THE RISK FACTORS OF METABOLIC SYNDROME AND NUTRITIONAL STATUS IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE: A CASE-CONTROL STUDY IN KERMANSHAH, IRAN

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ABSTRACT

Introduction*: Non-alcoholic fatty liver is the most common liver disease in the world that is associated with various metabolic complications. This study was conducted to determine the risk factors of metabolic syndrome and assess the nutritional status of patients with non-alcoholic fatty liver disease (NAFLD) in Kermanshah, Iran.*

Methods*: The present case-control study examined 250 patients in two groups of 125. The cases were selected through a convenience sampling of patients with NAFLD as per their positive ultrasound results and the controls were selected through a simple random sampling of those with negative ultrasound results. The data collection tools used were a demographic questionnaire and the Food Frequency Questionnaire. The NCEP/ATP-III definition of metabolic syndrome was used. Data were analyzed in Stata-11 using the Chi-square test, the t-test and the logistic regression.*

Results*: Triglyceride level was significantly higher in the patients with NAFLD compared to the healthy controls (33.33% vs. 14.41%; P=0.001). The waist-to-hip ratio was significantly lower in the control group (43.69% vs. 21.01%; P≤0.001). The prevalence of metabolic syndrome was 25.5% in the patients with NAFLD and 6.8% in the control group (P<0.001). Protein intake (OR: 0.29, 95% CI: 0.13-0.64) and vitamin E intake (OR: 0.65, 95% CI: 0.54-0.86) had a protective effect against the incidence of NAFLD.*

Conclusion*: The findings showed a high prevalence of metabolic syndrome in patients with NAFLD compared to the healthy subjects and revealed a significant relationship between fatty liver and metabolic syndrome. Ensuring an early diagnosis of NAFLD can help delay the complications of this disease, including metabolic syndrome.*

Key words*: Non-Alcoholic Fatty Liver Disease, Metabolic Syndrome, Nutrition, Triglyceride.*

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Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is a pathological excess of fat in the liver (steatosis) in the form of triglyceride (TG) that is not caused by alcohol. NAFLD shares the main features of metabolic syndrome, including obesity, hypertension, hyperlipidemia and insulin resistance. The pathogenesis of NAFLD is multi-factorial[(1)].

There is a mutual relationship between NAFLD and metabolic syndrome (MetS); in other words, the former is not only considered the hepatic manifestation of the latter, but also a common precursor to its incidence and to the development of its components[(2-3)].

NAFLD is the hepatic manifestation of metabolic syndrome[(4)] that can progress to more aggressive non-alcoholic steatohepatitis, cirrhosis and hepatocellular carcinoma[(5)].

Metabolic Syndrome (MetS) is a cluster of cardiometabolic disorders that are known be a risk factor for the development of atherosclerotic cardiovascular disease and stroke[6]. The development of this syndrome is associated with central obesity and insulin resistance. The major components of MetS include insulin resistance, central obesity, dyslipidemia and hypertension[7]. Increased plasma glucose and TG concentrations are key to MetS, and glucose and TG are also overproduced in NAFLD. The liver is thus a major determinant of these metabolic abnormalities[8]. NAFLD and MetS often occur simultaneously in the same individual and insulin resistance is assumed to play a key role in linking these conditions together. Nearly 90% of all NAFLD patients are reported to have more than one component of metabolic syndrome[9].

The global prevalence of NAFLD is 25.24%, with the highest prevalence observed in the Middle East and South America and the lowest in Africa[10]. In the United States, NAFLD is a significant health problem that affects 70 million adults, i.e. about 30% of the entire adult population in the US[11]. The prevalence of NAFLD and non-alcoholic steatohepatitis (NASH) varies from 2.9% to 7.1% in the general population in Iran[12-13]. Based on a report by the Iranian Ministry of Health, NASH is responsible for the death of 1% of the population over 15[14].

The etiology of NAFLD is explained by a complex interaction between genetic and environmental factors[15]. Of the environmental factors at play, dietary intake is an important one[16]. NAFLD is mostly common among obese or overweight people and those with signs of insulin resistance syndrome. Given that weight loss and maintaining the reduced weight are difficult in the long term[17], changing the dietary composition without necessarily reducing calorie intake may offer a more realistic and feasible alternative in the treatment of NAFLD(11). Examining the relationship between NAFLD and certain nutrients or the dietary composition is therefore crucial and this study was conducted to determine the risk factors of metabolic syndrome and assess the nutritional status of patients with non-alcoholic fatty liver disease in Kermanshah, Iran.

Materials and methods

This case-control study was conducted in Kermanshah in 2015. The case group consisted of patients with NAFLD selected through a convenience sampling of patients with a fatty liver according to their ultrasound results. The control group was selected through a simple random sampling of people who did not have a fatty liver in their ultrasound results. To take account of potential attrition, the sample size was determined as 125 per group and 250 overall based on previous studies and the prevalence of the different factors involved in the development of MetS. The study protocol was approved by the Ethics Committee of Kermanshah University of Medical Sciences (No: 92423).

Dietary Habits Assessment

Participants' food intake was assessed using the Food Frequency Questionnaire (FFQ); the validity and reliability of this tool have already been confirmed in Iran[18]. The FFQ consists of a list of 161 food items and their standard amounts in certain food groups, including bread and cereals, fruits, vegetables, meat and beans, milk and dairy products, salad and miscellaneous food items. The nutritional data obtained from the FFQ were analyzed in a software written in Visual Basic 6.0. The standard values for energy, folate, vitamin A, vitamin E and calcium were set based on Recommended Dietary Allowances (RDA) for different age groups. The RDA is 0.8 g per kg of body weight for protein and 25 g per day for fiber)[19]. To calculate the total energy of each food item from the total energy produced by proteins, carbohydrates and fats, each gram of protein, carbohydrate and fat was taken to give four, four and nine kilocalories of energy.

Blood Pressure Measurement

Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were measured in all the participants using a digital blood pressure measurement device. Hypertension is defined by the WHO as SBP ≥140 mmHg or DBP ≥90 mmHg or requiring antihypertensive medications.

Metabolic Syndrome Assessment

The third report of the National Cholesterol Education Program Adult Treatment Panel (2005) (NCEP/ATP-III) was used to define metabolic syndrome)[20].

Data Analysis

All the data were coded and entered into Stata-

11 and analyzed using descriptive (mean, standard deviation and percentage) and analytical (t-test, $\chi 2$, Mann-Whitney and logistic regression) statistics. The level of statistical significance was set at $P<0.05$.

Results

A total of 250 participants, 220 persons that completed information were analyzed, with a minimum age of 30 and a maximum of 65. The mean weight of the subjects was 82.1±16.9 kg in the case group (i.e. the patients with NAFLD) and 70.9±12.2 in the control group. The mean BMI was 30.41±5.7 kg/m2 in the case group and 26.41±3.8 in the control group, suggesting significant differences between the two groups in terms of BMI (P= 0.001).

A total of 44.66% of the cases and 12.45% of the controls had a BMI over 30 and were thus considered obese. SBP was 114.12±16.65 mmHg in the case group and 113.68±16.08 in the control group, suggesting the lack of significant intergroup differences in this variable.

Daily calorie intake was 2329.15±1319.38 in the case group and 2593.71±1944.25 in the control group. The amount of protein intake was 87.74±52.10 g in the case group and 97.007±75.55 in the control group, suggesting a significantly higher intake among the controls (P=0.02). Fiber intake was 23.12±14.57 g in the case group and 25.74±34.71 in the control group (Table 1).

Food Intake	Mean±SD			P-Value*
	Case Group	Control Croup	Total	
Energy (kcal)	2329.15±1319.38	2593.71±1944.25	2470.32±1685.69	0.5
Protein (g)	87.74±52.10	97.007±74.55	92.72±65.76	0.02
Fat (g)	93.44±60.51	107.32±87.12	100.90±76.13	0.2
Carbohydrate (g)	285.34±157.44	309.46±234.09	298.30±202.31	0.8
Fiber (g)	23.12±14.57	25.74±34.71	24.53±27.28	0.3
Vitamin A (µg)	992.53±811.18	1011.74±940.84	1002.85±881.24	0.8
Vitamin E (mg)	14.86±17.25	17.33±35.02	16.19±28.19	0.04
Folate (µg)	459.98±392.65	453.48±512.76	456.48±436.72	0.2
Calcium (mg)	3699±2222.65	3989.99±3608.80	3855.83±3042.72	0.7

Table 1: The mean daily food intake in the case and control groups.
**Using the Mann-Whitney test.*

A total of 39 (39.39%) of the cases and 31 (26.96%) of the controls received lower amounts of protein than the RDA and 69 (69.70%) of the cases and 86 (74.78) of the controls received lower amounts of vitamin E than the RDA (Table 2).

Food Intake	Lower than the RDA			Equal to or more than the RDA			P-Value**
	*Case Group	Control Group	Total	Case Group	Control Group	Total	
Protein (g)	39	31	70	60	84	144	0.053
	-39.39	(26.96)	-32.71	(60.61)	-73.04	-67.29	
Fiber (g)	64	81	145	35	34	69	0.36
	-64.65	(70.43)	-67.76	(35.35)	-29.57	-32.24	
Folate (µg)	55	70	125	44	45	89	0.43
	-55.56	(60.87)	-58.41	(44.44)	-39.13	-41.59	
Calcium (mg)	8	11	19	91	104	195	0.7
	-8.08	-9.57	-8.88	(91.92)	(90.43)	-91.12	
Vitamin A (µg)	46	58	104	53	57	110	0.56
	-46.46	(50.43)	-48.6	(53.54)	-49.57	-51.4	
Vitamin E (mg)	86	69	155	29	30	59	0.04
	-74.78	(69.70)	-72.43	(25.22)	-30.3	-27.57	

Table 2: The mean daily food intake compared to the RDA in the study groups.
**N (%); ** Using the Chi-square test*

Overall, the participants received 48.95±7.24% of their daily calories from carbohydrates, 36±6.18% from fats and 15±2.26% from protein; divided by group, these figures were 50±6.75%, 35±5.53% and 15±2.65% in the case group and 48±7.54%, 36.9±6.6% and 15±2.68% in the control group. The t-test showed significant differences between the two groups for fat (P=0.02) and carbohydrate (P=0.04) intake. Protein intake also differed significantly between the groups and protein was found to have a protective effect on the liver (OR: 0.29, 95% CI: 0.13-0.64). Vitamin E also had a protective effect against the incidence of fatty liver (OR: 0.65, 95% CI: 0.54-0.86).

Triglyceride level was significantly higher in the cases compared to the controls (33.33% vs. 14.41%). The waist-to-hip ratio (WHR) was significantly higher in the cases than in the controls (43.69% vs. 21.01%). Overall, the prevalence of MetS was 15.53% in the study population; divided by group, the prevalence was 25.5% in the case group and 6.8% in the control group, suggesting a significant intergroup difference in this regard (Table 3). The logistic regression analysis showed no statistically significant relationships between nutritional status and the incidence of MetS.

According to the ATP-III Criteria	Case Group N (%)	Control Group N (%)	Total N (%)	P-Value
BP ≥130/85 mmHg	12 (12.12)	14 (12.61)	26 (12.38)	0.943
FBS ≥100 mg/dl	6 (5.88)	2 (1.69)	8 (3.64)	0.092
TG >150 mg/dl	34 (33.33)	17 (14.41)	51 (23.18)	0.001
HDL <40 mg/dl	94 (92.16)	101 (58.59)	195 (88.64)	0.124
WHR >102 cm	45 (43.69)	25 (21.01)	70 (31.53)	<0.001
Metabolic Syndrome	26 (25.5)	8 (6.8)	34 (15.53)	<0.001

Table 3: The frequency and frequency percentage of metabolic syndrome components in the case and control groups.

Discussion

The prevalence of MetS was significantly higher in the patients with NAFLD compared to the healthy controls (25.5% vs. 6.8%). The WHR and triglyceride level were also higher in the cases than in the controls. In one study, the prevalence of MetS was reported as 51.4% in the patients with NAFLD[21]. Another study in Greece showed that 46.5% of the patients with NAFLD also have MetS and reported the most common abnormalities to be linked to a high waist circumference and a low HDL)[22]. The incidence of NAFLD is directly associated with the risk factors of MetS[23]. NAFLD can be a cause or a consequence of MetS, but the effect of MetS on NAFLD is significantly stronger than the effect of NAFLD on MetS[24]. In one retrospective study, the five-year health status of patients with fatty liver was associated with the development of the risk factors of MetS)[25]. NAFLD and MetS have synergistic effects on the incidence of atherosclerosis and their early diagnosis and treatment is therefore crucial)[26].

The mechanism by which fatty liver leads to MetS is not yet clear; however, it may be partly explained by noting that the regulation of hepatic lipid metabolism might be distinct from the regulation of glucose metabolism; for example, the overexpression of diacylglycerol acyltransferase 2 (DGAT2), which catalyzes the final stage of triacylglycerol (TAG) biosynthesis in the liver, increases hepatic steatosis, which is manifested as increased hepatic unsaturated long-chain fatty acyl-CoAs, ceramides, diacylglycerol and triacylglycerol (TG). Mice with an overexpression of DGAT2 showed no abnormalities in their glucose tolerance or insulin level, which supports the assumption that hepatic steatosis may not necessarily be caused by insulin resistance[27].

The development and treatment of fatty liver disease differ between different people and are related to various factors that can affect the risk of MetS. For example, variations in diet, physical activity, hepatic oxidative stress, cytokine production, the fluxes of fatty acids, the reductions in very low-density lipoprotein secretion and the changes in the intestinal microbiome are all associated with changes in NAFLD[28]. Additionally, an increase in free fatty acids (FFA), interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α) and other pro-inflammatory cytokines, which occurs with body fat tissue inflammation and changes in the adipose tissue function, are also associated with insulin resistance[29].

Diet plays an important role in the development and progression of NAFLD and MetS. The risk of metabolic syndrome is increased in patients with NAFLD with the consumption of red meat and refined grains[22]. Increasing carbohydrate intake will increase liver inflammation in patients with NAFLD. Short-term treatment with vitamin E reduces ALT level in NAFLD patients with MetS. Vitamin E is an antioxidant that prevents lipid oxidation and as a result free-radical formation too)[30]. One study reported that patients with NAFLD had a diet rich in saturated fat and cholesterol and poor in unsaturated fat, fiber and vitamin C)[31]. In the present study, the assessment of nutritional status in patients with NAFLD showed significant differences between the cases and the controls in the daily intake of protein and vitamin E, which are proposed as a protective factor against the incidence of NAFLD. The consumption of fiber, folate and calcium also differed between the two groups, but not significantly. Given the important role of nutrition in the development of NAFLD, more clinical studies should be conducted on this subject.

The diagnostic importance of NAFLD as a criterion for either the presence or future risk of metabolic syndrome needs to be more emphasized. From a therapeutic point of view, pathogenic interventions aiming to reverse NAFLD are a potentially rational approach to the prevention and treatment of metabolic syndrome and its associated complications.

Conclusion

The results of this study revealed a high prevalence of metabolic syndrome in patients with

NAFLD compared to healthy people and therefore show that a significant relationship exists between fatty liver disease and metabolic syndrome. Patients with NAFLD can prevent the development of metabolic syndrome by taking approaches such as weight control, proper nutrition and exercise. The early diagnosis of NAFLD helps delay the complications of the disease, including metabolic syndrome and heart disease.

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