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Mediterranean diet and the prevention of non-alcoholic fatty liver disease: results from a case-control study

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Abstract. – OBJECTIVE: Few studies report that Mediterranean dietary (MD) pattern has a beneficial role in the progression of non-alcoholic fatty liver disease (NAFLD). Evidence on its potential effect on the onset of disease are, however, scanty. With our study, we evaluated whether MD affects the risk of NAFLD with a large case-control study performed in Italy.

PATIENTS AND METHODS: Three hundred and seventy-one cases of NAFLD and 444 controls were questioned on the demographic data and their dietary habits before diagnosis. Additionally, information about lifestyles and other related diseases, such as hypertension and diabetes mellitus were collected. The MD adherence was assessed using a pre-defined Mediterranean Diet Score (MDS). Odds ratios (OR) and 95% confidence intervals (CI) were obtained using a multiple logistic regression model.

RESULTS: A high adherence to the MD is significantly associated with decreased risk of NAFLD (OR: 0.83 95% CI: 0.71-0.98). When the different MD components were examined separately, higher legumes consumption (OR: 0.62 95% CI: 0.38-0.99) and high fish consumption (OR 0.38 95% CI: 0.17-0.85) were reported to be protective against NAFLD.

CONCLUSIONS: Our study shows that a high adherence to the MD decreases the risk of NAFLD.

Key Words:
Epidemiology, Case-control, Mediterranean diet.

Introduction

The non-alcoholic fatty liver disease (NAFLD) is characterized by pathological accumulation of fat in the liver in the absence of excessive alcohol consumption or other causes of liver disease[1]. It can be presented either with lipid accumulation in the hepatocytes that exceeds 5% of the liver mass, a condition called non-alcoholic fatty liver (NAFL), or develop into non-alcoholic steatohepatitis (NASH), which is characterized by an inflammatory process that can eventually lead to cirrhosis or even hepatocarcinoma[2-5].

In recent years, NAFLD is becoming the most common liver disease worldwide[6-8]. It is closely associated with the Metabolic Syndrome (MetS) although it is not yet considered as one of its features (visceral adiposity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, low high-density lipoprotein (HDL) levels)[9]. Indeed, NAFLD affects about 20-30% of the population in the developed countries, 80-90% of obese adults, 30-50% of diabetes patients and 90% of patients with hyperlipidemia[7]. This high prevalence is considered to be caused mainly by unhealthy dietary habits, and particularly adherence to a high caloric diet that is rich in saturated fatty acids or simple carbohydrates[10,11].

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In the absence of a specific pharmacological therapy, the changing of lifestyle, including dietary regimen and physical activity, remains the main therapeutic option that gives positive results in NAFLD patients[12]. Weight loss diets alone could reduce hepatic steatosis but macronutrients composition of diet are becoming increasingly important, irrespective of the extent of weight loss[13]. The Mediterranean diet (MD) is characterized by high intake of monounsaturated fatty acids from olive oil, vegetables and fruits, plant proteins, whole grains, fish, low-fat dairy, moderate alcohol intake, and low red meat consumption[14]. MD has been already established to have a role in the prevention of NAFLD[15], as well as in slowing the disease processes in a number of diseases linked to NAFLD, such as diabetes mellitus, hyperlipidaemia, and coronary heart disease[16]. Furthermore, there is evidence[17] that MD, but also some of his components individually considered, have beneficial effects on every single feature of MetS. Moreover, several observational and intervention studies, as well as systematic literature reviews and meta-analyses[18-23], demonstrated the positive therapeutic effect of the MD alone or in combination with physical activity, particularly on NAFLD.

Despite the strong evidence[19] about the positive effects of diet on the course of the disease, there is still lack of consensus about which is the most effective macronutrient composition of NAFLD patients' diet. Additionally, although it is clear that the appropriate energy consumption is preventive, it is still not well established how the dietary composition could have a role in the onset of the disease[24,25]. Therefore, with our study we aimed to evaluate whether the adherence to MD is associated with a reduction risk of NAFLD within a case-control study in Italy.

Patients and Methods

Study Participants and Study Design

Patients were recruited at the Clinical Division of Internal Medicine, Gastroenterology and Hepatology of the Agostino Gemelli Teaching Hospital (Rome, Italy) from 2005 to 2017. Patient diagnosis of NAFLD was based on the presence of sonographic features of hepatic steatosis based on the presence of the bright liver pattern as recommended by the American Gastroenterology Association. Moreover, the diagnosis foresaw the absence of all the following factors: significant ethanol intake (20 g/day for females and 30 g/day for males); drug-induced liver disease within the last 5 years; autoimmune liver disease (manifested by positive serum antinuclear, liver/kidney microsomal, mitochondrial, smooth-muscle, and/or neutrophil cytoplasmic antibody titers); seropositivity for hepatitis B (HBs-Ag) or C infection and autoantibodies (anti-HCV IgG); fasting transferrin saturation (45%; low serum alpha1-antitrypsin levels; ceruloplasmin levels indicative of Wilson's disease, and/or DILI)[26]. Ultrasound determinations were performed by the same identical operator (GR) during the entire study period.

Inclusion criteria for controls required that the patients were admitted in the hospital during the same period of cases. Exclusion criteria were the presence of steatosis, fatty liver or metabolic disease. Controls were mainly blood donors or patients who underwent surgical interventions (laparoscopic cholecystectomy, appendicitis, inguinal hernia) and patients affected by chronic diseases as hypertension or chronic obstructive pulmonary disease.

Cases and controls were interviewed by trained medical doctors, following a structured questionnaire about demographics, medical history, family history of steatosis, alcohol and tobacco consumption, physical activity and other relevant lifestyle factors.

The collection of clinical and laboratory data was performed only from NAFLD patients. An informed consent was provided from all the participants according to the rules of the Ethical Committee of the University. We defined current smokers as individuals who were smoking at the time of the study or who had quit smoking within 1 year before the diagnosis for cases (1 year before the interview for controls). We defined former smokers those who had quit smoking more than 1 year before the diagnosis for the cases (1 year before the interview for the controls). Participants who had never smoked were defined as never smokers. Physical activity was defined as the number of times per week patients performed recreational or non-recreational physical activity.

Dietary Assessment and Mediterranean Diet Score

A validated food frequency questionnaire on food and beverages was used to assess dietary intakes of participants. The questionnaire has been already used in order to estimate the adherence to MD[27]; it focuses on dietary habits one year before diagnosis and includes 27 food and beverages items

The total energy intake was calculated based on all the items present in the questionnaire, accompanied with other data[28]. The Mediterranean Diet score (MDS) was used to assess the adherence to the MD pattern among cases and controls[29]. The MDS originally takes into account nine components of diet: fruit, vegetables, legumes, fish, meat and meat products, cereals, dairy products, alcohol and olive oil. For each component, a score from 0 to 2 is assigned to each participant, depending on the frequency of the consumption. As our questionnaire did not contain information on cereals, dairy products and olive oil, our score was based on six of the nine components of MDS. Thus, the final MDS range from a minimum of 0 point (lowest adherence) to a maximum of 12 point (maximum adherence).

For food groups typical of the MD (fruit, vegetables, legumes and fish) a score of 2 was assigned to the highest category of consumption, a score of 1 to the middle category, and a score of 0 to the lowest category. For food groups not typical of the MD (meat and meat products) a score of 0 was assigned to the highest category of consumption, a score of 1 to the middle category, and a score of 2 to the lowest. Finally, for alcohol consumption, a score of 0 was assigned to the highest category of consumption, a score of 2 to the middle category, and a score of 1 to the lowest.

Statistical Analysis

Descriptive statistics were used to describe the population included in the analysis. Pearson's Chi-square test was used to compare characteristics of cases and controls. Odds ratios (OR) and 95% confidence intervals (CI) of NAFLD were calculated for the MDS and the six components included in the MDS. We used unconditional logistic regression model adjusted for age, gender, total energy intake, diabetes status, smoking status, body mass index (BMI) and physical activity. All statistical tests were two-sided, and *p*-values < alpha (0.05) were considered statistically significant.

Statistical analysis was carried out using the Stata software (StataCorp. 2013. Stata Statistical Software: Release 13. StataCorp LP, College Station, TX, USA).

Table I. Characteristics of the 371 NAFLD cases and 444 controls. Fondazione Policlinico Universitario Agostino Gemelli, 2005-2017.

Characteristics	Cases (n=371)		Controls (n=444)		*p*-value[b]
	n	%[a]	n	%[a]	
Age (mean, SD)	59 (16.0)		45 (14.4)		
Gender					
Male	248	67.2	261	58.8	< 0.001
Females	121	32.8	183	41.2	
Cigarette smoking status					
Never	209	56.5	239	54.4	0.545
Former	83	22.4	113	25.7	
Current	78	21.1	87	19.8	
Alcohol drinking status					
Never	190	51.2	201	45.3	< 0.001
Former-Current	181	48.8	243	54.7	
Physical activity					
Never	129	34.9	216	49.4	< 0.001
< 1 times/day	128	34.6	130	29.7	
≥ 1 time/day	113	30.5	91	20.8	
Body mass index					
Underweight	13	3.5	47	10.6	< 0.001
Normal weight	78	21.0	192	43.3	
Overweight	170	45.8	117	26.4	
Obese	110	29.6	87	19.6	
Hypertension					
No	268	73.4	96	49.2	< 0.001
Yes	97	26.6	99	50.8	
Diabetes					
No	329	89.2	184	94.4	0.041
Yes	40	10.8	11	5.6	

[a]The percentages for each variable are computed based on the total number of non-missing observation;
[b]from χ^2-test.

Table II. Clinical features of the NAFLD patients by categories of the Mediterranean diet score (MDS).

Clinical parameters[a]	MDS[b]			
	0-5	6-7	>7	*p* for trend
Waist circumference – cm	101.6 (12.0)	99.9 (11.7)	100.7 (10.0)	0.351
Fasting glucose – mg/dL	98.7 (37.3)	97.3 (24.2)	99.9 (43.4)	0.519
Total cholesterol – mg/dL	200.6 (44.7)	198.7 (69.0)	195.9 (55.3)	0.175
HDL cholesterol – mg/dL	46.5 (16.4)	49.5 (17.6)	48.6 (14.5)	0.124
Triglycerides – mg/dL	158.1 (83.8)	135.8 (81.4)	142.0 (79.0)	0.045
GT – IU/L	64.2 (64.5)	67.8 (100.5)	73.6 (104.4)	0.337
AST – IU/L	40.5 (29.4)	37.6 (34.7)	34.1 (39.6)	0.019
ALT – IU/L	61.6 (43.3)	51.5 (34.3)	48.7 (49.1)	0.011
AST/ALT ratio	0.80 (0.5)	0.92 (0.8)	0.75 (0.3)	0.242

[a]Values are expressed as mean (standard deviation).
[b]The MDS, which ranges from 0 (minimal adherence) to 12 (maximal adherence), was categorized into 3 groups: 0-4, 5-7, and 8-12 points.

Results

We enrolled 371 NAFLD cases and 444 controls. Table I represents demographics, behavioural and clinical distribution of selected factors among cases and controls. There was a higher prevalence of man among cases and controls (67.2% and 58.8% respectively). The cases were significantly older than controls, and were more likely to be overweight or obese and to have diabetes. Table II reports the clinical features of NAFLD cases, expressed as mean level of waist circumference, fasting glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, gamma-glutamyl transferase (GT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) by categories of the MDS. Decreasing level of triglycerides, AST and ALT were observed for higher categories of the MDS ($p<0.05$). Table III represents the

Table III. Distribution of selected and behavioral variables by categories of the Mediterranean Diet Score (MDS), among 371 NAFLD cases and 444 controls.

	Cases				Controls			
	0-5	6-7	>7	p for trend	0-5	6-7	>7	p for trend
No. of subjects, n (%)	163 (43.9)	162 (43.7)	46 (12.4)		191 (43.0)	182 (41.0)	71 (16.0)	
Age (years) [mean (sd)]	41.7 (13.3)	46.2 (14.3)	49.9 (16.4)	<0.001	56.4 (17.0)	60.4 (15.2)	62.6 (14.2)	0.004
Male (%)	75% (68-81)	62% (55-69)	56% (41-70)	0.004	58% (51-65)	56% (49-63)	68% (56-78)	0.313
Current cigarette smokers (%)	25% (19-32)	18% (13-25)	18% (9-32)	0.128	20% (15-27)	20% (15-26)	19% (11-30)	0.813
BMI > 30 (%)	34.9% (28-43)	27.2% (21-35)	19.6% (10-34)	0.027	18.9% (14-25)	20.1% (16-27)	18.3% (11-29)	0.951
Physically inactive (%)[b]	41% (34-49)	35% (28-42)	13% (6-27)	<0.001	53% (46-60)	50% (43-58)	37% (26-49)	0.024
Hypertension (%)	21.1% (15-28)	31.9% (25-40)	27.3% (16-43)	0.112	49.5% (40-59)	52.6% (41-64)	50% (29-71)	0.821
Diabetes (%)	8.0% (5-13)	12.4% (8-19)	15.6% (7-29)	0.095	4.1% (1-11)	6.6% (3-15)	9.1% (2-33)	0.310

Values are expressed as mean (standard deviation) or percentage (95% confidence interval).
[a]The MDS, which ranges from 0 (minimal adherence) to 12 (maximal adherence), was categorized into 3 groups: 0-4, 5-7, and 8-12 points.
[b]Physically inactive were defined as those who not performed recreational or non-recreational physical activity.

Table IV. Odds ratios (ORs) and 95% confidence intervals (CIs) for NAFLD, according to six dietary components included in the Mediterranean diet score (MDS).

Dietary components[a]		Subjects n	%	ORb (95% CI)	Accuracy	Sensitivity	Specificity
MDS (as continuous)				0.83 (0.71-0.98)	80.1	91.5	58.6
Fruit score	0	164	20.1	1.00			
	1	509	62.5	0.67 (0.40-1.13)	78.9	90.7	59.6
	2	142	17.4	2.26 (0.97-5.29)			
Vegetables score	0	212	26.0	1.00			
	1	516	63.3	0.87 (0.54-1.40)	78.8	89.8	58.0
	2	87	10.7	1.81 (0.68-4.78)			
Legumes scorec	0	537	66.0	1.00	78.3	89.6	57.0
	1/2	277	34.0	0.62 (0.38-0.99)			
Fish score	0		371	45.6			
	1	329	40.4	0.67 (0.40-1.10) 1.00	78.8	89.8	58.0
	2	114	14.0	0.38 (0.17-0.85)			
Meat score	0	50	6.1	1.00			
	1	99	12.1	2.05 (0.65-6.52)	78.1	90.1	55.4
	2	666	81.7	1.90 (0.65-5.52)			
Alcohol score	0	55	6.7	1.00			
	1	573	70.3	1.76 (0.63-4.89)	79.2	89.3	60.1
	2	187	22.9	0.50 (0.17-1.44)			

[a]For fruit, vegetables, legumes, and fish, 2 points to the highest category of consumption, 1 point for the middle category and 0 point for the lowest category. Conversely, for meat 2 points for the lowest category, 1 point for the middle category and 0 point for the highest category of consumption. For alcohol (1 alcohol unit=12 g of alcohol), 2 points to the middle category (1-2 alcohol units/d), 1 point to the lowest category (<1 alcohol unit/d) and 0 point to the highest category of consumption (>2 alcohol units/d).
[b]Estimates from logistic regression adjusted for age, gender, total energy intake, diabetes status, smoking status, body mass index and physical activity.
[c]The legumes score was categorized in 2 classes because of the small number of individuals in the class = 2.

distribution of selected variables by categories of the MDS scores among cases and controls. In both groups, the older patients had significantly higher MDS (p<0.001 and p=0.004 respectively), while among cases only, males had lower adherence to MD compared to the females (p=0.004). NAFLD patients with BMI > 30 had significantly lower MDS scores (p=0.027). For both cases and controls, the percentages of patients physically inactive significantly decreased for higher categories of the MDS. Table IV reports the ORs and 95% CIs for NAFLD according to the MDS and to the different components of MDS. Adherence to the MD was significantly associated with a reduced risk of NAFLD (OR 0.83, 95% CI: 0.71-0.98). A high consumption of fish (OR 0.38, 95% CI: 0.17-0.85) and legumes (OR 0.62, 95% CI: 0.38-0.99) were significantly associated with decreased risk of NAFLD. No significant associations were reported for the other components of the MDS.

Discussion

In this study, we report that higher adherence to MD is associated with lower risk of NAFLD, when adjusting for age, gender and additional potential risk factors, such as total energy intake, diabetes status, smoking status, body mass index, and physical activity. In particular, high consumption of two components of MD, fish and legumes, were significantly associated with lower NAFLD risk. Several reviews and meta-analyses[30-32] have already documented the effect of nutrition in the ethology of NAFLD, showing that a diet rich in fat and sugar increases the risk of getting the disease. The MD has been already established as a preventive diet in many NAFLD related diseases, such as cardiovascular disease, diabetes and hypertension[7]. There is increasing evidence that MD is one of the best dietary patterns for NAFLD's prevention and therapy due to its capability of reducing liver fat without weight loss. Furthermore, the MD can also be effective in reducing liver steatosis and improving insulin sensitivity in patients with NAFLD[33]. However, there is still the need of more well-designed studies to evaluate these associations, as well as to define the exact macronutrients' composition that is most useful[18]. Even though most of this evidence on the effect of the MD on NAFLD is based on intervention studies that evaluated the use of MD pattern as a therapeutic option, our study is in line with the general conclusions about its potential beneficial effect on this disease. Implementing and pursuing lifestyle and dietary treatment for an asymptomatic and poorly known disease is quite difficult for most of the patients. Recently, Shira Zelber-Sagi et al[34] highlighted, on a cohort of 146 NAFLD patients, that more than a half of study participants did not feel to have fully understood what NAFLD is and that a better knowledge of the disease and his consequences was associated with better nutritional habits. To the best of our knowledge, only few studies evaluated the association between adherence to the MD and risk of NAFLD. Trovato et al[35] tested the effect of adherence to MD in 532 NAFLD patient and 667 controls: adherence score to MD resulted one of the most powerful independent predictors of fatty liver severity. Kontogianni et al[36] reported that adherence to MD was not associated with the risk of NAFLD, although a significant association was reported with lower degree of insulin resistance and severity of liver disease among NAFLD patients only. However, this study was conducted on a population lower than 150 subjects, which did not allow the possibility of adjustment for additional risk factors. Baratta et al[37] found an inverse relationship between MD and NAFLD in a sample of 584 patients; moreover, the authors observed an association between higher adherence to MD and lower insulin resistance among NAFLD patients only. Considering the specific components of the MD, our study reported that only high fish and legumes consumption were significantly associated with decreased risk of NAFLD. A higher consumption in fish, omega-3 fatty acids, as well as the dietary fibres and antioxidants present in the legumes, have been already reported to be protective and beneficial to NAFLD. Several studies[38,39] from the literature that the high fructose consumption increases the risk for NAFLD. In addition, the current studies demonstrated positive associations between higher vegetable, low meat and moderate alcohol consumption and the disease risk and development. However, our data did not report an association between these components individually. Given these results, it is likely that the beneficial role in the MD lies in the synergy among the nutrient foods from all of the individual components together, rather than the individual consumption.

In the era of precision medicine, even if the personalization of diet represents a goal for preventing the progression of metabolic disease[40,41], the adherence to the diet programme is still a key for the success of any preventive approach.

The main strength of our study was the large sample size that allowed us to test the association of the individual components of the MD and to adjust for several potential confounding factors.

However, some limitations of our study need to be considered. Firstly, the retrospective way in which the data for the cases were collected may have introduced recall bias, since the patients were asked to report the dietary habits referred to 1 year before the diagnosis. Additionally, we used a food frequency questionnaire for the assessment of the adherence to the MD which can be affected by measurement errors[42]. Lastly, we did not have information about three of the nine components of the MD: cereals, olive oil and dairy products. There is the possibility that this missing information could have affected the results by increasing or decreasing the association between MD adherence and NAFLD.

Conclusions

Our study showed that higher adherence to the MD decreases the risk of NAFLD. However, given some limitations of our study, additional studies that include all of the components of the MDS are needed in order to further explore this association.

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Authorship

LG and LM are the principal investigators of the study and responsible for study design and writing most of the manuscript. LG performed the statistical analysis and drafted the tables. KA and MAP contributed to data cleaning, analysis and interpretation. DA was involved in data entry. EM formulated the research question (together with SB). FM, MB, GM, CC and SR acquired the data and provided critical intellectual feedback to help revise the manuscript. AGM, AG and AL critically reviewed the project. SB and AG supervised the project. All authors have read and approved the final manuscript.

Conflict of Interests

The authors declare that they have no conflict of interest.

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