Govaresh/ Vol. 20, No.1, Spring 2015; 57-65.

Original Article

The Effect of 12 weeks Regular Physical Activity and Vitamin E in the Treatment of Non-Alcoholic Steatohepatitis: A Pilot study

Layli Eslami[1], Khatereh Isazadehfar[2], Maryam Karami[3], Laya Eslami[4], Farhad Rahmani-nia[5], Babak Nakhostinroohi[6]

[1] Assistant Professor, Department of Gastroenterology and Hepatology , Taleghani Hospital, Golestan University of Medical Science, Gonbad-e Kavus, Iran
[2] Assistant Professor, Department of Community Medicine, Imam Khomeini Hospital, Ardabil University of Medical Sciences, Ardabil, Iran
[3] Master of Science in Nursing, Faculty of Nursing, Shahid Beheshti University, Tehran, Iran
[4] Master of Science of Exercise Physiology,Faculty of Physical Education and Sport Sciences, University of Gilan, Rasht, Iran
[5] Professor and Dean of Faculty of P.E. and Sport Sciences, Department of Exercise Physiology, Islamic Azad University, Ardabil, Iran
[6] Assistant Professor, Department of Exercise Physiology, Ardabil Branch, Islamic Azad University, Ardabil, Iran

ABSTRACT

Background:
Despite the prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH), there was no treatment has been proven to be effective in these common diseases. Although many studies have shown that lifestyle modifications such as increasing physical activities and exercise could be effective in the treatment of these common diseases, the optimal strategy was still not determined. According to the beneficial effects of antioxidant agents in the treatment of NASH, vitamin E has been used for this purpose by some clinicians. We designed this study for assessing beneficial effects of regular physical activity on the biochemical and imaging responses in patients with NASH and comparing this with vitamin E as an accepted treatment for NASH.

Materials and Methods:
This study was Randomized and single-blind clinical trials were carried out in Gonbad-e Kavus through which a total of 30 consecutive patients with the ultra sonographic diagnosis of non-alcoholic steatohepatitis (NASH)were enrolled and randomized to one of the three groups: Vitamin E 800 mg/day, regular physical activity, or both.

Results:
In all treatment groups improvement in liver transaminases level, serum lipids and ultrasonographic grading of fatty liver occurred after three months of treatment. When these decrement was compared between the treatment groups, there was no statistically significant difference in the value of improvement between the three groups (ANOVA: $p>0.5$). I.e. all three interventions improved the biochemical and ultrasonographic finding of fatty liver in the same way. Both groups with regular exercise had significant mean weight loss in comparison with the vitamin E group (a mean decrease of 3.0 kg in exercise group, 5.8 kg in subjects on regular exercise plus vitamin E and 0.2 kg in vitamin E group, ANOVA: $p=0.04$).

Conclusion:
There were no significant differences between exercise and vitamin E alone or in combination regarding the reduction in the level of liver enzymes and sonographic evidences of fatty liver although both resulted in significant improvements in biochemical endpoints. This implies that physical activity could be considered as effective as vitamin E in the improvement of biochemical and ultrasonographic presentations of NASH and the addition of Vitamin E does not offer any benefits. According to the findings of this pilot study a full-powered study with a control group should be designed.

Keywords: NASH; NAFLD; Fatty Liver; Exercise; Vitamin E

please cite this paper as:
Eslami L, Isazadehfar K, Karami M, Eslami L,Rahmani-nia F,Nakhostinroohi B. The Effect of 12 weeks Regular Physical Activity and Vitamin E in the Treatment of Non-Alcoholic Steatohepatitis: A Pilot study. *Govaresh* 2015;20:57-65.

Corresponding author:
Layli Eslami, MD
Golestan University of Medical Science, Taleghani Hospital, North Khayyam Intersection, East Taleghani Avenue, Gonbad-e Kavus, Golestan province 49791-31983, Iran
Tel: +98 172 2292057
Fax:+98 172 2234988
E-mail: laylieslami@gmail.com
Received: 14 Dec. 2015
Edited: 08 Mar. 2015
Accepted: 09 Mar. 2015

INTRODUCTION

The burden of non-alcoholic fatty liver disease (NAFLD) was a significant clinical and public health issue worldwide. NAFLD was characterized by hepatic histological changes similar to alcohol-induced liver injury, in patients without significant alcohol consumption. A range of histological changes can be seen; some patients have steatosis only while others have hepatic steatosis with prominent necro-inflammatory changes (steatohepatitis) with or without associated fibrosis. Non-alcoholic

steatohepatitis (NASH) may lead to cirrhosis and end stage liver disease in a number of patients(1,2).

According to the "Practice Guideline by the American Gastroenterological Association" , the definition of NAFLD requires that there was evidence of hepatic steatosis, either by imaging or by histology and there were no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication or hereditary disorders(3).

Despite its prevalence, there was no treatment has been proven to be effective in NAFLD/NASH. A major reason was a lack of understanding of the pathogenetic mechanisms. General measures of risk reduction, such as weight loss in the obese patients, effective treatment of hyperlipidemia and diabetes mellitus (if present) are usually recommended(4-9).

Many studies have shown that lifestyle modifications such as weight loss and increased physical activity was vital component to the treatment of NAFLD and metabolic Syndrome(4,10-12). The importance of various protocols of endurance and resistance exercise with or without medical intervention has been evaluated in many studies; however, the optimal strategy was not yet determined(12-22).

On the other hand, most of the patients with the diagnosis of NAFLD have conditions related to the metabolic syndrome such as obesity, hypertension and cardiovascular disease which makes almost impossible for these patients to participate in most protocols of the exercise programs.

The Borg Rating of Perceived Exertion (RPE) was a way of measuring physical activity intensity level(22). Perceived exertion was how hard the patient feels like the body is working. It was based on the physical sensations a person experiences during physical activity, including increased heart rate, increased respiration or breathing rate, increased sweating, and muscle fatigue. Although this was a subjective measure, a person's exertion rating may provide a fairly good estimate of the actual heart rate during physical activity(23). This method can be used for the measurement of physical activity even in the patients with co-morbidities. This could be suitable for NASH patients too.

According to the two hypothesis in the pathogenesis of NASH, the first hit involves accumulation of excess fat in the liver cells due to insulin resistance and leads to hepatic steatosis. The second hit concerns oxidative stress that causes lipid peroxidation and activates inflammatory cytokines resulting in NASH(24).

Vitamin E, a fat-soluble vitamin were believed to be an important antioxidant, can ameliorate the effects of free radicals(25-26).

There were several studies that have experimented on the use of antioxidants such as Vitamin E for the treatment of NAFLD or steatohepatitis. Based on some experiences that vitamin E could improve the level of liver transaminases and fibrosis score, it has been used for the treatment of NASH by some hepatologists(4,27-30).

In this pilot study, we compared the effect of regular physical activity and high dose of Vitamin E alone and combination in the improvement of biochemical and ultrasonographic of NASH.

METHODS AND MATERIALS

The study was carried out in Gonbad-e Kavus, Golestan, Iran. A total of 30 consecutive patients with the diagnosis of non-alcoholic steatohepatitis (NASH) were enrolled into the study. Recruitment started in September 2012. Participants of any sex or ethnic origin diagnosed with NASH were included on the basis of the following criteria:

- Age between 20-55 years old
- Ultrasonographic evidence of hepatic steatosis together with increased in serum ALT to above 1.5 times the upper limit of normal (ULN) i.e. 19 U/L in women and 30 U/L in men in two separate measurements with at least 3 months interval.
- Daily alcohol intake less than 10 g in women and 20 g in men.

Patients were excluded from the study if they had one of the followings:

- Diagnosis of hepatitis B, hepatitis C, autoimmune hepatitis, and genetic liver diseases such as Wilson's disease and hemochromatosis.
- Participants presenting one or more causes that are commonly associated with secondary NAFLD; i.e., drugs, surgical procedures, environmental toxins, and total parenteral nutrition
- Any disease or condition which might prohibit physical activity
- Uncontrolled hypertension (blood pressure more than 140/90 mmHg)
- Presence of any diagnosed malignancy
- Presence of any co-morbid illness including heart failure, renal failure, respiratory failure, Corpulmonale, psychological disorder, or thyroid disorders
- Any type of Drug abuse

- Lactation, pregnancy or planning for pregnancy in the next 12 months
- Use of any type of vitamin E supplementation
- Being a professional athlete or doing regular exercise

The study complies with the Declaration of Helsinki. The Ethics Committee of the Faculty of Sport Sciences and Physical Education of Guilan University approved the protocol and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Study design: This study was a prospective and randomized trial with three groups. Subjects underwent an assessment of body weight, height, and blood pressure at the initial evaluation and at the completion of treatment 12 weeks later. Blood samples were obtained for assessment of complete blood count, fasting levels of lipids, glucose, liver aminotransferases and alkaline phosphatase.

Degree of fatty liver infiltration was assessed by ultrasound. The severity of steatosis is graded as mild (I), moderate (II), or severe (III)(31-34).

All subjects, received lifestyle advice. This included a verbal advice for weight loss, consumption of low fat diet and an increase in physical activity. There were no specific guidelines for how the patients should lose their weight. Participants were allowed to continue their regular drugs based on their previous disease but were discouraged from adding other drugs that are used for non-alcoholic steatohepatitis to their regimen.

In the case of newly diagnosed hypercholesterolemia (LDL>130 mg/dl), treatment with Atorvastatin 20 mg daily and in the case of hypertriglyceridemia (Serum TG level>200 mg/dl), Gemfibrozil 300 mg twice a day was initiated. In patients with elevated blood glucose level (FBS> 126 mg/dl) treatment with metformin 500mg/day was started.

There was no significant difference between groups in the number of patients with hyperlipidemia, impaired glucose tolerance test and need for receiving these medications (ANOVA: $p>0.5$), therefore patients which had received these medications have not been excluded from the study.

The planned sample size was 30 subjects, with equal assignments to each of the three study groups (10 per group). Subjects who met all eligibility criteria and provided written informed consent were randomly -using computer random number generation program- assigned to one of three treatment groups for 12 weeks:

Group A: receiving oral vitamin E with dose of 400 mg twice a day

Group B: receiving a regular and planned physical activity as the intervention group; physical activity was assessed objectively using a validated scale; i.e., the Borg's Rating of Perceived Exertion (RPE) scale. Borg's RPE scale which was provided by Borg is commonly used for rating of perceived effort during physical exercise in ergonomics and rates from 6 to 20 (Table 1).

Patients were advised to start exercise (walking for at least 20 min, 3 days a week) with the Borg's Rating of Perceived Exertion (RPE) scale of at least 9. They could raise the Borg's RPE scale up to 14 during the study period and were advised to increase the duration of exercise from 20 minutes up to 60 minutes if they wished.

Group C: Oral vitamin E with a dose of 400 mg twice a day plus regular physical activity as performed by group B.

A printed checklist was given to participants in group B and C and subjects were asked to record the duration and the intensity (based on Borg's RPE scale) of their regular activity in the checklist.

Allocation sequence was hidden in sealed envelopes and was controlled by another person who was independent to the study; so the participant's allocation could not been foreseen for the investigators. After randomization, subjects were visited every four weeks for assessment of the tolerability to the study drugs and also for evaluation of maintaining the regular activity based on the previously given check list. Because of the type of interventions, it was not possible for either the participants or the investigators to be blinded to the treatment groups.

Study outcomes: The primary outcome of this study was to assess the efficacy of regular and planned physical activity in improving of the biochemical and/or ultrasonographic evidence of NASH within a 12-week period. The secondary endpoint was to assess the safety of such intervention.

Statistical analysis: The primary analysis was an intention-to-treat analysis, SPSS was used to analyze the data. A 2-factor analysis of variance (ANOVA) one-way analysis of variance test was performed for the analysis of qualitative variables; Chi-square test was used for analysis of quantitative variables. P values of less than 0.05 were considered to indicate statistical significance. This study was a pilot study so

Table 1: **Instructions for Borg Rating of Perceived Exertion (RPE) Scale**

Scales	Expressions
6	No exertion at all
7-8	Extremely light
9-10	Very light: corresponds to "very light" exercise. For a healthy person, it is like walking slowly at his or her own pace for some minutes
11-12	Light
13-14	Somewhat hard: on the scale is "somewhat hard" exercise, but it still feels OK to continue.
15-16	Hard (heavy)
17-18	Very hard: is very strenuous. A healthy person can still go on, but he or she really has to push him- or herself. It feels very heavy, and the person is very tired.
19	Extremely hard: on the scale is an extremely strenuous exercise level. For most people this is the most strenuous exercise they have ever experienced.
20	Maximal exertion

sample size was not calculated. Extraction of data from the questionnaires and analyzed them was performed by a person who was blinded to the treatment groups.

RESULTS

A total of 30 patients aged 23 up to 55 years, 10 (33.3%) men and 20 (66.7%) women, were enrolled between October 2012 and April 2013.

There was no significant difference between the three groups with respect to demographics characteristics, clinical, laboratory and ultrasonographic data at baseline (Table 2). All subjects completed the study.

Serum biochemical levels:

Decrease in mean aspartate aminotransferase, alaninetransferase and alkaline phosphatase levels among subjects in all intervention groups were seen after treatment. Improvement in the level of aspartate aminotransferase and alaninetransferase was statistically significant in the subjects receiving vitamin E (Table 3). However, there was no significant difference in the amount of improvement between the three groups.

Serum lipids:

The serum level of the triglycerides, total cholesterol, and LDL-C was decreased in the subjects of all treatment groups. Among these, decrement in the triglycerides level was statistically significant in all groups after the treatment; however, there was no significant difference in the mean value of decrement between the intervention groups. It's because almost the same numbers of patients in each group has hyperlipidemia and thus received medication for.

Metabolic factors:

A minor non-significant change occurred in the fasting serum glucose after 12 weeks of treatment in the groups, as mentioned before patients received Metformin if they had hyperglycemia. Both groups with regular exercise had significant mean weight loss in comparison with the vitamin E group (a mean decrease of 3.0 kg in exercise group, 5.8 kg in subjects on regular exercise plus vitamin E and 0.2 kg in vitamin E group, ANOVA: p=0.04)

Although there was significant decrease in the mean BMI of all groups after treatment; this decrement was not significantly different between the groups.

Ultrasonographic grade:

Statistically non-significant improvement in the ultrasonographic finding of fatty liver has been occurred in few patients of each group (p value=0.359). There is no significant difference in the level of improvement between different groups. Table 4 shows sonographic degrees of liver fat accumulation before and after treatment according to the treatment groups:

Exercise:

Table 5 shows the number and percentage of RPE scales which patients started to exercise with.

A number of patients gradually increased the duration of their physical activity according to the given checklist and some of them also increased the degree of Borg's scale during the treatment.

Some other patients continued their activity with the same duration and intensity (p value=0.133). Several statistical analyses were made to assess the effect of exercise intensity and duration on the levels of liver enzymes and sonographic changes in patients (Table 5).

There was a significant statistical correlation between the intensity of the physical activity; i.e., Borg's RPE score and the mean reduction in the levels of blood cholesterol, LDL, and alkaline phosphatase in the studied groups. Based on Post Hoc Analyses, with increasing the intensity of physical activity from score 8 to 14, a significant further reduction occurred in cholesterol, LDL, and alkaline phosphatase levels, particularly in the treatment group B (Table 6).

Table 2: **Baseline characteristics of study subjects ***

Characteristic	Vitamin E (n=10)	Exercise (n=10)	Exercise plus Vitamin E (n=10)	Total(n=30)	*p* value
Age (yr)	42.4±8.1	43.6±9.7	39.6±6.4	41.9±8	0.545
Female sex (%)	50	90	60	66.7	0.142
Turkmen Ethnic (%)	40	30	30	33.3	0.698
Alanin aminotransferase (U/liter)	60.30±36.61	58.30±27.24	56.60+15.02	58.40±26.81	0.958
Aspartate aminotransferase (U/liter)	35.50±12.96	43.20±17.92	38.90±12.96	39.20±14.63	0.515
Alkaline phosphatase (U/liter)	225.20±26.28	215.00±54.74	211.90±51.10	271.37±54.21	0.857
Triglycerides (mg/dl)	190.80±86.21	151.20±67.20	213.60±112.93	185.20±91.40	0.314
Total Cholesterol (mg/dl)	215.90±23.81	209.90±36.15	191.20±33.04	205.67±34.54	0.256
High-density lipoprotein	37.70±6.94	48.90±12.67	34.54±7.70	40.38±11.07	0.095
Low- density lipoprotein	135.50±27.48	130.00±33.35	119.32±29.17	128.27±29.84	0.483
Fasting serum glucose(mg/dl)	91.11±24.41	105.20±26.59	106.80±26.71	101.38±26.01	0.372
Weight (kg)	77.60±13.83	78.30±9.88	94.50±22.53	83.47±17.61	0.074
Body-mass index**	28.66±3.44	30.14±3.37	32.76±5.74	30.52±4.52	0.121

*Plus–minus values are Means±SD.
**The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 3: **Mean decrease in the level of aspartate aminotransferase, alanintransferase and alkaline phosphatase levels**

Intervention group		Aspartate aminotransferase	Alanine aminotransferase	Alkaline phosphatase
Vitamin E	Before treatment	60.3	35.5	225.2
	After trePatment	33.7	25.4	194.6
	Mean decrease	26.5	10.1	30.6
	p value	0.001	0.02	0.06
Regular exercise	Before treatment	58.3	43.2	215.0
	After treatment	19.2	18.8	170.1
	Mean decrease	39.1	24.4	44.9
	p value	0.50	0.15	0.30
Vitamin E plus regular exercise	Before treatment	56.6	38.9	205.3
	After treatment	34.2	30.4	161.8
	Mean decrease	22.3	8.5	23.4
	p value	0.80	0.94	0.80

DISCUSSION

Despite the high and increasing prevalence of hepatitis induced by non-alcoholic fatty liver, no definitive cure has been found for this common disease so far. In addition to general measures such as weight loss and effective treatment of hyperlipidemia and diabetes, various pharmacologic and non-pharmacologic treatments are also recommended.

Being overweight is considered as an important risk factor for the disease. In our study, only 3.3 percent of patients have body mass index (BMI) lower than 25. In 83.3 percent of patients, BMI was between 25 and 35, and in 13.3 percent of them, it was over 35.

We advised all study subjects to lose their weight. Although no specific diet was prescribed to the patients, the BMI was significantly reduced in

Table 4: Sonographic grading of fatty liver before and after treatment

Treatment group		Normal	Grade I	Grade II	Grade III
Vitamin E (A)	Before treatment	0	1	7	2
	After treatment	1	3	6	0
Regular physical activity (B)	Before treatment	0	0	9	1
	After treatment	2	4	4	0
Vitamin E and Regular physical activity (C)	Before treatment	0	0	5	5
	After treatment	0	3	5	2

Table 5: Number and percentage of RPE scales of Borg's in the patients

Borg's RPE scale	Number of patients	Cumulative percentage
8	15	71.4
10	2	81
12	2	90.5
14	1	100

Table 6: Mean reduction in the level of biochemical markers considering the intensity of exercise

Mean reduction	Patients who start and continue the physical activity with Borg's scale of 8	Patients who start and continue the physical activity with Borg's scale of 14	*p* value
Cholesterol	32.6	37.16	0.01
LDL	17	36.7	0.03
AlkPhos	33	55	0.015

patients of all three groups after the study, which was irrelevant to the type of intervention.

Among pharmacologic treatments of fatty liver, the effect of vitamin E in various studies has been shown. In our study, after three months of regular use of vitamin E in the Group A, the liver enzyme levels significantly reduced. In our study, sonographic evidence of fatty liver also reduced after treatment with vitamin E. Similarly, reduction in aminotransferases with vitamin E was noted in a controlled trial which compared vitamin E alone to vitamin E with pioglitazone; however, histologic improvement was only seen with combined therapy(29).

Another prospective, double-blind, randomized, placebo-controlled trial with a total enrollment of 49 patients was performed in 2003 by Harrison et al. All patients were randomized to receive either vitamins E and C (1000 IU and 1000 mg, respectively) or placebo daily for six months. Vitamin treatment resulted in a statistically significant improvement in fibrosis score. No changes were noted in inflammation with treatment and no improvement in necroinflammatory activity or ALT was seen with this combination drug therapy(28).

Histologic changes of fatty liver were not assessed in our study. The usefulness of using regular doses of vitamin E in improvement of histological evidence of fatty liver was found in a large study by Sanyel et al. in 2010. In this clinical trial, non-diabetic patients with fatty liver disease were randomly divided into three groups of treatment with Pioglitazone (30 mg/day), treatment with Vitamin E (800 international units/day), and placebo for 96 weeks. Overall improvement in liver histology was clearly higher in vitamin E group than the placebo group, while such a significant improvement was not observed in the Pioglitazone group(35).

Treatment with antioxidant supplements showed a significant, though not clinically relevant, amelioration of aspartate aminotransferase levels but not of alanine aminotransferase (ALT) levels, as compared to placebo or other interventions in a meta-analysis published in 2007. Gammaglutamyltranspeptidase was decreased, in the treatment arm. Radiological and histological data were too limited to show any definite conclusions on the effectiveness of these agents. The authors noted that the results of this review is not sufficient enough to strongly advice the antioxidant supplements for treating NAFLD or NASH due to the small number of trials, their low methodological quality, the variability in clinical and histological assessment, and the number of different antioxidant supplements which were tested(30).

Many clinicians are now using vitamin E in the treatment of non-alcoholic fatty liver hepatitis. However, according to the above-mentioned review and another meta-analysis by Miller (36)which showed that long-term use (over one year) of high-doses of vitamin E can increase the overall mortality, focusing on other antioxidant treatments and physical activity could be useful. In addition to the beneficial

effect of regular physical activity on fatty liver, it does not have any side effects and could have many other useful effects on the other systems.

Many studies have shown the effectiveness of the various types of exercise; i.e., endurance and resistance programs, on the radiologic and biochemical presentations of fatty liver.

Hallsworth et al. randomized 19 healthy subjects with MRI diagnosed NAFLD to take part in 45–60 minutes of resistance exercise three times a week for 8 weeks, or to be in a control group. For minimizing the effect of weight loss, if the patients lost more than 5% of their body weight, they were excluded from the study. Results showed that there was a 13% decrease in intrahepatic fat, recorded by MRI, in the intervention group with no change in the control group. There was an improvement in insulin resistance but no change in ALT or blood lipid levels(14).

Similarly, Sullivan et al. recruited and randomized 18 participants with NAFLD in which the intervention group was required to carry out 30–60 minutes of exercise five times a week. MRI was used to determine the intrahepatic fat content, which showed a mild decrease in the intervention group compared to the control. Decrease in ALT occurred which was correlated with the decrease in intrahepatic fat in the intervention group(15).

These results are in contrast with the results of the study by Tarnopolsky in which healthy NAFLD patients have participated in a moderate intensity program of endurance exercise (stationary bike cycling). After a 3-month period of endurance exercise, improvements in fitness (maximal oxygen consumption) and reduction in waist circumference were noted in both the lean and obese groups, regardless of sex. No change in BMI was seen. Hepatic lipid content, as measured by CT (liver attenuation), did not change post exercise, regardless of group or sex. Furthermore, no improvement in liver enzymes or insulin resistance was observed, and no measurement of lipid profile was discussed in the trial(17).

Previous studies that were designed based on the effect of physical activity on fatty liver were carried on healthy population with relatively heavy endurance or resistance exercise. Doing such exercises would not be possible for most patients with fatty liver; since, according to risk factors for fatty liver, the possibility of other concurrent diseases such as osteoarthritis in obese people, heart disease in diabetics, etc. is high. Thus, this study was designed based on Borg's scale and according to the patient's ability to exercise.

In our study, in both groups treated with regular physical activity, there was a significant reduction in the content of liver fat based on ultrasound results (table 3). These results are in agreement with previous studies, while they are inconsistent with the results of Michael Doris study on 41 patients with NASH with evaluating the effects of endurance exercise. In this study, the liver fat content measured by CT scan did not change substantially after 3 months of exercise. Likewise, no significant changes occurred in the levels of liver enzymes(37).

In our study the reduction in the levels of liver enzymes was seen in the groups after three months of treatment, this decrement was even higher in AST levels (table 2). Considering the high level of AST as a marker of disease progression to liver fibrosis, perhaps its further decline in physical activity group is a sign of slowdown of cirrhosis(38).

As described above, more reduction in the levels of cholesterol, LDL, and alkaline phosphatase was seen parallel to the increase of the exercise intensity. However, the intensity of the exercise has no impact on levels of liver enzymes and sonographic evidence of fatty liver.

There was no significant difference between treatment groups in the baseline demographic characteristics, diet type, levels of liver enzymes, other blood biochemical tests and the degree of fat accumulation on ultrasound; i.e., the role of these factors as confounder becomes less in this study.

In general, the following points are noteworthy from this study:

- Although three-month treatment with high dose vitamin E decreases the levels of liver aminotransferases and liver fat content in NASH patients, we could not say that this decrement is just because of Vitamin E; weight loss and treatment of other metabolic abnormalities such as hyperlipidemia and hyperglycemia might had a significant effect on the results.
- The effect of vitamin E on liver histology was not evaluated here.
- Performing heavy endurance or resistance exercise is not necessary for all patients; planned and regular physical activity in any intensity could improve the biochemical and ultrasonographic evidence of fatty liver. The benefits of exercise on liver histology cannot be judged based on this study.
- The use of vitamin E for three months is safe with no complications.

Study limitations:

- This study was designed as a pilot study to conduct a RCT with a larger sample size. Despite the high value of the study type (RCT), the small sample size precludes a definitive announcement on the results of the study.
- The short duration of the study is a limitation. Perhaps greater effects from all three interventions would be more apparent if the study period was extended.
- Histological assessment of liver is an important goal in the treatment of fatty liver. Liver Biopsy was not performed in this study because of short duration of the study; three-month period is shorter than being useful for evaluating the effect of the treatment on histology.

CONCLUSION

There were no significant differences between treatment groups regarding the reduction in the level of the liver enzymes and sonographic evidence of fatty liver. This implies that physical activity could be considered as effective as vitamin E in improving of biochemical and ultrasonographic presentations of NAFLD. According to the possible side effects of long-term use of vitamin E and the undeniable benefits of physical activity, we could conclude that regular physical activity can be recommended for the patients unwilling to take medications who seek low-risk methods in the treatment of fatty liver. On the other hand, the majority of the studies using just exercise interventions for the treatment of NAFLD/ NASH -such as our trial- has shown that exercise does improve liver markers of steatosis. We conclude that designing clinical trials with large sample sizes could help clinicians to plan and define a suitable exercise

REFERENCES

1. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999;116:1413-9.
2. Brunt EM. Nonalcoholic steatohepatitis: definition and pathology. *Semin Liver Dis* 2001;21:3-16.
3. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Am J Gastroenterol* 2012;107: 811–26.
4. Eslami L, Merat S, Nasseri-Moghaddam S. Treatment of Non-Alcoholic Fatty Liver Disease (NAFLD): A Systematic Review. *Middle East J Dig Dis* 2009;1:89-99.
5. Angelico F, Burattin M, Alessandri C, Del Ben M, Lirussi F. Drugs improving insulin resistance for non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis. In: *Cochrane Database Syst Rev* 2007;1:CD005166.
6. Angulo P, Lindor KD. Treatment of non-alcoholic steatohepatitis. *Best Pract Res Clin Gastroenterol* 2002;16:797–810.
7. Younossi ZM, Diehl AM, Ong JP. Nonalcoholic fatty liver disease: an agenda for clinical research. *Hepatology* 2002;35:746-52.
8. Wang RT, Koretz RL, Yee HF Jr. Is weight reduction an effective therapy for nonalcoholic fatty liver? A systematic review. *Am J Med* 2003;115:554-9.
9. Eslami L, Merat S, Malekzadeh R, Nasseri-Moghaddam S, Aramin H. Statins for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. In: *Cochrane Database of Syst Rev* 2013;12: CD008623.
10. Hickman IJ, Jonsson JR, Prins JB, Ash S, Purdie DM, Clouston AD, et al. Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. *Gut* 2004; 53:413-9.
11. Dixon JB, Bhathal PS, Hughes NR, O'Brien PE. Nonalcoholic fatty liver disease: Improvement in liver histological analysis with weight loss. *Hepatology* 2004; 39:1647-54.
12. Bradford V, Dillon J, Miller M. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease. *Hepat Med* 2013;6:1-10.
13. Kistler KD, Brunt EM, Clark JM, Diehl AM, Sallis JF, Schwimmer JB. NASH CRN Research Group Physical activity recommendations, exercise intensity, and histological severity of nonalcoholic fatty liver disease. *Am J Gastroenterol* 2011;106:460–8.quiz 469.
14. Hallsworth K, Fattakhova G, Hollingsworth KG, Thoma C, Moore S, Taylor R,et al. Resistance

exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. *Gut* 2011;60:1278–83.

15. Sullivan S, Kirk EP, Mittendorfer B, Patterson BW, Klein S. Randomized trial of exercise effect on intrahepatic triglyceride content and lipid kinetics in non-alcoholic fatty liver disease. *Hepatology* 2012; 55:1738–45.
16. Fealy CE, Haus JM, Solomon TP,Pagadala M, Flask CA, McCullough AJ,et al. Short-term exercise reduces markers of hepatocyte apoptosis in nonalcoholic fatty liver disease. *J ApplPhysiol* 2012;113:1–6.
17. Tarnopolsky MA, Rennie CD, Robertshaw HA, Fedak-Tarnopolsky SN, Devries MC, Hamadeh MJ. Influence of endurance exercise training and sex on intramyocellular lipid and mitochondrial ultrastructure, substrate use, and mitochondrial enzyme activity. *Am J Physiol* 2007;292:R1271 –8.
18. Bae JC, Suh S, Park SE,Rhee EJ, Park CY, Oh KW, et al. Regular exercise is associated with a reduction in the risk of NAFLD and decreased liver enzymes in individuals with NAFLD independent of obesity in Korean adults. *PLoS One* 2012;7:e46819.
19. St George A, Bauman A, Johnston A, Farrell G, Chey T, George J. Independent effects of physical activity in patients with nonalcoholic fatty liver disease. *Hepatology* 2009;50:68–76.
20. St George A, Bauman A, Johnston A, Farrell G, Chey T, George J. Effect of a lifestyle intervention in patients with abnormal liver enzymes and metabolic risk factors. *J Gastroenterol Hepatol* 2009;24:399–407.
21. Gerber L, Otgonsuren M, Mishra A, et al. Non-alcoholic fatty liver disease (NAFLD) is associated with low level of physical activity: a population-based study. *Aliment PharmacolTher* 2012;36:772–781.
22. Borg, G. Perceived Exertion as an indicator of somatic stress. Scand J Rehabil Med 1970;2:92-8.
23. Mackenzie, B. (2003) Borg Scale. In:http://www.brianmac.co.uk/borgscale.htm
24. Chitturi S, Farrell GC. Etiopathogenesis of nonalcoholic steatohepatitis. *Semin Liver Dis* 2001;21:27–41.
25. Traber MG, Stevens JF. Vitamins C and E: beneficial effects from a mechanistic perspective. *Free Radic Biol Med* 2011;51:1000–13.
26. Hoofnagle JH, Van Natta ML, Kleiner DE, Clark JM, Kowdley KV, Loomba R, et al. Vitamin E and changes in serum alanine aminotransferase levels in patients with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2013;38:134–43.
27. Bugianesi E, Gentilcore E, Manini R, Natale S, Vanni E, Villanova N, et al. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. *Am J Gastroenterol* 2005;100:1082–90.
28. Harrison S, Torgerson S, Hayashi P, Ward J, Schenker S. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. *Am J Gastroenterol* 2003; 98:2485–90.
29. Sanyal A, Mofrad PS, Contos MJ, Sargeant C, Luketic VA, Sterling RK, et al. A pilot study of vitamin E versus vitamin E and pioglitazone for the treatment of nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol* 2004; 2:1107–15.
30. Lirussi F, Azzalini L, Orando S, Orlando R, Angelico F. Antioxidant supplements for non-alcoholic fatty liver disease and/or steatohepatitis. In: *Cochrane Database Syst Rev* 2007;1:CD004996.
31. Rofsky NM, Fleshaker H. CT and MRI of diffuse liver disease. *Semin Ultrasound CT MR* 1995;16:16-33.
32. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology* 2002; 123:745-50.
33. Poonam M, Zobair M. Abdominal ultrasound for diagnosis of nonalcoholic fatty liver disease (NAFLD). *American Journal of Gastroenterology* 2007;102:2716-7.
34. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. *J Hepatol* 2009;51:433-5.
35. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis. *N Engl J Med* 2010;362:1675-85.
36. Miller ER, Pastor-Barriuso R, Dalal D, Riemersma RA, Apple LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005;142:37-46.
37. Michaela DC, Imtiaz SA, Mazen HJ, Mark TA. Effect of Endurance Exercise on Hepatic Lipid Content, Enzymes, and Adiposity in Men and Women. *Obesity (Silver Spring)* 2008;16:2281-8.
38. Parkes J, Guha IN, Roderick P, Rosenberg W. Performance of serum marker panels for liver fibrosis in chronic hepatitis C. *J Hepatol* 2006;44:462-74.