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Effects of Nonlinear Resistance Training with Curcumin Supplement on Liver Enzymes in Men with Non-Alcoholic Fatty Liver Disease

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Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) has been recently very common; however, there is no definitive treatment for it. The present study aimed to investigate the effects of nonlinear resistance training with curcumin supplement on liver enzymes in men with non- alcoholic fatty liver disease.

Methods: Forty-eight men with obesity and non-alcoholic fatty liver disease (mean age: 38.24 ± 6.59 years and BMI: 29.27 ± 4.43 kg.m-^{2}) were selected and randomly divided into 4 groups including resistance training (RT), resistance training with curcumin supplement (RTCS), curcumin supplement (CS) and placebo (P). Before and after the protocol blood samples were taken to investigate the alanine aminotransferase (ALT), aspartate aminotransferase (AST) and Alkaline phosphatase (ALP) levels. One-way analysis of variance (ANOVA), paired sample t- test and Tukey post hoc test were used to analyze the data ($p<0.05$).

Results: The results indicated significant difference between groups in ALT ($p=0.0001$) and AST ($p=0.0001$) levels following 12 weeks of exercise and supplement interventions. Post-hoc multiple comparison of ALT and AST was significant between RT and RTCS groups with CS and P groups ($p=0.0001$). ALP levels was not significantly different between groups ($p=0.05$).

Conclusion: It seems that nonlinear resistance training with curcumin supplement improves the liver enzymes in men with non-alcoholic fatty liver disease.

Keywords: Curcumin, Resistance Training, Liver Enzyme, Fatty Liver

Introduction

Liver as one the main organs of human body regulates hormonal activities and metabolism during rest, exercise and recovery with its different enzymes (1). Under normal conditions, the liver receives 27 percent of bloodstream (2). However, liver disease is also common, for example the prevalence of fatty liver disease in 40 to 50 years old is 39 percent (3). Although it is a silent disease with no or few clinical symptoms (4), sometimes fatigue, lethargy and right upper quadrant abdominal pain are reported (5). In non-alcoholic fatty liver disease (NAFLD), fat deposits in the liver cells, particularly triglyceride (6). The main cause of prevalence of NAFLD is not discovered (7); however, obesity, low physical activity, a diet high in fat foods and low antioxidants can lead to NAFLD (8). The possibility of its prevalence in obese people is more than 70-90 percent (9). There is no definitive pharmaceutical drug to treat it and the focus of treatments has been on metabolic syndrome (10). Nevertheless, the effective guidelines include physical activity, weight loss and surgical methods to decrease obesity because the most effective cure for NAFLD is to reduce weight (11). Despite the consequences of obesity, nonstandard severe weight loss in a short period of time can trigger inflammation of the liver and intensify the fatty liver (12). In order to predict NAFLD, blood test can be used to measure alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) and also the ultrasound can be used to detect the accumulation of fat hepatocytes (13). In spite of the effectiveness of physical exercise in the treatment of NAFLD (11), its role has not been fully discovered and studies that examine the effect of physical activity on NAFLD are limited (14). A study has shown that physical exercise can reduce insulin resistance, ALT level and improve the metabolism of fat-glucose (15). Damore et al. (16) also found that resistance training may cause to decrease liver fat, subcutaneous fat, and increase insulin sensitivity. On the other hand, taking supplements with antioxidants can enhance the liver function. Curcumin as an antioxidant supplement belonging to the ginger family (Zingiberaceae) and is the main ingredient in turmeric, an Indian spice derived from the rhizomes of Curcuma Longa (17). Some studies regarding the biologic effects of curcumin have suggested some of its health benefits such as anti-fungal, anti-bacterial, anti-viral, anti-proliferative, anti-inflammatory and pro-apoptotic effects (18). Anti-inflammatory activities of this material are to prevent generating pro-inflammatory cytokines including interleukin-1 (IL- 1), tumor necrosis factor alpha (TNF- α) and the synthesis of Nitric Oxide (NO). Even though the mechanism of the anti- inflammatory effects of curcumin has not been completely determined (19). With respect to the crucial significance of liver function in human health and paucity of the related studies on prevention and treatment of NAFLD and the absence of a definitive cure, it is essential to examine and apply non-pharmaceutical solutions such as exercise and herbal supplements. This study aims at examining the effects of concurrent nonlinear resistance training with curcumin supplement on liver enzymes in men with non-alcoholic fatty liver disease.

Methods

In this study, a quasi-experimental method with a pretest-posttest design was used. The participants were men suffering from NAFLD recruited from patients visiting some physicians' offices in Esfahan. Estimation of the number of participants was performed via single proportion formula with 95 percent interval confidence and the estimated sample number was 48. Forty-eight men with overweight and non-alcoholic fatty liver disease selected and were randomly divided into 4 groups including resistance training (RT) group (age: 37.91 ± 7.23 years, n=12), curcumin supplement (CS) group (age: 38.45 ± 6.83 years, n=12), resistance training with curcumin supplement (RTCS) group (age: 39.25 ± 5.87 years, n=12) and placebo (P) group (age: 37.36 ± 6.43 years, n=12). The groups RT and RTCS received 12- week of non-linear resistance training. Each session took about 45- 60 minutes, three days a week (nonconsecutive) lasting 12 weeks. The subjects in groups CS and RTCS were asked to take one curcumin capsule (Curcumin 80 mg as Nanomicelle produced by Minoo Pharmaceutical Co.) (19) Daily after breakfast and also subjects in group P were asked to take one placebo (3 g dextrose) capsule per day after breakfast for 12 weeks. The dietary intake was controlled via a food frequency checklist in combination with traditional lecture- based and paper- based instructions according to the classical food pyramid. Inclusion criteria consisted of men with NAFLD, which was confirmed by ultrasound. The accumulation of liver triglyceride exceeded 5 % in the subjects. The spectrum of NAFLD ranged from grade I to grade II, and grade III. The exclusion criteria were as follows: smoking, alcohol usage (more than 30 g/day) (20- 21), cardiovascular disease, metabolic and genetic disease, hepatitis, mellitus diabetes, chronic disorders, taking special drugs such as statins, hepatotoxic medications intake, having a special dietary program, allergy to curcumin, fasting hyperglycemia, having a cancer record. Before participating in the investigation, the participants were informed about the risks of the protocol and each participant signed an institutionally approved informed consent document. All participants were asked to complete the physical activity readiness questionnaire (PAR-Q: British Columbia ministry of health, 1978) to determine their health background. Blood samples (5 cc) were obtained from the antecubital vein in sitting condition in the morning between 7:00 a.m. and 9:00 a.m. after 12- hour fast. The samples were drawn 48 hours before training protocol and 48 hours after that and heparinized. Ultrasonography was conducted in the morning from 8:00 to 11:00, 24 hours before training protocol. To ultrasonography from liver, the color Doppler ultrasonography machine (ESAOTE My lab 40, Italy) was used. All subjects were controlled regarding exclusion criteria. The blood samples drawn before and after training protocol were analyzed on that day in the laboratory.

ALT, AST, ALP levels were measured using biochemical analysis kits (Pars Azmoon Chemical co., Iran). The sensitivity of kits was 4 IU/L for ALT, 2 IU/L for AST, and 3 IU/L for ALP. The photo absorbance change per minute was up to 0.16 for ALT and AST, and up to 0.25 for ALP. To analyze liver enzymes, the auto biochemical analyzer (Mindray BS 800, China) was used. The nonlinear resistance training program used in this study has been proposed by Kraemer and Fleck (Tables 1 and 2) (22, 23). In order to evaluate 1 repetition maximum (1RM), the subjects were asked to report to the gym in two preliminary sessions before starting the training protocol and after the warm-up the 1RM measurement was performed using the Brzycki's equation (24). The equation is as follows:

$$1\text{RM} = \frac{weight\ lifted}{(1.0278 - (0.0278 \times number\ of\ repetitions))}$$

The warm-up consisted of working out with a steady bicycle for 10 minutes and five minutes of light stretching exercises. Subcutaneous fat thickness was measured using caliper (AC-6575 model) in the abdominal, thigh, and pectoral points on the dominant side of the body (25). Body composition device (Tanita BC-418) was used to measure each subject's weight and the body mass index (BMI) and total fat while they were wearing the minimum clothes and no shoes after 12 hours fasting. All data analyses were performed using SPSS (Version 22.0. Armonk, NY: IBM Corp). The data were analyzed regarding normality of distribution (Shapiro–Wilk), homogeneity (Levene), and were reported as mean ± standard deviation. One-way analysis of variance (ANOVA) was used to compare the changes of each variable before and after intervention between the groups and the Tukey post hoc was employed to find where the differences occured if the ANOVA indicated significant interactions between groups. Also, paired sample t- test was used to compare pre-test and post- test values in each group. All alpha- levels were set at $p \leq 0.05$ for all statistical comparisons.

Results

Anthropometric characteristics of the subjects and their body composition before and after the intervention are displayed in Table 3. Paired t-test results indicated significant reduction on waist circumference (t=4.85, p=0.002; t=4.79, p=0.003), subcutaneous abdominal fat thickness (t=5.02, p=0.001; t=5.91, p=0.001) and body fat percentage (t=3.92, p=0.03; t=3.98, p=0.022) in RT and RTCS groups, respectively (Table 4).

Table 1. Nonlinear resistance training program *

Exercise	Very Light	Light	Moderate	Heavy	Very Heavy
Knee extension	†40/20×1	60/15×2	75/10×3	90/4×3	95/2×4
Bench press	40/20×1		75/10×3	90/4×3	95/2×4
Incline bench press		60/15×2			
Seated row	40/20×1	60/15×2	75/10×3	90/4×3	95/2×4
Dead lift	40/20×1	60/15×2	75/10×3	90/4×3	95/2×4
Pully crunches	1×20	2×20	3×15	3×18	3×20
Lat pull-downs		60/15×2			
Calf raise	40/20×1	60/15×2	75/10×2	90/4×2	
Hamstring curl	40/20×1	60/15×2	75/10×2	90/4×2	
Press behind neck	40/20×1	60/15×2	75/10×2	90/4×2	
Upright row	40/20×1	60/15×2	75/10×2	90/4×2	
Arm curl	40/20×1	60/15×2	75/10×2	90/4×2	

*Length of rest period: very light=1 minutes; light and moderate=1-2 minutes; heavy=3-4 minutes; very heavy=5-7 minutes.
†1set×20 repetitions, 40% 1RM.

Table 2. The intensity of 12- weeks nonlinear resistance training*

			Week									
	1	2	3	4	5	6	7	8	9	10	11	12
Workout Sequence												
Day 1	L	L	M	VL	M	L	VL	H	L	M	L	VL
Day2	M	VL	H	H	M	M	M	VL	L	M	M	H
Day3	L	H	L	L	H	H	L	M	VH	VL	VL	L

*L=light-intensity workout; M=moderate- intensity workout; VL=very light- intensity workout; H= heavy-intensity workout; VH= very heavy-intensity workout. An active rest day was used after any workout

Table 3. Anthropometric characteristics of subjects before and after protocol implementation.

Variables	Time	Group			
		RT	RTCS	CS	P
Age (year)	Pre- test	35.54±7.12	38.19±4.52	37.41±5.17	33.37±6.21
	Post- test	-------	-------	-------	-------
BMI (kg/m^2)	Pre- test	28.34±3.89	30.27±4.34	29.88±4.49	28.59±5.01
	Post- test	28.45±4.79	30.17±3.98	29.12±5.45	28.25±4.31
BF%	Pre- test	24.14±4.11	24.87±4.62	21.44±5.3	23.57±4.31
	Post- test	21.32±4.39	21.79±5.5	22.35±4.21	23.24±3.78
Fat mass (kg)	Pre- test	21.44±6.87	19.55±6.4	18.58±5.27	18.76±4.17
	Post- test	19.44±6.13	18.33±4.22	19.43±6.41	19.33±6.31
Waist circumference (cm)	Pre- test	97.81±7.23	99.56±7.79	98.21±8.09	99.87±8.43
	Post- test	93.55±8.59	95.31±8.34	98.67±9.54	99.23±8.61
Hip circumference (cm)	Pre- test	103.67±5.95	106.4±6.04	104.37±5.4	106.21±6.34
	Post- test	102.89±6.77	105.95±6.76	104.79±4.33	105.51±7.39
Abdominal subcutaneous fat (mm)	Pre- test	36.45±6.34	38.67±7.89	38.72±8.11	38.6±8.47
	Post- test	32.11±6.85	33.44±9.35	38.66±7.25	39.61±7.62
Pectoral subcutaneous fat (mm)	Pre- test	25.33±8.15	25.76±8.43	25.46±7.69	24.32±8.53
	Post- test	25.23±8.43	24.21±8.31	25.1±7.44	24.68±9.47
Thigh subcutaneous fat (mm)	Pre- test	29.21±7.73	28.66±7.43	28.17±6.38	28.08±9.57
	Post- test	28.64±8.42	27.44±8.20	28.32±8.77	27.88±9.44

RT: resistance training; RTCS: resistance training with curcumin supplement; CS: curcumin supplement; P: placebo

Table4. The results of one way ANOVA and paired sample t- test for comparison within and between groups at different phases of measurement

Variable	Group	Time	M±SD	$Mean_{diff}$	t	F
ALT	RT	Pre test	57.7±12.3	13.2±4.1	t=11.27, p=0.0001*	F=69.9, p=0.0001*
		Post test	44.5±10.3			
	RTCS	Pre test	58.2±14.1	16.3±4.9	t=10.59, p=0.0001*	
		Post test	41.5±10.3			
	CS	Pre test	56.8±14.8	1.5±1.2	t=1.02, p=0.32	
		Post test	56.2±14.4			
	P	Pre test	57.5±12.4	0.7±0.9	t=1.23, p=0.24	
		Post test	57.1±12.4			
AST	RT	Pre test	51.8±14.6	6±2.9	t=7.03, p=0.0001*	F=31.4, p=0.0001*
		Post test	45.8±12.9			
	RTCS	Pre test	53.7±13.2	7.9±3.3	t=8.07, p=0.0001*	
		Post test	45.8±10.7			
	CS	Pre test	52.2±12.4	0.5±0.9	t=1.44, p=0.17	
		Post test	51.8±11.8			
	P	Pre test	53.1±13.4	0.5±0.9	t=0.0001, p=1.00	
		Post test	53.1±13.5			
ALP	RT	Pre test	188.1±15.2	4.3±3	t=3.97, p=0.002*	F=2.52, p=0.07
		Post test	184.1±13.7			
	RTCS	Pre test	180.7±12.7	2.6±2.4	t=3.81, p=0.003*	
		Post test	178.1±10.8			
	CS	Pre test	186±13.6	3.5±3	t=3.60, p=0.004*	
		Post test	182.6±11			
	P	Pre test	183.3±12.6	1.6±0.88	t=2.64, p=0.023*	
		Post test	182.1±11.8			

* Significant at p≤0.05
RT: resistance training; RTCS: resistance training with curcumin supplement; CS: curcumin supplement; P: placebo

Table5. The result of Tukey post hoc test to compare ALST, AST and ALP between groups

Variable	Group	Group	Mean Difference	Std. Error	Sig.
ALT_{diff}	RT	RTCS	-3.08	1.34	0.11
		CS	11.66	1.34	0.0001*
		P	12.50	1.34	0.0001*
	RTCS	CS	14.75	1.34	0.0001*
		P	15.58	1.34	0.0001*
	SC	P	0.83	1.34	0.92
AST_{diff}	RT	RTCS	-1.91	0.95	0.2
		CS	5.41	0.95	0.0001*
		P	5.50	0.95	0.0001*
	RTCS	CS	7.33	0.95	0.0001*
		P	7.41	0.95	0.0001*
	CS	P	0.08	0.95	1.000
ALP_{diff}	RT	RTCS	1.66	1.01	0.36
		CS	0.83	1.01	0.84
		P	2.66	1.01	0.056
	RTCS	CS	-0.83	1.01	0.84
		P	1.00	1.01	0.76
	CS	P	1.83	1.01	0.28

* Significant at p≤0.05
RT: resistance training; RTCS: resistance training with curcumin supplement; CS: curcumin supplement; P: placebo

According to results of one way ANOVA test it was found that ALT levels were significantly different in four groups ($F= 69.72$, $p=0.0001$), Significant difference was found among four groups in AST levels as well ($F=31.43$, $p=0.0001$) nevertheless ALP levels were not significantly different between groups ($F=2.52$, $p=0.07$) (Table 4). Tukey's post hoc test revealed that ALT and AST levels were significantly decreased in RT and RTCS groups in comparison with CS and P groups ($p\leq0.05$) but ALT and AST levels were not significantly different between RT and RTCS groups ($p\geq0.05$) (Table 5).

Discussion

The present study investigated the effects of 12- week nonlinear resistance training with curcumin supplement on liver enzymes in men with NAFLD. It was found that non-linear resistance training per se and concurrently with curcumin supplement intake can reduce insulin resistance and that was accompanied with high sensitivity to insulin and decrease of ALT and AST levels. The findings of the present research were in line with those revealed by Hallsworth et al. (26). They found that resistance training caused a 13 % reduction of liver fat without weight loss which can be due to change in sensitivity to insulin, lipids transmit and energy balance. De Piano et al. (27) showed that resistance and aerobic training in obese men with NAFLD caused a decrease in ALT enzyme. Alie et al. (28) found that eight-week of resistance training reduced ALT, AST and GGT in obese men. Also previously we showed that 12 week nonlinear resistance training with curcumin supplement can reduce ALT and AST levels in women with NAFLD (29). In return, according to the research conducted by Slentz et al. (30), although resistance training does not have significant effects on weight, liver fat, visceral fat and ALT, aerobic training does, because it is known that resistance training has lower caloric expenditure than a similar amount time spent in vigorous aerobic training. Also aerobic exercise training can significantly reduce visceral fat and consistently improves insulin sensitivity (30). Bacchi et al. (31) showed that resistance training does not have any effect on ALT, AST and GGT enzymes in diabetic patients with NLFLD. In the present study, ALT and AST enzymes levels improved. Improvement in hepatic lipid depositions can be due to changes in sensitivity to insulin, lipids transmit, fat oxidation and increase availability glucose to the body based on a rise in the expression of GLUT4. (11). Our findings support results achieved by Hallsworth that showed eight weeks resistance training improved NLFLD and HOMA-IR with no effect of weight (26). The levels of ALT and AST decreased in resistance training and resistance training with curcumin supplement groups. In comparison, taking curcumin per se did not have any significant effect. The post hoc test did not show any significant difference between resistance training group and resistance training with curcumin supplement group. Therefore, it can be concluded that non-linear resistance training could improve liver function and the effects of curcumin supplement intake was not very significant. Increasing the duration of curcumin intake may yield different results but more research is needed. Some research reports show that curcumin can have inhibitory action on JAK-STAT signaling pathway in inflammation (21). A study reveals that curcumin significantly inhibits the phosphorylation of STAT1 and STAT3 in microglia activated with gangliosides and interferon-γ (INF- γ) (21). Adhesion of monocytes in the inflammation area plays a crucial role in the inflammatory responses. Curcumin prevents from adherence of monocytes to human epithelial cells. Tumor necrosis factor- alpha (TNF-α) causes to increase the expression of vascular cell adhesion molecule- 1 (VCAM- 1), intercellular adhesion molecule- 1 (ICAM- 1) and endothelial cell leukocyte adhesion molecule- 1 (ELAM- 1) on monocytes. Curcumin inhibits this due to its effect on nuclear factor kappa-light-chain-enhancer of activated B cells (NF_{KB}) (32). Curcumin inhibits the production of inflammatory cytokines expressed by LPL and can promote the performance of phagocytic macrophages in non-inflammatory conditions (33). Disilvestro et al. (34) found that low doses of curcumin lipidated extraction cause changes such as reduction in ALT levels in middle-aged individuals but in this research we did not see any changes in liver enzymes in that group with curcumin usage. ALP enzyme can transfer metabolites such as fats across cell membrane to generate aerobic energy, that shows liver's role in gluconeogenesis (35) and lipid peroxidation (33) processes. The most part of energy was used to resistance training supplied from anaerobic way, so in this research ALP level did not change significantly. This study has some limitations. Low number of participants and the short duration of study can affect the results and it is more reliable to measure liver fat and its enzyme levels via biopsy.

Conclusion

In conclusion, 12- week non-linear resistance training accompanied with curcumin supplement intake can decrease ALT and AST levels in men with NAFLD and improve their liver function. With regarded to findings of this research, it can be concluded that this improvement is more likely the outcome of non-linear resistance training rather than curcumin supplement intake.

Ethical issues

No applicable.

Authors' contributions

All authors equally contributed to the writing and revision of this paper.

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