Original article

Adherence to Mediterranean diet in Crohn's disease is associated with better quality of life, lower disease activity and less systemic inflammation

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Abstract

Objective: Since the Mediterranean diet (MD) is a dietary pattern with several health benefits, but adherence and its effects in patients with Crohn's Disease (CD) have not yet been investigated, the objectives of the present study were a) to assess the adherence to MD in patients with CD and b) to examine the association of adherence to MD with quality of life, disease activity and inflammatory markers.

Design: Outpatients with CD were enrolled in this protocol. Medical history, disease activity, dietary intake, habitual Mediterranean Diet (MedDiet) score, anthropometric measurements and Inflammatory Bowel Disease Questionnaire (IBDQ) were recorded. Blood samples were collected for quantification of biochemical and inflammatory indices. Statistical analysis was conducted with the SPSS software.

Results: A total of 86 patients with CD were enrolled: 41 in relapse (5≤ Harvey Bradshaw Index ≤14) and 45 in remission (Harvey Bradshaw Index ≤4). Adherence to MD was greater in patients with inactive disease. The MedDiet score correlated positively with the IBDQ ($p=0.008$) and negatively with disease activity ($p<0.001$).

Conclusion: Adherence to MD is associated with improved quality of life in CD patients. Counselling regarding the MD could therefore be of importance in patients with CD to improve quality of life and reduce disease activity.

Summary "box"

What is already known about this subject?

- Nutrition seems to play a role both in the development and the management of IBD.
- Mediterranean diet (MD) is a dietary pattern with several health benefits.
- Adherence to MD and its effects in patients with Crohn's Disease (CD) have not yet been investigated.

What are the new findings?

- Adherence to MD is positively associated with improved quality of life and negatively with disease activity.
- Adherence to MD is greater in patients with inactive CD compared with active CD.

How might it impact on clinical practice in the foreseeable future?

- Counseling regarding the Mediterranean diet should be considered in patients with CD as a dietary treatment approach to improve quality of life and reduce disease activity.

Keywords: Mediterranean diet; Crohn's disease; Quality of life; Systemic Inflammation

INTRODUCTION

Inflammatory Bowel Disease (IBD) - a chronic gastrointestinal condition including Crohn's Disease (CD) and Ulcerative Colitis (UC) - is considered a global challenge (Ng et al., 2018). Patients experience periods of relapse and remission, while the prolonged nature of IBD affects health-related quality of life, economic productivity and social function.

Nutrition seems to play a role both in the development and the management of IBD. Western diets may increase the risk for IBD, while Mediterranean diet (MD) may exhibit a protective effect (Gentschew & Ferguson, 2012; Hou et al., 2011).

Some dietary patterns have been of interest in IBD, such as low-FODMAP diet (Gibson, 2017) and specific-carbohydrate diet (SCD) (Suskind et al., 2016). Overall, patients in remission are encouraged to follow a balanced diet, while in acute phases individual intolerances should be considered in alleviating symptoms. However, drastic exclusion of foods should be avoided as there is a high risk for nutritional deficiencies, and reliable achievement of remission is anyway not established (Forbes et al., 2017).

The Mediterranean diet (MD) is a dietary regimen characterised by relatively high consumption of olive oil, legumes, grains, vegetables, fruits, nuts and seeds, a moderate consumption of fish, poultry and dairy foods, but low consumption of processed foods, and of red and processed meat. Its proportionally high contents of monounsaturated fatty acids, omega-3 polyunsaturated fatty acids, dietary fibre and phytochemicals together confer the beneficial anti-inflammatory and antioxidant properties that have been documented against chronic diseases (Martinez-Gonzalez & Martin-Calvo, 2016). Additionally, MD adherence has been found to beneficially affect the gut microbiota and associate metabolome (De Philippis et al., 2016). Since CD is a chronic disease

characterised by inflammation and oxidative stress, MD could potentially be beneficial for patients and is advocated by IBD clinicians in some parts of the world. Greek CD patients are typically advised by clinicians not to exclude specific food groups and try to consume foods from different food groups. However, no specific recommendation as regards MD is given, since this dietary regimen has not been formally investigated regarding its effect on CD.

Thus, the aims of the present study were: a) to assess the habitual adherence to MD in patients with CD and b) to examine the association of adherence to MD with quality of life, disease activity and inflammatory markers.

MATERIALS AND METHODS

Ethics

The protocol was reviewed and approved by the Harokopio University Ethics Committee (49/29-10-2015) and the study was conducted according to the principles of the Declaration of Helsinki of 1975. Laboratory techniques were standardised and the personnel were trained according to Good Clinical Practice.

Participants

Enrolment was stimulated through an announcement to the *Hellenic Society of CD and UC patients*. Outpatients with endoscopically proven CD were enrolled subject to certain inclusion and exclusion criteria. Adult males and females were included. Patients were excluded in case of positive stool culture for enteric pathogens or Clostridium difficile toxin or when they had undergone bowel surgery ≤3 months prior to screening. Additionally, clinically significant short bowel syndrome, the presence of an intra-abdominal abscess or a fistula with clinical or radiological evidence of an associated abscess, ileostomy and colostomy were set as exclusion criteria. Enteral or parenteral nutrition, alcohol or drug abuse, vitamin or inorganic supplement use in the 6 months prior to screening, a vegan or macrobiotic diet in the 5 years prior to screening, any malignancy in the year prior to screening or cancer survivors <10 years, the presence of serious cardiovascular disease, peptic ulcer, pregnancy, and lactation were considered as exclusion criteria. After receiving full information about the study, participating patients provided written Informed Consent, a copy of which was given to the individual. Patients were recruited between May 2016 and June 2017. The study took place in

Athens, Greece.

Assessment of patients

Medical history*:* A gastroenterologist recorded the medical history, including general information (e.g. allergic reactions, smoking habits, etc.) as well as specific data regarding CD (i.e. brief history of CD, age of diagnosis, complications, treatment). Assessment of disease severity was based on the Harvey-Bradshaw Index (HBI) (Harvey & Bradshaw, 1980).

Dietary assessment:

Adherence to MD was evaluated by an experienced dietitian using the MedDiet scoring method, which is based on the inherent characteristics of the MD (Supplementary material, Table S1). This score was recorded for the mean frequency of consumption of each food group in the past 6 months. MedDiet food groups include non-refined cereals, fruit, vegetables, legumes, potatoes, fish, meat and meat products, poultry, full fat dairy products, as well as olive oil and alcohol. For the consumption of items presumed to be close to the Mediterranean Dietary pattern (i.e. those suggested on a daily basis or more than 4 servings/week; non-refined cereals, fruits, vegetables, legumes, olive oil, fish, and potatoes) the dietitian would assign: a score of 0 for no consumption; 1 for reported consumption of 1-4 servings/month; 2 for 5-8 servings/month; 3 for 9-12 servings/month; 4 for 13-18 servings/month; and a score of 5 for more than 18 servings/month. For the consumption of foods that are distant from the MD the scores are assigned on a reverse scale. For example, for alcohol the score is 5 for consumption of less than 100 ml of alcoholic beverages/day, 0 for consumption of more than 700 ml of alcoholic beverages/day and 4-1 for consumption of 300, 400-500, 600 and 700 or 0

ml of alcoholic beverages/day, respectively. The calculation is based on the central role of wine consumption (approx. 12% ethanol) in the Mediterranean diet and 100ml of alcoholic bevarages is equivalent with 12g of ethanol. According to this rating scale, the MedDiet score ranges from 0 to 55 with higher values indicating greater adherence (Panagiotakos et al., 2006).

An experienced dietitian recorded the 24-hour recall dietary intake and assessed the macronutrient and micronutrient composition of the diet with the software package Nutritionist Pro™ (Axxya Systems).

Quality of life assessment*:* Quality of life was assessed with the Inflammatory Bowel Disease Questionnaire (IBDQ). The IBDQ includes 32 questions about bowel habit, social, systemic and emotional performance and is scored from 32 to 224 points. Higher scores indicate a better quality of life (Guyatt et al., 1989).

Blood sample collection*:* Standard blood sampling (20mL) took place. After collection, blood samples were centrifuged at 3000rpm for 10 minutes at 4°C for plasma and serum isolation. All samples were stored at -80°C until further analysis.

Anthropometric assessment: Body weight was measured to the nearest 0.1 kg. Height was measured with a standard stadiometer to the nearest millimetre. Both measurements were performed twice. Body Mass Index (BMI) was also calculated.

Laboratory analyses

Biochemical analyses*:* Serum iron (Fe), albumin, glucose, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides and plasma fibrinogen were quantified with an automatic biochemical analyser. Routine laboratory tests included also serum amylase, lactate dehydrogenase (LDH), glutamic-oxaloacetic

transaminase (SGOT), glutamic-pyruvic transaminase (SGPT), γ-glutamyl transferase (γ-GT), alkaline phospatase (ALP) and C-reactive protein (CRP).

Serum interleukin (IL)-6 and IL-10 were measured by sandwich ELISA (Biotek PowerWave XS2; R&D Systems, Inc. for IL-6, OriGene Technologies, Inc. for IL-10).

Statistical analysis

Data are expressed as mean ± standard deviation (SD). The differences between two independent groups were analysed using Student's t-test for normally distributed variables and Mann-Whitney U test for those not normally distributed. Spearman's correlation tests were used for the correlation analysis. For parameters with a significant bivariate association with the MedDiet score, multivariate linear regression models were applied. A P value ≤ 0.05 was considered as significant. Statistical analysis was conducted with the SPSS software (SPSS for Windows, version 21.0, SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 86 patients diagnosed with CD met our inclusion criteria. Table 1 shows the clinical and demographic characteristics of those with active and inactive disease. As expected, the HBI was significantly lower in inactive disease ($p<0.001$), whereas the IBDQ score was higher in inactive disease ($p<0.001$). The biochemical indices are presented in Table 2. Active CD patients had significantly higher levels of fibrinogen ($p=0.039$) and IL-6 ($p=<0.001$), and lower levels of IL-10 ($p=0.025$).

With respect to adherence to MD, the MedDiet score was higher in patients with inactive CD than in those with active disease (26.8±5.0 vs 30.2±5.8, $p=0.005$). Also, protein intake ($p=0.015$) and vitamin C ($p=0.003$) levels were individually higher in the remission group (Table 3).

Correlation analyses were conducted for HBI and inflammatory markers with the MedDiet score, regardless of remission/relapse status, and the significant associations are presented in Table 4. There was a significant negative correlation of the MedDiet score with HBI ($r = -0.400$, $P < 0.001$) and CRP levels ($r = -0.268$, $P = 0.027$), while there was a positive correlation of MedDiet score with IBDQ ($r = 0.291$, $P = 0.008$). No significant correlation was observed between the MedDiet score and IL-6 ($p=0.125$) or between MedDiet and IL-10 ($p=0.137$).

Significantly correlated parameters were tested in a linear regression model with an adjustment for age, sex and BMI. HBI showed a highly significant negative linear correlation with the MedDiet score - B = -0.190 [95%CI: -0.252 to -0.128], ($p=0.003$), whereas IBDQ showed a positive linear correlation with MedDiet score - B = 1.342 [95%CI: 0.778-1.906], $p=0.020$).

Energy intake, carbohydrate, protein, cholesterol, saturated fatty acid, fat, calcium,

selenium and iron intake were significantly higher and caffeine intake was significantly lower in males with inactive CD than in females (Supplementary material, Table S2).

DISCUSSION

IBD often compromises the nutritional status of patients. Currently international guidelines recommend no specific diet for IBD. The effects of the Mediterranean Diet - a dietary regimen with several health benefits attributed to its anti-inflammatory and antioxidant components – has hitherto been inadequately explored in IBD patients.

Herein, we identified a higher MedDiet score in patients with inactive CD. Although no cut-off values exist in the MedDiet score such that patients could be classified as adherent or non-adherent, it is evident that patients in remission are more likely to be following a MD. A plethora of different diet scores has been developed in order to study overall dietary patterns rather than taking a single nutrient approach to various health outcomes. The large scale of the MedDiet score is considered to render it more informative when compared with small-scale scores that fail to capture the extremes and the inherent characteristics of a pattern or a behaviour, or which may not give good predictions in cases where the outcome is of a continuous rather than binary nature (Panagiotakos et al., 2006).

In this study the MedDiet score was negatively associated with HBI and CRP, while it was positively associated with IBDQ. When we adjusted for age, sex and BMI, HBI showed a highly significant negative linear correlation with the MedDiet score, while IBDQ showed a positive linear correlation with MedDiet score. Thus, we hypothesise that as adherence to the MD increases, disease activity decreases, leading to an improved quality of life. Another study assessing adherence to MD in CD patients in remission using a different tool, namely an adapted 13-item PREDIMED Mediterranean Diet Score (P-MDS) showed that only few patients met those criteria for MD, and that overall scores were generally low (Taylor et al., 2018). The association of adherence to

MD with quality of life in CD may however explain the benefits of low-FODMAP diet in CD (Prince et al., 2016), as the latter is replicating in part the MD pattern.

Our results correspond to those of studies evaluating the association of the MD with other chronic inflammatory entities. Veronese and colleagues (2016) showed that adherence to the MD is associated with better quality of life, decreased pain, disability and depressive symptoms in patients with osteoarthritis, and adherence to the MD was associated with better quality of life in patients with type 2 diabetes (Alcubierre et al., 2016).

Our protocol has both strengths and limitations. According to our knowledge this is the first study that has evaluated adherence to MD and its association with disease activity and quality of life in patients with CD. The MedDiet score is a validated tool that allows for the prediction of disease risk better than other scores, and was developed to achieve analysis of a holistic dietary pattern rather than a single nutrient approach to health outcomes. The IBDQ, which is the most widely used tool to assess the quality of life in IBD patients (Alrubaiy et al., 2015) is similarly validated, in Greek as well as in English (Pallis et al., 2001) and is well respected. The limitations from the modest number of participants and the indirect assessment of dietary intake using 24 hour recall, are well compensated by the fact that only a single experienced dietitian undertook the interview and assessment to avoid biases.

Conclusion

This study shows for the first time that greater adherence to MD is associated with improved quality of life in CD patients and it is negatively associated with disease activity. Thus, dietary assessment of CD patients applying simple but validated tools

and counselling regarding the MD are likely to be important in the nutritional management of CD. Future studies should address implementation of these conclusions.

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Statement of Authorship

All authors contributed to the design, analysis and interpretation of the study. Patients were recruited by EP, CA and ACK. The dietary assessments were performed by EP. All authors contributed to the writing of the final manuscript, with which all are in agreement.

Conflict of Interest Statement. The authors declare that they have no conflicts of interest.

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Table 1. Demographic characteristics and clinical features of active and inactive CD patients

	Active (N=41)	**Inactive (N=45)**	***P***
Age (years)	41.5±16.5	37.4±11.5	0.366
Sex (female : male)	23:18	18:27	
BMI (kg/m^2)	23.0±5.2	24.8±4.2	**0.011**
Smoking habit (n%)	15 (36.6%)	16 (35.6%)	
Marital status			
Married	20	20	
Unmarried	20	22	
Divorced	1	3	
Education			
1-9 years	4	8	
10-12 years	9	9	
>12 years	28	28	
Extend of disease			
Colonic	2	5	
Ileocolonic	14	15	
Ileal	17	11	
Other	8	14	
Current medical treatment			
Mesalazine	9	15	
Azathioprine	9	15	
Corticosteroids	17	11	
Harvey-Bradshaw index (HBI)	7.3±2.4	2.5±1.2	**<0. 001**
IBDQ	144.9±24.0	176.1±25.6	**<0.001**

Table 2. Biochemical indices according to disease activity.

	Active (N=41)	**Inactive (N=45)**	***P***
IL-6 (pg/mL)	16.7±16.4	4.8±6.6	**<0.001**
IL-10 (pg/mL)	4.9±1.4	5.6±1.6	**0.025**
CRP (mg/L)	8.9±9.5	7.0±10.6	0.103
Amylase (IU/L)	66.2±20.7	71.2±26.7	0.515
Fibrinogen (mg/dL)	294.1±71.7	259.4±73.7	**0.039**
Fe (µg/dL)	66.3±67.1	67.1±34.0	0.250
Glucose (mg/dL)	84.4±12.4	89.0±15.7	0.170
Total cholesterol (mg/dL)	168.4±44.0	171.7±45.7	0.809
HDL (mg/dL)	50.5±14.8	50.8±13.4	0.910
LDL (mg/dL)	92.1±34.8	98.3±39.7	0.587
Triglycerides (mg/dL)	128.8±90.9	112.8±62.0	0.246
Albumin (g/dL)	3.9.±1.3	4.2±0.7	0.439
SGOT (IU/L)	16.2±9.4	18.6±8.6	0.065
SGPT (IU/L)	19.2±14.5	19.3±9.6	0.344
γ-GT (IU/L)	20.9±14.5	27.2±64.4	0.590
Alkaline phosphatase (IU/L)	67.1±23.8	67.4±36.8	0.541
Lactate dehydrogenase (U/L)	141.4±31.1	148.7±32.5	0.321

Values are presented as mean±SD
Differences between groups were analysed by Mann-Whitney U test or Student's test

Table 3. Mediterranean diet score and dietary habits according to disease activity in Crohn's disease.

	Active (N=41)	**Inactive (N=45)**	***P***
MedDiet score	26.8±5.0	30.2±5.8	**0.005**
Energy intake (kcal)	1812.1±646.8	2069.0±825.2	0.309
Carbohydrates (g)	204.7±85.7	215.4±108.4	0.982
Proteins (g)	78.3±33.3	100.1±42.2	**0.015**
Fats (g)	77.2±40.3	87.1±43.8	0.313
Cholesterol (mg)	306.4±420.1	288.8±176.1	0.433
Saturated FA (g)	25.2±13.4	27.2±15.7	0.548
Monounsaturated FA (g)	33.2±21.1	37.3±23.0	0.272
Polyunsaturated FA(g)	12.2±8.0	13.4±8.2	0.407
Oleic acid (g)	27.9±20.0	31.1±21.5	0.326
Linoleic acid (g)	9.4±7.1	10.5±7.5	0.384
Linolenic acid (g)	1.15±0.8	1.20±0.8	0.473
Eicosapentaenoic acid (g)	0.09±0.3	0.07±0.2	0.926
Docosahexaenoic acid (g)	0.14±0.5	0.15±0.4	0.795
Trans FA (g)	0.8±1.9	0.4±0.7	0.714
β-Carotene (µg)	1421.1±2875.3	1739.9±2959.5	0.493
α-Carotene (µg)	292.8±697.4	471.7±1137.8	0.238
Lycopene (µg)	4947.0±14561.9	4357.8±7278.0	0.585
Vitamin C (mg)	46.6±53.1	146.5±490.5	**0.003**
Calcium (mg)	755.4±439.1	900.3±508.5	0.192
Iron (mg)	11.0±4.3	14.1±7.1	0.058
Vitamin D (µg)	3.3±7.2	2.7±3.0	0.631
Vitamin E (mg)	0.8±1.8	0.6±1.2	0.465
a-Tocopherol (mg)	5.9±4.3	6.9±5.5	0.507
Vitamin K (µg)	57.8±75.0	66.3±66.3	0.300
Selenium (µg)	100.8±50.6	124.7±70.6	0.077
Fiber(g)	13.3±8.2	18.8±13.2	0.089
Glucose (g)	7.5±6.8	10.7±8.9	0.075

Lactose (g)	4.5±8.8	4.0±5.8	0.434
Fructose (g)	9.1±9.1	13.3±12.7	0.118
Caffeine (mg)	225.2±450.3	313.2±504.0	0.473

Values are presented as mean±SD. Differences between groups were analysed by Mann-Whitney U test or Student's test
FA: fatty acids

Table 4. Correlation analysis between the MedDiet score and disease activity indices and CRP in CD patients.

	CD patients (N=86)	***P***
IBDQ	0.291	**0.008**
HBI	-0.400	**<0.001**
CRP (mg/L)	-0.268	**0.027**