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Efficacy of Traditional Persian Medicine-Based Diet on Non-Alcoholic Fatty Liver Disease: A Randomized, Controlled, Clinical Trial

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Abstract

Background: Regarding the preventive approaches of traditional Persian medicine (TPM) in the management of chronic diseases such as fatty liver, we evaluated the effect of a TPM-based nutritional style on liver enzymes levels and fatty liver grade in patients with non-alcoholic fatty liver.**Materials and Methods:** Patients were randomly assigned to receive either a three-month TPM-based diet as the intervention group or received the low-fat, low-calorie diet as the control group. The primary outcome measure was changes in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Secondary outcome measures were changes in fatty liver grade (fatty tissue infiltration in liver by using ultrasound imaging) and changes in patients' body mass index (BMI). All outcome measures were evaluated at the baseline, at six weeks, and at three months after intervention.**Results:** Regarding within-group changes in outcome measures' mean values, there was a significant reduction in ALT serum level, AST, BMI, and fatty liver grade after intervention, compared with baseline in both groups of study ($P< 0.001$). The results of between-group analyses showed significant decreases in both mean body mass index and mean fatty liver grade between the intervention group compared to the control group at the end of intervention ($P<0.037$ and $P<0.003$, respectively).**Conclusion:** This randomized open-label controlled clinical trial demonstrated that the traditional Persian medicine-based nutritional style, used as a non-pharmacological remedy, could reduce body weight and improve fatty liver grade in patients suffering from non-alcoholic fatty liver disease.
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Introduction

Nonalcoholic fatty liver disease (NAFLD) is the presence of liver steatosis when other causes of hepatic fat accumulation are not present [1]. NAFLD may progress and lead to cirrhosis [2]. NAFLD has a worldwide prevalence (about 20%) and is the most common liver disease in Western countries [3]. In a population-based study carried out in Iran, the prevalence of NAFLD was reported to be 21.5%, while in other studies, this prevalence varied from 2.9% to 7.1% in the general population. It seems that the screening criteria for NAFLD in these studies were not as accurate as in the recent study [4, 5]. Multiple therapies, from lifestyle modification to pharmacological therapy, have been suggested for the treatment of NAFLD [6, 7]. Moreover, risk factor adjustment, such as weight, dyslipidemia and diabetes control, is commonly recommended [8, 9]. Since the pathogenesis of NAFLD remains unknown, there is no established successful therapy for it. Therefore, further work is clearly needed to enhance our evidence for this condition. Over the past decades, increasing interest in the use of complementary and alternative medicine has arisen for the treatment of chronic diseases such as fatty liver [10-13]. Traditional Persian medicine (TPM) as a medical alternative has been practiced among Iranian people since ancient times [14–16]. From TPM's viewpoint, there are several therapeutic strategies available to treat hepatic diseases, ranging from lifestyle modification to herbal therapy [17–20]. The six fundamental plans for the prevention of diseases, which were called "*Setteh-e-Zarurieah*" (comprising taking care of six essential factors: weather, diet and nutritional style, physical activities, sleep and wakefulness, exertion of unnecessary materials from the body, and mental and spiritual status), were considered to be TPM's main disease prevention approach. According to this point of view, for example, wet climate, overeating, cold and wet foods and fruits (such as yogurt, watermelon, curd, potage, cucumber, sour dough), oversleeping, lack of exercise, and waste retention may lead to excessive cold and wet qualities in the body. This condition can result in disorders which are compatible with arthralgia, fatty liver, dyspepsia, gastroesophagial reflux, lower limb edema, constipation, and weakness. In TPM, three main methods are applied in treatment, including lifestyle (changes in the aforementioned *Setteh-e-Zarurieah*), herbal drugs, and practical manners such as massage, venesection, and leech therapy. Adjustment of *Setteh-e-Zarurieah* was considered to be a preventive approach prior to herbal therapy, or what is now known as lifestyle changes in current medicine [21–25]. Regarding the preventive approaches of TPM in the management of chronic diseases such as NAFLD [21, 26–29], and due to lack of evidence on the clinical effects of these preventive approaches for NAFLD management, we designed a randomized, controlled clinical trial to try to evaluate the effect of the TPM-based diet and nutritional style (as one of the six essential factors of *Setteh-e-Zarurieah*, from the standpoint of TPM) on liver enzyme levels and fatty liver grade in patients with NAFLD.

Materials and Methods

Study Design

This study was a randomized, double arm, open label, active-controlled clinical trial that started in November 2014 and finished in May 2016 at the Mashhad University of Medical Sciences. In this trial, we evaluated the effect of TPM-based diet and nutritional style on the fatty liver grade and the liver enzyme levels in patients with NAFLD. No changes occurred to methods after trial commencement.

Sample Size Calculation

Regarding the objectives of former similar studies, and by taking into account a two-sided significance level of 0.05 and a power of 80%, the sample size was calculated for 15 patients in each group for a total of 30 patients [30, 31].

Participants

Inclusion criteria for participants enrolled in this study were men and women aged 20 to 60 years, with non-alcoholic fatty liver (grades 1–2) diagnosed by ultrasound imaging. These were the patients referred to

Ghaem Hospital's gastrointestinal and nutrition clinic and its traditional medicine clinic, both located at the Mashhad University of Medical Sciences. It is to be noted that signing an informed consent form was required. Exclusion criteria were: diabetes, cardiovascular diseases, hypertension, overweight (BMI greater than 27), familial hyperlipidemia, alcohol consumption, drug addiction, breastfeeding, pregnancy, renal stones, gallstones, an active or previous infection with hepatitis B or C, acute liver disease, major surgery during the last 6 months, any surgery on the liver and gallbladder or general anesthesia drugs during the study, rapid weight loss during the last 3 months for any reason, patients undergoing a special diet or engaging in exercise for weight loss or gain, and those losing weight.

Randomization

Forty-three eligible patients were randomized in two parallel groups. Then, patients were randomly assigned to one of the groups using a simple block randomization method, which was carried out by applying NCSS (statistical software). Only the statisticians were blind to patient allocation.

Intervention

Sonographic assessment was done with the device model Siemens 40 with the Acuson 15 L8 transducer after 8 hours of fasting by a radiologist who was not aware of either the patient's medical case files or their liver biochemical tests. When diagnosis of fatty liver was confirmed by a gastroenterologist, the patients were divided into two groups. Patients were randomly assigned to receive either a three-month TPM-based diet as the intervention group or the low-fat, low-calorie diet as the control group. Participants in the intervention group received TPM-based dietary commands by a written list of hot- and cold-natured foods along with related recipes for a period of three months. According to TPM, each food affects organ metabolism rates. This effect is different from calorie generating of foods' ingredients. When a food decreases the mean metabolism rate, especially before the final ingredients' metabolism, it is traditionally called cold-natured food. Yoghurt, cheese, watermelon, tomatoes, lentils, mung beans, and spinach are some examples of cold-natured foods. Peas, butter, meat, beans, bananas, and apples are some examples of hot-natured foods. To better understand the concept of hot- and cold-natured foods, please refer to previous studies [14, 22, 32–34]. Those in the control group received a low-fat and low-calorie diet for three months. Controls were put on a 500 kcal per day deficit on daily energy needs. In this diet, participants received 60% carbohydrates, 20% protein, and 20% fat. The participants were prevented from weight changing by any out-of-the-protocol-study diet and physical activity during the trial period. They were asked to come to the clinic twice a month. BMIs were calculated; if a participant lost more weight than the designed protocol, he/she was asked why the reason and were advised to follow the suggested program.

Outcome Measures

The primary outcome measure in this trial was changes in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) liver enzyme levels. Blood samples were taken after 12–14 hours overnight fasting at the baseline, six weeks, and three months after intervention in two groups by using the International Federation of Clinical Chemistry (IFCC)-approved method. Secondary outcome measures were changes in fatty liver grade (fatty tissue infiltration in liver by using ultrasound imaging) and changes in patients' BMI. Any observed adverse event was also considered as the secondary outcome. No changes were made to trial outcomes after the trial commenced.

Safety Assessment

In order to detect potential patient complaints, all patients were followed by physicians every two weeks. Weight and blood pressure measurements were also carried out by the physicians.

Ethical Issues

The trial was in compliance with the Declaration of Helsinki (1989 revision) and was reviewed, approved, and monitored by the Mashhad University of Medical Sciences ethics committee (Reference number:

922501.1.1109). The trial was also registered in the Iranian Registry of Clinical Trials with the following code: IRCT2014081518807N1. All of the participants signed an informed consent form prior to enrollment in the study.

Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS software Version: 15). All data were described by mean ± standard deviation (SD) or number (percentage). Chi-square and Mann–Whitney U tests were used for statistical comparison of baseline characteristics. Repeated measurement ANOVA was used to determine the changes in outcomes between the two groups of the study. A P-value less than 0.05 was considered significant.

Results

From November 2014 to May 2016, 83 volunteers were assessed for eligibility. Forty-three patients who met the inclusion criteria and consented to participate in the study were divided into two groups. Twenty-one patients were assigned to the intervention group to receive a TPM-based diet, and 22 patients were assigned to the control group to receive a low-fat, low-calorie diet for a period of three months. Three patients in the intervention group and 4 patients in the control group were subsequently excluded from the study because they did not fully adhere to the study protocol. Figure-1 is a flowchart of the groups' distribution, recruitment, intervention, follow-up, and analysis. The mean age of participants was 42.22 ± 8.89 and 42.83 ± 9.53 years in intervention and control groups, respectively (P = 0.844). Moreover, the male/female ratio was 9/9 and 11/7 in the intervention and control groups, respectively (P=0.502). No significant differences were observed in baseline demographic data between the two groups of the study except a significant difference that was observed be-

Table 1. Mean ± SD for AST, ALT, BMI, and Fatty Liver Grade in Intervention and Control Groups Before and After the Intervention

		Intervention	Control	P-Value
AST (U/L)	Baseline	37.72 ± 13.19	52.61 ± 29.59	0.143
	6 weeks	28.94 ± 7.64	39.22 ± 15.99	0.021
	12 weeks	24.22 ± 6.29	27.39 ± 7.20	0.169
	P-value	< 0.001	< 0.001	
ALT (U/L)	Baseline	37.56 ± 10.83	62.67 ± 52.07	0.252
	6 weeks	28.00 ± 8.79	44.28 ± 24.37	0.013
	12 weeks	24.67 ± 7.42	28.56 ± 7.75	0.133
	P-value	< 0.001	< 0.001	
BMI (kg/m^2)	Baseline	25.97 ± 1.28	24.38 ± 2.55	0.013
	6 weeks	25.48 ± 1.24	23.97 ± 2.31	0.006
	12 weeks	24.97 ± 1.27	23.70 ± 2.19	0.037
	P-value	< 0.001	< 0.001	
Fatty liver grade	Baseline	1.44 ± 0.51	1.61 ± 0.50	0.317
	6 weeks	1.22 ± 0.42	1.56 ± 0.51	0.040
	12 weeks	0.50 ± 0.51	1.22 ± 0.54	0.003
	P-value	< 0.001	< 0.001	

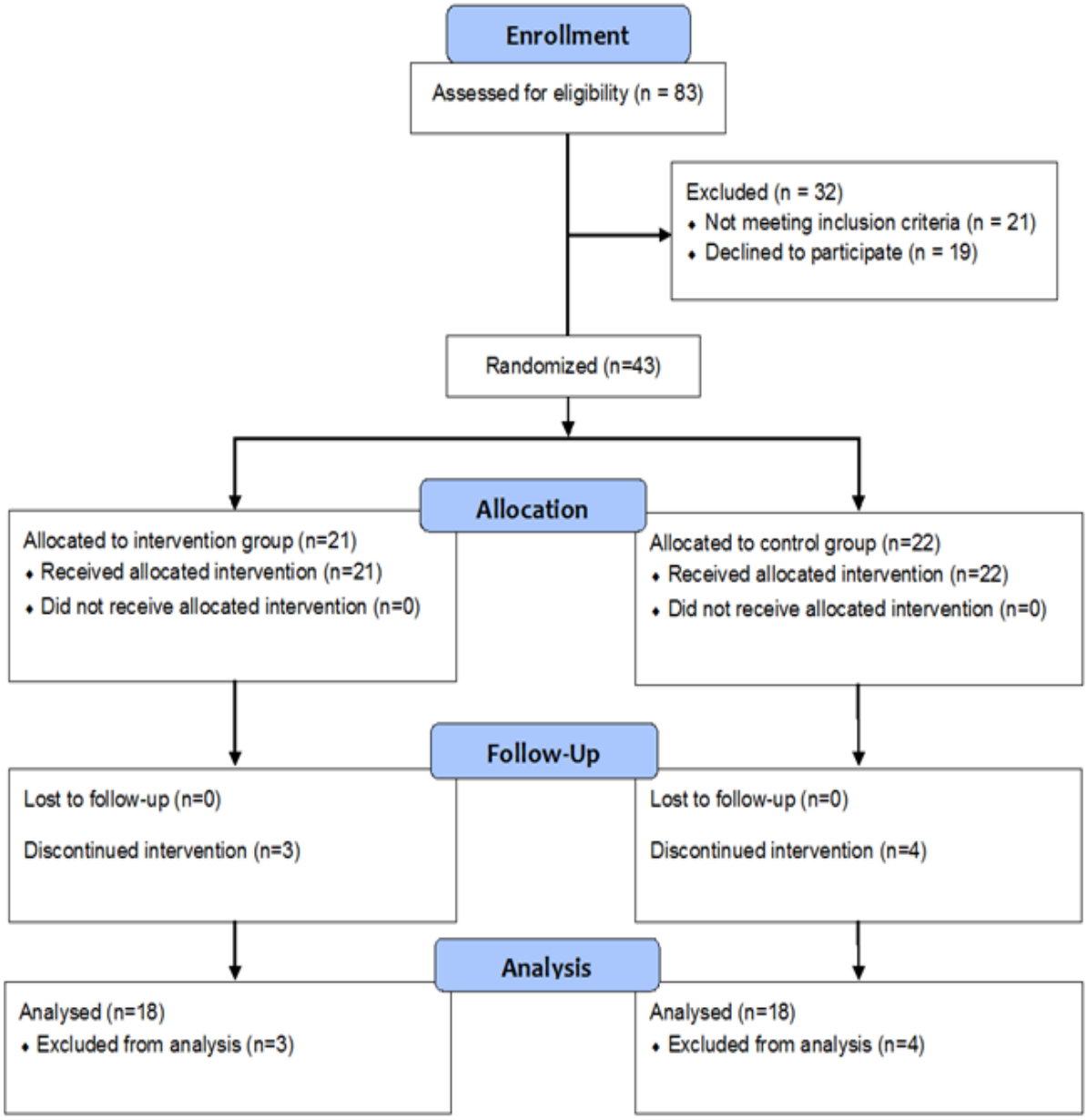

Figure 1. CONSORT flowchart of study

tween the study groups in term of baseline BMI (25.97 ± 1.28 versus 24.38 ± 2.55; P=0.013). Regarding within-group changes in the mean values of outcome measures, there was a significant reduction in the serum level of AST and ALT, BMI, and fatty liver grade after intervention compared with the baseline in both groups of study (P<0.001). The results of between-group analysis, as demonstrated in Table-1, showed a significant decrease in mean body mass index and mean fatty liver grade between the intervention group compared to the control group at the end of intervention (P<0.037 and P<0.003, respectively).

Safety and Tolerability

There was no observed adverse event in either group.

Discussion

In the present trial, we evaluated the effectiveness of the nutritional style based on TPM on NAFLD via an open-label randomized controlled clinical trial. Although both TPM diet and low-fat, low-calorie diet could improve all of the study's outcome measures, the TPM diet is demonstrated to have better effects on reducing mean body mass index and on fatty

liver grade in patients suffering from NALFD, compared to a low-fat, low-calorie diet. Efficacy of lifestyle modifications such as physical exercise, weight loss, and dietary changes for prevention and management of NAFLD have been evaluated in previous studies. Huang *et al*. in a pilot study, suggested that dietary intervention could be effective in improving histology in patients with biopsy-proven non-alcoholic steatohepatitis [35]. This issue was confirmed by Promrat *et al*. in a randomized controlled trial; they showed that a 7% to 10% weight reduction, achieved through a combination of diet, exercise, and behavior modification, can lead to significant improvements in liver chemistry and in the histological activity of NAFLD [6]. Studies have shown that even weight loss brought about by surgery can improve the state of NAFLD patients [36].

John *et al*. proved that weight loss after laparoscopic adjustable gastric band surgery could improve abnormal liver histological features in severely obese patients [37]. Weight loss due to caloric restriction leads to hepatic triglycerides content reduction and to decreased gluconeogenesis, which consequently would lead to a reduction in alanine aminotransferase [38]. In fact, hepatic fat content reduction in weight loss reflects the mobilization of hepatic lipid stores as an energy source and as a contributor to the related ketosis, leading to improved liver function [39]. Wong *et al*. in a randomized, controlled, clinical trial with an acceptable sample size, demonstrated that a community-based lifestyle modification program was effective in reducing and normalizing liver fat in NAFLD patients. They showed that a dietician-reinforced lifestyle intervention, which included advice for diet and required participation in moderate intensity exercise 3 times per week, was superior to general recommendations to lose weight for 12 months. While the effect is proportional to the degree of weight loss, a substantial proportion of patients with weight loss of 3% or more have a remission of NAFLD [40]. Previous studies reported that even without weight loss, Mediterranean diet reduces liver steatosis and improves insulin sensitivity in an insulin-resistant population with NAFLD [41–43]. It is reported that the effect of the Mediterranean diet is gradual and favorable and is independent of other lifestyle changes [43]. The authors of a UNESCO report noted that the Mediterranean diet is a set of traditional practices, knowledge, and skills passed on from generation to generation, providing a sense of belonging and continuity to the concerned communities [44]. Some studies have reported that the traditional diets, which include a high proportion of vegetables, could reduce incidence of chronic diseases and promote health and life expectancy in older people [45]. To the best of our knowledge, this is the first clinical trial on the effects of a TPM-based diet and nutritional style on NALFD. But we compared this study with other studies in which evaluation had been made of diet, though the diet and the resulting weight reduction had not been related to TPM. The result of our study was compatible with previous study results: both TPM diet and low-fat, low-calorie diet could reduce patients' weight and also could improve biochemical markers and sonographic fatty liver grade. The main difference between this study and previous studies was this study's use of the TPM diet to cause weight loss. This diet originates from TPM. Also, TPM is a complementary and alternative medicine branch and is based on humoral theory [14, 34]. In this diet, mostly cold-natured foods such as dairy and pickles are restricted; instead, taking hot-natured foods and spices is to be increased. Ardekani *et al*. demonstrated that the opinions of traditional philosophers about temperaments have a strong scientific fundament in modern medicine [46]. Panchal, in her thesis, explained the potential health benefits of traditional spices in the symptoms of metabolic syndrome and nonalcoholic steatohepatitis [47].

Limitation

Even with the randomized controlled trial design in our study, we had some limitations that should be pointed out to achieve a consistent perspective of our trial's results. The small sample size was the main problem in our study. Another important limitation was the lack of more accurate objective indices, such as liver biopsy, for the assessment

of patients' fatty liver grade. However, due to the ethical considerations, it was difficult to take liver biopsies. In addition, this study was an open-label study that might possibly have some bias. Although designing a placebo arm for such a study may not be possible, the absence of the placebo comparator arm is another methodological problem in this study.

Conclusion

This randomized open-label controlled clinical trial demonstrated that a traditional Persian medicine-based diet, used as a non-pharmacological remedy, could reduce body weight and improve fatty liver grade in patients suffering from nonalcoholic fatty liver disease.

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Conflict of Interest

The authors declare that they have no competing interests and anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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