# Dietary Intervention in Clinical Improvement of Nonalcoholic Fatty Liver Patients

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**Abstract** Nonalcoholic fatty liver disease (NAFLD) is related to lifestyle practices including dietary intake and sedentary lifestyle. The common treatment is directed towards weight loss, which is usually difficult to be achieved or maintained. Therefore, a nutritional intervention program aiming at improving the metabolic health not only focusing on weight loss was conducted. Total of 110 patients referred to the hepatology outpatient clinic in the Main Alexandria University Hospital were selected based on ultrasound examination. Data about dietary intake, habits, and practices, and lifestyle practices were collected. Body composition measurements, laboratory investigations, clinical examination and measuring liver fat by ultrasound were assessed. A Mediterranean diet reduced in total carbohydrates, very low in refined sugars, rich in vegetables, moderate in fruits and low fat dairy, with more incorporation of fish, legumes, olive oil, nuts and seeds; was used for 12 weeks and different exercise advices were provided to patients. A significant reduction in the amount of liver fat, together with improvement in lipid profile, liver enzymes, blood pressure, fasting blood glucose and waist circumference were reported. The criteria of metabolic syndrome and gastrointestinal tract symptoms were improved among the majority of patients, with moderate reduction in body weight 5-6%. Liver fat content estimated by ultrasound was associated with the amount of dietary fat and carbohydrate intake, eating meals at irregular times, and unhealthy cooking methods. Nutrition intervention with Mediterranean diet has significant positive impact on metabolic health of NAFLD patients.

*Keywords: NAFLD, Mediterranean diet, liver enzymes, exercise, metabolic health, lifestyle, carbohydrates, follow up study*

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## 1. Introduction

Nonalcoholic fatty liver (NAFL) is an emerging disease worldwide and poses a heavy health-related cost burden to the liver as well as increased risks of other metabolic diseases. [1] The higher prevalence of nonalcoholic fatty liver diseases (NAFLD) was found to follow the increasing trends of obesity and diabetes worldwide. Its pathogenesis is not fully elucidated, and until now there is no effective treatment that addresses the progression of the disease; and the associated metabolic disturbances. [2] The adoption of sedentary lifestyle, and the consumption of energy dense diets were associated with central obesity, insulin resistance and other features of metabolic syndrome, as NAFLD is considered the liver presentation of metabolic syndrome. [3]

In Egypt, there is no national estimation of the prevalence of the disease. However, with the increased prevalence of overweight and obesity in Egypt, [4] the

poor quality of the Egyptian diet, [5] and the lack of physical activity, all constitute significant risks for many health conditions and chronic diseases. Indeed, the actual prevalence of NAFLD is difficult to estimate as it is generally silent and relying on different diagnostic modalities including liver enzymes, liver biopsy or radiological examinations, all can give different prevalence. [6] A successful management plan requires a multidisciplinary teamwork. However, the awareness of health risks of NAFLD and its complications is low in the general population, and the health risks are not properly diffused among non-hepatologists [7,8].

Evidence supports that dietary pattern may be related to the development of NAFLD. Therefore, dietary intervention could be beneficial in NAFLD treatment aiming at reduction of energy intake and weight loss. [9,10] However, there is no consensus regarding the best dietary intervention to treat NAFLD. Different dietary patterns [11,12,13,14] had been investigated as well as different dietary supplements. [15] However, the general guidance of the Mediterranean diet may be specifically beneficial in

patients with fatty liver and metabolic syndrome. This beneficial effect of Mediterranean diet goes beyond weight loss to further management of the metabolic disturbances and body fat distribution. [16]

Indeed, macronutrient composition is not the only determining dietary factor in intrahepatic triglycerides accumulation and the associated metabolic disturbances, but the frequency and timing of eating food has a role in the pathogenesis and in the treatment too. [13,14]

As the debate of different dietary treatment is not solved with different contribution of dietary macronutrients, and dietary practices and habits with the absence of an effective treatment strategy for NAFLD, an intensive nutritional intervention program aiming at improving the metabolic health of patients and not merely focusing on weight loss became a significant research issue.

## 2. Subjects and Methods

### 2.1. Study Design and Sampling

One group pretest posttest design was used to conduct this intervention study on 110 patients with mild to moderate nonalcoholic fatty liver disease (NAFLD) who referred to the outpatient Hepatology clinic in the Main University Hospital in Alexandria University over a period of two years from 2014 to 2016. All patients suffering from viral hepatitis, liver cirrhosis or fibrosis or other liver diseases, diabetes mellitus, chronic kidney diseases or endocrine disorders, cancers, or receiving hormonal or chemotherapy treatment were excluded from the study as well as pregnant or lactating females. Sample size was estimated based on a detectable change of 25% in liver fat before and after intervention (11.7±1.9% and 8.8±1.8%) [11] and using an effect size of 0.25 and a 5% error and 80% power, the resulting sample size was 110 patient. Patients' consent was obtained and all details of the study was explained to patients. Patient's identity and privacy was highly respected and all patients had the right to withdraw at any time.

### 2.2. Data Collection

#### 2.2.1. Initial Assessment

Initial interviewing of patients was conducted to collect data about patients' personal characteristics (sex, age, residence, education, and marital status) and lifestyle practices (daily sleeping hours and practicing exercise). Educational level was categorized into 3 groups, low, middle, and high.

Data about dietary habits and practices including eating breakfast, time gap between getting up and eating breakfast, times of eating meals, eating chicken skin/meat fat, type of dairy products, type of added fat, and number of coffee/tea cups per day was collected. Food frequency questionnaire was designed to assess the frequency of consumption of different foods and beverages. The frequency of intake of common dietary portions of 47 food categories has been assessed per day, per week or per month. Each patient was asked to keep a food diary for 3 non consecutive days of dietary intake of foods and drinks. A 24-hour dietary recall of food intake [17,18] was assessed for each patient to recheck accuracy of recording.

Using the Egyptian Food Composition Tables, [19] dietary intake data were evaluated and total intake of energy and macronutrients were estimated for each patient.

Based on Gibson, [20] patient's height and waist was estimated. Body weight and body composition was determined using In Body 270 Biospace body analyzer to determine body weight, fat mass, muscle mass, water content. Clinical assessment of patients including physical examination, blood pressure measurements, laboratory analysis that included evaluation of liver enzymes, lipid profile, fasting blood glucose and uric acid. [21]

Patients were subjected to abdominal ultrasound examination, and the amount of fat deposited in the liver was evaluated by the hepatorenal index (HRI). [22] By using a Toshiba machine (Japan) and scanning the right upper quadrant by a curvilinear probe with a frequency of 3.5-5 MHz. The Image J software was used for calculation of HRI (National Institutes of Health: rsb.info.nih.gov/ij/index. html). Using the Measure function, mean brightness is calculated within both the liver and the right kidney, excluding the central sinus fat. The average liver brightness was divided by the average kidney brightness to produce the HRI. This calculation was repeated at different levels for a total of three HRI values that were averaged to produce a final HRI value.

#### 2.2.2. Dietary Intervention Program

Each patient had received an individually prescribed balanced dietary regimen adapted from the Mediterranean Diet, [18,23] with moderate carbohydrate restriction (40-45% of total energy), dietary fat intake 35-40%, and protein intake 15-20%. Patients were followed every two weeks for a period of 3 months. Dietary advices were directed toward control of portion sizes and selection of food groups aiming at reduction of simple sugars, refined carbohydrates, and energy dense foods in addition to saturated fats.

The dietary intake of grains was controlled, 6-8 servings/day and where mainly whole grain cereals as whole grain bread. The main source of added fat in the diet was olive oil, 70 % of fat intake. The consumption of high fat dairy products as cheddar cheese and cream was discouraged. Also added butter did not exceed 5-10gm /day, while other types of added oils do not exceed 2 tablespoons, according to calorie deficit needed. The intake of seeds and nuts was allowed on daily bases. And 2 tablespoons of grounded flax seeds were recommended daily.

The consumption of vegetables was highly encouraged in each meal and snack. 8-10 serving /day of fresh and cooked vegetables was advised. The intake of fruits was controlled between 2-3 servings /day. No free consumption of fruits between meals and all varieties according to seasons were accepted, but in a controlled portions. Dairy consumption was allowed, with the choice of low fat types, and yogurt intake was recommended 2-3 times /day.

Patients were advised to never consume more than one type of cheese in one meal, eat fish 3 times /week, legumes 2-3 times /week, poultry 1-2 times /week, while red meat was restricted to once /month. Egg consumption was allowed 3/week.

To achieve a gradual weight loss for obese patients, a calorie deficit ranges from 500-800 kcal of the estimated daily energy requirement [24,25] has been used. In

patients with very high caloric intake the reduction of 800 calories was from their actual caloric intake to facilitate changes and obtain a gradual weight loss.

As for coffee intake, it was not specifically encouraged. The quality of coffee consumed, the timing of intake and the total amount were discussed with patients to ensure good quality with no effect on sleeping schedules. Using the brands that containing creamers were discouraged. All juices or carbonated beverages were not allowed. Tea and plant infusions were allowed. Also drinking water was encouraged by providing tips for changing the taste of water as adding lemon, mint, or apple slices. The prescribed diet was discussed with each patient in individual sessions that included discussions about dietary habits and practices. Each visit lasted for 45 minutes for each patient.

We used different descriptive photos and videos in the clinic to facilitate health education to the patients. Including, description of NAFLD causes and risks, the concept of healthy nutrition, food groups, and practicing exercise. Other healthy lifestyle parameters were emphasized including good sleep and stress management.

### 2.2.3. Physical Activity Instructions

According to each patient physical and clinical condition, physical activity was encouraged. Therefore, practicing physical exercises was discussed including a combination of moderate- to- high intensity exercises, as follows: [26] Aerobic exercises as walking, jogging, stair climbing or swimming 20 minutes to be increased gradually to 30 minutes, 5 days/week. Patients with knee problems were instructed to start exercise on a chair with the guidance of y-tube videos they watched in the clinic. Other patients without knee problems were instructed to walk every day 30 minutes with moderate intensity even at home, however, dancing or going to the gym were preferred for some young patients. For all patients, abdominal exercises were discussed with different modifications according to health condition as doing the exercise while standing or sitting or wall push-ups. Resistance training was discussed with patients using some weights from 500 grams to one kilo, to be performed 1-2 days per week. If dumbbells were unavailable, lifting a ball or a small bottle of water or the body weight as push-up on a wall was advised. Videos from y-tube were used as well as some applications that can be downloaded on smart phones to encourage some modification of exercise.

### 2.2.4. Follow up

Regular consultations for each patient were planned every 2 weeks for a duration of 3 months. In each visit, we assessed food intake by 24 hour recall. Also, each patient was asked to keep a record of any deviation of the dietary regimen, practicing exercise, and difficulties encountered. The feelings of fatigue, somnolence, and headache, bowel habits and different dyspeptic symptoms were assessed in each follow up visit. Blood pressure, abdominal waist circumference, body weight and body composition were measured. Practicing exercise and all types of physical activity was assessed and reinforced, also suggesting alternatives for difficulties encountered. Problematic dietary practices were discussed for each patient as breakfast eating, added sugar, coffee and tea drinking, late sleepers, long day workers and skipping meals.

By the end of the third month of follow up, patients were subjected to reevaluation of all parameters including dietary intake, clinical assessment, laboratory investigations and radiological examination. The Radiologists were kept blind as regarding patient identity in evaluating the HRI, as they were unaware whether the patient was initially evaluated or had completed the follow up period.

### 2.3. Statistical Analysis

Data management was conducted using the Statistical Package for Social Science (SPSS) version "20" software (Chicago, Illinois, US) for tabulation and analysis. Frequency tables and cross tabulations were used to present the results of categorical data and were analyzed using Chi Square Test or Fisher's Exact Test. Quantitative data were summarized by the arithmetic mean and standard deviation. Paired t-test was used to compare the data of 2 independent groups (means) before and after dietary intervention. For all analyses $P$ value $< 0.05$ was used to detect statistically significant difference. The changes in the blood pressure and anthropometric measurements were estimated using the following equation: (initial visit – next visit)/initial visit X 100. The readings of HRI were categorized, considering $\leq 1.2$ as normal. Improvement in the HRI was considered when there is a decrease in the level even if not reaching the normal value.

Two linear multiple regression analysis models; the enter and stepwise methods; were tested by using HRI as dependent variable to determine the factors that have significant impact on HRI before and after intervention.

## 3. Results

Table 1 shows the descriptive characteristics of the studied sample. A total of 110 NAFLD patients were participated in this study aged 42.25 ± 11.72 years. There were more females enrolled in the study, most patients were from urban area, married, and highly educated.

**Table 1. Descriptive characteristics of the studied sample**

| Variable | No (%) (n=110) |
|---|---|
| Sex | |
| Males | 43 (39.1) |
| Females | 67 (60.9) |
| Age (years) | |
| 20-40 | 53 (48.2) |
| 40-60 | 48 (43.6) |
| 60+ | 9 (8.2) |
| Mean SD[a] | 42.25 11.72 |
| Residence | |
| Urban | 84 (76.4) |
| Rural | 26 (23.6) |
| Marital status | |
| Married | 79 (71.8) |
| Single | 68 (28.2) |
| Education | |
| Low-Middle | 35 (31.8) |
| High | 75 (68.2) |

SD[a]: Standard deviation.

Table 2 shows the dietary and lifestyle habits and practices. As 71.0% of patients reported eating breakfast before intervention that increased to 92.7% and more patients were eating it earlier with follow up. Also, 38.2% of patients reported eating meals at fixed times before intervention, which increased to 42.7% with intervention. A significant decrease was detected in the intake of chicken skin/meat fat and full cream dairy products with follow up. Also, the type of added fat was changed, with reduction in the intake of butter/ghee, margarine, corn/sunflower oils, and cotton/soy oil; meanwhile, there was more incorporation of olive oil. The intake of coffee/tea was mainly moderate <2 cups among nearly half of the patients (47.2% before intervention and 57.35 after intervention). As for practicing exercise, before intervention only 17.3% of patients were practicing exercise and was mainly walking, that increased to 60.0% of patients with intervention. The majority of patients had sleeping hours from 6-8 hours.

Table 3 shows highly significant reduction in the mean intake of total energy, dietary carbohydrates, fat and protein after intervention. Carbohydrates constituted 53.18±9.85% of dietary energy intake before intervention, while after intervention it constituted 44.74±7.56% of intake. Meanwhile, the contribution of fat and protein to dietary energy intake after intervention were significantly increased. Table 3 shows also the results of biochemical blood analyses before and after intervention. Concerning liver enzymes, the mean level of AST and ALT decreased significantly with intervention. As for AST/ALT ratio, there was insignificant change in the mean level with intervention. While the mean level of GGT were decreased yet it was statistically insignificant. Concerning FBG, the mean level decreased after intervention with statistically significant difference. As for uric acid, despite the majority of the studied patients (82.0%) had normal blood level (2-6 mg/dl), the mean uric acid level decreased after intervention yet it was statistically insignificant. The table shows also the blood lipid profile before and after intervention. Total cholesterol, LDL, and TG levels had decreased significantly after intervention. High density lipoprotein (HDL) level was increased throughout intervention yet it was statistically insignificant.

Table 4 shows the clinical evaluation before and after intervention. Before intervention, patients were complaining of chronic fatigue, chronic headache, somnolence as well as different dyspeptic symptoms related to meals, constipation, and diarrhea that were significantly decreased after intervention. Also the metabolic syndrome criteria, [27] were present among 68.2% of patients before intervention that significantly decreased to 31.8% with intervention.

**Table 2. Dietary and lifestyle habits and practices (n=110)**

| Habits and practices | Before No (%) | After No (%) | *P*-value* |
|---|---|---|---|
| **Eating breakfast** | | | |
| Yes | 78 (71.0) | 102 (92.7) | 0.010 |
| No | 32 (29.0) | 8 (7.3) | |
| **Time gap between getting up and eating (hours)** | | | |
| ½ | 41 (37.4) | 61 (55.5) | 0.019 |
| 2- | 32 (29.0) | 39 (35.5) | |
| 3+ | 37 (33.6) | 10 (9.0) | |
| **Fixed times of meals** | | | |
| Yes | 42 (38.2) | 47 (42.7) | 0.005 |
| No | 62 (56.4) | 63 (57.3) | |
| **Eating chicken skin/meat fat** | | | |
| Yes | 29 (26.4) | 11 (10.0) | 0.000 |
| No | 81 (73.6) | 99 (90.0) | |
| **Dairy products consumption** | | | |
| Not consumed | 7 (6.4) | 1 (0.9) | 0.000 |
| Full cream | 61 (55.4) | 36 (32.7) | |
| Low fat/skimmed | 42 (38.2) | 73 (66.4) | |
| **#Type of added fat** | | | |
| None | 5 (4.5) | 5 (4.5) | |
| Butter / Ghee | 86 (78.0) | 56 (50.5) | |
| Margarine | 26 (23.6) | 13 (11.8) | 0.000 |
| Corn / Sunflower oil | 95 (86.4) | 45 (41.0) | |
| Olive oil | 17 (15.4) | 53 (48.2) | |
| Cottonseed /Soy oil | 15 (13.6) | 3 (2.7) | |
| Cream | 1 (0.9) | 1 (0.9) | |
| **Coffee/Tea (cups/day)** | | | |
| None | 12 (10.9) | 3 (2.7) | |
| ≤2 | 52 (47.2) | 63 (57.3) | 0.000 |
| 3- | 34 (31.0) | 37 (33.6) | |
| 5+ | 12 (10.9) | 7 (6.4) | |
| **Practicing Exercise** | | | |
| Yes | 20 (18.2) | 66 (60.0) | 0.012 |
| No | 90 (81.8) | 44 (40.0) | |
| **Daily Sleeping Hours** | | | |
| ≤5 | 34 (30.9) | 36 (32.7) | 0.001 |
| 6 | 67 (60.9) | 69 (62.8) | |
| 9+ | 9 (8.2) | 5 (4.5) | |

#Multiple responses, *P<0.05: significant, *P*- value based on Chi squared test

**Table 3. Daily intakes of energy and macronutrients and biochemical blood parameters before and after intervention**

| Item | Before | | After | | P- value* |
|---|---|---|---|---|---|
| | Mean SD[a] | | Mean SD | | |
| **Daily Intake** | | | | | |
| **Energy (kcal)** | 3252.65 | 1078.89 | 1998.31 | 669.24 | 0.000 |
| **Carbohydrate (g)** | 460.89 | 321.80 | 228.48 | 100.71 | 0.000 |
| **Fat (g)** | 114.63 | 50.07 | 77.71 | 29.26 | 0.000 |
| **Protein (g)** | 129.08 | 62.74 | 96.17 | 34.00 | 0.000 |
| **Contribution of macronutrients in energy (%)** | | | | | |
| **Carbohydrate** | 53.18 | 9.85 | 44.74 | 7.56 | 0.000 |
| **Fat** | 31.86 | 9.14 | 34.95 | 8.0 | 0.003 |
| **Protein** | 15.805 | 4.406 | 20.21 | 6.06 | 0.000 |
| **Biochemical blood parameters** | | | | | |
| **AST [b](U/L)** | 27.32 | 12.52 | 21.32 | 11.21 | 0.000 |
| **ALT[c] (U/L)** | 34.06 | 19.96 | 23.65 | 15.08 | 0.000 |
| **AST/ALT ratio** | 0.941 | 0.30 | 0.992 | 0.55 | 0.296 |
| **GGT[d] (U/L)** | 37.96 | 27.24 | 29.93 | 51.40 | 0.153 |
| **FBG[e] (mg/dl)** | 102.42 | 13.92 | 92.94 | 13.39 | 0.000 |
| **Uric Acid (mg/dl)** | 5.33 | 1.59 | 4.72 | 1.32 | 0.484 |
| **Total Cholesterol (mg/dl)** | 210.96 | 9.23 | 186.75 | 34.91 | 0.000 |
| **LDL[f] (mg/dl)** | 147.23 | 41.77 | 127.01 | 40.10 | 0.000 |
| **HDL[g] (mg/dl)** | 43.43 | 9.18 | 44.82 | 8.35 | 0.051 |
| **TG[h] (mg/dl)** | 145.55 | 77.68 | 112.71 | 54.01 | 0.000 |

SD[a]: standard deviation, aspartate aminotransferase (AST)[b], alanine aminotransferase (ALT)[c], gama glutamyl transferase (GGT)[d], fasting blood glucose (FBG)[e], low density lipoprotein (LDL)[f], high density lipoprotein (HDL)[g], triglycerides (TG)[h]. *P <0.05: significant, P- value based on Paired t test.

**Table 4. Clinical evaluation before and after intervention (n=110)**

| Clinical evaluation | Before No (%) | After No (%) | P-value* |
|---|---|---|---|
| **Chronic Fatigue** | 80 (72.7) | 35 (31.8) | 0.000 |
| **Chronic Headache** | 65 (59.0) | 30 (27.3) | 0.000 |
| **Somnolence after eating** | 62 (56.4) | 36 (32.7) | 0.006 |
| **Dyspepsia** | 62 (56.4) | 15 (13.6) | 0.003 |
| **Constipation** | 30 (27.3) | 13 (11.8) | 0.000 |
| **Diarrhea** | 20 (18.2) | 5 (4.5) | 0.000 |
| **Metabolic syndrome criteria** | | | |
| **Present** | 75 (68.2) | 35 (31.8) | 0.000 |

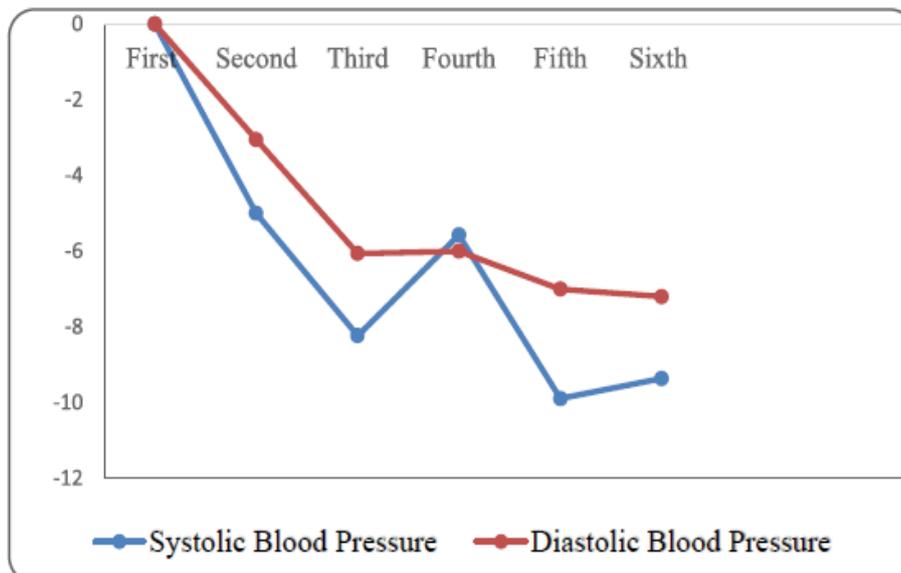*P<0.05: significant, P- value based on Chi squared test.



**Figure 1.** Percent changes in the mean levels of measured blood pressure with follow up
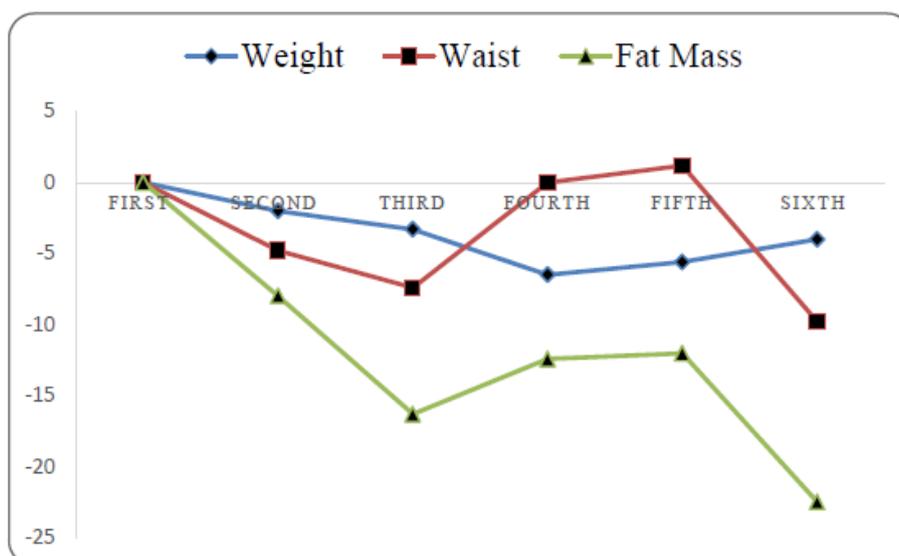
**Figure 2.** Percent changes in the mean values of measured body weight, waist, and body fat mass with follow up
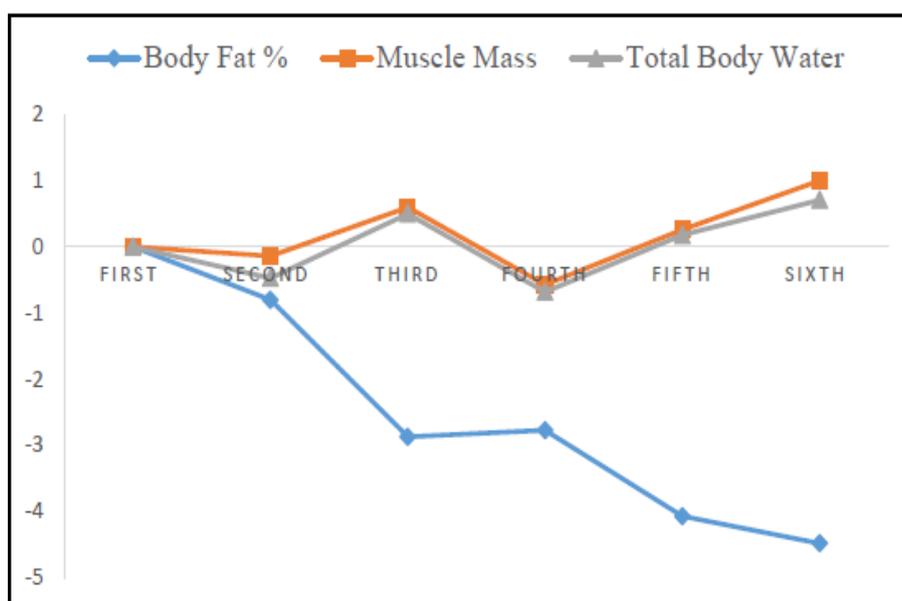


**Figure 3.** Percent changes in the mean values of measured body fat %, muscle mass and total body water with follow up

As shown in Figure 1, comparing the mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the initial visit (128.48/88.6 mm/Hg) with each follow up visit, there was a highly significant decreasing trend in recorded measurements (P=0.000).

Figure 2 shows the percent changes in the mean values of measured body weight, waist and body fat mass with follow up. A significant decreasing trend was detected in body weight and waist circumference from second to third visit (-2-3%) with slight increase detected in fourth and fifth visits. However, by reaching the sixth visit, marked decline was detected (-4-5%). As for changes in body fat mass, more decreasing trend was observed throughout the whole follow up experience (-12-13%), *p=0.000*.

Figure 3, shows the percent change in the mean values of measured body fat %, muscle mass and total body water with follow up. Slight changes had occurred in muscle mass and total body water, with one percent increase by the end of the sixth visit, meanwhile, much decrease was observed in body fat percent significantly.

Table 5 shows the Hepatorenal index before and after intervention. Before intervention, 43.2% of patients had HRI 1.4, 28.4% had HRI 1.6, 14.7% had HRI 1.8, and 13.7% of them had HRI 2+. While after intervention, 39.7% had normal HRI (≤1.2), 9.1% had HRI 1.6, 4.5% and 5.7% had HRI 1.8 and 2+ respectively, *p*=0.000. The mean value of HRI decreased from 1.48 ± 0.26 before intervention to 1.26 ± 0.29 after intervention which were highly significant changes, *p*=0.000.

**Table 5. Hepatorenal index (HRI) before and after intervention (n=88)**

| HRI | Before No (%) | After No (%) | *P*-value* |
|---|---|---|---|
| Normal (≤1.2) | 0 (0.0) | 35 (39.7) | |
| 1.4 | 38 (43.2) | 36 (41.0) | |
| 1.6 | 25 (28.4) | 8 (9.1) | 0.000 |
| 1.8 | 13 (14.7) | 4 (4.5) | |
| 2+ | 12 (13.7) | 5 (5.7) | |
| Mean SD | 1.48 0.26 | 1.26 0.29 | 0.000 |

*\*P<0.05: significant, P- value based on Chi squared test and paired t test.*

Figure 4 (a) before intervention, showing the liver markedly hyper-echoic (brighter) compared to the renal parenchyma, reflecting fatty liver (HRI=1.8). Figure 4 (b) after intervention, marked diminution of the hepatic echogenicity, which is only mildly hyper-echoic compared to the renal parenchyma (HRI=1.1).

Figure 5 shows the improvement in HRI with follow up. The HRI of only 30.0% patient did not improve while HRI of 70.0% patient was decreased.

Table 6 shows the results of the multiple linear regression analyses which revealed that before intervention, liver fat content estimated by ultrasound (HRI) was positively correlated with total blood cholesterol, ALT level, amount of dietary fat intake, and was significantly higher among males. Also, it was negatively correlated with eating meals at fixed times. While after intervention, HRI was positively correlated also with total blood cholesterol level, ALT level and amount of carbohydrate intake, while a negative correlation was detected with HDL, and healthy cooking methods.
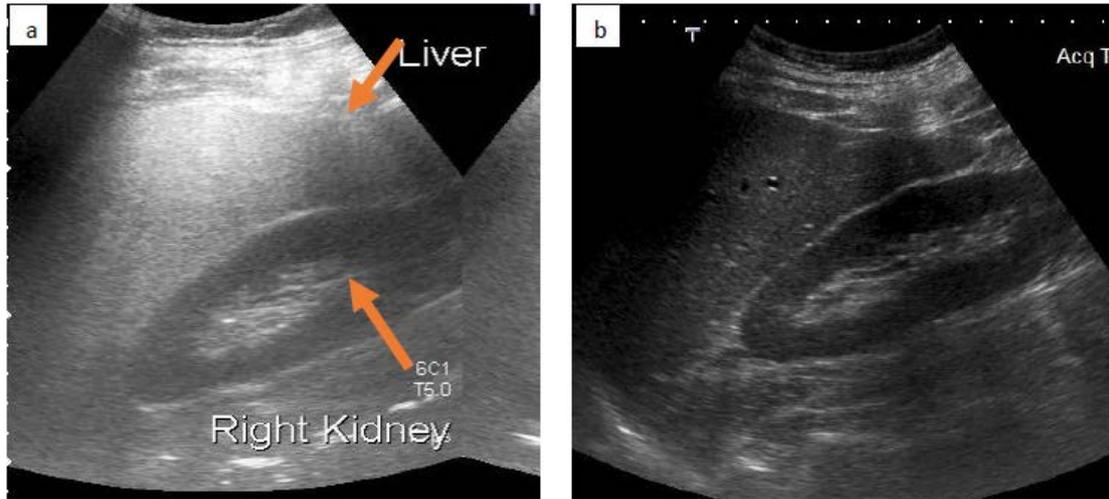


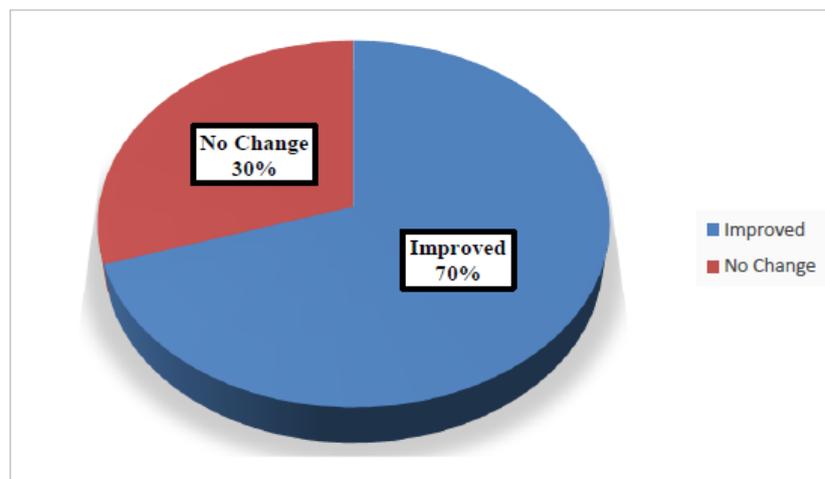**Figure 4.** (a-b) Ultrasound view of the right hypochondrium



**Figure 5.** The improvement of HRI with follow up

**Table 6. Multiple Linear Regression analysis using HRI[a] as dependent variable before and after intervention**

| Model | Unstandardized coefficients | | Standardized coefficients | t | *P*-value |
|---|---|---|---|---|---|
| | B | Std.Error | Beta | | |
| **Before intervention** | | | | | |
| **Total cholesterol** | 0.003 | 0.001 | 0.466 | 2.905 | 0.005 |
| **Dietary fat intake** | 0.002 | 0.001 | 0.317 | 2.271 | 0.026 |
| **ALT[b]** | 0.004 | 0.001 | 0.297 | 3.294 | 0.001 |
| **Male sex** | 0.146 | 0.046 | 0.29 | 3.209 | 0.002 |
| **Fixed times of meals** | -0.108 | 0.044 | -0.212 | -2.482 | .015 |
| **(R[2] = 0.445, *P* = 0.000\*)** | | | | | |
| **After intervention** | | | | | |
| **Total cholesterol** | 0.005 | 0.002 | 0.599 | 3.457 | 0.001 |
| **HDL[c]** | -0.01 | 0.005 | -0.257 | -2.196 | 0.034 |
| **Carbohydrate intake** | 0.001 | 0.000 | 0.352 | 3.385 | 0.001 |
| **Cooking method** | -0.327 | 0.115 | -0.299 | -2.833 | 0.006 |
| **ALT** | 0.005 | 0.002 | 0.235 | 2.315 | 0.024 |
| **(R[2] = 0.493, *P* = 0.000\*)** | | | | | |

Hepatorenal Index (HRI)[a], alanine aminotransferase (ALT)[b], high density lipoprotein (HDL)[c].

# 4. Discussion

The Mediterranean diet has been linked to better health and life expectancy over many years. [28] The association between adherence to the Mediterranean diet and NAFLD are in the focus of attention, as a number of reviews examined this association. [15,16,29] An inverse correlation was previously observed between following the principals of Mediterranean diet and ALT level, insulin levels, stage of fibrosis, and severity of steatosis in NAFLD. [30] Indeed, olive oil has been demonstrated to have several beneficial effects on metabolic syndrome and NAFLD. [31,32]

In the current study, we examined a diet based on the Mediterranean diet, with moderate decrease in carbohydrate, 40-45% of energy intake, and olive oil was the main source of added fat together with nuts and seeds. Our program was consistent with Rayn et al, [33] who had tested the effect of 2 types of diet on NAFLD patients. Mediterranean diet with 40% energy from fat mainly olive oil and plenty of omega-3 sources, 40% from carbohydrate, and 20% from protein, versus the American Heart Association Diet (AHA) [34] with 30% fat, 50% carbohydrate, and 20% protein. They got significant decrease in fatty liver (39.0%) detected by magnetic resonance spectroscopy, improvement in blood pressure levels, glycemic control, and waist circumference without significant weight loss of their patients, all within 3 months.

Indeed, changing the type of carbohydrate is very important issue, Misciagna et al. [35], documented that using a low glycemic Mediterranean diet has an inverse correlation with NAFLD progression, even without caloric restrictions. Changing the type and amount of carbohydrate with more inclusion of olive oil and omega-3 fats could be used as a guidance for health education of the public, thus helping them following healthy diet without strict medical supervision.

As suggested by the American Gastroenterological Association guidelines, [36] focusing on "Treating the patient" by lifestyle changes, including nutritional counseling and physical activity, and/or weight loss is worth studying as there is no one unified approach for all patients and diet needs to be tailored according to personal conditions. Initially, the mean intake of dietary carbohydrate was $53.18\% \pm 9.85$ of caloric intake, which was in concordance with the USDA dietary guidelines of carbohydrate intake of adults, as being in the range of 45-60% of intake. [37] However, previous studies confirmed that patients with nonalcoholic steatohepatitis (NASH), or with metabolic syndrome, were more likely consuming high carbohydrate (51.0%) and moderate fat content (34.0%) diets, [38] which could question the utility of dietary guidelines in NAFLD. Indeed, this was confirmed in the present study with the results of the regression analysis that revealed a significant and direct correlation between the amount of carbohydrate intake and the level of fatty liver estimated by HRI which signifies the importance of the quantity of carbohydrate intake in NAFLD treatment as the mean intake of carbohydrates decreased to 228.48 grams $\pm 100.71$ constituting $44.74\% \pm 7.56\%$ of intake after intervention.

The mean caloric intake of studied patients before intervention was higher than the caloric intake detected in other studies. [39] Indeed the increase in body weight can reflect this high energy intake, as the initial mean body mass index (BMI) was $36.75 \pm 6.29$ kg/m$^2$, which was in agreement of Mohemad et al., [40] (BMI=36.03±5.39kg/m$^2$), while much higher than BMI detected by Zelber-Sagi et al, [39] ($30.2 \pm 4.6$kg/m$^2$). Therefore, a moderate caloric restrictions were implemented, which is the standard practice in NAFLD patients care. [41,42,43]

Nutrition is not only nutrients, but it covers more than that. Eating breakfast was highly addressed in the study as healthy composition and timing of breakfast were positively changed with intervention. Although large percentage of patients reported eating breakfast before intervention, they were unaware of the proper timing, or composition of this meal. The patients were advised to eat breakfast as early as possible, and preferably at home, as a previous study [44] found that daily breakfast intake not exceeding 2 hours of getting up leads to greater physical activity during the morning, whereas eating after 12:00 PM resulted in partial dietary compensation with greater energy intake later in the day which amounted to 550 kcal increase. The reason of this higher amount of intake was attributed to the feeling of lethargy and fatigue. [44]

In the current study, some patients reported previous trials to lose weight or decreasing dietary fat intake by skipping meals, omitting breakfast or replacing it with small sized cookies, coffee, tea, fruit juices and sugars. Therefore, these patients were suffering from early hunger and sudden loss of energy in the mid noon that necessitate frequent eating of snacks rich in energy and carbohydrates. Unfortunately they believed that it was a healthy practice, which signifies the importance of proper nutritional counseling. A similar practice of breakfast skipping among obese Egyptian mothers was previously reported, and was related to increased body weight. [45]

Also breakfast composition was emphasized to contain more protein, fat and less carbohydrate which was consistent with Chandler-Laney et al, [46] who compared 2 types of diets; high carbohydrate/low fat breakfast, versus low carbohydrate/high fat breakfast. Low carbohydrate/high fat breakfast was associated with less hunger 3-4 hours after eating.

Regular or consistent meal patterns are thought to be beneficial for the health. However, the scientific evidence relating meal patterns with health is limited. Limited number of trials have provided evidence for the regularity of eating, and found that regular meal patterns could have beneficial effects on cardio-metabolic risk factors. [47,48] In addition, recent follow up study revealed that irregular intake of energy, both at lunch and breakfast, was associated with an increased risk of metabolic syndrome. [49] This was evident in the current study, as results of the regression analysis revealed the existence of an inverse correlation between the amount of fat deposited in the liver and eating meals and snacks at fixed times.

Cardiovascular disease (CVD) was demonstrated to be the main cause of death in NAFLD, [1,50] as patients had mostly atherogenic dyslipidemia with metabolic syndrome criteria. [51] With dietary intervention, gradual reduction in blood pressure, in both systolic and diastolic measurements was detected. Meanwhile, total cholesterol, LDL, and TG were significantly decreased, with small increase detected in HDL level, as well as, much

improvement in fasting blood glucose level. In addition, blood cholesterol was found to have a direct and positive correlation with HRI both before and after intervention, while HDL level was inversely correlated with HRI after intervention only. These beneficial effects of dietary intervention on blood lipids and blood glucose as well as liver fats, are in agreement with Ryan, et al. [33]

There is close association between the degree of NAFLD and increased body weight. Indeed, diagnosing NAFLD among obese persons is a marker of metabolic abnormalities. [51] In the current study, the initial weight, BMI and waist circumferences were much higher than normal ranges and was similar to Wasfy et al., [52] findings. However, with follow up a decreasing trend was detected in body weight, body fat mass and waist circumferences. These results were close to Kirk et al., [41] who found significant improvement in metabolic health and fatty liver with 7% of weight loss on moderately caloric restricted diet. While, in the current study, weight loss did not exceed 5-6% with great loss of body fat mass and more preservation of total muscle mass and body water due to good exercise practicing. The results are in agreement with similar improvement in body composition with practicing high intensity interval training and following Mediterranean diet that Dunn et al, [54] found.

The functional role of food is very evident in the preservation of gastrointestinal balance [55] as some regimens are beneficial [56] while others can trigger different functional disorders. [57] Also the health of the gastrointestinal tract and gut microbiota were previously reported to have close relationship with hepatic enzymes level. [58] Diets rich in simple carbohydrates, poor in vegetables, rich in fats with sedentary life and irregular sleep pattern might induce dysbiosis with release of endotoxins and stimulation of inflammatory mediators that leads to liver insult. [59]

Liver enzymes (ALT, AST and GGT) rise whenever liver cells are affected. According to the standard upper limit of normal liver enzymes, the majority of patients in the current study had normal levels which was consistent with a study conducted in Italy. [60] However, the upper limit of normal had been questioned in a previous study especially among obese patients. [61] Indeed, in the present study ALT level was found to have a direct and significant correlation with the amount of liver fat by HRI which was in agreement with findings of Ryan et al, [33] and might signify the concept of healthy ranges of enzymes rather than normal ranges especially among obese persons.

Dealing with different lifestyle practices is a multidisciplinary task. [60] As having adequate sleep is an important aspect of health and lifestyle that have different hormonal control on food intake, [62] but changing the sleeping habit is not a simple issue. Therefore, we focused on modifying the habit of eating dinner late, providing different dietary alternatives away from sugar dense snacks, and preventing very late intake of caffeine containing drinks. Also the quality of coffee was a priority with total omission of creamer containing coffee and less frequent intake of filtered coffee. This was in agreement with other studies conducted on the risk of liver fibrosis and coffee consumption. [63,64]

The beneficial effect of exercise on body weight, and all liver enzymes is undeniable [65], therefore, practicing exercises in the current study was highly encouraged taking in consideration different socioeconomic, health status, and physical limitations of patients. The benefit of exercise in fatty liver management goes beyond weight loss, [65] that can normalize ALT levels in NASH patients [66] and may help improve different metabolic disturbances. [67,68] All types of exercises are beneficial in decreasing visceral fat and improving metabolic profiles, even without a concomitant weight loss. [69] Indeed, the compliance of practicing exercise in NAFLD patients may be even lower compared to other patients due to fatigue sensation and excessive daytime sleepiness, but gradual increase in physical activity and decreasing sedentary time [70] is a must in NAFLD management. Suffering from chronic fatigue, somnolence, excessive day time sleepiness and some cognitive problems as memory and concentration problems could have significant effect on the poor quality of life experienced by patients with NAFLD. The severity of these symptoms were not previously reported to be associated with biochemical or histological parameters of liver disease severity nor related to the degree of insulin resistance. [71] In the current study, nutritional intervention were found to have a great positive impact on much of these symptoms.

Using ultrasound in evaluation of liver fat is very common in the clinical practice and in different study settings. [72,73] In the present study, HRI was used in initial assessment and after intervention to evaluate changes in the amount of liver fat. A positive and strong correlation was previously confirmed between the HRI and percentage of fat detected by liver biopsy. [22] The value ≤1.2 was considered as level of normal which was lower than Webb et al., [74] limit of normal 1.4, but in agreement with Marshal et al. [22] The target was to examine the percentage of patients achieving a decrease in fat content by HRI, which was achieved among 70% of the followed patients, and 39.7% of patients had achieved normal HRI after intervention. The utility of using noninvasive measurements of liver fat including the HRI to evaluate patients and determining who should undergo liver biopsy could prevent unnecessary invasive procedures, save patients' time, prevent side effects and complications, as well as cost reduction especially with limited health resources.

Before intervention, liver fat content estimated by ultrasound was positively correlated with total blood cholesterol, ALT level, dietary fat intake, and was significantly higher among males. Also, it was negatively correlated with eating meals at fixed times. While after intervention, HRI was positively correlated also with total blood cholesterol level, ALT level and carbohydrate intake, while a negative correlation was detected with HDL, and healthy cooking methods. These differed from Xia et al., [75] as they found positive association between HRI and waist circumference, hip circumference, AST, triglycerides, and fasting glucose levels while these factors were not associated with HRI in the current study. However, this may signify some ethnic differences between Egyptian and Chinese populations studied. Also, to our knowledge, this index was not used previously to assess nutritional implications in fatty liver.

Indeed different obstacles were encountered in this study such as the highly restricted inclusion criteria, as there were more patients who had viral hepatitis, diabetes,

cancers or taking different hormones. Practicing outdoor exercise was mostly difficult for female patients, due to social un-acceptance, embarrassment, perceived old age and time. The intervention based on restriction of carbohydrates was sometimes a problem, especially for emotional eaters, night eaters, very low income and those who work all day out as the accessibility to healthy alternatives were a problem among these patients. Also, telling patients to restrict bread intake, bread sticks, cookies and added sugar was sometimes not convincing. The reason of seeking nutritional advice was focused only on weight loss as the concept of medical nutritional management is unavailable in the context of patients' care generally and in NAFLD patients specifically. When we tried to highlight the metabolic improvement and positive health results, some patients were not accepting the explanation especially for weight loss resistance. Misunderstanding of previous advices concerning patient's health status stand as a barrier of acceptance; for example: patients with osteoarthritis should not perform exercises, and eating fruits is safe, irrespective of the amount. Unfortunately, some data of body composition analyses as well as ultrasound examinations were lost due to technical problems as well as refusal of some patients to perform the final assessment. NAFLD patients perceived themselves healthy and having fatty liver is not perceived as a significant disease by itself which made it difficult to convince some of them to participate in this work.

## 5. Conclusions and Recommendations

Diagnosis of NAFLD is an early alarm of metabolic upset of the body. Proper nutritional counseling can improve not only the liver status but can prevent a lot of forthcoming diseases and enhance the nutritional status of patients. Following a moderately carbohydrate restricted diet based on the Mediterranean diet with moderate caloric restriction was found to have a significant positive impact on NAFLD and metabolic health of patients, all within 12 weeks of follow up. The amount of liver fat content estimated by ultrasound was found to be associated with dietary fat and carbohydrate intake, eating meals at irregular times, and unhealthy cooking methods. Therefore, patients with NAFLD should be encouraged to follow a healthy lifestyle including proper diet and exercises aiming at better health not just focusing on body weight loss.

## Abbreviations

NAFL, Nonalcoholic fatty liver. NAFLD, Nonalcoholic fatty liver diseases. HRI, Hepatorenal index. SPSS, Statistical Package for Social Science. AST, Aspartate aminotransferase. ALT, Alanine aminotransferase. GGT, Gama glutamyl transferase. FBG, Fasting blood glucose. LDL, Low density lipoprotein. HDL, High density lipoprotein. TG, Triglycerides. SBP, Systolic blood pressure. DBP, Diastolic blood pressure. AHA, American Heart Association Diet. USDA, U.S. Department of Agriculture. NASH, Nonalcoholic steatohepatitis. BMI, Body mass index. CVD, Cardiovascular disease. SD, Standard deviation.

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