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Lifestyle Modification through Dietary Intervention: Health Promotion of Patients with Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Background: Prevalence of non-alcoholic fatty liver disease (NAFLD) is more common worldwide and no certain treatment apart from lifestyle modification has been established yet. Available data consistently show that energy intake is significantly higher in patients with NAFLD than in individuals with no evidence of fatty liver. Changing nutritional behaviors seems to be the primary approach for treatment, simultaneously addressing all the clinical and biochemical defects. This study was aimed to examine the effects of two different composition of low energy diet (diet I *vs.* diet II) on non-alcoholic fatty liver disease patients.
Methods: In this double-blind randomized controlled trial, 44 ultrasonography-proven overweight non-alcoholic fatty liver disease patients were divided into two groups and received two low-energy diets (-500 kcal less than energy requirement individually) inc. diet I (Carbohydrate: Fat: Protein: 55:25:20) and diet II (Carbohydrate: Fat: Protein: 40:40:20) for six weeks. Anthropometric and biochemical measures as well as liver enzymes were assessed after 12 hours fasting.
Results: After diet I and diet II, weight decreased significantly (%1.82 and %2.45, respectively). Liver enzymes and echogenicity decreased significantly by both diet I and diet II. Mean of triglyceride concentration decreased (%18.09) after diet II (P=0.023), while there was no significant change after diet I. Significant correlations were found between changes in aspartate aminotransferase with triglyceride and LDL-C diet I.
Conclusion: Low energy diets can decrease liver enzymes regardless of their composition, while diet II seems to be more effective than diet I in reduction of weight and triglyceride level.
Keywords: Non-alcoholic fatty liver disease, Low energy diet, Obesity

Introduction

Modern societies nowadays have a life-style that is much different from our ancestors, probably as a result of cultural changes. This lifestyle is more sedentary combined with dietary indiscretion, which has contributed to the worldwide epidemic of obesity and non-alcoholic fatty liver disease (NAFLD). NAFLD is a clinicopathologic

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disease [1], with remarkably increasing not only in the western societies but also in developing countries parallel to increasing obesity [2-4].

NAFLD is characterized by lipid accumulation in the liver as well as overweight or obesity and underlying insulin resistance and is associated with lifestyle [5]. Therefore, therapeutic lifestyle modifications are strongly recommended for patients with NAFLD. Even when efficacious pharmacologic interventions are identified, lifestyle changes will likely represent an adjuvant treatment because new drugs are inevitably expensive and may have unanticipated adverse effects after prolonged use. These lifestyle modifications typically consist of both dietary intervention and physical activity goals. Unfortunately, the goal of regular physical activity is hard to be achieved in an environment of busy daily routines that seem to preclude time for exercise [6]. Therefore, it seems logical that dietary advice would form the cornerstone of therapy for these patients. Diet-induced weight loss would be expected to have a number of inter-related beneficial effects on NAFLD [7]. Lifestyle intervention with diet and increased physical activity result in weight loss, and improvement in liver enzymes as well as insulin resistance [8]. The overproduction of triglycerides in the liver especially during obesity may be associated with high intake of dietary carbohydrate [9, 10]. Evidence show that low-energy diets could reduce liver size and improve the function of liver by weight loss [11-15]. These types of diets could be based on either dietary guidelines or by manipulating the macronutrient percent from energy. For example, comparison between low-energy diets vs. low carbohydrate diet has shown greater weight loss with low carbohydrate diet [16, 17].

A clinical trial on five NAFLD patients has revealed that ketogenic (very low carbohydrate) diet over six months resulted in weight loss and histologic improvement of fatty liver disease [18]. It seems that usefulness and feasibility of such very restricted carbohydrate diet may be questionable for NAFLD; also, patient compliance seems to be very important [19]. However, being on a moderately low carbohydrate diet by reducing energy intake appears to be effective on pathogenesis of NAFLD by reducing the fat accumulation in the liver. On the other hand, dietary fat also influences the fat content of the liver; furthermore, increased triglyceride deposition in the liver may be a result of the excessive influx of free fatty acids [20,21], but which type of dietary interventions or changes in diet could alter liver fat is not clear.

In this study, we aimed to examine the effect of a non-pharmacological dietary intervention, namely hypocaloric diets with different composition in the management of liver steatosis and lipid profile in patients with NAFLD.

Materials & Methods

This study was a randomized controlled trial (registered code @ IRCT: IRCT138811203320N1) on 44 patients with NAFLD confirmed by ultrasonography and assessment of liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in 2008. Patients with liver diseases such as Wilson's disease, autoimmune liver diseases, hemochromatosis, hepatitis C virus infection and alcoholic fatty liver were excluded. In addition, patients with hepatotoxic drugs, lipid lowering and blood pressure medication, oral contraceptive pills and estrogen were excluded. The Ethics Committee of Tabriz University of Medical Sciences granted approval this research and informed consent was signed by all patients.

Anthropometric measurements inc. weight and height were assessed by the same trained assessor using scale (to the nearest 100g) and tape (to the nearest 0.5

cm) and body mass index (BMI) was estimated.

Habitual diet was assessed before the study using a food frequency questionnaire in order to design proper hypocaloric diet. Blood samples were obtained after 12-14 hours fasting at baseline. A detailed lipid profile (inc. total cholesterol (TC), LDL-C, HDL-C, lipoprotein a), ALT and AST were measured by enzymatic colorimetric assay. Ultrasonography was used for determining fatty liver for all patients by the same sonographist. Hepatobiliary ultrasonography was performed using Sonoace X4 Medison (South Korea) and the grade of echogenisity was defined based on Joseph A.E.A. et al. [22].

Hypocaloric diet was designed by estimating the energy requirements regarding the age, gender, ideal body weight, height and activity level. Patients were randomly allocated into two groups: (1) diet I (C:F:*P* 55:25:20) and (2) diet II (C:F:*P*: 40:40:20) that was given as eating plans with some substitutes for participants. The level of physical activity was defined as light, moderate and heavy and all subjects were asked not to change it over the study period.

All patients followed the prescribed diet for a 6 week period by receiving instruction to record their daily dietary intake for 3 days, including a weekend day. A trained dietitian handled dietary data, received and analyzed records with a computer-based data evaluative system using Nutritionist III software. Average nutrient intakes of 3 days were used for statistical analysis to confirm obeying the prescribed diet. All measurements and assays were repeated at the end of the study.

All continuous data were checked for normal distribution. T-student or Mann-Whitney U-test was applied for comparison of anthropometric and biochemical parameters between the two diets. While changes over time for each diet were tested using paired-*t* test and Wilcoxon test for systemic and asymmetric distributed continuous variables. *P* value less than 0.05 was defined as statistically significant.

Results

The mean age was 38.00±8.10 yr in diet I and 40.64±8.33 yr in diet II group. There was no significant difference between two groups in terms of age. Both groups were matched for demographic (Table 1), anthropometric and biochemical factors at baseline. As shown in Table 1, based on baseline data, both of the two intervention and control groups were similar and significant difference was not found between them.

Following diet I, there was a significant weight loss as well as reduction in ALT and AST concentration, and liver echogenicity.

Although the mean of triglyceride level decreased from 192.77 mg/dl to 172.95 mg/dl and level of HDL-C increased from 46.77 mg/dl to 48.59 mg/dl but the differences were not statistically significant. No significant changes were found for other lipid profile components after diet I. Diet II revealed a similar reduction in anthropomethric measures (82.45 kg to 80.34 kg for weight) as well as a reduction in ALT and AST levels. Triglyceride level reduced from 207.09 mg/dl to 167.27 mg/dl (*P*=0.023) (Table2).

Both diets resulted in improvement of liver steatosis as main outcome, (7 of 22 patients) (*P*=0.016), while total recovery was in 5 and 3 out of 7 patients in diet I and diet II consumers, receptively. The effect of two diets on weight and metabolic parameters was similar (Table 3). Significant correlations were found between changes in AST and triglyceride level (*r*=0.462, *P*=0.035) and LDL-C (*r*=0.497, *P*=0.022) in diet I consumers.

Table1: Demographic features of the two groups at baseline

	Diet I* **n (%)**	**Diet II**** **n (%)**	***P*†**
Male	12(54.5)	10(45.5)	0.670
Married	20(90.9)	22(100)	0.306
Up to High school education	12(54.5)	10(45.4)	0.831
Nonsmokers	16(72.7)	20(90.9)	0.459
Housewife	8(36.4)	10(45.5)	0.400
Employed	6(27.3)	10(45.5)	

* Diet I (C:F:*P* 55:25:20), **Diet II (C:F:*P*: 40:40:20)
†Independent samples t-test, *P* values <0.05 was considered as significant.

Table2: The effects of diet I and diet II on anthropometric and biochemical parameters and hepatic steatosis

		Diet I*			Diet II**		
		Before	**After**	***P***	**Before**	**After**	***P***
Weight(kg)		81.75±11.49	80.27±11.45	<0.001	82.45±11.90	80.34±11.04	<0.001
BMI† (kg/m^2)		28.99±2.72	28.45±2.57	<0.001	29.21±2.61	28.48±2.41	<0.001
Triglycerides (mg/dl)		192.77±97.34	172.95±77.98	0.172	207.09±79.28	167.27±93.95	0.023
Cholesterol (mg/dl)		194.68±39.63	190.77±27.33	0.596	191.59±32.33	191.59±29.44	1.000
LDL-C (mg/dl)		104.73±22.10	104.41±15.71	0.932	104.45±25.21	104.04±21.98	0.940
HDL-C (mg/dl)		46.77±7.90	48.59±7.94	0.214	48.36±10.78	49.68±8.69	0.496
Lipoprotein (a) (mg/dl)		34.67±16.28	35.67±16.51	0.227	34.65±14.14	33.40±13.76	0.251
ALT (IU/L)		35.86±20.34	26.77±12.45	0.020	38.05±16.62	29.14±13.50	0.009
AST (IU/L)		27.57±12.34	20.76±5.04	0.006	27.00±10.07	21.95±5.67	0.020
Grade of hepatic steatosis (n)	Grade 0	0	5	0.011*	0	3	0.014††
	Grade 1	15	11		11	14	
	Grade 2	5	6		11	5	
	Grade 3	2	0		0	0	

* Diet I (C:F:*P* 55:25:20), **Diet II (C:F:*P*: 40:40:20)
† BMI: Body Mass Index, LDL-C: Low Density Lipoprotein-Cholesterol, HDL-C: High Density Lipoprotein-Cholesterol, AST: Alanine Aminotransferase, AST: Aspartate Aminotransferase
*Paired samples t-test, Wilcoxon test, *P* values <0.05 was considered as significant.

Table 3: Mean and standard deviation of change (%) after diet I and diet II

	Diet I* **(%)**	**Diet II**** **(%)**	***P****
Weight(kg)	-1.82±1.32	-2.45±2.20	0.257
BMI † (kg/m2)	-1.82±1.32	-2.45±2.20	0.257
Triglycerides (mg/dl)	-3.41±33.47	-18.09±32.32	0.147
Cholesterol (mg/dl)	0.50±17.91	0.85±11.58	0.939
LDL-C (mg/dl)	2.12±17.14	3.84±27.84	0.805
HDL-C (mg/dl)	4.90±14.28	4.44±14.56	0.916
Lipoprotein(a) (mg/dl)	3.81±12.70	-2.60±12.16	0.107
ALT (IU/L)	-11.63±52.63	-18.06±33.65	0.640
AST (IU/L)	-2.99±89.63	-4.60±34.57	0.062

* Diet I (C:F:*P* 55:25:20), **Diet II (C:F:*P*: 40:40:20)

† BMI: Body Mass Index, LDL-C: Low Density Lipoprotein-Cholesterol, HDL-C: High Density Lipoprotein-Cholesterol, AST: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ALP: Alkaline phosphatase

*Independent samples t-test, *P* values <0.05 was considered as significant.

Discussion

NAFLD is associated with some components of metabolic syndrome and CVD risk factors. Over the past decade, it became apparent that NAFLD in some patients is a progressive disorder, leading to cirrhosis and liver failure [23]. Several studies have shown beneficial effects of dietary modification, weight loss and exercise in reducing insulin resistance and normalizing ALT in patients with NAFLD. Weight reduction through lifestyle modifications is usually recommended as the first-line therapy. However, the effectiveness and optimal treatment approach has yet to be defined [24, 25]. Low-calorie diet parallel to exercise and weight loss has been shown to have favorable effect on body composition [25-27].

In this RCT, diet I resembled to healthy diet, while diet II was similar to western diet. Six- week dietary intervention with diet I and diet II led to significant improvement in liver functional test as well as sonographic findings in patients with NAFLD. In our study, both low calorie diets resulted in a significant decrease of weight, liver enzymes and hepatosteatosis but the magnitudes of the effect of diet I and diet II treatment were similar not only for biochemical parameters but also for liver steatosis.

The number of studies that assessed the effect of diet therapy alone on liver histology is limited. But several studies have shown that low calorie diets can affect liver function tests favorably. De Luis et al. [3] found that a low calorie diet (1520 kilocalorie) could decrease AST and ALT levels on obese patients significantly. Indeed, a low calorie diet (25 kcal/ kg Ideal Body Weight) resulted in improving the liver enzymes by means of 1.6 kg weight loss for 8 weeks [28]. Our findings are similar to these data. This study also showed that both low calorie diets could decrease liver enzymes similarly, which may be due to low sample size in each diet. Ryan et al. [29], in a study on obese insulin-resistant patients showed a greater decrease in serum ALT concentration after diet II (45% of energy from fat) in comparison with diet I.

Weight reduction in the present study for both diets was less than other studies (1.82-2.45 kg over 6 weeks). Because of difference in the energy intake and intervention period among studies, it would be better to judge about the results after adjusting for study duration. De Luis

[3], Okita [27] and Yamamoto [30] showed 0.17 kg to 0.38 kg per week weight reduction, which are in agreement with our findings (0.25 kg/ wk). It was thought that great weight loss (to %10 body weight) results in improvements in liver enzymes, but it has recently been shown that even low weight loss (0.5-3.00 kg) could effectively improve liver functions [31].

Studies on the effect of diet therapy and specially macronutrient composition changes on hepatosteatosis are scarce. However, the effects of carbohydrates on the development of NAFLD differ depending on the carbohydrate type; increased hepatic fat is attributed to high-glycemic index foods in both rodents and humans [9]. Similarly, simple carbohydrates, such as fructose, increase fat deposition via stimulation of hepatic de-novo lipogenesis and reduction of lipid oxidation. The underlying mechanisms may involve the activation of transcription factors. Fat intake widely leads to hepatic fat deposition in rodents but few data are available on humans. Both carbohydrates and fat trigger inflammatory factors, which are closely related to metabolic disorders and NAFLD [9].

There is little information on how protein quantity, quality, and composition affect NAFLD. It is known that protein deficiency or malnutrition can cause steatosis [32, 33]. Considering that the total protein content and quality are typically high in the average American diet, protein deficiency is highly unlikely in NAFLD patients. Reversely, an excessive intake of protein may cause glomerular sclerosis, intrarenal capillary hypertension, and eventually renal malfunction in certain vulnerable individuals who have underlying renal insufficiency [34 –38]. Studies of high protein intakes and their possible effects on NAFLD are lacking.

Independent of dietary macronutrient composition, the present study showed that low-calorie diets can improve hepatosteatosis via improvement of insulin sensitivity and resulting depletion of liver triglycerides.

The strength of this study is the design as a randomized controlled clinical trial. This methodology in contrast to the previous studies can show the more accurate measure of the effect of the calorie and diet composition on NAFLD improvement and its complication. Low sample size and relatively short follow-up period seems to be the most important limitations for the present studies as they estimated sample size using the results of previous studies.

In conclusion, our study indicated that lifestyle modification through diet might affect hepatosteatosis. It established that hypocaloric diet was effective in lowering liver enzymes, improving lipid profile and anthropometric measures among NAFLD patients; moreover, diet II (Carbohydrate: Fat: Protein: 40:40:20) seems to be more effective than diet I in reduction of weight and triglyceride level as well as anthropometric measures and lipid profile in NAFLD patients. Further studies are warranted to evaluate the effects of dietary modification through macronutrient composition or calorie restriction on NAFLD.

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