренировок (пирамидальные и непрерывные аэробные тренировки), составил с 1 августа 2024 г. по 28 февраля 2025 г.

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Abstract

Purpose: The effect of choosing the type of exercise — the first-line conservative non-pharmacological therapy in managing non-alcoholic fatty liver disease (NAFLD) — on improving liver enzymes has not been fully investigated.: This was a comparative trial aimed to examine the response of liver enzymes to pyramidal progressive-intensity (interval) versus continuous moderate-intensity aerobic training in NAFLD women. **Materials and Methods:** Thirty-eight NAFLD women were randomized into a pyramidal training group (n=19) and a group of continuous moderate-intensity exercise (n=19). Both groups followed a reviewed 12-week low-calorie diet and received exercise training thrice weekly. Besides body mass index (BMI) and abdominal circumference (AC), NAFLD patients' serum alanine transaminase enzyme (ALTE), alkaline phosphatase enzyme (ALPE), high-density lipoprotein (HDL), aspartate transaminase enzyme (ASTE), triglycerides (TGs), and gamma-glutamyl-transpeptidase enzyme (GGTE) were assessed before and after 12 weeks. **Results:** Significant improvements in all outcomes occurred after finishing both training forms. The pyramidal aerobic form produced more significant and pronounced improvements in the tested outcomes compared to the other form of exercise, moderate-intensity aerobic exercise. **Conclusion:** Both training forms, moderate-intensity aerobic exercise or pyramidal training, significantly improved NAFLD patients' ALTE, BMI, ASTE, HDL, GGTE, AC, ALPE, and TGs, but the pyramidal form of exercise is more efficient than the continuous moderate-intensity form.

Key words: pyramidal exercise; aerobic exercise; liver enzymes; lipid profile; non-alcoholic fatty liver disease

Conflict of interests

The authors state that this work, its theme, subject and content do not affect competing interests

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

Consenting of NAFLD women, ethical approval of conducting medical/clinical research (P.T.R.E.C/012/004669), and universal recommendations of Helsinki were applied. In this NAFLD trial, the period designed for conducting the exercise program (pyramidal versus continuous aerobic exercises) was from 1st August 2024 to 28 February 2025.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is the local fat deposition/deposition in the liver's hepatocytes of more than 5% of hepatic cells' volume/size [1-3]. The estimated incidence of NAFLD is 47 cases/patients per 1,000 subjects [4].

The pathogenesis of NAFLD may be related to genetic predisposing factors and/or clinical conditions such as insulin resistance, metabolic syndrome, obesity, and/or type 2 diabetes mellitus [5]. These conditions may accelerate the development/accumulation of macrovesicular hepatic fat which may be accompanied by local hepatic inflammation, signs of local hepatic injury, and variant hepatic fibrosis. Fibrosis disrupts normal hepatic architecture. This disruption leads to an impairment of hepatic functions. This fibrosis-induced hepatic impairment may predispose the development of hepatic cirrhosis and the risk of malignant transformation into hepatocellular carcinoma [6].

With the lack of effective/approved drugs, leaving NAFLD without management accelerates the development of cardiovascular/metabolic diseases, low work productivity, poor patients' quality of life, and rapid sensation of tiredness/exhaustion [7].

Lifestyle changes (exercise training with or without reduction of dietary calories) are considered the initial/main step of NAFLD management [8]. Exercise — as a first-line lifestyle modification treatment for NAFLD — is currently applied mainly as aerobic exercise [9]. Aerobic exercise, particularly walking, is a low-cost non-pharmacological option that is an easy exercise tool that may be handled by NAFLD patients, applied irrespective of place, and managed to improve NAFLD-associated cardiovascular complications. Despite these good characteristics/features of aerobic exercise, its usual continuous form may induce rapid fatigue/discomfort (due to depletion of glycogen stores and/or overuse of slow-twitch muscle fibers) and poor long-term compliance or adherence [10].

On the other hand, pyramidal training, a form of aerobic exercise that is applied in a nearly interrupted form with a gradual progression of the intensity from low to high intensity during the same session, is a relatively new exercise tool that could be used to improve cardiovascular risk factors. The mix between low intensity — which is directed to use local fat as a source of energy — and high intensity — which is directed to use carbohydrates as a source of energy and avoid overuse of slow-twitch muscle fibers — explain the preference of using pyramidal training compared to other forms of training (such as low or moderate intensity exercises) in treating cardiovascular risk factors such as obesity and dyslipidemia [11].

However, the most effective exercise prescription (needed frequency, type, intensity, and total time of

exercise session) for the enhancement/improvement of NAFLD remains unclear/unexplained. Moreover, given the high prevalence of NAFLD-inducing cardiovascular disorders, the effect of choosing exercise type on liver enzymes has not been fully compared, especially for pyramidal training. So, this comparative trial aimed to investigate the response of liver enzymes to pyramidal versus continuous moderate-intensity aerobic training in NAFLD patients.

Materials and methods

Design

A randomized controlled pyramidal-versus-aerobic exercise trial.

Settings

Outpatient clinic of internal medicine which is affiliated to Meetghamr General Hospital.

Inclusion criteria

The diagnosis of NAFLD was thoroughly confirmed by a gastroenterologist and a radiologist. Both of them confirmed the presence of NAFLD after applying abdominal ultrasonography. Ultrasonography detected the presence of hepatic steatosis without an evidence of secondary causes such as alcohol consumption or viral hepatitis. The patients (38 women) who were aged 37-51 years old and had a body mass index (BMI) $> 30 \text{ kg/m}^2$ to $< 35 \text{ Kg/m}^2$ were called to participate in this exercise trial.

Exclusion criteria

The presence of orthopedic surgeries, deformities, and trauma that limit the accurate performance of exercise training declined patients from participation in this exercise trial. Also, recent or current engagement in exercise trials or weight loss trials declined patients from participation. History of cardiovascular, metabolic, systemic, endocrine, autoimmune, psychic, neurological, renal, viral, or malignant disorders declined patients from participation in this exercise trial. Also, the authors prevented the engagement of pregnant or lactating females.

Randomization

Concealed sealed envelopes containing the names of NAFLD women were prepared by a physiotherapist who did not show any intention of participating as an author in this exercise trial and he did not show the passion to know the cause of randomizing the women. This

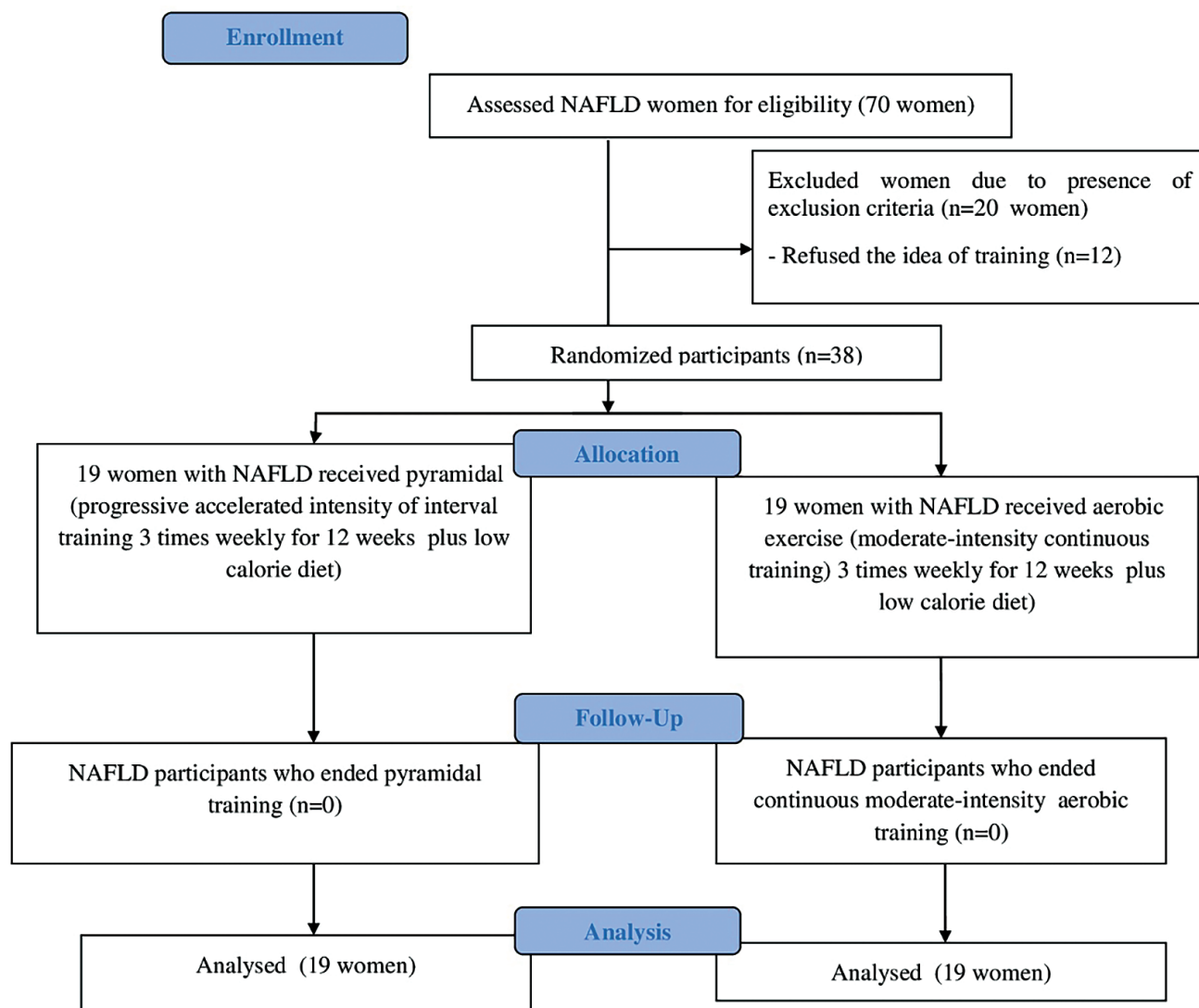


Figure 1. Flow chart of women with NAFLD

physiotherapist equally randomized NAFLD women into a pyramidal training group (PTG, $n=19$) and a group of continuous aerobic exercise (GCAE, $n=19$) (**Figure 1**). Exercise sessions in both groups were repeated thrice weekly for 12 weeks. Additionally, both groups followed a reviewed low-calorie diet. Before starting pyramidal training or continuous aerobic exercise, unfolding the concealed sealed envelopes was executed via an independent researcher.

Interventions

Low-calorie diet

Patients adhered to the by-last-author-reviewed low-calorie diet after subtracting 500 kilocalories from women's resting metabolic rate (RMR). The Harris-Benedict equation — the equation used to estimate RMR — was utilized as follows: $RMR = 655.1 + (9.59 \times \text{NAFLD women's body mass in kg}) + (1.85 \times \text{NAFLD women's height}$

in cm) — $(4.67 \times \text{NAFLD women's age in years})$ [12]. Besides fats (20–30%), carbohydrates (55–65%) and proteins (10–15%) constituted the ration of macronutrients of NAFLD women's low-calorie diet [13].

NAFLD patients were advised to drink a large amount of fresh water or low-carbohydrate fresh drinks. Charts listing carbohydrate levels/amounts in different foods such as vegetables and dairy products were provided to all NAFLD patients. The supplied specific charts listing carbohydrate levels in appropriate food choices and meal plans were compatible with NAFLD patient's individualized preferences.

Aerobic training (moderate-intensity continuous exercise)

Walking was executed by NAFLD women on an electronic treadmill in the form of warm-up phase (the first phase of walking performed at 40–60% of NAFLD women's maximal heart rate, MHR, for 5 minutes), middle

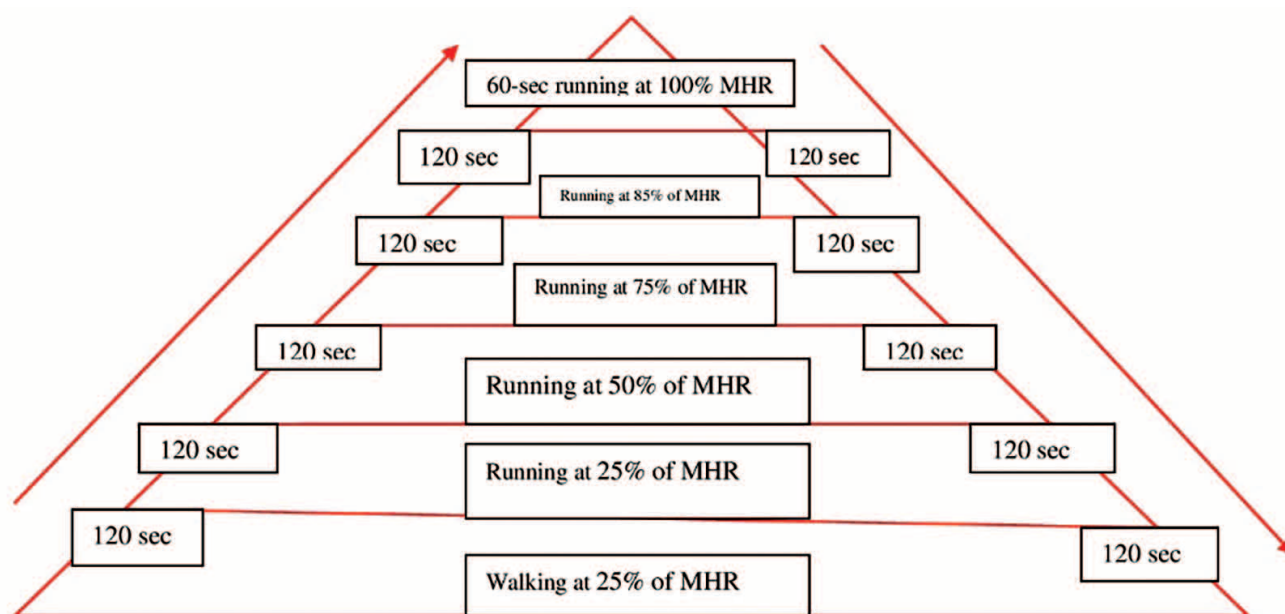


Figure 2. The protocol of the executed pyramidal training

phase (the second phase of walking performed at 60-75 % of NAFLD women's MHR for 50 minutes), and cooling-down phase (the third and final phase of walking which imitated the same features of warming-up phase) [14].

Pyramidal training

The 42-minute pyramidal exercise — the accelerated progressive-intensity interval training — was executed in two 21-minute cardio-training running on an electronic treadmill, with 10-minute rest between exercises and an intensity ranged from 25-100% of MHR of NAFLD women's MHR [12] (Figure 2). The training was conducted according to Karvonen's heart rate formula calculation. Ten-minute warming-up (before the pyramidal training) and 10-minute cooling-up (after the pyramidal training) were conducted in the form of light running and/or light stretching exercises [15]. To be noted, before starting the first session of the pyramidal training, a cardiopulmonary exercise test was applied to every patient who received a pyramidal training to prevent probable side effects of high-intensity exercise.

Outcomes

NAFLD patients' serum alanine transaminase enzyme (ALTE) was measured in both groups. The authors of this study designed this enzyme as the primary outcome of this clinical exercise trial. Secondary outcomes were serum levels of NAFLD patients' alkaline phosphatase enzyme (ALPE), high-density lipoprotein (HDL), aspartate transaminase enzyme (ASTE), triglycerides (TGs), and gamma-glutamyl-transpeptidase enzyme (GGTE).

Also, BMI and abdominal circumference (AC) were assessed as anthropometric secondary outcomes of this clinical exercise trial.

Blinding

Details of this study were not explained to the clinical biochemistry physician or assistants who analyzed serum liver enzymes.

Sample size

Thirty NAFLD patients were needed to complete this pyramidal-vs-continuous exercise trial. The effect size of the G*power analysis was 0.94. This effect size was for NAFLD patients' serum ALT (the primary outcome of this clinical exercise trial). To manage the G*power analysis (at a power of 80%), a pilot test was conducted on eight patients with NAFLD in every group. The authors of this pyramidal-vs-continuous exercise trial raised the number of NAFLD participants to 38 NAFLD patients (the ratio of the estimated increase in NAFLD patients' number was 25% to avoid the idea of dropout).

Statistical analysis

Using SPSS 18, paired test was used to assess the significant-inducing changes of selected exercises on BMI, AC, ALPE, GGTE, ALTE, ASTE, HDL, and TGs within groups. Concerning pre-treatment or post-treatment between-group parity of data (AC, ALPE, GGTE, ALTE, ASTE, HDL, TGs, and BMI), the significant

difference was tested via unpaired test. Age, as one of demographic data, was compared before application of both exercises to assess significant difference using the unpaired test. Authors used the applied statistical tests (paired or unpaired tests) due to the normal distribution of tested data.

Results

Before starting the pyramidal training or the continuous aerobic exercise, parity of between-group pre-treatment age, AC, BMI (**Table 1**), ALPE, GGTE, ALTE, ASTE, HDL, and TGs of NAFLD patients was not significant (**Table 2**).

Also, after ending the pyramidal training or the continuous aerobic exercise, within-group parity of AC, BMI, ALPE, GGTE, ALTE, ASTE, HDL, and TGs showed a significant improvement. The improvement level of outcomes in the PTG was higher than the improvements in GCAE (**Table 2**).

Also, after ending the pyramidal training or the continuous aerobic exercise, between-group parity of AC, BMI, ALPE, GGTE, ALTE, ASTE, HDL, and TGs showed a significant improvement toward the PTG (**Table 2**). The outcomes of this study revealed significant improvement after the application of both types of exercises with a superiority to the application of pyramidal training.

Discussion

This clinical exercise trial confirmed the role of pyramidal or continuous moderate-intensity aerobic exercise in improving NAFLD-associated dyslipidemia and elevation of liver enzymes with a more novel favorable effect of pyramidal aerobic training over continuous moderate-intensity intensity.

Regarding the liver enzymes' improvement after adherence to the moderate-intensity exercise program of this study, gained strength of immunity, regular release of anti-inflammatory/anti-oxidative markers, and increased fight against further inflammation or oxidative stress of new hepatocytes [14] may explain the exercise-induced improvement in GGTE, ALTE, ALPE, or ASTE.

Correction of high levels of liver enzymes means that the progressive hepatic steatosis and cirrhosis started to be limited. The limitation of hepatic steatosis/cirrhosis is associated with decline in cardiovascular risk factors in addition to the control of disturbed lipid metabolism [14].

Regarding tested lipids' improvement after adherence to the two regular exercise programs of this study, exercise-induced utilization of visceral fat as an energy supply or fuel during exercise increases general and local

fat loss/lipolysis via the repeated stimulation of sympathetic activity and hormonal production (e.g. growth hormone). Exercise increases the production of enzymes (e.g. lipoprotein A and lipoprotein lipase enzymes) that not only increase catabolism of TGs but also improve their removal from the bloodstream to be utilized by exercising skeletal muscles [16-18].

Previous reports mentioned more favorable effect of high-intensity exercise over moderate-intensity exercise on lowering the risk of cardiovascular diseases by improving AC, TGs, HDL, and metabolic syndrome components [19]. The reported improvement in metabolic syndrome may improve fatty liver and its indicators (elevated liver enzymes).

Again, parallel to the presented pyramidal training results, performing this form of exercise over an eight-week training period in Egyptian women with obesity produced significantly improved HDL, TGs, BMI, and AC [12]. Again, in another recent study, regular adherence to pyramidal aerobic exercise for eight weeks fights against the development of liver disorders in patients with type 2 diabetes mellitus (via the significant lowering of ALTE and ASTE) [20].

Consistent with the above-mentioned idea of the superiority of high-intensity (interval) training over moderate-intensity training in controlling cardiovascular risk factors, a recent study confirmed this superiority after the more pronounced improvement in ALT, lipids, body composition, and percentage of body fat in obese college students [21]. Again, improvement in steatosis and fibrosis (both are considered as a progression of NAFLD) was more evident in patients with NAFLD who received high-intensity (interval) training compared to those who received the moderate-intensity continuous form of training [22].

The idea was also confirmed again in an experimental study that reported that high-intensity interval training produces more reduction in visceral fat and local fat accumulation compared to continuous low-intensity training in female rats fed a high-fat-containing diet [23]. Another experimental study reported that lipid profile and liver enzyme (ALPE, GGTE, ASTE, and ALTE) improved significantly more in diabetic rats that received high-intensity training compared with rats that received exercise training performed in continuous low-intensity form [24]. Another experimental study reported that high-intensity (interval) training was more favorable than moderate-intensity training in preventing/controlling hepatic fat accumulation in rats with diet-induced obesity (via rebuilding genetic levels of mRNA included in hepatic lipogenesis) [25]. Again, the ability of high-intensity (interval) training to control/reduce intrahepatic fat accumulation is more significant than the reduction obtained from moderate-intensity exercise in rats with NAFLD [26].

Table 1. Demographic data before aerobic exercises

Data	Group of pyramidal training	Group of continuous aerobic training	P value
Age (years)	45.15±4.19	47.10±4.74	0.187
Body mass index (kg/m ²)	31.95±1.43	32.91±1.54	0.054
Abdominal circumference (cm)	110.52±8.03	116.47±11.27	0.069

Note. Data (expressed as mean±SD) of this table (Table 1) are non-significant (P value >0.05)

Table 2. Outcomes (results of training)

Results of outcomes	Group of pyramidal training	Group of continuous aerobic training	P value (between trained groups)
Body mass index (kg/m²)	Mean ± SD	Mean ± SD	
Before training	31.95±1.43	32.91±1.54	0.054
After training	29.74±1.36	31.74±1.51	0.001*
p-value (within trained group)	< 0.001*	< 0.001*	
Abdominal circumference (cm)	Mean ± SD	Mean ± SD	
Before training	110.52±8.03	116.47±11.27	0.069
After training	100.63±7.28	110.10±10.61	0.0028*
p-value (within trained group)	< 0.001*	< 0.001*	
Alanine transaminase (U/L)	Mean ± SD	Mean ± SD	
Before training	44.73±5.49	48.10±6.22	0.0851
After training	33.63±5.40	41.89±5.91	0.0001*
p-value (within trained group)	< 0.001*	< 0.001*	
Asparate transaminase (U/L)	Mean ± SD	Mean ± SD	
Before training	35.94±6.01	39.42±5.42	0.069
After training	28.05±5.32	34.84±5.41	0.0004*
p-value (within trained group)	< 0.001*	< 0.001*	
Alkaline phosphatase (U/L)	Mean ± SD	Mean ± SD	
Before training	168.21±17.31	178.15±15.33	0.0691
After training	150.68±15.10	168.89±15.32	0.0007*
p-value (within trained group)	< 0.001*	< 0.001*	
Gamma-glutamyl transferase (GGT) (U/L)	Mean±SD	Mean±SD	
Before training	38.68±5.74	42.31±6	0.064
After training	31.78±4.82	38.57±5.77	0.0004*
p-value (within trained group)	< 0.001*	< 0.001*	
Triglycerides (mg/dl)	Mean ± SD	Mean ± SD	
Before training	173.05±23.14	189.52±31.76	0.076
After training	150.52±22.42	175.47±32	0.0085*
p-value (within trained group)	< 0.001*	< 0.001*	
High-density lipoprotein (mg/dl)	Mean ± SD	Mean ± SD	
Before training	43.57±4.32	40.94±4.15	0.0636
After training	49.63±4.20	43.36±4.34	0.0001*
p-value (within trained group)	< 0.001*	< 0.001*	

SD: Standard deviation; *: data are significant (P value < 0.05)

Also, in obese rats involved in 12-week training, HDL improvement was greater in training performed as high-intensity (interval) exercise compared to continuous low-intensity one [27].

The idea was confirmed again in a recent study that included overweight/obese children. This study reported that exercise performed in high-intensity intervals has more positive effects than exercise performed in a continuous and moderate-intensity form because the high-intensity interval exercise produced higher improvement in overweight/obese children's serum lipids [28].

Also, in subjects aged 19.5 ± 0.6 years, eight-week exercise performed in high-intensity interval cycling has more positive effects on AC, waist-hip ratio, and the sum of skinfolds than exercise performed in continuous and moderate-intensity cycling [29]. Again, in obese adolescent females, high-intensity interval training achieved a better improvement in lipids, AC, and percentage of body fat compared to moderate-intensity exercise [30].

Again, despite similar energy consumption, postprandial fat oxidation and TGs significantly improved with a higher percentage after one session of high-intensity exercise compared to one session of moderate-intensity exercise in healthy young subjects [31]. Again, compared to moderate-intensity training, a high-intensity (interval) form of exercise is more efficacious in local and general fat reduction in obese females, partly due to the interval-training-induced greater release/production of lipolytic hormones [32].

Opposite to us, in sedentary overweight/obese adults, no difference in the efficacy of liver fat reduction or visceral fat reduction by either 8-week aerobic exercises' dose or intensity due to the small number of trained adults [33]. Contradicting the results, although there was a significantly improved percentage of body fat, weight, BMI, and AC, 12-week aerobic exercise (running) did not improve ALTE and ASTE in inactive obese Iranian women may be due to the relatively low pre-treatment values of these enzymes [34]. Also, in disagreement with us, both forms of training, high-intensity (interval) and continuous low-intensity exercise did not show a significant change/improvement in obese adults due to the relatively short period of exercise (eight weeks) [35].

Limitations

Follow-up of results (ALTE, BMI, ASTE, HDL, GGTE, AC, ALPE, and TGs) was achieved in this clinical exercise trial, so it must be searched in future NAFLD trials. Other studies are required to advance the benefits of pyramidal training in controlling NAFLD-related evaluation of this study's outcomes via investigating molecular biomarkers, conducting longer intervention studies, or exploring broader health outcomes.

Conclusion

This study reported a more novel favorable effect of pyramidal aerobic training over continuous moderate-intensity intensity in controlling liver enzymes and lipids in NAFLD patients.

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