Hepat Mon. 2017 May; 17(5):e45339. doi: 10.5812/hepatmon.45339.

Published online 2017 May 9. **Research Article**

How Does Addition of Regular Aerobic Exercises, Influence the Efficacy of Calorie-Restricted Diet in Patients with Non-Alcoholic Steatohepatatis (NASH)?

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Received 2017 January 23; **Revised** 2017 March 05; **Accepted** 2017 April 04.

Abstract

Background: Nonalcoholic fatty liver (NAFLD) is a worldwide, leading cause of chronic liver disease, not yet approved medical treatment standards. The aim is to assess the effects of aerobic exercise sand calorie-restricted (CR) diet on many clinical and laboratory findings in patients with Nonalcoholic Steatohepatatis (NASH).

Methods: In Randomized controlled trial study, in Mashhad, between February 2010 - August 2011, Twenty-five patients with NASH, in ranging ages of 18 - 55, were randomly selected to be divided in to two groups, who received CR-diet and aerobic exercise (n = 12) and CR-diet alone (n = 13). We measured Anthropometric indices, cardio-respiratory fitness, and biochemical profiles in three steps, in baseline, and after 8 - 12 weeks of intervention. We measured hepatic steatosis and patient's quality of life by ultra-sonography and short form (questionnaire) 36 in three steps. Data was then analyzed by paired and independent samples T Test.

Results: We observed a significant improvement in BP, FBS, TG, HOMA-IR, ultra-sonography grading of steatosis and quality of life, only in patients who received aerobic exercises. (P value 0.021, 0.005, 0.006, 0.042, 0.010 and 0.012). Waist circumference, waist-to-height ratio, serum ALT and peak oxygen consumption improved in both groups; however, improvement was significantly, higher in patients who received aerobic exercises (P value 0.027, 0.011, 0.020 and 0.020). Body weight, BMI, body fat percentage and AST improved in both groups but they were not significantly different. No significant changes noted in total cholesterol, LDL and HDL in groups.

Conclusions: Add of aerobic exercises to CR diets can, not only enhance the therapeutic effects of calorie-restricted diet, but also bring more benefits in patients with NASH.

Keywords: Physical Activity, Low-Calorie Diet, Insulin Resistance, Non-Alcoholic Fatty Liver Disease

1. Background

Non-Alcoholic fatty liver disease is a common health problem in the world. Prevalence, in western countries is 20% to 30% (1). There are conditions that result to serious consequences of simple steatosis to Steatohepatatis, fibrosis and even cirrhosis (2). Non-alcoholic Steatohepatatis (NASH) is commonly and closely associated with obesity, sedentary lifestyle, metabolic syndrome, Type-two diabetes mellitus, hyperlipidemia, hyperinsulinemia, hyperglycemia and hypertension (3-8).

The pathogenesis of NASH is not fully elucidating up to now. The most widely accepted theory is the two-hit hypotheses: The first hit is the accumulation of hepatic fat which is secondary to insulin resistance (9). Oxidative stress can cause the second hit. This promotes the initiation of reactive oxygen species, inflammatory cytokines, and adipocytes such as (tumor necrosis factor-alpha (TNF α), leptin, and adiponectin) (10). In addition, a further component, or "third-hit" added inadequate hepatocyte proliferation as the oxidative stress, that, inhibits the replication of mature hepatocytes (5). Nevertheless, insulin resistance is the major pathogenic cause of implication in both, liver fat accumulation and disease progression (7, 8).

Up to now, there are no approved medication standard for treatment of NAFLD or NASH (5, 10). Indirect pharmacological therapy includes, metformin, pioglitazone and thiazolidinedione to reduce insulin resistance. Razavizade

et al. had seen significantly decrease in serum level of LFT (liver function test), fasting glucose, Cholesterol, LDL, HOMA-IR and increase of serum level of HDL after four month intervention with Metformin and Pioglitazone (11). Vitamins C and E plus many other drugs such as gemfibrozil, clofibrate and acetyl cysteine, reduce the oxidative damage (5, 6). More emphasis is now, on lifestyle modification by acquiring, healthy dietary habits and routine regular exercises which are safe and effective (3, 6, 12, 13).

Peta et al., showed that a lower physical activity associated with a higher liver fat content (3). Several studies also have reported a significant inverse relationship between the level of cardio respiratory fitness and hepatic fat contents (4, 14). Nikroo et al. showed that addition of low-calorie diet to aerobic exercise was more effective in the improvement of quality of life and that decrease of grading of ultrasonography features in patients with NASH (15). It was found that inverse association between fitness categories and the prevalence of NAFLD is independent upon body mass index (BMI), visceral fat content and waist circumference (WC) (14). A significant relationship was seen between the severity of histological injuries and decreased peak oxygen consumption (VO_2peak) in overweight and obese patients with NAFLD (16).

In this randomized clinical trial, we aimed to assess the efficacy of addition of regular aerobic exercises to calorie-restricted diets in management of NASH. We compared anthropometric indices, Insulin resistance index, transaminase levels and lipid profiles, Peak oxygen consumption, Ultra sonographic hepatic steatosis grading as well as quality of life in two groups of patients who received calorie-restricted diet with and without regular aerobic exercises.

2. Methods

2.1. Study Design

In a randomized controlled clinical trial, twenty-five male adult patients which diagnosed NASH, by Ultrasound were enrolled and randomly assigned to one of the groups who received either CR-diet and aerobic exercises (n = 12), or, CR-diet alone (n = 13). In ultrasound method based on the difference of hepatic-renal echo contrast, brightness, deep attenuation, vascular blurring, is divided into six grades. The cases of grade > 1 are defined as a diagnosis of fatty liver (17).

We recruited patients from gastroenterology and clinical nutrition clinics at Ghaem and Imam Reza general hospitals, Mashhad, Iran. Research was between, February 2010 to August 2011. The study protocol approved by the research ethics committee of Mashhad University (no 89878, trial identifier at clinical trials.gov IRCT201104286319N1) and was conducted in accordance with the guidelines of the declaration of Helsinki.

2.2. Selection of Patients

All the patients that we chose, had a ranging age of 18 - 55 years old. The level of their ALT were more than 1.5 times, the upper limit of normal, for a minimum period of three months, and evidence of fatty liver on liver ultrasonography. Patients were excluded, where, they had history of significant alcohol consumption (> 20 gr/day for women and > 30 gr/day for men), and other liver diseases (viral hepatitis B and C, autoimmune hepatitis, Celiac disease, Wilson's Disease, α1-antitrypsin deficiency and hemochromatosis). Also, we excluded all the patients which had medical problems such as (hypothyroidism, ischemic heart disease, renal failure and use of hepatotoxic drugs).

2.3. Testing and Outcome Variables

2.3.1 Anthropometry

At the baseline, we recorded anthropometric indices including weight (Wt.), height (Ht), waist circumference (WC), hip circumference (HC), body fat percentage (BF%), body mass index (BMI), and waist-to-hip ratio (WHR) as well as blood pressure including systolic (SBP) and diastolic (DBP) and cardio respiratory fitness including peak oxygen consumption (VO_2peak). Height measured to significant level 0.5 cm. The patients standing on bare feet and against the wall, looking straight forward, at full expiration. Circumference of waist (WC) measured at the midpoint of the lowest rib to the top of pelvic. The width of hip circumference (HC) at the widest portion of buttocks measured. Weight measured with light clothing and bare feet to significant level 0.1 kilogram. Body-fat percentage rated by a body-fat meter (Inbody-720, South Korea), using an impedance method. BMI calculated by dividing weight in kilograms by the square of height in meters. Waist/hip ratio calculated by dividing the waist circumference on the hip circumference. The blood pressure measured, using a mercury sphygmomanometer (Riester exacta CE 0124, Germany). Peak oxygen consumption measured by Bruce test, using a treadmill (Technogym, Italy) with unit of mL/min/Kg.

At the same time, six ml blood was drawn from brachial vein after 12 and 24 hours of fast. We cheeked Fasting blood sugar (FBS) with a 24-channel automated chemical analyzer, using standard reagents measured serum alanine Aminotransphrase (ALT), aspartate Aminotransphrase (AST), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG) and Insulin. Insulin resistance (IR) was determined by HOMA index (fasting insulin (mIU/mL) $\times$ FBS (mg/dL)/22).

A radiologist expert assessed grade of fatty liver by using Ultrasonic at the base line, in fasting state. He was looking for evidence of portal hypertension. The liver was scanned in two different view sight: A sub xiphoid view, for evaluating liver echogenicity and portal vein branches, and a sub costal view for comparing echogenicity of liver parenchyma with right kidney cortex using a 5 MHz curved array transducer. They reported degree of fatty liver as follow; grade 1: Mild increased liver echogenicity with normal visualization of diaphragm and intrahepatic vascular borders; grade 2: Moderate increased liver echogenicity with slight decreased visualization of diaphragm and intrahepatic vascular margins; grade 3: Severe increased liver echogenicity with poor or non-visualization of diaphragm and vessel borders (18).

We evaluated quality of life by short form 36 (SF-36) questionnaire, that, validated widely used, and has shown good psychometric properties (19, 20). The SF-36 questionnaire consists of 36 questions that stands for eight subscales: physical function (PF), Role limitations due to physical health (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), and mental health (MH). An overall physical health score (physical component scale (PCS)) and mental health score (mental component scale (MCS)) are derived from the subscale scores.

In this study, diet was individualized after the measurement of body composition and calculation of daily energy requirements of patients. The patients were controlled and managed by nutritionist, regularly. Calorie-restricted diet in both groups included 500 kilocalories (kcal) of energy less than the estimated daily energy requirement. The percentage distribution of macro nutrients consisted of 60% carbohydrate, 25% fat and 15% protein with emphasize on selecting variety of all food groups and reducing saturated fat intake and simple sugar consumption. The aerobic training program designed according to guideline of American college of sports Medicine (ACSM) and performed by professionally qualified instructors (21). Exercises programs were individualized, under the supervision of experienced exercise physiologists, which allowed participants to achieve their target heart rate reserve (HRR).It consisted of walking, jogging or running, for a period of 8 weeks/ 3 days a week. The time of exercises were 35 to 50 minutes (15 minutes of warm up, 10 to 25 minutes of aerobic exercise and 10 minutes of cool down), with 55% - 60% of HRR during each training session. The first session of aerobic exercise lasted for 10 minutes and the next sessions, one minute added to every aerobic exercise, so in the end of sixth, seventh and eighth weeks, duration of aerobic exercises was maintained in 25 minutes.

2.4. Post-Intervention Assessment

For the patients in both groups repeated anthropometric and biochemical measurements and tests were done in the eighth and twelve-week of intervention. Hepatic steatosis and quality of life reassessed at the end of twelve-week intervention. To prevent the acute effects of exercises, blood test was done two days after completion of intervention.

2.5. Statistical Analysis

Data analyzed by SPSS statistical software version 11.5. Descriptive data expressed as mean $\pm$ standard deviation (SD). Before statistical analysis, normal distribution and homogeneity (Equality of Variances) of the variances were evaluated using Kolmogorov-Smirnov (K-S) and Levene's tests. Paired samples and independent samples T Test were applied for comparison within each group and between the two groups, respectively. P value less than 0.05 was considered the significance level.

3. Results

Twenty-three patients of twenty-five, finished intervention. One of the participants in CR diet groups, because of non-compliance with the intervention, was withdrawn. We depicted Baseline clinical and biochemical characteristics of patients in Table 1.

The age, height, weight and BMI of patients in the CR diet group were 35.64 $\pm$ 9.22, 173.75 $\pm$ 5.9 cm, 98.26 $\pm$ 19.99 kg and 32.58 $\pm$ 6.62 kg/m^2, respectively. The values in the CR diet-exercises groups, were 38.67 $\pm$ 7.36, 174.1 $\pm$ 5.04 cm, 92.19 $\pm$ 15.09 kg and 30.37 $\pm$ 4.5 K/m^2, in respect. There were no significant differences, statistically, comparing these two groups. K-S test and independent-samples T Test revealed a normal distribution of data in both groups.

Table 2 shows, mean differences of variables, in post-intervention exercises, plus diet groups After 8 weeks. We observed significant reduction in weight, BMI, WC, WHR, BF, SBP, DBP, ALT, AST, TG, FBS, Insulin and HOMA-IR. A significant increase was also observed in VO_2peak ($P < 0.05$).

In the diet restriction group, while VO_2peak increased, Weight, BMI, WC, WHR, BF and TG showed reduction ($P < 0.05$). When comparison was made, between the two groups, there were a significant difference in WC, WHR, ALT, AST, FBS and VO_2peak ($P < 0.05$). There were nonsense variations in weight, BMI, BF, SBP, DBP and TG ($P > 0.05$) and there was a trend toward lower insulin level, although, considerable differences observed in Insulin ($P = 0.054$) and HOMA-IR ($P = 0.066$). But between the both groups, no significant differential shown, statistically ($P < 0.05$).

Table 1. Baseline Characteristics of All Study Subjects in Both Groups

Variables	Groups	Baseline, (Mean ± SD)	Tolerance	P Value[a]	P Value[b]
Age, y	D + E	38.67 ± 7.36	25 - 49	1.000	0.392
	D	35.64 ± 9.22	25 - 50	0.850	
Height, cm	D + E	174.1 ± 5.04	165 - 184	0.806	0.877
	D	173.75 ± 5.9	160 - 181	0.876	
Weight, kg	D + E	92.19 ± 15.09	79 - 131	0.481	0.418
	D	98.26 ± 19.99	73 - 132.4	0.537	
BMI, kg/m^2	D + E	30.37 ± 4.5	25.2 - 41.45	0.891	0.358
	D	32.58 ± 6.62	23.95 - 44.5	0.445	
WC, cm	D + E	105.5 ± 8.6	92 - 120	0.999	0.386
	D	109 ± 11.3	87 - 133	0.733	
WHR	D + E	0.99 ± 0.06	0.9 - 1.09	0.805	0.501
	D	0.97 ± 0.05	0.86 - 1.07	0.547	
BF, %	D + E	30.11 ± 5.57	19.8 - 39.8	0.937	0.149
	D	35.1 ± 9.96	20.1 - 52.1	0.749	
SBP, mmHg	D + E	127.2 ± 11.6	108 - 142	0.750	0.495
	D	124 ± 10.15	98 - 136	0.550	
DBP, mmHg	D + E	85.8 ± 4.04	79 - 90	0.700	0.513
	D	84.6 ± 5.2	72 - 90	0.845	
ALT, U/L	D + E	86.42 ± 21.2	62 - 131	0.695	0.397
	D	77.27 ± 29.2	60 - 160	0.279	
AST, U/L	D + E	50.92 ± 13.03	23 - 71	0.925	0.962
	D	51.18 ± 13.24	32 - 85	0.433	
TC, mg/dL	D + E	200.1 ± 43.16		958	0.188
	D	170.1 ± 61.77		0.649	
LDL, mg/dL	D + E	124.1 ± 39.26		0.851	0.700
	D	130.2 ± 35.15		0.852	
HDL, mg/dL	D + E	32.35 ± 4.93	19 - 38	0.524	0.197
	D	34.45 ± 2	31 - 38	0.955	
TG, mg/dL	D + E	179.7 ± 32.6	120 - 220	0.648	0.305
	D	192.4 ± 24.2	164 - 240	0.628	
FBS, mg/dL	D + E	103.25 ± 4.6	95 - 110	0.543	0.430
	D	101.45 ± 6.06	95 - 112	0.869	
Insulin, mIU/mL	D + E	13.99 ± 12.5	7.5 - 52	0.208	0.529
	D	11.48 ± 3.8	6.8 - 19.5	0.913	
HOMA - IR	D + E	3.6 ± 3.25	1.95 - 13.5	0.207	0.510
	D	2.9 ± 1	1.6 - 4.9	0.617	
VO_2peak, mL.kg.min	D + E	25.33 ± 5.4	20 - 40	0.326	0.317
	D	22.82 ± 6.37	13 - 31	0.884	

Abbreviations: D, Diet; D + E, Diet Along with Exercise.
[a] Result of K-S t-test.
[b] Result of Independent samples t-test.

Metabolic syndrome is, a combination of hypertension, hyperlipidemia, obesity and types 2 diabetes. Current study suggests the severity of NASH increasing, in relation to increase number of domains of MS (3, 5, 6, 8).

3.1. Anthropometry

Our findings on patients with NASH suggests that, after 8 weeks of diet modification, with emphasis on calorie-restriction, with and without addition of regular aerobic exercises, reduce in Weight, BMI, WC, WHR and BFP, could be observed. In addition, there were differences in WC and WHR between the two groups after the completion of our studies. Which showed that, diet with aerobic exercises are more effective on reducing of WC and WHR.

3.2. Biochemistry

After 8 weeks, we detected that, diet modification alone significantly reduced TG. But there was no reduction in TC,

Table 2. Change in Physical and Biochemical Parameters After 8 Weeks of Intervention in Two Groups[a]

Variables	Diet + Exercise, N = 12				Diet, N = 11				T value	P Value[b]
	Pre-test	Post-test	Change percent	P value[c]	Pre-test	Post-test	Change percent	P value[c]		
Weight, kg	92.19 ± 15.09	86.8 ± 12.8	-5.85	0.002†	98.26 ± 19.99	94.93 ± 18.65	-3.4	0.002†	1.284	0.213^{NS}
BMI, kg/m^2	30.37 ± 4.5	28.62 ± 4.81	-5.76	0.002†	32.58 ± 6.62	31.43 ± 6.08	-3.53	0.002†	1.118	0.276^{NS}
WC, cm	105.5 ± 8.6	97.92 ± 6.83	-7.18	0.000†	109.2 ± 11.3	105.73 ± 11.06	-3.2	0.000†	3.501	0.002†
WHR	0.99 ± 0.06	0.95 ± 0.06	-4.05	0.000†	0.97 ± 0.05	0.96 ± 0.05	-1.03	0.009†	3.39	0.003†
BF, %	30.11 ± 5.57	25.97 ± 4.91	-13.75	0.000†	35.1 ± 9.96	32.34 ± 10.15	-7.86	0.001†	1.604	0.124^{NS}
SBP	127.2 ± 11.6	122.2 ± 7.36	-3.93	0.043†	124 ± 10.15	119.5 ± 8.5	-3.63	0.110^{NS}	0.164	0.872^{NS}
DBP	85.8 ± 4.04	82.3 ± 3.2	-4.08	0.021†	84.6 ± 5.2	82.4 ± 3.8	-2.6	0.067^{NS}	0.163	0.447^{NS}
ALT, U/L	86.42 ± 21.2	43.17 ± 19.35	-50.05	0.000†	77.27 ± 29.2	71.73 ± 34.78	-7.17	0.318^{NS}	3.72	0.001†
AST, U/L	50.92 ± 13.03	30.25 ± 7.864	-40.6	0.000†	51.18 ± 13.24	47 ± 16.71	-8.17	0.236^{NS}	3.117	0.005†
TC, mg/dL	200.1 ± 43.16	188.8 ± 23.7	-5.65	0.436^{NS}	170.1 ± 61.77	180.9 ± 29.1	+6.35	0.558^{NS}	0.984	0.336^{NS}
LDL, mg/dL	124.1 ± 39.26	125.3 ± 18.37	+0.97	0.903^{NS}	130.2 ± 35.15	119.73 ± 32.3	-8.04	0.168^{NS}	-0.98	0.338^{NS}
HDL, mg/dL	32.3 ± 4.9	32.2 ± 5.25	-0.31	0.929^{NS}	34.5 ± 2	34.65 ± 4.95	+0.43	0.915^{NS}	0.140	0.89^{NS}
TG, mg/dL	179.7 ± 32.6	146.7 ± 57.03	-18.36	0.007†	192.4 ± 24.2	132 ± 49.8	-31.4	0.000†	-1.94	0.66^{NS}
FBS, mg/dL	103.25 ± 4.6	92.7 ± 10.02	-10.22	0.003†	101.45 ± 6.06	98.8 ± 6.3	-2.6	0.252^{NS}	2.23	0.037†
Insulin	13.99 ± 12.5	6.53 ± 3.36	-53.32	0.036†	11.48 ± 3.8	11.43 ± 5.55	-0.44	0.979^{NS}	2.043	0.054^{NS}
HOMA-IR	3.6 ± 3.25	1.5 ± 0.77	-58.33	0.039†	2.9 ± 1	2.75 ± 1.23	-5.17	0.721^{NS}	1.194	0.066^{NS}
VO_2peak	25.33 ± 5.4	31.67 ± 5.3	+25.03	0.000†	22.82 ± 6.37	24.82 ± 6.705	+8.76	0.001†	-5.83	0.000†

Abbreviations: BF%, Body Fat Percent; DBP Diastolic Blood Pressure; WHR, Weight Height Ratio, HOMA-IR, (HOMA Index (Fasting Insulin (m IU/mL) × FBS (mg/ dL) /22); NS, Not Significant; SBP Systolic Blood Pressure; TC Total Cholesterol.
[a] Values are expressed as mean (SD).
[b] Independent samples t-test.
[c] Paired sample t-test.

LDL, HDL FBS, ALT and AST, in calorie-restricted and aerobic exercise group, the reduction in FBS, TG, AST and ALT was more visible, but, there was not any improvement in HDL. In addition, there was a different in ALT, AST and FBS between the two groups, which expressed that, calorie-restriction along with aerobic exercises, is more effective in decreasing ALT, AST and FBS.

3.3. Hormone, HOMA, Blood Pressure and Fitness

In dietary modified group, and in the group with exercises plus DR, VO_2peak increased, but, only in the group with exercises plus DR were showed decrease in SBP, DBP, Insulin and HOMA. In addition, there was a significant difference in VO_2peak, between the two groups after the completion of our study. Therefore, insulin resistance (= HOMA) as the major pathogenic factor and AST/ALT as the diagnostic markers of NASH were not significantly affected by 8 weeks of dietary modification. This reveals that changes in weight, WC, BFP, TG and VO_2peak on their own might not be sufficient to cause improvements in patients with NASH.

In the diet group while VO_2peak had increased significantly, only weight, BMI, WC, WHR, BF and TG showed significant reduction ($P < 0.05$). When comparison is made between the two groups, there are significant differences in WC, WHR, ALT, AST, FBS and VO_2peak ($P < 0.05$). There are only subtle variations in weight, BMI, BF, SBP, DBP and TG ($P > 0.05$). A trend toward lower insulin level was shown. Although considerable differences are observed in Insulin ($P = 0.054$) and HOMA-IR ($P = 0.066$) between the two groups, they were not statistically significant ($P < 0.05$).

4. Discussion

We observed improvements in BP, FBS, HOMA-IR, Ultrasonography grading of steatosis, and up grading qualification of life only, in patients who received aerobic exercises with diet restriction. (P value 0.021, 0.005, 0.006, 0.042, 0.010 and 0.012). In the diet restriction group while VO_2-peak had increased, only weight, BMI, WC, WHR, BF and TG showed significant reduction ($P < 0.05$). Body weight, BMI, WC, Body fat percentage and AST, improved clearly in diet restriction with and without exercises. No explicit changes noted in total cholesterol (TC), LDL and HDL in both groups.

The result of our study about diet restriction, agreed with Benjaminov et al. (2007) (22). This study isn't, however, all agree with Okita et al. (2001) (23) and Tendler et al. (2007) (24).

Benjaminov et al. (2007) study is generally on the effects of low-carbohydrate diets, on 14 severe obese patients (age range of 24 to 45 years), with NAFLD, who were Bariatric surgery candidates, for a short time (4 weeks). They got to the similar results (reduction of weight, BMI, HDL, as well as, a reducing in liver fat content and liver size,

Table 3. Quality of Life Parameters after 12 Weeks of Intervention in Two Groups[a]

Variables	CR Diet + Exercise (N = 12)			CR Diet Alone (N = 13)			
	Pre-test	Post-test	P Value*	Pre-test	Post-test	P Value*	P Value**
PCS	45.93 ± 9.2	54/35 ± 4.1	0.012†	48.73 ± 12	53.58 ± 6.3	0.242^{NS}	0.445^{NS}
MCS	42.51 ± 9.6	48.68 ± 13.2	0.076^{NS}	40.38 ± 10.3	47.05 ± 8.7	0.101^{NS}	0.903^{NS}
PF	47.73 ± 10.7	55.76 ± 1.4	0.031†	48.73 ± 11.8	53.97 ± 4.3	0.236^{NS}	0.591^{NS}
RP	38.25 ± 14.2	49.79 ± 11.5	0.034†	44.73 ± 13	46.51 ± 9.9	0.721^{NS}	0.143^{NS}
BP	53.92 ± 9.3	56.72 ± 7.3	0.284^{NS}	52.01 ± 13.9	58.21 ± 10.2	0.168^{NS}	0.459^{NS}
GH	42.59 ± 8.2	52.42 ± 7.9	0.004†	42.57 ± 10	47.91 ± 8.8	0.022†	0.208^{NS}
VT	48.87 ± 8.7	57.02 ± 9.6	0.001†	48.98 ± 10.3	60.32 ± 5.6	0.016†	0.405^{NS}
SF	45.78 ± 8.2	50.2 ± 10.5	0.182^{NS}	46.27 ± 12.6	55.07 ± 4	0.082^{NS}	0.409^{NS}
RE	38.06 ± 16.5	45.66 ± 14.5	0.09^{NS}	32.92 ± 14.2	36.87 ± 14.6	0.476^{NS}	0.545^{NS}
MH	42.79 ± 11.5	50.41 ± 10.8	0.055^{NS}	44.53 ± 12.1	52.43 ± 11.2	0.112^{NS}	0.96^{NS}

Abbreviations: BP, Body Pain; GH, General Health; MH, Mental Health; MCS, Mental Component Score; NS, Not Significant; PCS, Physical Component Score; PF, Physical Functioning; RE, Role Limitations Due to Emotional Problems; RP, Role Limitations Due to Physical Health; VT, Vitality; SF, Social Functioning.
[a]Values are expressed as mean (SD).

particularly, of left lobeon CT scan images). However, they did not observe any significant changes in FBS, TG, LDL and ALT. This matter might be because of period of time.

The studies by Okita et al. (2001) evaluated the effectiveness of moderately energy-restricted (25 kcal/kg) diets, on liver-function tests and anthropometric measurements, in patients with NASH for a longer duration. Their research, after 24 weeks, showed improvements in BMI, WC, ALT and AST, as well as, Ultra sonography appearance of the diseases (23). Although Okita et al. intervened in their research, with restriction of energy in taking from Carbohydrates, they increased the intake of vitamin A, vitamin C, and vegetables. Tendler et al. (2007) after six months of a low-carbohydrate, ketogenic diet observed significant weight loss and histological improvement of fatty liver disease (24).

The contrast observed here could be due to different factors such as the duration, quality and intensity of dietary modifications as well as individual and ethnic variations. It could also be a result of longer duration of intervention. At the previously mentioned studies, longer duration of dietary modification (more than 8 weeks) might cause significant changes in AST and ALT of NASH patients.

The results of this study about diet plus exercise are in agreement with Ueno et al (1997) (25), Hickman et al. (2004) (26), Suzuki Ayako et al. (2005) (27), Sreenivasa Baba et al. (2006) (2), Cinar et al. (2006) (28), Akyuz et al. (2007) (29), Wang et al. (2008) (30) Promrat et al. (2010) (31). They had exercise and diet restriction both in all patients and they didn't have control groups.

In study other are in disagreement with my study (28, 30, 32, 33). Kate hallsworth et al. had only drug intervention (vitamin E) but Kittichachi and Shah had life style intervention and D + E same as our study. In study of Kate only hepatic TG, intra hepatic fat and HOMA were decrease but after diet restriction and exercise in our study were decrease Weight, BMI, WC, BF, FBS and TG.

There was a significant difference in WC, WHR, ALT, AST, FBS and VO_2peak between the two groups after the completion of our study. Although not significant statistically, there was a considerable difference in HOMA/IR and insulin as well. Therefore, addition of aerobic exercise to diet in patients with NASH produces a more positive impact on the efficacy of therapy.

Overall, those who have a higher level of physical activity have a much better cardio-respiratory fitness compared to those with those of a lower level (21). In this study, we observed a 25.3% increase in VO_2peak of patients who engaged in aerobic training in addition to diet which was significantly higher than those receiving diet alone. Previous studies have shown a significant and reverse relationship between the level of cardio-respiratory fitness and the quantity of hepatic fat in patients with NAFLD and NASH (21). Aerobic exercise can increase hemoglobin in the blood, myoglobin in myocytes and increase in size and number of mitochondria and enzymes involved in aerobic energy synthesis and the number of capillaries supplying each muscle fiber (32). All of these factors can play a positive role in the reduction of hepatic fat content as well as an improvement in the pathologic indices of NASH (9).

Insulin resistance has a close association with many factors involve in the development of metabolic syndrome. It is currently postulated as the major pathophysiological factor in NASH even in the absence of obesity and diabetes type two (2, 5, 25, 34). Studies have found a reverse relationship between insulin sensitivity and hepatic fat accumulation (34-36).

Resistance to insulin is caused by reducing signal

transmission of insulin because of down-regulation of insulin receptors (insulin receptor substrate or IRS-1) and competitive utilization of free fatty acids in the blood (2). Hormone-sensitive lipase (HSL) is normally suppressed by insulin which is a state of resistance can enhance lipolysis leading to a release of fatty acids from endogenous sources. Plasma concentration of fatty acids is directly associated with their entry into hepatocyte and therefore liver starts accumulating lipids (33).

IRS-1 and the carrier protein GLUT4 mediate glucose uptake by the muscle tissue. An aerobic exercise of adequate intensity and duration positively affects insulin sensitivity through increasing the levels of IRS-1 and GLUT4 mRNA in muscle cells. This improves glucose utilization and in turn reduces the amount of lipid entry into hepatocyte (2). Aerobic activity also stimulates lipid oxidation and hinders lipogenesis within the liver (2, 33, 35).

In summary aerobic exercise can lead to increased insulin sensitivity and hepatic lipid oxidation as well as decreased activity and inhibition of lipogenic enzymes. They all contribute to a reduction of hepatic fat. This can explain the significant reduction of serum ALT levels of patients in the group with added aerobic training. Regular aerobic exercise seems to have a significantly positive impact on the prevention and treatment of NASH (2, 33, 35).

Kate et al. (28) and Hickman et al. (22) had exercise intervention in NASH patients that observed decrease of insulin and HOMA level same as this study. Kittichai et al. had life style change intervention and they didn't have decrease in insulin level and HOMA but Nobili et al. and Wang et al. (14) had decrease of insulin and HOMA with change in life style and diet. This is in disagreement with our study.

Waist circumference indicates the amount of visceral fat deposition and has a significant association with the level of serum transaminases (especially ALT), hepatic fat accumulation and incidence of NAFLD and NASH (11, 17). It is also associated with insulin resistance, hyperlipidemia, hyperglycemia, diabetes type two and metabolic syndrome which all play a role in the development of fatty liver disease (11). It is believed that the visceral adipose tissue has a higher degree of insulin resistance and therefore is more prone to lipolysis. The subsequent release of fatty acids into the bloodstream results in hepatic lipid accumulation (11).

Regular exercise increases metabolism of the visceral fat stores and causes a redistribution of fat stores throughout the body (indicated by reduction in WC) with the resultant increased sensitivity to insulin within the adipose tissue. This decreases the release of free fatty acids and hence their deposition within the liver as well as improved beta-oxidation of fatty acids within the live (2, 9).

Studies suggest a lower risk of type 2 diabetes and an increased level of serum HDL with regular exercise which are both important risk factors for the decrease of NASH (2).

4.1. Limitation

Unfortunately, individual difference and genetically particulars was not with control of researchers. We had low sample size and only 12 weeks intervention in this issue.

Acknowledgments

This study was funded by the research ethics committee of Mashhad University that project code number was 89878. All staff of laboratory Jahad Daneshgahi Mashhad and school of sport Sciences of the Ferdowsi University of Mashhad would be appreciated. I sincerely thank all of the patients who participated in this research project.

Footnote

Trial Identifier: Trial Identifier at ClinicalTrials.gov: IRCT201104286319N1.

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