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Inflammatory potential of diet and risk of ulcerative colitis in a case-control study from Iran

Nitin Shivappa[1,2], **James R. Hébert**[1,2], **Samaneh Rashvand**[3], **Bahram Rashidkhani**[3], and **Azita Hekmatdoost**[4]

[1]Cancer Prevention and Control Program, University of South Carolina, Columbia, SC 29208, USA

[2]Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC 29208, USA

[3]Department of Community Nutrition, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute (WHO Collaborating Center), Shahid Beheshti University of Medical Sciences, Tehran, Iran

[4]Department of Clinical Nutrition and Dietetics, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background—Diet and inflammation have been suggested to be important risk factors for ulcerative colitis (UC).

Objectives—In this case-control study conducted in Iran, we examined the ability of the dietary inflammatory index (DII) to predict UC.

Methods—This case-control study included 62 UC cases and 124 controls hospitalized for acute non-neoplastic diseases. The DII was computed based on dietary intake assessed by a previously validated food frequency questionnaire. Multivariable logistic regression models were used to estimate odds ratios (ORs) and the DII was analyzed as both continuous and as tertiles. Energy was adjusted using the residual method.

Results—Subjects with higher DII scores (i.e., with a more pro-inflammatory diet) had a higher risk of UC, with the DII being used as both a continuous variable ($OR_{continuous}$ 1.55, 95% confidence interval, CI, 1.04–2.32; one unit increase corresponding to ≈18% of its range in the current study) and as tertiles ($OR_{tertile3vstertile1}$ 2.58, 95%CI 1.03–6.48, P_{trend}=0.04).

Address correspondence and reprint requests to: Prof. Bahram Rashidkhani, Phone: (0098) 9127388016, Fax: (0098)(21) 22376467, ; Email: rashidkhani@yahoo.com, ; Email: b_rashidkhani@sbmu.ac.ir and Dr Azita Hekmatdoost, ; Email: a_hekmat2000@yahoo.com

Disclosure: Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI.

Conflicts: All authors declare no conflict of interest.

Conclusions—These results indicate that a pro-inflammatory diet is associated with increased risk of UC.

Introduction

Chronic inflammation, which is characterized by the continuous presence of inflammatory cytokines in circulation and in the tissues, is known to play a key role in the development of inflammatory bowel disease (IBD) (1–3). It has been shown that chronic inflammation is important in triggering the development of ulcerative colitis (UC) (4), which is characterized by pain in the lower left abdomen, diarrhea, weight loss, rectal bleeding (5), and frequent relapses and remissions (6). In general, UC is a disease caused by a complex interaction of environmental, genetic, and immunoregulatory factors (7). Diet may influence gut inflammation through several biologically plausible mechanisms, including antigen presentation, change in prostaglandin balance, and alteration of the microflora (8). Several studies have examined the association between dietary intake and food groups and UC (9–11).

Diet represents a complex set of exposures that often interact, and whose cumulative effect modifies both inflammatory responses and health outcomes. A literature-derived, population-based dietary inflammatory index (DII) was developed to assess the inflammatory potential of an individual's diet (12), and has been validated with various inflammatory markers, including C-reactive protein (12, 13), interleukin-6 (14, 15), and homocysteine (15). Additionally, the DII has been shown to be associated with the glucose intolerant component of metabolic syndrome in American police officers (13); shift work status in a large population-based survey in the USA (13); asthma in Australia (14); obesity measures in Spain (16) and colorectal, pancreatic and prostate cancers (15, 17–19).

Our hypothesis is that a higher DII score (indicating a pro-inflammatory diet) is associated with increased risk of incident UC. In the current study, we thus examined this putative association using a case-control study conducted in Iran. This provided original information on an Iranian population where dietary and lifestyle habits and awareness of diet-related health issues are different from those in North America and Europe.

Methods and Materials

Study Population

A case-control study based on patients newly diagnosed (<6 months) with UC was carried out. Overall, 62 new cases of UC and 124 healthy controls between 20 and 80 years of age were studied. Participants were recruited from a referral hospital in Tabriz during 2013. The medical records of all cases were reviewed to confirm the diagnosis. In addition, UC patients reporting history of any other gastrointestinal illness, carcinoma, and autoimmune disease, other inflammatory and infectious disorders were excluded. Controls were patients visiting the outpatient orthopedic clinics of the same hospitals. Controls were frequency-matched with cases on sex and age (10-yr groups). Only those controls without a concurrent history of any gastrointestinal illness/symptoms (irritable bowel syndrome, gastroesophageal reflux, diarrhea, abdominal pain, etc.), or condition likely to be related to dietary habits including

diabetes, cardiovascular disease, gout, and hyperlipidemia, were recruited. Face-to-face interviews were conducted by a trained interviewer in private. Participants completed questionnaires on demography, medical history, medications, diet, alcohol, smoking, appendectomy, helicobacter pylori, education, and family history of UC. In terms of maximal education attained for analysis we stratified according to attainment: primary, secondary, and tertiary (i.e., having attended at least high school). Weight was measured with subjects standing without shoes and was recorded to the nearest 1kg. Height was measured while subjects were in a standing position without shoes, using a non-stretch tape meter fixed to a wall and was recorded to the nearest 1 cm. Body mass index (BMI) was then calculated by dividing weight (in kilograms) by the square of height (in meters).

Informed consent was obtained from each participant prior to enrollment. The study protocol was approved by the ethics committee at the National Nutrition and Food Technology Research Institute of Shahid Beheshti University of Medical Science.

Assessment of Diet and Dietary Inflammatory Index

Information on usual diet was measured by country-specific food frequency questionnaires (FFQ) that was modified to include Iranian food items (20). This semiquantitative FFQ acquired information on 168 foods. Previously, it has shown relative validity and reproducibility in Iranian adults and appeared to be an acceptable tool for assessing dietary intakes in this population (21). Dietary habits of cases one year prior to diagnosis and controls one year before the interview were collected. Nutrient consumption was then calculated using the Nutrient Composition of Iranian Foods (NCIF) (22) supplemented with the USDA Food Composition Data. The consumption of alcohol was not asked to our participants due to their cultural beliefs and concomitant low levels of intake, and therefore was not included in the analysis.

FFQ-derived dietary data were used to calculate DII scores for all participants. The DII is based on literature published through 2010 linking diet to inflammation. Individuals' intakes of food parameters on which the DII is based are then compared to a world standard database. A complete description of the DII is available elsewhere (18). A description of validation work, including DII derived from both dietary recalls and a structured questionnaire similar to an FFQ and related to interval values of hs-CRP, also is available (15). Briefly, to calculate DII for the participants of this study, the dietary data were first linked to the regionally representative world database that provided a robust estimate of a mean and standard deviation for each parameter (18). These then become the multipliers to express an individual's exposure relative to the "standard global mean" as a z-score. This is achieved by subtracting the "standard global mean" from the amount reported and dividing this value by the standard deviation. To minimize the effect of "right skewing" (a common occurrence with dietary data), this value is then converted to a centered percentile score. The centered percentile score for each food parameter for each individual was then multiplied by the respective food parameter effect score, which is derived from the literature review, in order to obtain a food parameter-specific DII score for an individual. All of the food parameter-specific DII scores are then summed to create the overall DII score for every participant in the study (18). A total of 27 food parameters were available from the FFQ and

therefore could be used to calculate DII. The include carbohydrate, protein, total fat, fiber, cholesterol, saturated fat, mono-unsaturated fat, poly unsaturated fat, omega-3, omega-6, niacin, thiamin, riboflavin, vitamin B12, vitamin B6, iron, magnesium, selenium, zinc, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, beta carotene, onion and pepper.

Group comparisons by each factor were done using χ^2 analysis, significance level was set at $\alpha = 0.05$. Various study characteristics were examined across the DII expressed as continuous and as tertiles using *Student t*-test or χ^2 test for continuous and categorical variables, respectively. Energy adjustment was done using the residual method. The DII was analyzed both as a continuous variable and as tertiles; odds ratios and 95% confidence intervals (OR; 95% CI) were estimated using logistic regression models, adjusting only for age and energy, and then fitting a model with additional adjustment for sex, education, BMI, family history of IBD, appendectomy, smoking, H.*pylori* infection and non-steroidal anti-inflammatory drug (NSAID) use. Statistical tests were performed using SAS® 9.3 (SAS Institute Inc., Cary, NC); all p values were based on two-sided tests.

Results

The DII score in this study ranged from −2.69 (most anti-inflammatory score) to +2.70 (most pro-inflammatory score). Table 1 shows the distribution of the 62 cases of UC and 124 controls according to selected variables. By design, age and sex distributions were similar in cases and controls (Table 1). Each identified case of UC was clinically confirmed by a physician. The data were 100% complete for all cases and controls. Education, cigarette smoking, family history of UC and BMI was similar between UC and controls, while there was a significant difference between two groups on energy intake, sex and H.*pylori* infection. Study characteristics across categories of DII are provided in Table 2. There were no major differences in sociodemographic factors and other lifestyle habits across DII categories.

Odds ratios (OR) and 95% confidence intervals (CI) for the risk of UC are shown in Table 3. Results obtained from modeling DII as a continuous variable in relation to risk of UC showed a positive association after adjustment for age and energy (OR=1.46; 95% CI=1.02–2.10) and in the multivariate analyses analysis (OR=1.55; 95% CI=1.04–2.32). When analysis was carried out with DII expressed as tertiles, and adjusting for age and energy, there was no significant association observed with UC. After multivariable adjustment, subjects in tertile 3 were at 158% higher odds of having UC compared to subjects in tertile 1 ($OR_{tertile3vs1}$ =2.58; 95% CI=1.03–6.48, P_{trend}=0.04).

Discussion

In this case-control study, we found that subjects with the higher DII (i.e., those who had the most pro-inflammatory diets) were at increased risk of developing UC, a result supporting our hypothesis that consuming a more pro-inflammatory diet is associated with an increased risk of UC. In a previous case-control study conducted in the same catchment area in which this study was based, we found that higher consumption of total fat, oleic acid, saturated fat, total PUFA, trans fat, MUFA, and linoleic acid were significantly associated with increased

risk for UC; however, no statistically significant association was detected between the risk of UC and intake of n-3 PUFAs or cholesterol (23). Previously, the DII has been shown to be associated with reduced bone mineral density (24) and esophageal squamous cell cancer (25) in similar Iranian populations.

Consumption of food items such as vegetables and fruits have been shown to reduce inflammation (26), while others, such as red and processed meat, increase inflammation (27). This is the first study conducted in Iran to examine the association between inflammatory potential of diet and UC. It also is the first time the DII has been tested with UC as an outcome. Previous studies have shown different dietary components to have varying effect on UC (10, 28). A multicenter case-controls study in Japan showed UC to be positively associated with sweets and inversely associated with vitamin C (28). In the Nurse's Health Study, a high intake of dietary long-chain n-3 PUFAs was associated with a reduced risk of UC; in contrast, high intake of trans-unsaturated fats were associated with an increased risk of UC (10), and no association was observed with dietary fiber intake (29). Although, the above results gives an idea about the effect of specific food items and nutrients, they do not provide information on the inflammatory potential of an entire diet, which would be the cumulative effect of all these nutrients and food items. The DII was developed to assess this, by placing a person's diet on a continuum from maximally pro-inflammatory diet to a maximally anti-inflammatory diet (12). In formulating the DII, a different approach was taken by focusing on the functional effects of foods and nutrients. As such, it relies on reviewing and scoring of the peer-reviewed literature on the subject of diet and inflammation. Moreover, it standardizes individuals' dietary intakes of pro- and anti-inflammatory food constituents to world referent values, which results in values that are not dependent on idiosyncrasies of the units of consumption (e.g., simply expressing exposure in micrograms instead of milligrams) and can be used for comparison across studies.

One of the possible mechanisms for the observed direct association of the DII with UC is through the effect of pro-inflammatory diet on mucosal inflammation, which is characterized by the increased production of cytokines from the dendritic cells of lamina propria of the colon (30). Diet also plays an important role in the epithelial barrier function, which in turn has an effect on mucosal inflammation (31).

Potential limitations of this study include reliability and validity of the estimation of average food intakes which were based on the relatively limited number of food items (168 items, which is moderately long for an FFQ). As with other case–control studies, recall bias is possible. In case–control studies, there is the possibility that cases may recall their diets differently after UC diagnosis (32–34). However, recall bias is minimized by interviewing patients within six months of diagnosis and standardizing the interview protocol. Also, using the same clinic controls and administering validated FFQs by trained interviewers might have further reduced the recall bias and improved the comparability of information between cases and controls. As in most case–control studies, selection bias also is possible. Among the possible limitations of the present study is the use of the same clinic controls, who may have different dietary habits and lifestyle when compared with the general population (i.e., they may have modified their diets due to gastrointestinal symptoms). Furthermore, we are not entirely able to rule out residual confounding due to imprecise measurement or the

omission of important covariates (35, 36). We know that such estimates may be plagued by disease-independent response sets, such as social approval and social desirability (37–39). These were not measured in the study, nor do we know how they would function in Iranian culture. Another limitation is the non-availability of inflammatory markers to validate DII with in this study. These might have shed additional light on the etiology of UC, which is an autoimmune disorder.

As with many diseases, ulcerative colitis has a complicated, non-linear, natural history that does not lend itself easily to epidemiologic study. As an autoimmune disorder UC goes through periods of heightened inflammatory activity followed by periods of remission. The inability to account for this kind of pattern is exacerbated by the fact that this is a case-control study. Clearly, it was not possible to conduct repeat assessments of either diet or UC over a long enough period of time to determine the impact of diet on this process. This would require an entirely different, and much more expensive, study design.

Despite potential weaknesses, there are several strengths that should be considered in evaluating our study. An important strength is the high participation rate (>95%) of individuals in our research. This might be of particular importance because food intakes are often associated with factors such as BMI, smoking and socioeconomic status that are, in turn, related to response. Besides, where economic resources have been severely limited, food intake is closely linked to income, so that even small economic inequalities directly influence the diet. This might increase dietary differences across the population

In conclusion, we found that subjects who consumed a more pro-inflammatory diet were at increased risk of UC compared to those who consumed a more anti-inflammatory diet. Thus, encouraging intake of more anti-inflammatory dietary factors, such as plant-based foods rich in fiber and phytochemicals, and reducing intake of pro-inflammatory factors, such as fried or processed foods rich in saturated fat or trans-fatty acids, appears to be a good strategy for reducing risk of UC. However, more studies have to be conducted to replicate these results and this association has to be explored in studies with multiple assessments of diet and UC status.

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Table 1

Characteristics of patients in an Iranian Ulcerative Colitis Case-Control Study, 2013 (n=186).

Characteristics	Cases	Controls	P-value
	***N* =62**	***N* =124**	
Age, (years): mean ± sd	37.4 ± 13.6	36.2.±11.9	0.53
Energy intake (kcal); mean ± sd	2902.3±643.3	2590.8±585.2	0.001
Sex, n (%)			<0.001
Male	27 (43.6)	54 (43.6)	
Female	35 (56.4)	70 (56.4)	
BMI, kg/m^2 mean ± sd	24.8 ± 4.1	25.7±3.7	0.14
Dietary Inflammatory Index (DII): mean ± sd			
Unadjusted	0.18 ± 0.92	−0.09 ± 0.94	0.07
Adjusted[c]	−0.04±0.44	−0.36±0.47	0.05
Smoking[a] n (%)			0.71
Yes	6 (9.7)	10 (8.1)	
No	56 (90.3)	114 (91.9)	
Education n (%)			0.17
Primary education	7 (11.3)	6 (4.8)	
Secondary education	28 (45.2)	69 (55.7)	
Tertiary education	27 (43.5)	49 (39.5)	
Helicobacter pylori infection n (%)			<0.001
Yes	7 (11.3)	1 (0.8)	
No	55 (88.7)	123 (99.2)	

[a] ANOVA-test was used for continuous variables;

[b] Chi-square test was used for categorical variables

[c] Adjusted for age, energy, sex, education, BMI, family history of IBD, appendectomy smoking, H.pylori infection, NSAID use

Table 2

Participant characteristics by level of dietary inflammatory index (DII), Iranian Ulcerative Colitis, Case-Control Study (n=186), 2013

Continuous variables (mean ± SD)	**Tertile 1 <−0.43**	**Tertile 2 −0.43 to 0.36**	**Tertile 3 >0.37**	**P-Value[a,b]**
Age (years)	38.4±14.0	36.4±10.7	35.1±12.2	0.13
Body mass Index (kg/m^2)	25.3±3.7	25.2±3.8	25.7±4.0	0.62
Sex (%):				0.90
Males	41.9	45.9	42.9	
Females	58.1	54.1	57.1	
Smoking (%)				0.65
Non-smoker	91.9	93.4	88.9	
Current smoker	8.1	6.6	11.1	
H.pylori infection (%)				0.41
No	93.6	98.4	95.2	
Yes	6.4	1.6	4.8	
Education (%)				0.62
Primary Education	8.1	4.9	7.9	
Secondary education	58.1	52.5	46.0	
Tertiary education	33.9	42.6	46.0	

[a] ANOVA -test was used for continuous variables;

[b] Chi-square test was used for categorical variables

Table 3

Odds ratios and confidence intervals for the association between DII and Ulcerative Colitis, Iranian Case-Control Study (n=186), 2013

	Dietary Inflammatory Index OR (95% CI)			P-Value	DII (Continuous)[a] OR (95% CI)	P-Value
DII	**Tertile 1 <−0.43**	**Tertile 2 −0.43 to 0.36**	**Tertile 3 >0.37**			
Age and energy adjusted	1 (ref.)	1.57 (0.70, 3.51)	2.00 (0.89, 3.51)	0.09	1.46 (1.02, 2.10)	0.04
Multivariate-adjusted [b]	1 (ref.)	2.00 (0.81, 4.92)	2.58 (1.03, 6.48)	0.04	1.55 (1.04, 2.32)	0.03

[a] one unit increase corresponds to ≈15% of its range in the current study.

[b] Adjusted for age, energy, sex, education, BMI, family history of IBD, appendectomy smoking, H.pylori infection, NSAID use.