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Dietary intake and its relationship with non-alcoholic fatty liver disease (NAFLD)

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Abstract.
BACKGROUND: Non-alcoholic fatty liver disease is becoming the most common cause of liver disease worldwide. However, there are few reports about the intake of various nutrients in nonalcoholic fatty liver disease.
OBJECTIVE: The aim of this study was to identify the characteristics of dietary intake and their associations with NAFLD.
METHODS: This case-control study was performed on 280 subjects (140 patients with NAFLD and140 healthy subjects) who attended nutrition clinic, Ghaem Hospital, Mashhad, Iran. Dietary intake was assessed using an Iranian semi-quantitative food frequency questionnaire. Dietary intake was compared with data reported by clinically healthy individuals. Regression models were fitted to assess the relation between dietary patterns and non- alcoholic fatty liver disease.
RESULTS: The means (and SD) age of the samples were 39.3 ± 11.4 years for NAFLD group and 38.6 ± 11.3 years for the controls. After adjustment for total energy intake, NAFLD group had higher carbohydrate intake (235.60 ± 31.12 g vs. 222.47 ± 21.18 g, $P < 0.001$). However, the consumption of vitamin E, folate and potassium was significantly less in patients than controls ($P < 0.001$.(After adjusting for confounders, higher intake of carbohydrate was significantly associated with an increased risk for NAFLD (OR = 4.15, 1.66–10.38; $P < 0.05$), While higher intake of fat, vitamin A and folate was significantly associated with lower odds of the disease ($P < 0.05$).
CONCLUSIONS: It seems that within an Iranian population, there may be an association between diet and NAFLD. A large-scale trial and more prospective studies are yet warranted.

Keywords: Non-alcoholic fatty liver disease, carbohydrate, food frequency questionnaire, nutrient intake

1. Background

Nonalcoholic fatty liver disease (NAFLD) is associated with high body mass index (BMI), insulin resistance (IR) and has been known as a predictor of coronary artery disease and diabetes mellitus (DM) in all range of ages [1]. The prevalence of obesity and type 2 diabetes mellitus has augmented over the past two decades; so at this period of time NAFLD is the most important cause of liver injury in the world [1]. Some cases of NAFLD may progress to cirrhosis, risking complications of hepatocellular carcinoma and liver failure, moreover it is becoming an increasingly usual indication for liver transplant [2]. Some papers indicate that the pathogenesis initiates with

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insulin resistance leading to hepatic steatosis. This will result in increased level of oxidative stress in the body, and in some individuals it will be the cause of steatohepatitis (NASH), fibrosis and cirrhosis [3]. Literature have revealed that NAFLD affects 20 to 30 percent of adults in western societies [4], also 12 to 24 percent of subjects in Asian countries [5]. Dietary changes and increases in physical activity level are the first line of treatment [6]. It has been proposed that dietary composition plays an important role in NAFLD pathogenesis; thus, modifying dietary patterns may constitute a therapeutic method even in the absence of body mass index reduction [7]. Some papers stated that a positive correlation between increased consumption of cholesterol [8], saturated fatty acids (SFA) [8], total fatty acids [9], and a high n-6/n-3 fatty acid ratio [9] with the NAFLD. By contrast, others reported an association between NAFLD and a lower intake of polyunsaturated fats [8] and total lipids [10]. Although a direct association between carbohydrate intake and NAFLD [10, 11] was previously shown, however, the pattern of dietary and nutrient intake in NASH remains rarely investigated and controversial [9]. Most of the reported dietary determinants of NAFLD are not investigated in the Middle East [12]. Central adiposity and high body mass index is widespread among Asian population which may be associated with pathology of NAFLD in this area [13, 14]. Obviously, more investigation is required on the effect of dietary intake on patients with NAFLD [11]. Considering the lack of knowledge regarding the diet of NAFLD patients in Iran, we undertook this study to identify the characteristics of the dietary intake in NAFLD patients compared with healthy subjects. Therefore, our aim was to identify the characteristics of dietary intake and their associations with NAFLD.

2. Patients and methods

2.1. Subjects

Approximately 43.6% ($n = 122$) of the individuals were males and 56.4% ($n = 158$) were females. This case-control study was performed on 280 subjects (140 NAFLD patients and 140 healthy subjects) who were attending nutrition clinic, Ghaem Hospital, Mashhad, Iran from September 2012 to April 2013. Patients with NAFLD were those who were referred to Ghaem Hospital and with increased level of Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST), also NAFLD was confirmed by sonography.

In case group, inclusion criteria were the presence of NAFLD which was confirmed by sonography and increasing level of ALT and AST.

NAFLD group were new cases and they were not treated before the study. The exclusion criteria comprised of other causes of liver disease (namely alcohol intake 20 g/day, markers of chronic B or C hepatitis virus infections, auto-immune hepatic disorders, Wilson disease, hemochromatosis, and alpha-1-antitripsin deficiency), no use of steatogenic medications within the past six months, no exposure to hepato toxins, and no history of bariatric surgery [15]. We also excluded pregnant and lactating women and subjects who had previous dietary counseling.

2.2. Clinical, laboratory and ultrasound investigations

The anthropometric data included height (m), weight (kg), and body mass index (kg/m^2). Weight was determined using a digital scale (in kilograms, to the nearest tenth), and height was recorded (in centimeters, to the nearest tenth) using a wall stadiometer. Both were measured with subjects wearing light indoor clothes and no shoes. Overweight status was defined as having a body mass index >25 and <30 kg/m^2, and obesity was defined as having a body mass index >30 kg/m^2 [16].

2.3. Routine biochemical analysis

A full fasted lipid profile, comprising total cholesterol, triglycerides, Low-Density Lipoprotein Cholesterol (LDL-C) and High-Density Lipoprotein Cholesterol (HDL-C), was determined for each subject. Serum lipid and Fasting Blood Sugar (FBS) concentrations were measured by enzymatic methods. Liver biochemistry was taken after an overnight fast.

2.4. Fatty liver diagnose

Fatty liver was diagnosed by abdominal ultrasound using standardized criteria [15]. The abdominal ultrasound was performed in controls using the same equipment and by the same operator, who was unaware of the clinical and laboratory results.

2.5. Assessment of other variables

Other information such as age, demographic data, medical history and medication use were gathered by questionnaires.

2.6. Dietary assessment

Dietary intake was assessed using a semi-quantitative food frequency questionnaire (FFQ) as representative of the usual intake over the previous month. This questionnaire, includes a list of 160 Iranian food items and was designed by the department of nutrition of the Medical school, Mashhad University of Medical Sciences [17]. In order to analyze completed FFQs, first we scanned all pages of the FFQs and then the first software rode the selected choices on the scanned pages of the FFQ and delivered an external file with TXT format. This software was written with Delphi7 programing language [17]. Then the second software was used to analyze the data resulted from the first software and to deliver these data in a SPSS file [18] containing the food items which have been eaten; [19] grams of each food item that have been eaten; [20] amount of consumed energy, macronutrients, fiber, and some micronutrients (vitamin A, vitamin E, folate, and potassium). The dietary variables selected for the purpose of this study were crude, and total energy adjusted intake of micro and macro nutrients [21]. An adjustment was made for total energy intake through the residual method as an alternative to use nutrient densities to control for confounding by total energy intake and to remove extraneous variation due to total energy intake. Regression analysis was used to compute residuals of nutrient intake by removing the variation caused by total energy intake. In this procedure, the nutrient intakes of the subjects in a group are regressed on their total energy intakes [22]. The residuals from the regression show the differences between actual intake and the intake predicted by total energy intake [23–25]. Total energy-adjusted nutrient intakes were calculated as the residuals from the regression model, with absolute nutrient intake as the dependent variable, and total energy intake as the independent variable [23].

2.7. Statistical analysis

SPSS software (version 11.5, Chicago, IL, USA) was used for statistical analysis and the significance level was determined as $P < 0.05$. Kolomogrov-Smirnov test was used to evaluate the normality of data. To compare nutrients intake as well as biochemical parameter among case and control groups, independent sample *t*-test or the Mann-Whitney U test were used as appropriate. Multiple logistic regression was used for assessing the association between dietary intake and NAFLD.

3. Results

There were a total of 280 participants, 43.6% ($n = 122$) males and 56.4% ($n = 158$) females. The means (and SD) age of the population samples were 39.3 ± 11.4 years for NAFLD group and 38.6 ± 11.3 years for the healthy group.

3.1. Clinical, demographic and anthropometric data for subjects in both groups

Table 1 shows the mean and standard deviation for clinical and biochemical parameters in the healthy subjects and NAFLD group. Weight, BMI, fasting blood glucose (FBG), lipid profile, ALT and AST were significantly different between the groups ($p < 0.01$); patients had a higher ALT and AST level compared with healthy group. Furthermore subjects with NAFLD were significantly more obese than those without NAFLD ($p < 0.01$).

Table 1
Clinical and biochemical characteristics of the individuals with and without non-alcoholic fatty liver disease

Variables	NAFLD		Total
	Positive ($n=140$)	Negative ($n=140$)	($n=280$)
Age (y(	39.3 ± 11.41	38.6 ± 11.31	39.0 ± 11.35
Weight (Kg)	88.1 ± 19.21	$69.1 \pm 11.32^{**}$	87.1 ± 18.5
BMI (kg/m^2)	32.4 ± 6.46	$25.2 \pm 3.56^{**}$	28.8 ± 6.34
Total Chol (mg/dl)	210.7 ± 37.05	$184.7 \pm 34.34^{**}$	196.9 ± 37.87
HDL-C (mg/dl)	48.1 ± 9.96	$51.9 \pm 10.00^{*}$	50.2 ± 10.15
LDL-C (mg/dl)	122.6 ± 32.25	$107.7 \pm 24.43^{**}$	114.6 ± 29.24
y TG (mg/dl)	133(97–201)	93(72–133)**	112(80–148)
FBG (mg/dl)	111.0 ± 36.44	$92.6 \pm 14.92^{**}$	101.3 ± 28.74
ALT (U/L)	66.5 ± 22.27	$22.1 \pm 8.82^{**}$	42.6 ± 27.58
AST (U/L)	49.3 ± 14.47	$21.9 \pm 5.73^{**}$	34.4 ± 17.30
Current Smoking (%)	8.6%	2.9%*	5.7%
Diabetes Mellitus (%)	21%	6.1%*	13%

Values expressed as mean ± SD for normally distributed data, and median and interquartile range for non-normally distributed data. Between groups comparisons were assessed by parametric statistical analysis for normal distributed data and nonparametric test for non-distributed data. Abbreviations: NAFLD, Non-Alcoholic Fatty Liver Disease; BMI, Body Mass Index; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; TG, Triglyceride; FBG, Fasting Blood Glucose; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; $^{*}p<0.05$, $^{**}p<0.001$.

3.2. Comparison of the crude and total energy adjusted intake of nutrients between the NAFLD (+) and NAFLD (−) subjects

Table 2, shows the crude intake and total energy adjusted intake of the nutrients. We found significant difference in crude and total energy adjusted intake of nutrients between the two groups ($p<0.01$) except for adjusted intake of fiber ($p=0.12$) and vitamin A ($p=0.10$).

3.3. Associations between ALT and AST with crude and energy adjusted nutrient intake

To determine the relationship between ALT and AST with the crude and total energy adjusted intake of the nutrients, Spearman's (Table 3) correlation coefficient was used. As can be seen from Table 3, p-value for all factors for both ALT and AST were significant, except for protein, ($p=0.16$, $r=-0.09$) and ($p=0.10$, $r=-0.10$), fiber, ($p=0.55$, $r=-0.03$) and ($p=0.93$, $r=0.005$) and for vitamin A, ($p=0.17$, $r=-0.08$) and ($p=0.29$, $r=-0.06$) for ALT and AST respectively. For this set of data, Spearman's coefficient was highest for carbohydrate ($r_{ALT}=0.50$, $r_{AST}=0.52$) and energy intake ($r_{ALT}=0.44$, $r_{AST}=0.49$) in both ALT and AST.

3.4. Multivariate analysis of the association between nutrition and NAFLD

Associations between nutrients intake and NAFLD are shown in Table 4. When intakes of nutrients were stratified to tertiles, those in the highest tertile for the carbohydrate intake had a 4.47 times greater odds of NAFLD (OR 4.47;95% CI 2.39–8.33; $P<0.001$) compared with those in the lowest tertile. Moreover, after adjustment for total calorie intake, BMI, smoking, triglyceride and HDL-C, these associations were still significant (model 2).

Table 2
Nutritional intake characteristics of the patients with and without non-alcoholic fatty liver disease

Variables		NAFLD	
		Positive ($n = 140$)	Negative ($n = 140$)
Crude Intake	Energy (kcal)	2426.8 (2041.8–3160.0)	1702.7 (1455.1–1993.2)**
	Fat (gr)	106.3 (86.2–130.0)	77.7 (64.5–93.7)**
	Carbohydrate (gr)	288.8 (229.4–358.0)	180.9 (160.4–226.4)**
	Protein (gr)	89.1 (74.3–108.5)	68.3 (54.2–82.5)**
	Fiber (gr)	20.0 (14.4–26.0)	13.2 (10.3–17.8)**
	Potassium (mg)	3407.6 (2730.1–4389.4)	2598.9 (2049.5–3129.8)**
	Folate (μg)	493.0 (328.6–638.5)	374.8 (294.2–538.4)**
	Vitamin A (μg)	828.7 (592.5–1171.2)	535.7 (410.6–789.1)**
	Vitamin E (mg)	8.8 (6.1–16.9)	6.3 (4.4–12.6)**
Total energy adjusted	Fat (gr)	85.8 (77.6–94.5)	90.5 (85.6–96.0)**
	Carbohydrate (gr)	237.0 (218.0–255.6)	221.7 (206.5–237.3)**
	Protein (gr)	74.7 (66.3–83.7)	77.0 (70.8–83.6)*
	Fiber (gr)	15.4 (12.6–18.1)	15.8 (13.9–18.1)
	Potassium (mg)	2707.6 (2400.3–3211.1)	3028.9 (2761.4–3242.0)**
	Folate (μg)	350.3 (244.3–508.5)	452.4 (356.2–544.6)**
	Vitamin A (μg)	617.8 (466.8–942.5)	679.5 (575.3–830.1)
	Vitamin E (mg)	6.8 (3.8–12.1)	9.31 (7.86–12.79)**

Dietary intakes were adjusted for total energy intake through the residual method as an alternative to using nutrient densities to control for confounding by total energy intake and to remove extraneous variation due to total energy intake, regression analyzes was used to compute residuals of nutrient intake by removing the variation caused by total energy intake. *$p < 0.05$, **$p < 0.001$. Abbreviation: NAFLD, Non-Alcoholic Fatty Liver Disease.

Table 3
Correlation (r) between ALT and AST with crude and energy adjusted nutrient intake

Variables		ALT (U/L)	AST(U/L)
Crude Intake	Energy (Kcal)	0.44***	0.49***
	Fat (gr)	0.36***	0.43***
	Carbohydrate (gr)	0.50***	0.52***
	Protein (gr)	0.34***	0.38***
	Fiber (gr)	0.35***	0.41***
	Potassium (mg)	0.33***	0.40***
	Folate (μg)	0.16**	0.20**
	Vitamin A (μg)	0.31***	0.36***
	Vitamin E (mg)	0.26***	0.30***
Total energy adjusted	Fat (gr)	−0.19**	−0.13*
	Carbohydrate (gr)	0.22***	0.18**
	Protein (gr)	−0.09	−0.10
	Fiber (gr)	−0.03	0.005
	Potassium (mg)	−0.17**	−0.14*
	Folate (μg)	−0.23***	−0.21***
	Vitamin A (μg)	−0.08	−0.06
	Vitamin E (mg)	−0.21***	−0.23***

Correlations were assessed using Spearmen correlation coefficients. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase.

Table 4
Adjusted multiple logistic regression models of nutrients intake and risk of non-alcoholic fatty liver disease

Nutrients Intake		Odds Ratio (95% CI)			*P*value
		T1(ref.)	T2	T3	
Carbohydrate (gr)	Model 1	1.00	1.41 (0.78–2.55)	4.47 (2.39–8.33)	<0.001
	Model 2	1.00	0.87 (0.35–2.16)	4.15 (1.66–10.38)	<0.008
Protein (gr)	Model 1	1.00	0.39 (0.21–0.70)	0.61 (0.34–1.10)	0.10
	Model 2	1.00	0.23 (0.09–0.60)	0.52 (0.21–1.27)	0.15
Fat (gr)	Model 1	1.00	0.26 (0.14–0.48)	0.33 (0.18–0.61)	<0.001
	Model 2	1.00	0.23 (0.09–0.60)	0.30 (0.12–0.75)	0.01
Fiber (gr)	Model 1	1.00	0.40 (0.22–0.72)	0.58 (0.32–1.05)	0.07
	Model 2	1.00	0.40 (0.22–0.72)	0.61 (0.33–1.10)	0.10
Vitamin A (μg)	Model 1	1.00	0.29 (0.16–0.53)	0.69 (0.38–1.25)	0.23
	Model 2	1.00	0.26 (0.10–0.65)	0.32 (0.13–0.80)	0.01
Vitamin E (mg)	Model 1	1.00	0.93 (0.45–1.91)	0.46 (0.20–1.06)	0.07
	Model 2	1.00	1.29 (0.40–4.16)	0.35 (0.08–1.51)	0.16
Folate (μg)	Model 1	1.00	0.52 (0.26–1.04)	0.43 (0.19–0.97)	0.04
	Model 2	1.00	0.38 (0.12–1.18)	0.19 (0.04–0.80)	0.02
Potassium (mg)	Model 1	1.00	0.72 (0.35–1.48)	0.40 (0.13–1.21)	0.10
	Model 2	1.00	1.09 (0.35–3.34)	0.42 (0.08–2.21)	0.30

Model 1: Adjusted for total energy intake. Model 2: Adjusted for model 1 plus BMI, smoking, triglyceride and high-density lipoprotein cholesterol, by using multivariate regression model, and the stepwise forwards selection procedure. Abbreviations: CI, confidence interval; T, tertile.

In contrast, after adjusting for cofounders, those in the highest tertile for fat, vitamin A and folate had lower odds of NAFLD compared with those in the lowest tertile (model 2).

4. Discussion

This study was carried out to determine the association between dietary intake, as well as anthropometric and biochemical indices among NAFLD patients and its comparison with healthy group. The outcome of the present study indicated that dietary intake may be associated with NAFLD. NAFLD group have higher intake of calories and carbohydrate, but lower intake of fat. Furthermore, serum level of liver enzymes, lipid profiles and fasting blood glucose are also higher among NAFLD patients. In regard to anthropometric parameters, patients with NAFLD had higher body mass index and weight. Our findings are in keeping with previous studies; they revealed that simple carbohydrate and refined grains were consumed more by the NAFLD patients [26–29]. Studies in the field of nutrition and NAFLD have focused on the detrimental effects of fats [26, 27, 29]. However, there are some disagreement regarding the role of carbohydrate and fat in the etiology of NAFLD [26, 27]. Although a review paper showed that high fat diet could quickly develop the NAFLD [30]. Nevertheless, Solga et al. showed that higher fat intake was significantly associated with lower odds of inflammation in NAFLD subjects [11]. Furthermore, some authors indicate that the different kinds of fat are related to NAFLD [31].

However, recent studies on dietary intake of NAFLD patients revealed different outcomes [9]; Musso et al. stated saturated fat and cholesterol-rich diets with poor in polyunsaturated fat, fiber, vitamins C and E [8] were associated with the presence of the disease; whereas the other author emphasized the association between higher carbohydrate intake with significantly higher odds of inflammation [11]. Up to now, the pattern of dietary intake in NASH remains rarely investigated and controversial [9].

NAFLD is common in both obese or overweight individuals and those with IR [32]. While low-energy diets are well known to be helpful for the treatment of obese subjects [33], the role of dietary composition remains debatable [34],

and some authors believe that low-fat diets are needless [35] or even detrimental [36]. According to the outcomes of this survey, carbohydrate intake may be more responsible compared to fat intake in the etiology of NAFLD. Moreover, the types of fat intake may also be significant as revealed in previous studies [26, 27, 37, 38]. In the current study, there was no difference between the two groups regarding protein intake. Up to now, the effects of protein intake on NAFLD have been poorly considered and remains controversial [37]. In this field, studies are mainly restricted to rodents [37]. Some study showed that, an augmentation in dietary protein content, reduce the risk of hepatic fat accumulation during a high-fat diet both in human and animal models [39–42]. However, some authors indicate that the protein malnutrition also may lead to steatosis [43–45]. In this study, intake of vitamin E was lower in patients with NAFLD. Our results are in keeping with previous studies that also confirmed lower antioxidant intake in patients with NAFLD [46].

We found that NAFLD group had lower consumption of potassium and folate. But there were no significant differences in their vitamin A and fiber intake in comparison to healthy subjects.

In this study patients had higher levels of serum lipid profile, liver enzymes and fasting blood glucose. There are numerous reports regarding to these abnormalities among patients with NAFLD [47, 48]. A current study revealed that serum levels of lipid profiles are also correlated with the presence of NAFLD [49]. Therefore, it is prominent to investigate the biochemical indices of patients with NAFLD in different zones of the world [37].

There are some methodological limitations in this survey. It would be better if the diagnosis of NAFLD had been established by liver biopsy in NAFLD patients. Additionally, the probability of both memory and reporting bias in dietary assessment should not be ignored, particularly when considering subjects, such as obese individuals, who have awareness regarding “healthy diets”. The routine dietary intake of the patients may be affected by diagnosis of their disease. We have considered only a limited number of dietary parameters. It would be better if more nutrients, specially the different kinds of fat intake were analysed. As we previously said some studies showed that types of fat intake may also be significant. Just a few studies have reported the role of dietary composition in NAFLD pathogenesis, but their results are relatively ambiguous [8–11, 50–52]. Consequently, we strongly recommend undertaking more prospective model surveys in future to clarify this correlation.

In conclusion, our NAFLD group had higher energy and carbohydrate intake; while, fat intake was lower in this group compared with healthy subjects. Also the consumption of vitamin E, folate and potassium were lower in NAFLD group. We found that, carbohydrate intake directly related, but fat, vitamin A and folate intake were inversely related to NAFLD. Thus, by considering the limitations of the present study, it appears that the dietary intake may be correlated with NAFLD. A large-scale trial and more prospective studies are yet warranted.

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Ethical standards

Each subject gave informed written consent to participate in the study, which was approved by the Mashhad University of Medical Sciences Ethics Committee.

Conflict of interest

None.

Implication for health policy/practice/research/medical education

It is shown that dietary composition plays an important role in NAFLD; thus, lifestyle interventions are the first-line prevention and treatment for NAFLD. A large-scale trial and more prospective studies are yet warranted.

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