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ORIGINAL ARTICLE

The effect of a fruit-rich diet on liver biomarkers, insulin resistance, and lipid profile in patients with non-alcoholic fatty liver disease: a randomized clinical trial

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ABSTRACT

Background: Despite confirmed dietary approaches to improve the Non-Alcoholic Fatty Liver Disease (NAFLD), the effect of fruits on NAFLD is not clear. The present study aimed to investigate the effect of a fruit rich diet (FRD) on liver steatosis, liver enzymes, Insulin resistance, and lipid profile in patients with NAFLD.

Methods: Eighty adults with NAFLD participated in this randomized controlled trial. The participants were randomly assigned to the FRD group with consumption of at least 4 servings of fruits daily or the control group with fruits consumption of less than 2 servings/day. The grade of steatosis, serum levels of liver enzymes including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), glucose, and homeostatic model assessment for insulin resistance (HOMA-IR) were measured at the baseline and at the end of the study.

Results: After 6 months of intervention, the FRD group had significantly higher BMI (31.40 ± 2.61 vs. 25.68 ± 2.54, $p < .001$), WC (113.5 ± 10.7 vs. 100.5 ± 7.5, $p < .001$), the grade of steatosis, ALT (89.1 ± 92.9 vs. 32.0 ± 19.2, $p < .001$), AST (74.5 ± 107.8 vs. 24.0 ± 8.5, $p < .001$), ALP (273.4 ± 128.5 vs. 155.0 ± 43.9, $p < .001$), GGT (92.7 ± 16.2 vs. 21.2 ± 7.7, $p < .001$), TC (206.1 ± 40.5 vs. 172.7 ± 42.4, $p < .01$), LDL (126.9 ± 32.3 vs. 99.8 ± 29.8, $p < .001$), glucose (115.5 ± 30.0 vs. 97.7 ± 19.0, $p < .01$), and insulin resistance (7.36 ± 4.37 vs. 2.66 ± 1.27, $p < .001$), and lower HDL (41.4 ± 8.9 vs. 53.8 ± 15.1, $p < .001$) compared to the control group. Adjusting for BMI and calorie intake did not change the results.

Conclusion: The results of the present study indicated that consumption of fruits more than 4 servings/day exacerbates steatosis, dyslipidemia, and glycemic control in NAFLD patients. Further studies are needed to identify the underlying mechanisms of the effects of fruits on NAFLD.

Clinical trial registration: This trial was registered at Iranian randomized clinical trial website with IRCT registration no. IRCT20201010048982N1on October 15, 2020.

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Non-alcoholic fatty liver disease; fruit; steatosis; insulin resistance

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is characterized by the accumulation of fat in the hepatic parenchymal hepatocytes at more than 5% of the liver weight, in people without a history of high alcohol consumption. NAFLD can lead to a variety of histological problems, from steatosis to inflammation, fibrosis, cirrhosis, and eventually liver cancer [1,2] Epidemiologic studies reported that NAFLD is the most prevalent liver disease with an estimated prevalence of 25% worldwide, and a highest rate in South America and the Middle East [3–5]. In recent years, the mortality rate from chronic liver diseases increased and it was 10th cause of death worldwide in 2019 [6–8]. It has been reported that the NAFLD along with fibrosis increases the mortality rate by 30% [9].

Currently, MR is gold standard to detect steatosis. Biopsy is gold standard for NASH. Since the liver biopsy is an invasive and expensive procedure, it is not suitable for general screening, and the other methods such as ultrasonography, computed tomography (CT), and magnetic resonance (MRI) may be used to evaluate the amount of liver fat [10]. Ultrasound is a tool for early detection of fatty liver disease, which is less sensitive and specific for grade 1 of steatosis compared to grade 2 and 3 of non-alcoholic fatty liver [11]. The sensitivity and specificity of ultrasound to detect hepatic fat content decreases in people with high body mass index (BMI) and increases with the high degree of fat penetration in the liver and BMI between 18.5 and 30 kg/m^2 [12,13]. At least 33% of steatosis is optimal for the diagnosis of NAFLD by ultrasonography. It is identified 33% of fat is from liver biopsy (Grade 1, 5–33%) but not 33%of fat is from MRI-PDFF [14].

The pathology and molecular mechanisms of NAFLD has not been yet well understood. Macro-vesicular steatosis is

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the result of high intake of dietary fat or increased hepatic synthesis of fatty acids [1]. Impaired regulation of fatty acids and consequent steatosis is mainly associated with elevated levels of insulin, which can make the liver more vulnerable to oxidative damage [15]. In addition, patients with NAFLD often suffer from other disorders such as hypertriglyceridemia and hypertension [16].

Diet is among the most critical risk factors for the onset, development, and treatment of NAFLD and its metabolic comorbidities. The dietary risk factors for NAFLD include high intake of saturated fatty acids (SFA), trans fatty acids (TFA), simple carbohydrates (CHO), sweetened beverages, and fructose [17]. Whereas reducing caloric intake and increasing the intakes of choline, soy protein, carotenoids and dietary anthocyanins can decrease the risk of NAFLD [18].

Fruit and vegetable consumption is well recognized to be inversely related to various insulin resistance-related illnesses. These results raise the question among researchers whether high consumption of fruits and vegetables can also prevent NAFLD. Fruits and vegetables are high in vitamins and minerals. Some vitamins and active compounds, such as B vitamins, phytochemicals, and polyphenols in fruits and vegetables, have been shown to have positive effects on NAFLD in some studies by exerting antioxidant and anti-inflammatory effects [19]. On the other hand, fruits and vegetables, are rich sources of soluble and insoluble fiber. Numerous studies have shown that high-fiber diets have preventive and therapeutic effects against NAFLD [20,21]. Also, it has been reported that some dietary patterns, such as the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet [22], which contain high amounts of fruits and vegetables, have shown positive effects against NAFLD [23]. Despite positive results in some studies, other studies had conflicting results. For example, one study in Korea found that only vegetables consumption, not fruits, was inversely associated with NAFLD prevalence. These findings are partly supported by studies using dietary pattern analysis: NAFLD prevalence was positively associated with a 'fruits' pattern [24,25]. One of the concerns about high fruit consumption is the high levels of fructose in the fruit, which has the ability to convert to fatty acids and aggravate NAFLD. Fructose has been shown to be involved in the pathogenesis of metabolic syndrome and fatty liver through various mechanisms [26]. So, the effect of different types of fruits on NFLD is not yet clear.

Observational studies have found conflicting results on the relationship between fruit consumption and NAFLD prevalence [25,27]. To the best of our knowledge, no clinical trial has studied the effect of a fruit-rich diet (FRD) on liver function in patients with NAFLD. This study aimed to evaluate the effect of FRD on liver steatosis, liver enzymes, insulin resistance, and lipid profile in patients with NAFLD.

Materials and methods

Study design and participants

A randomized controlled trial was performed to investigate the effect of the FRD for 6 months on NAFLD outcomes. The sample size was calculated according to the study of Cantero et al. on the effect of fruit fiber consumption on liver index (effect size = 0.05) [28] and the α and 1-β were considered equals to 0.05 and 0.90, respectively. Eighty people were recruited between October 2020 to March 2021 from patients with NAFLD referred to the gastrointestinal and liver clinic in Imam Khomeini University Hospital in Urmia, Iran. The written informed consent forms were collected from all participants before entering the study. The participants in the FRD group were recommended to consume at least 4 servings of fruits per day and the control group was asked not to consume more than 2 servings of fruit per day. Inclusion criteria were defined as age older than 18 years, BMI between 18.5 and 29.9 kg/m^2, and presence of grade 2 or 3 of NAFLD confirmed by a gastroenterology and liver specialist. Individuals with viral hepatitis, diabetes mellitus, mental disorders, not-treated hypothyroidism, renal diseases, heart failures, bone diseases, gastrointestinal diseases (such as celiac), alpha1-antitrypsin deficiency, history of alcohol consumption, using of nonsteroidal anti-inflammatory drugs (NSAIDs), cholesterol-lowering drugs (such as statins), phenytoin, carbamazepine, and barbiturates (such as phenobarbital), following a certain diet; pregnant and breastfeeding women, and as well as menopause women, and smokers (smoking more than 5 cigarettes/week), were excluded. Also, those who received less than 4 servings of fruits in the intervention group or more than 2 servings of fruits in the control group were excluded from the analyses. Totally, 32 males (16 in FRD group and 16 controls) and 40 females (20 in FRD group and 20 controls) participated in the study. Two participants lost to follow-up. In addition, 2 of them discontinued participating in the study. Four participants were excluded from the study due to low compliance.

The flowchart of participants' enrollment is presented in Figure 1. The stratified blocked randomization was performed by an independent statistician by the grade of NAFLD, age, and gender. A blinded person to the aims of the study and patients' baseline status assigned participants to the FRD and control groups using sealed envelopes. The category of fruits was based on colored fruits, dried fruits, and other fruits. To eliminate the effect of pesticides on NAFLD, participants were recommended to peel the fruits or consume after 20–30 min soaking in water. For the same consumption of other food groups, both groups were advised to follow the recommendations of the Food and Agriculture Organization (FAO) for Iranians [29].

At the baseline, data on gender, age, level of education, family size, duration of NAFLD (according to the patient's self-expression), physical activity, energy intake, type and dose of medication, herbal medicines and dietary supplements, marital status, place of residence, income, other chronic disease histories, and familial history of the disease was collected using a general questionnaire. Anthropometric measurements and ultrasonography were performed at the start and end of the study. Five mm of venous blood samples were also collected at the baseline and after the intervention to conduct biochemical assessments. To ensure the consumption of fruits within the recommended range, as

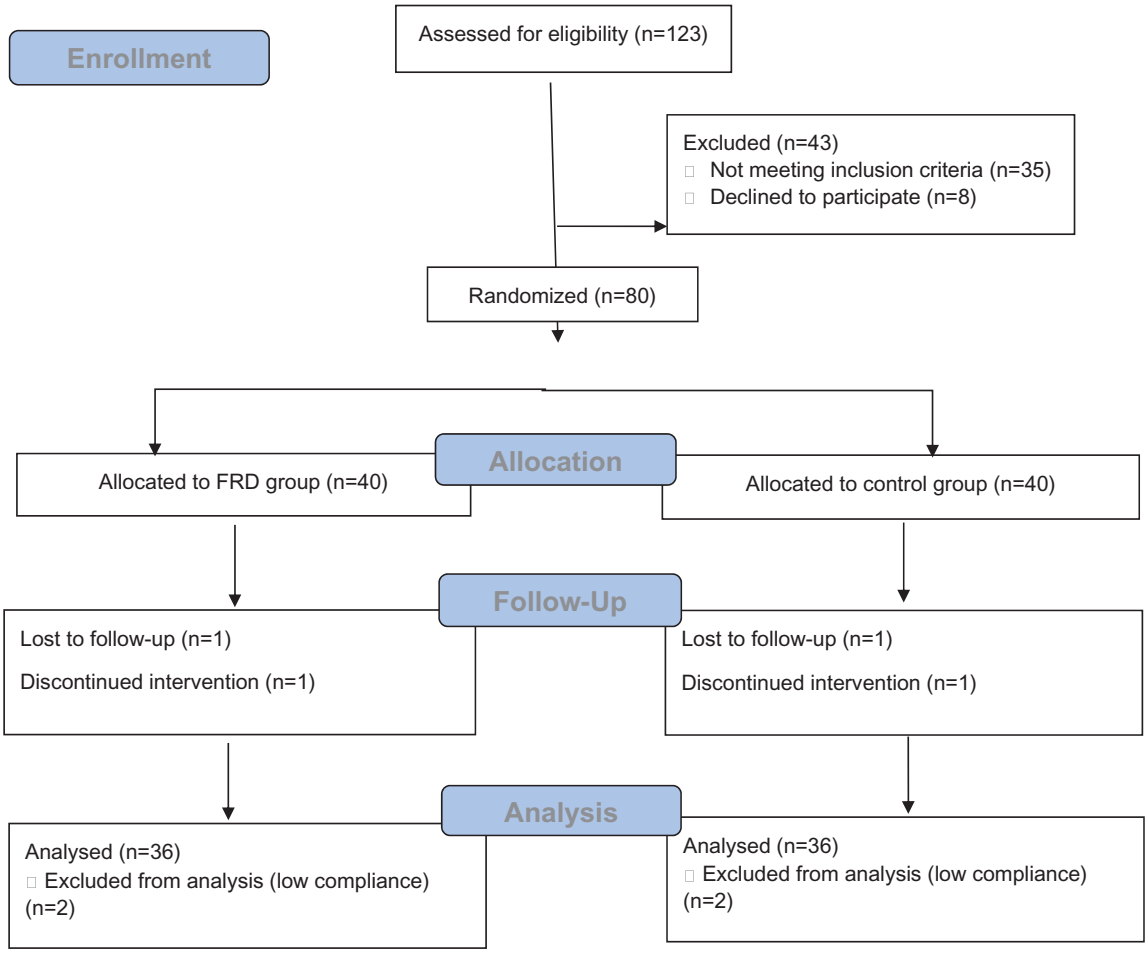

Figure 1. The CONSORT flow diagram of the study participants.

well as assessing of other food groups consumption, three 24-hours food recalls (two non-consecutive days and one day off) were taken from individuals each month. In addition, the physical activity was assessed using the international physical activity questionnaire (IPAQ) every month [30]. Patients were followed using phone call every week and the necessary reminders were made.

Biochemical assessments

The blood samples were collected at the baseline and end of the study between 7:00 and 9:00 am, after 12 h of fasting. Blood samples were centrifuged at 4000 rpm for 10 min and the isolated serums were stored at −80° C until biochemical analysis. Measurement of serum insulin levels was performed using the enzyme-linked immunosorbent assay (ELISA) kits (Pars Azmoon Co, Tehran, Iran). Serum concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL-c), high-density lipoprotein (HDL-c), Glucose, insulin were assessed using BT1500 autoanalyzer (Biotecnica Instrument SpA, Rome, Italy). The following formulas were used to calculate, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and Quantitative Insulin-Sensitivity Check Index (QUICKI):

$$\mathrm{HOMA-IR} = [(\text{Fasting Serum Glucose, mmol/L}) \times \text{Fasting Serum Insulin, } \mu\mathrm{IU/mL})]/22.5$$

$$\mathrm{QUICKI} = [1/(\log(\text{Fasting Serum Insulin}) + \log(\text{Fasting Serum Glucose}))]$$

Liver steatosis assessment

The liver condition was evaluated following at least 6 h of fasting by an experienced radiologist. To assess the severity of steatosis the ultrasonography (Siemens ACUSON S2000 Siemens Healthcare, Erlangen, Germany) was performed with previously described methodology [31]. The amount of fat accumulation is associated with an increase in the degree of echogenicity in ultrasound. Accordingly, steatosis was divided into 4 degrees: grade 0 with normal echogenicity, grade 1 or mild in which the echogenicity of the liver increases and the ability to see blood vessels and sound penetration in the liver tissue is normal, grade 2 or moderate in that the vascular wall are seen vaguely and the sound penetration is reduced, and grade 3 or severe, in which the arteries are

difficult to see and the sound penetration is very limited. Due to a lower sensitivity and specificity of ultrasonography in diagnosis of grade 1 steatosis, in the present study only people with grades 2 or 3 were recruited. Also, this method is most accurate at BMI between 18.5 and 30, so the participants were recruited in the same range. The size of the liver was also divided into large and normal by the radiologist based on its appearance.

Anthropometric measurements

A digital scale and stadiometer were used to assess the weight and height of the patients with a precision of 100 gr and 0.1 cm, respectively. Measurements were performed with the minimal dress and without shoes. To calculate the BMI, the weight (kg) was divided by the square of height (m^2). Waist Circumstance (WC) was measured using a flexible tape at the midpoint of the lowest rib and the iliac crest hip bone. All measurements were repeated 3 times, and the mean of measurements was used to confirm the test reliability.

Statistical analyses

Quantitative and qualitative variables were compared between the groups using independent sample t-test and chi-square and were presented as mean ± SD and frequency (%), respectively. Also, the paired sample t-test was used to compare the values before and after the study. To calculate the change of dietary intakes, baseline values were subtracted from mean intakes of each food groups throughout the 6 months. The normality of the quantitative variables was evaluated using the Kolmogorov–Smirnov test. Moreover, the repeated measure ANOVA was used to compare the change in dietary intake and physical activity in different time frames (baseline, 1st, 2nd, 3rd, 4th, 5th, and 6th months). The analysis of covariance (ANCOVA) was used to adjust the effect of change in energy intake (Model 1), further adjustments for change in bread and cereals, meats, vegetables, dairies, and oils intake (Model 2), and further adjustments for BMI change (Model 3). Statistical analyses were conducted using SPSS software version 25 (IBM Corp. IBM SPSS Statistics for Windows, Armonk, NY). The p-value $< .05$ was considered statistically significant.

Results

The baseline general characteristics of the participants are presented in Table 1. The mean age of the participants was 46.25 ± 9.80 years. No significant difference was found between age, education status, family size, duration of disease, gender, and marital status between the intervention and control groups ($p > .05$).

Table 2 presents the dietary intake and physical activity of the participants during the study. At baseline, both the intervention and control groups received fewer calories than they required per kilogram of body weight (1900.98 ± 160.37 vs. 1624.93 ± 163.97 kcal/d). During the study, the mean ± SD intakes of fruits in the FRD and control groups were 6.96 ± 0.61 and 1.65 ± 0.17 serving/day, respectively. At the end of the study, there was a significant increase in fruits ($p < .001$), bread and cereals ($p < .001$), meats ($p = .002$), vegetables ($p = .01$), dairies ($p = .001$), fats and oils ($p < .001$), and energy intake ($p < .001$) and a significant decrease in sugars intake ($p = .001$) compared to the baseline in the FRD group. In the control group, a significant decrease in fruit intake ($p < .001$) and increase in the intake of bread and cereals ($p < .001$), meats ($p = .015$), vegetables ($p < .001$), dairies ($p < .001$), sugars ($p < .001$), fats and oils ($p < .001$), and energy intake ($p < .001$) was observed after 6 months compared to the baseline. Regarding to the change of dietary intake during the study, between-group analysis identified that the FRD group compared to the control group consumed more daily servings of fruits (+3.59 vs. −.95, respectively, $p < .001$) and less daily servings of sugar (−1.93 vs. +0.46, respectively, $p < .001$). In contrast, a higher intake of vegetables was observed in the control group, compared to the FRD group (+2.29 vs. +0.75, respectively, $p < .001$). The mean change of other food groups and energy were not significantly different between two groups. There was no difference in physical activity change between two groups during the study ($p = .792$) (Figure 2).

Table 3 presents comparison of the mean ± SD of the liver enzymes between two groups at the baseline and end of the study. At the end of the study, there was a significant increase in the serum levels of ALT, AST, ALP, GGT compared to the baseline in the FRD group ($p < .001$). In contrast, there was a significant decrease in all liver enzymes in the control group after the study compared to the baseline ($p < .001$). After 6 months, the FRD group had higher serum levels of ALT, AST, ALP, and GGT compared to the control group. Adjustments for the effect of change in BMI, energy, bread and cereals, meats, vegetables, dairies, sugars, fats, and oils intake did not change the results.

Regarding to lipid profile, the FRD group had higher levels of TG ($p < .001$), total cholesterol ($p < .001$), and LDL-c ($p < .001$), and a lower level of HDL-c ($p < .001$) after 6 months of intervention compared to the baseline. In the control group, a decrease in TG ($p = .003$), TC ($p < .001$), and LDL-c ($p < .001$) and an increase in HDL-c ($p < .001$) was observed after 6 months of intervention compared to the baseline. Between-groups analysis showed that the FRD group had a higher level of TG ($p < .001$), total cholesterol ($p = .001$), and LDL-c ($p < .001$) and lower levels of HDL-c ($p < .001$) at the end of the study compared to the control group. However, the difference between the two groups in the LDL-c was not significant after adjusting for changes in BMI ($p = .17$). Adjustment for changes in energy and dietary intake and BMI did not change the results for the other variables.

In terms of glycemic profile, a significant increase was found in the serum glucose ($p < .001$), insulin ($p < .001$), and HOMA-IR ($p < .001$) and a significant decrease was found in QUICKI ($p < .001$) in the FRD group after the intervention compared to the baseline. The control group had a significant reduction in the glucose ($p < .001$), serum insulin

Table 1. General characteristics of the non-alcoholic fatty liver disease participants.

Variable	Total ($n = 72$)	FRD[a] ($n = 36$)	Control ($n = 36$)	p[b]
Age (years)	46.25 (9.80)	47.39 (10.29)	45.11 (9.28)	.33
Education (years)	7.71 (5.14)	7.50 (5.15)	7.92 (5.20)	.73
Family size (numbers)	4.29 (1.22)	4.39 (1.29)	4.19 (1.16)	.50
Disease duration	3.53 (1.65)	3.39 (1.55)	3.67 (1.75)	.48
Monthly income (Million Tomans)	3.42 (0.99)	3.14 (0.79)	3.69 (1.09)	.02
Gender				
Female	40 (55.6)	20 (55.6)	20 (55.6)	1.00
Male	32 (44.4)	16 (44.4)	16 (44.4)	
Marital status				
Married	71 (98.6)	36 (100)	35 (97.2)	1.00
Single	1 (1.4)	0 (0.0)	1 (2.8)	
BMI (kg/m^2)				
Baseline	28.07 (2.26)	28.37 (2.09)	27.78 (2.43)	.27
6th month	28.54 (2.57)	31.40 (2.61)	25.68 (2.54)	<.001
WC (cm)				
Baseline	108.4 (9.65)	10.9.7 (11.3)	107.1 (8.0)	.28
6th month	107 (9.1)	113.5 (10.7)	100.5 (7.5)	<.001

Data are presented as mean (SD) for quantitative and frequency (%) for qualitative variables. [a]FRD, fruits rich diet; [b]Calculated using independent sample t-test or chi-square.

($p < .001$), and HOMA-IR ($p < .001$), and a significant increase in the QUICKI ($p < .001$) at the end of the study compared to the baseline. Following 6 months of intervention, the FRD group had a higher glucose, serum insulin, and HOMA-IR and a lower QUCKI compared to the control group. The between-groups difference in the glucose was not statistically significant after adjusting for BMI changes ($p = .06$). Other results were not changed after adjustment for changes in energy and dietary intakes and BMI.

Regarding to the effects of the intervention on anthropometric measurements, the results showed a significant increase in weight, BMI, and WC in the FRD group after 6 months of intervention compared to the baseline ($p < .001$). The control group had a significant decrease in all of these variables ($p < .001$). At the baseline, there was no difference between the two groups in weight ($p = .82$), BMI ($p = .35$), and WC ($p = .10$). However, at the end of the study the FRD group had a higher weight ($p < .001$), BMI ($p < .001$), and WC ($p < .001$).

Figure 3 shows the frequency of subjects with a mild, moderate, or severe grade of steatosis in two groups. Before study (Figure 3(A)) there was no difference between groups in the grade of steatosis. After 6 months of the intervention, the frequency of severe and moderate steatosis was significantly higher in the FRD group (Figure 3(B)) ($p < .001$).

As shown in Figure 4(A), there was no significant difference in the size of the liver before the study. At the end of the study (3B), most of the participants in the FRD group had a large liver, but the size of the liver in the control group was normal ($p < .001$).

Discussion

The present study investigated the effect of a fruit rich diet compared to the low-fruit diet on liver steatosis, lipid profile, glycemic control, and anthropometric measurements patients with in NAFLD. After 6 months of the intervention, exacerbation of steatosis, dyslipidemia, and glycemic disorders were observed in the FRD group. In contrast, patients in the low fruit diet gruop had an improvement in their condition.

There are limited randomized clinical trials on the relationship between fatty liver and fruit consumption. Cantero, I. et al. [28] reported that calorie restriction along with fruit fiber intake (≥8.8 g/day) improved fatty liver index, hepatic steatosis index, and serum levels of GGT, ALT, and AST in obese patients with NAFLD. In the mentioned study, in addition to intervention with fruit intake, the intake of fiber and energy and the distribution of macronutrients of total caloric value (40% carbohydrate, 30% protein, and 30% lipids in intervention group vs. 55% carbohydrate, 15% protein, and 30% lipids in control group) were also altered, and each of these changes could have an independent effect on fatty liver. In addition, the dietary habits were changed, with at least 7 meals/day in the intervention group compared to the 5 meals/day in the control group. Therefore, the observed changes cannot be attributed only to the intake of fruits.

There are other reports of improvements in hepatic function or lipids metabolism due to intake of specific compounds of fruits. Previous studies found the hepatoprotective effect of antioxidants including polyphenols, carotenoids, glucosinolates, and fibers [32–34]. For example, resveratrol, which is found in the family of plums and grapes, can increase the oxidation of fatty acids [35], and Quercetin is a flavonoid found in a variety of plants, including berries, had antioxidant activities [36]. Moreover, anthocyanins found in many fruits have shown some anti-liver damage activity in experimental studies [37]. Carotenoids are other substances that generally accumulate in the liver and can prevent liver damage. Also, due to the role of carotenoids in regulating the polarization activity of macrophages, they can prevent the formation and progression of nonalcoholic steatohepatitis (NASH) [38]. Despite this evidence, contradictory results have also been obtained in some studies. Fakhoury-Sayegh et al. [25] in a case-control study found that a fruit-rich dietary pattern (more than 2–3 serving/day of fruits and >20 gr/day of fructose) was directly related to NAFLD. Earlier, Kobayashi et al. [39] reported that people with fatty liver were more likely to eat fruits and sweets than people with diabetes. In addition, Xia et al. [40] found in a study on 27,000 people reported that consuming oranges seven times a week was associated with an increased risk of fatty liver.

Table 2. Comparison of dietary intakes and physical activity between FRD and control groups at the baseline and following intervals[a].

Variable[b]	FRD ($n = 36$)	Control ($n = 36$)	p[c]
Total fruits (servings/day)			
Baseline	3.37 (1.16)	2.61 (1.17)	.007
1st month	7.27 (1.28)	1.64 (0.40)	<.001
2nd month	7.23 (1.43)	1.60 (0.47)	<.001
3rd month	6.88 (1.35)	1.51 (0.46)	<.001
4th month	7.09 (1.59)	1.75 (0.40)	<.001
5th month	6.64 (1.12)	1.61 (0.42)	<.001
6th month	6.66 (0.76)	1.81 (0.37)	<.001
Change[d]	3.59 (1.26)	−0.95 (1.19)	<.001
p[e]	<.001	<.001	
Colored fruits (servings/day)			
Baseline	1.61 (0.47)	1.43 (0.50)	.126
1st month	2.15 (1.53)	0.53 (0.56)	<.001
2nd month	3.11 (1.85)	0.70 (0.80)	<.001
3rd month	2.70 (1.44)	0.36 (0.54)	<.001
4th month	3.20 (2.34)	0.94 (0.78)	<.001
5th month	4.03 (1.61)	1.26 (0.67)	<.001
6th month	4.93 (1.50)	1.56 (0.59)	<.001
Change	1.74 (1.14)	−0.53 (0.56)	<.001
p[d]	<.001	<.001	
Dried fruits (servings/day)			
Baseline	0.65 (0.49)	0.44 (0.47)	.071
1st month	2.61 (2.11)	0.20 (0.50)	<.001
2nd month	2.20 (1.93)	0.31 (0.54)	<.001
3rd month	2.24 (2.03)	0.21 (0.43)	<.001
4th month	1.88 (2.05)	0.31 (0.46)	<.001
5th month	1.49 (1.36)	0.11 (0.29)	<.001
6th month	1.04 (1.08)	0.19 (0.40)	<.001
Change	1.26 (1.14)	−0.21 (0.55)	<.001
p[d]	.056	<.001	
Other fruits (servings/day)			
Baseline	1.11 (0.54)	0.73 (0.62)	.009
1st month	2.45 (2.61)	0.90 (0.74)	.001
2nd month	1.84 (1.94)	0.64 (0.79)	.001
3rd month	1.96 (1.98)	0.83 (0.61)	.002
4th month	1.91 (2.39)	0.47 (0.56)	.001
5th month	1.12 (1.49)	0.27 (0.48)	.002
6th month	0.89 (1.48)	0.07 (0.27)	.002
Change	0.59 (1.29)	−0.20 (0.61)	.002
p[d]	.023	<.001	
Cereals (servings/day)			
Baseline	8.81 (1.26)	8.47 (1.00)	.201
1st month	10.54 (1.25)	10.64 (1.51)	.757
2nd month	10.31 (1.36)	10.06 (1.36)	.448
3rd month	10.80 (1.48)	10.40 (1.19)	.213
4th month	10.64 (1.52)	10.22 (1.46)	.235
5th month	10.37 (1.51)	10.40 (1.06)	.924
6th month	10.44 (1.27)	10.17 (1.15)	.351
Change	1.70 (1.44)	1.84 (1.16)	.637
p[d]	<.001	<.001	
Meats and poultry (servings/day)			
Baseline	4.31 (0.68)	4.41 (0.79)	.581
1st month	5.30 (1.34)	5.29 (1.14)	.973
2nd month	4.98 (1.31)	4.95 (1.05)	.918
3rd month	5.34 (1.36)	5.05 (1.48)	.388
4th month	5.48 (1.27)	4.76 (1.30)	.020
5th month	5.37 (1.37)	4.66 (1.26)	.028
6th month	4.90 (1.23)	4.81 (1.03)	.737
Change	0.91 (1.03)	0.50 (0.93)	.085
p[d]	.002	.015	
Vegetables (servings/day)			
Baseline	4.48 (1.12)	3.02 (1.69)	<.001
1st month	5.03 (1.18)	5.35 (1.21)	.257
2nd month	5.43 (1.14)	5.22 (1.25)	.462
3rd month	5.11 (1.02)	5.62 (1.14)	.050
4th month	5.36 (1.06)	5.38 (1.20)	.935
5th month	5.20 (1.16)	5.04 (1.12)	.574
6th month	5.28 (1.12)	5.31 (1.45)	.922
Change	0.75 (1.06)	2.29 (1.73)	<.001
p[d]	.010	<.001	
Dairies (servings/day)			
Baseline	1.65 (0.48)	1.42 (0.60)	.081
1st month	2.16 (0.86)	2.36 (0.73)	.288
2nd month	2.31 (0.86)	2.06 (0.85)	.231
3rd month	2.17 (0.69)	2.25 (0.82)	.630
4th month	2.35 (0.84)	2.32 (0.84)	.901
5th month	2.19 (0.75)	2.53 (0.85)	.080
6th month	2.47 (0.78)	2.48 (0.86)	.978
Change	0.62 (0.76)	0.91 (0.75)	.109
p[d]	.001	<.001	
Sugars (servings/day)			
Baseline	5.18 (1.90)	2.88 (1.24)	<.001
1st month	3.12 (0.90)	3.31 (1.13)	.428
2nd month	3.40 (1.20)	3.49 (0.87)	.719
3rd month	3.34 (1.07)	3.05 (0.77)	.203
4th month	3.33 (1.02)	3.21 (0.82)	.589
5th month	3.23 (0.99)	3.33 (0.81)	.636
6th month	3.05 (1.04)	3.70 (0.82)	.004
Change	−1.93 (2.26)	0.46 (1.21)	<.001
p[d]	.001	<.001	
Fats and oils (servings/day)			
Baseline	4.22 (0.88)	4.13 (0.76)	.645
1st month	5.72 (1.03)	5.88 (1.07)	.527
2nd month	5.70 (1.12)	5.59 (1.16)	.678
3rd month	5.77 (1.00)	5.22 (1.21)	.042
4th month	5.45 (1.00)	5.58 (1.19)	.621
5th month	5.82 (0.94)	5.73 (1.06)	.707
6th month	5.38 (1.23)	5.59 (1.18)	.458
Change	1.42 (1.01)	1.47 (1.12)	.845
p[d]	<.001	<.001	
Energy intake (kcal/day)			
Baseline	1900.98 (160.37)	1624.93 (163.97)	<.001
1st month	2306.89 (213.50)	2018.60 (254.84)	<.001
2nd month	2321.2 (193.7)	1959.3 (221.7)	<.001
3rd month	2293.8 (169.7)	1955.8 (205.1)	<.001
4th month	2299.9 (193.9)	1968.0 (180.9)	<.001
5th month	2276.8 (185.6)	1981.4 (161.3)	<.001
6th month	2226.2 (207.5)	2024.5 (164.7)	<.001
Change	487.9 (623.9)	359. (179.3)	.240
p[d]	<.001	<.001	
Physical activity (METs.hr/day)			
Baseline	32.86 (0.93)	32.71 (0.78)	.471
1st month	32.91 (1.14)	32.59 (1.17)	.242
2nd month	32.44 (1.05)	32.50 (1.06)	.819
3rd month	32.52 (1.06)	32.66 (1.16)	.599
4th month	33.07 (0.96)	32.66 (1.08)	.093
5th month	32.81 (1.04)	32.66 (1.00)	.559
6th month	32.86 (0.87)	32.24 (2.20)	.122
Change	−0.09 (1.03)	−0.15 (1.14)	.792
p[d]	.131	.827	

[a]FRD, fruit-rich diet. [b]Data are presented as mean (SD). [c]Calculated using independent sample t-test. [d]The difference between baseline and mean of six values during study. [e]Calculated using repeated measure ANOVA to compare intakes during six months.

In the present study, the participants were not obese and no calorie restriction was considered. Since the weight loss is one of the first approaches in controlling fatty liver [3], it is probably important to consider the weight reduction of participants in addition to the other procedures or treatments to control NAFLD. In the present study, there was an increase in the BMI of the FRD group and a decrease in the control group. A cross-sectional study showed that controlling for the effect of BMI eliminates the association between fruit intake and NAFLD [41]. However, the present study showed that the main findings on the adverse effects of fruits in patients with NAFLD are independent from changes in the BMI, energy or other food group's intake. More clinical trials should investigate the interaction between fruit consumption and weight changes on the consequences of NAFLD.

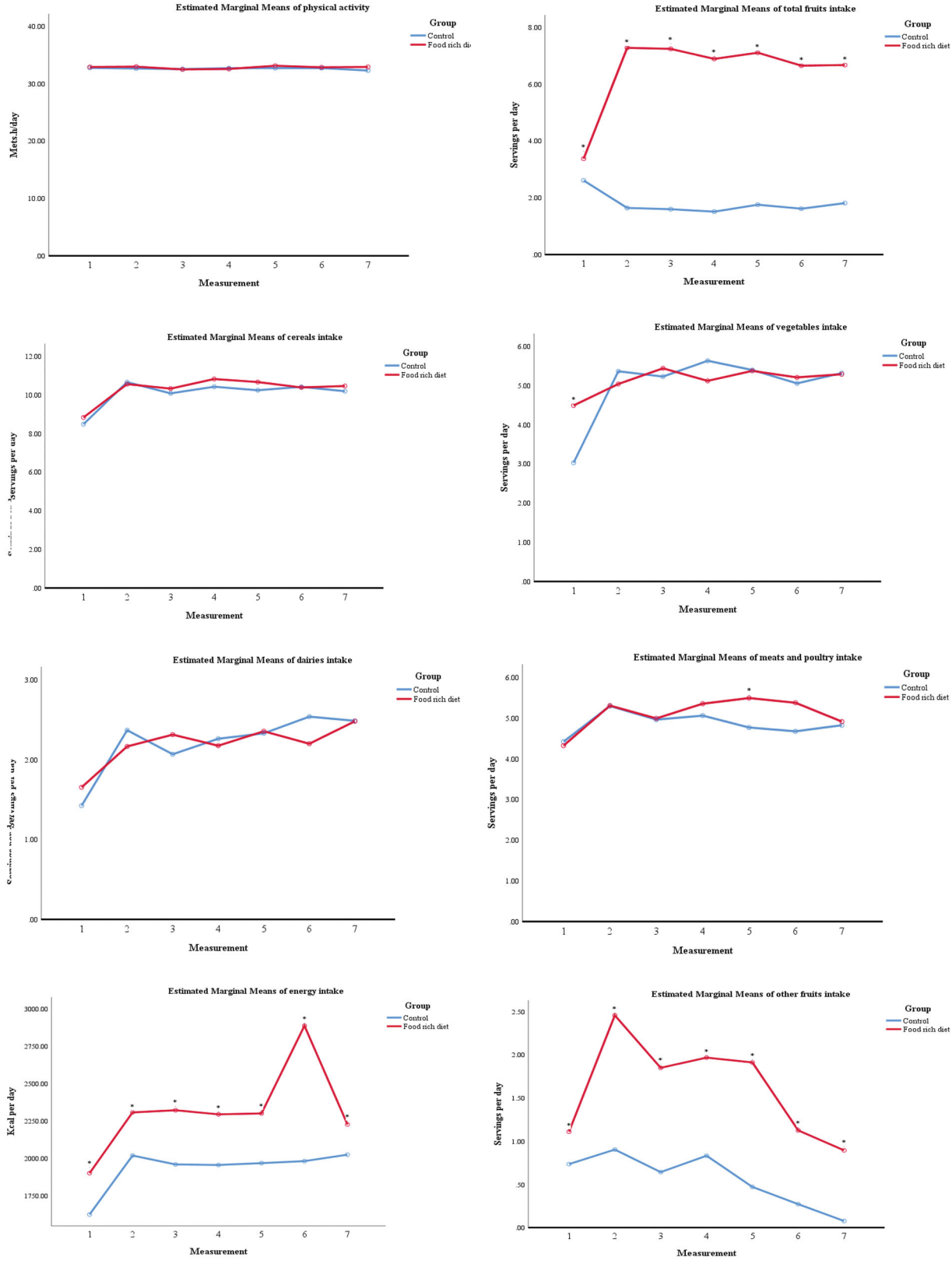

Figure 2. Dietary intake and physical activity of the participants during the study.

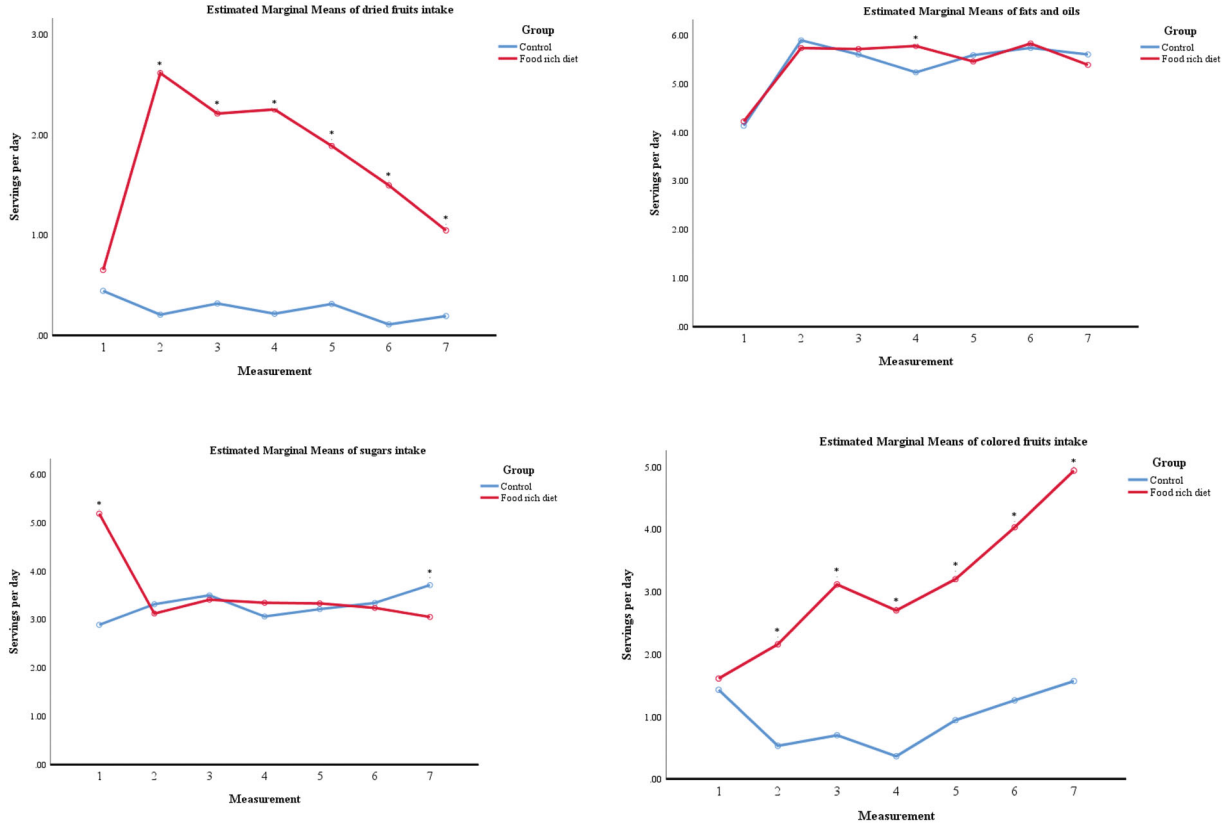

Figure 2. Continued.

On the other hand, some observational studies found a lower intake of fruits in patients with NAFLD [42]. However, dietary habits and eating behaviors are other important factors in NAFLD patients [43]. It is important to consider the intake of other food groups. In the present study, an increase of more than 2 servings/day of vegetable and about 0.5 serving of sugars and a decrease of about 1 serving/day of fruits were observed in the control group. In contrast, in the FRD group the intake of sugars decreased about 2 servings/day and an increase was observed in the consumption of fruits and vegetables 3.6 and 0.75 servings per day, respectively. Although some beneficial effects of reduced fruit intake could attributed to increased intake of vegetables [5]. Fruit consumption may play a more important role in the accumulation of fats in the liver in FRD group due to the lipogenic potential of fructose which can downregulate the fatty acids oxidation compared to the glucose. There is an evidence that fructose leads to a greater increase in liver fat content than glucose [44]. Decreased fatty acid oxidation in skeletal muscle induces the free fatty acids flux to the liver, thereby increasing the hepatic fat deposition [45]. On the other hand, fructose may increase hepatic fat content through de novo lipogenesis from acetate [46]. After absorption, glucose is mainly metabolized by peripheral tissues, while fructose is transported directly to the liver. Due to the lack of feedback control, fructose is metabolized faster and enters the path of lipogenesis compared to the glucose [47]. Also, fructose induces lipogenesis more efficiently than glucose through upregulation of carbohydrate-responsive element-binding protein (ChREBP) and sterol regulatory element-binding protein 1c (SREBP1c) signaling pathways in the hepatocytes [48]. In addition, fructose may intensify bacterial growth in the small intestine, which increases endotoxin levels in the portal vein and can lead to inflammation the NASH [49]. Some studies indicated that fructose restriction decreases steatosis and serum levels of hepatic enzymes [50]. However, an inverse association between NAFLD and fructose intake was reported in a cross-sectional study [27].

To the best of our knowledge, limited studies investigated the effect of fruit intake on NAFLD outcomes. Clinical trial design, stratified randomization, including only grade 2 and 3 of NAFLD, limiting the participants to a range of BMI between 18.5 and 29.9 kg/m^2 (which eliminates the diagnostic bias of ultrasound), and controlling for the effect of changes in BMI, energy, and dietary intake are the strengths of the present study. However, some limitations should be noted. First, this study was performed on non-obese patients with grade 2 and 3 fatty liver and the results cannot be generalized to obese patients or patients with other grades of fatty liver. Second, the effect of fruits on NAFLD may be influenced by BMI. However, we adjusted the effects of BMI and calorie intake in different models. It is plausible to determine participants' fruit daily servings based on the individual energy requirement in future studies. Third, as with other nutritional studies, there is a probability of over-or under-reporting of dietary intake. Fourth, due to the lack of analysis of nutrients received by patients, it is not possible to determine which of the fruit components caused by the effects observed in this study. Further longitudinal studies on the effect of different components of fruits in NAFLD are needed

Table 3. Comparison of liver enzymes, lipid profile, and glycemic control between FRD and control groups at the baseline and after six months[a].

Variable[b]	FRD ($n = 36$)	Control ($n = 36$)	p[c]	Model 1[d]	Model 2[e]	Model 3[f]
ALT (IU/L)						
Baseline*	38.1 (25.3)	50.0 (35.7)	.02	0.03	0.029	0.01
6th month*	89.1 (92.9)	32.0 (19.2)	<.001	<0.001	<0.001	<0.001
Changes*	51.0 (83.3)	−18.0 (26.1)	<.001	<0.001	<0.001	<0.001
p[g]	<.001	<.001				
AST (IU/L)						
Baseline*	26.8 (11.0)	36.5 (19.8)	.01	0.01	0.01	0.01
6th month*	74.5 (107.8)	24.0 (8.5)	<.001	<0.001	0.01	<0.001
Changes*	47.7 (104.1)	−12.5 (16.8)	<.001	<0.001	0.01	<0.001
p[g]	<.001	<.001				
ALP (IU/L)						
Baseline*	189.4 (73.2)	211.1 (80.7)	.16	0.26	0.17	0.24
6th month	273.4 (128.5)	155.0 (43.9)	<.001	<0.001	<0.001	<0.001
Changes*	84.0 (95.9)	−56.1 (62.7)	<.001	<0.001	<0.001	<0.001
p[g]	<.001	<.001				
GGT (IU/L)						
Baseline*	40.8 (26.4)	55.9 (73.2)	.43	0.90	0.44	0.84
6th month*	92.7 (161.2)	21.2 (7.7)	<.001	<0.001	<0.001	<0.001
Changes*	51.9 (143.5)	−34.7 (70.8)	<.001	<0.001	0.04	<0.001
p[g]	<.001	<.001				
TG (mg/dl)						
Baseline	183.2 (100.8)	242.5 (109.6)	.02	0.01	0.03	0.20
6th month*	248.6 (125.0)	153.5 (84.4)	<.001	<0.001	<0.001	<0.001
Changes*	65.4 (123.6)	−88.9 (79.9)	<.001	<0.001	<0.001	<0.001
p[g]	<.001	.01				
TC (mg/dl)						
Baseline	174.6 (35.5)	209.4 (38.7)	<.001	0.01	<0.001	0.02
6th month	206.1 (40.5)	172.7 (42.4)	.01	0.01	0.01	0.01
Changes	31.6 (28.6)	−36.7 (35.9)	<.001	<0.001	<0.001	<0.001
p[g]	<.001	<.001				
LDL-c (mg/dl)						
Baseline	99.9 (29.4)	120.7 (29.3)	.01	0.01	0.01	0.06
6th month	126.9 (32.3)	99.8 (29.8)	<.001	0.01	0.17	0.01
Changes	26.9 (27.5)	−20.9 (27.4)	<.001	<0.001	0.01	<0.001
p[g]	<.001	<.001				
HDL-c (mg/dl)						
Baseline	50.4 (11.1)	42.1 (10.2)	.01	0.01	0.01	0.05
6th month	41.4 (8.9)	53.8 (15.1)	<.001	0.01	0.01	<0.001
Changes	−9.0 (8.0)	11.7 (11.5)	<.001	<0.001	<0.001	<0.001
p[g]	<.001	<.001				
glucose (mg/dl)						
Baseline	96.9 (9.4)	119.1 (49.9)	.01	0.01	0.01	0.03
6th month	115.5 (30.0)	97.7 (19.0)	.01	0.01	0.06	0.01
Changes	18.6 (25.7)	−21.4 (39.0)	<.001	<0.001	0.01	<0.001
p[g]	<.001	<.001				
Insulin (μU/ml)						
Baseline*	14.0 (5.7)	18.0 (14.1)	.13	0.19	0.11	0.99
6th month*	26.6 (15.9)	11.5 (6.4)	<.001	<0.001	<0.001	<0.001
Changes*	12.5 (15.3)	−6.5 (12.6)	<.001	<0.001	<0.001	<0.001
p[g]	<.001	<.001				
HOMA-IR						
Baseline*	3.32 (1.41)	4.92 (3.45)	.01	0.01	0.01	0.33
6th month*	7.36 (4.37)	2.66 (1.27)	<.001	<0.001	<0.001	<0.001
Changes*	4.03 (4.24)	−2.26 (3.13)	<.001	<0.001	<0.001	<0.001
p[g]	<.001	<.001				
QUICKI						
Baseline	0.32 (0.02)	0.31 (0.02)	.01	0.01	0.01	0.29
6th month	0.29 (0.01)	0.33 (0.02)	<.001	<0.001	<0.001	<0.001
Changes	−0.03 (0.02)	0.02 (0.01)	<.001	<0.001	<0.001	<0.001
p[g]	<.001	<.001				
Weight (kg)						
Baseline	79.4 (9.9)	78.2 (9.7)	.59	0.71	–	0.82
6th month	86.4 (9.5)	71.7 (10.2)	<.001	<0.001	–	<0.001
Changes	7.0 (3.0)	−6.5 (2.8)	<.001	<0.001	–	<0.001
p[g]	<.001	<.001				
BMI (kg/m^2)						
Baseline	28.37 (2.09)	27.78 (2.43)	.27	0.42	–	0.35
6th month	31.40 (2.61)	25.68 (2.54)	<.001	<0.001	–	<0.001
Changes	3.03 (1.36)	−2.09 (1.13)	<.001	<0.001	–	<0.001
p[g]	<.001	<.001				
WC (cm)						
Baseline	109.7 (11.3)	107.1 (8.0)	.28	0.65	–	0.10
6th month	113.5 (10.7)	100.5 (7.5)	<.001	<0.001	–	<0.001
Changes	3.9 (2.5)	−6.6 (5.0)	<.001	<0.001	–	<0.001
p[g]	<.001	<.001				

[a]FRD, food-rich diet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; TC, total cholesterol; TG, triglyceride; LDL-c, low-density lipoprotein; HDL-c, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; QUICKI, Quantitative Insulin-Sensitivity Check Index. [b]Data are presented as mean (SD). [c]Calculated using independent sample t-test. [d]Calculated using ANCOVA, adjusted for change in energy intake. [e]Calculated using ANCOVA, further adjustments for change in bread and cereals, meats, vegetables, dairies, and oils intake. [f]Calculated using ANCOVA, further adjustments for BMI change. [g]Calculated using paired sample t-test. *Log-transformed were entered into the analysis.

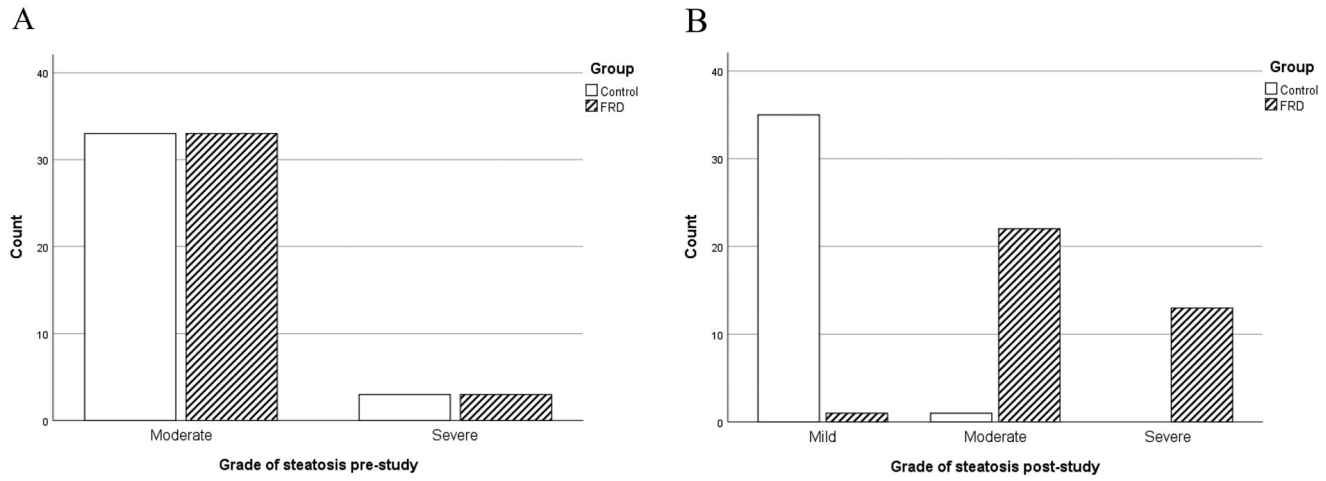

Figure 3. The grade of steatosis according to sonography in two groups before (A) and after (B) study. The *p*-value of difference between groups were 1.000 and <.001 at the baseline and after study, respectively.

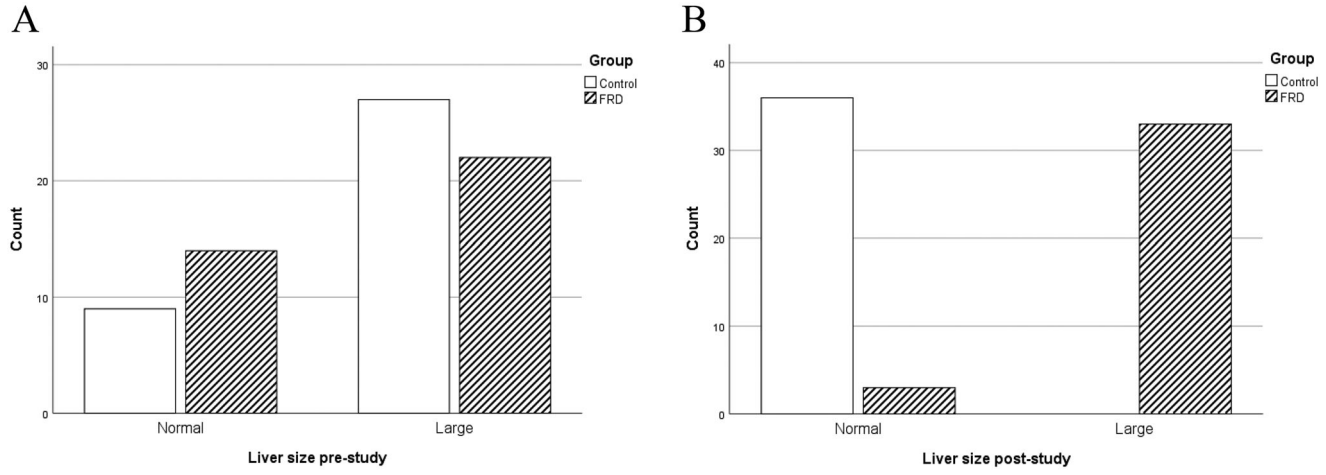

Figure 4. The liver size according to sonography in two groups before (A) and after (B) study. The P-value of difference between groups were 0.312 and <0.001 at the baseline and after study, respectively.

to confirm these finding and to identify the underlying mechanisms.

Conclusion

In conclusion, the present study found that 6 months of intervention with FRD exacerbated steatosis, dyslipidemia, and glycemic control of NAFLD patients. It is possible that excessive fruit consumption makes worse the condition of patients with fatty liver. According to the findings of the study, fruits intake increases the fat content of the hepatocyte probably through the lipogenic effect of fructose. To clarify the issue, more studies specifying a range for fruit intake (with minimum and maximum values) and considering obese patients and patients with different grades of fatty liver are warranted.

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Ethics approval and consent to participate

The present study was conducted following the deceleration of Helsinki and was approved by Ethics committee at the Urmia University of Medical Sciences, Urmia, Iran (Ethic number: IR.UMSU.REC.1398.535, Date: 02/03/2020).

Author contributions

The authors' responsibilities were as follows MA and FA: conceived and designed the study and collected of blood sample and analyzed the data; KS: provided material and technical support, FA: wrote the manuscript; MA: critically revised the manuscript for important intellectual content; all authors: read and approved the final manuscript.

Disclosure statement

The authors declare no competing interests.

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Availability of data and material

Datasets used and/or analyzed during the current study are available from the corresponding author on reasonable requests.

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