ORIGINAL PAPERS

Diet as an environmental trigger in inflammatory bowel disease: a retrospective comparative study in two European cohorts

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ABSTRACT

Background and aims: inflammatory bowel disease development has been associated with several environmental factors, among which, diet can play a key role, probably due to a westernized lifestyle. However, its involvement in the pathogenesis of inflammatory bowel disease (IBD) is difficult to demonstrate. The aim of this study was to analyze dietary composition in a Romanian and Belgian population with IBD.

Methods: an observational retrospective comparative study was performed using two European cohorts (Romanian and Belgian). The IBD group included 76 Romanian and 53 Belgian patients with an IBD diagnosis, while the control group included a total of 56 healthy people (35 Romanians and 21 Belgians). All subjects were interviewed and asked to fill in a questionnaire regarding diet.

Results: in the entire IBD cohort (Romanian + Belgian), a significantly increased consumption of sweets (OR 3.36 [95 % CI 1.6,7]), processed and high fat meat (OR 2.5 [95 % CI 1.4, 4.7], fried food (OR 9.5 [3.8, 23.6]), salt (OR 2.8 [1.5, 5.3]), ice cream (OR 3.25 [1.1, 9.8]), mayonnaise (OR 3.49 [1.1, 10.3]), margarine (OR 5.63 [1.64, 19.33]) and chips/nachos/other snacks (OR 2.3 [0.97, 5.73]) were found compared to the healthy control group. The intake of seeds, nuts (OR 0.26 [0.14, 0.52]) and yoghurt consumption (OR 0.44 [0.23, 0.83]) was lower in the IBD group compared to the control group.

Conclusion: a westernized diet with increased consumption of sweets, processed food, high fat meat, fried food, salt, margarine, snacks, ice cream and mayonnaise seems to be a risk factor for IBD in Romanian and Belgian IBD patients. Intake of seeds, nuts and yoghurt may be a protective factor.

Keywords: Inflammatory bowel diseases. Crohn's disease. Ulcerative colitis. Diet.

BACKGROUND AND AIMS

Inflammatory bowel diseases (IBD), mainly Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory conditions of the gastrointestinal tract. The interaction between environmental factors and normal intestinal commensal microbiota in IBD patients can lead to an inappropriate immune response that results in chronic inflammation (1,2).

IBD was primarily recognized in westernized countries following the rise of the industrial revolution. The incidence

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of IBD dramatically increased during the 20th century with a significant prevalence in developed nations such as Canada, the United States and Western Europe (3). As individuals move from areas of low to high prevalence, first-generation offspring acquire the same risk of developing IBD as the local population (4). This shift in risk suggests that changes in environment, in addition to genetic predisposition, contribute to the development of IBD.

Several environmental factors have been associated with IBD, such as smoking, hygiene, microorganisms, oral contraceptive pills, non-steroid anti-inflammatory drugs, antibiotics, appendectomy, diet, breastfeeding, vitamin D, stress and ambient air pollution (5). However, a clear mechanism by which these environmental risk factors interact to cause IBD has not been elucidated (5). Furthermore, most risk factors have not been consistently demonstrated across different studies. A low-fiber, high-carbohydrate and fat-rich diet seems to play a role in the development of IBD via mechanisms related to insulin resistance, alteration of intestinal permeability, stimulation of proinflammatory pathways and the generation of dysbiosis (8,9). The prospective ECCO-EpiCom study of patients with IBD in 31 European countries has shown a higher number of western-associated risk factors in Eastern Europe, including high-sugar and low-fiber diets (8). Belgium has a high incidence of IBD. A study published in 1998 reported a mean annual incidence per 10(5) of 4.5 for CD and 3.6 for UC, while in Romania the incidence of IBD is much lower, 0.5 per 10(5) for CD and 0.97 per 10(5) for UC (6,7).

The aim of this project was to analyze dietary composition and patterns in a retrospective comparative Romanian-Belgian study, enrolling 2 groups of patients with inflammatory bowel disease (IBD).

METHODS

Type of study

An observational retrospective case-control study was performed using two cohorts, one from Romania and one from Belgium.

Patients

All IBD patients admitted to the Gastroenterology Outpatient Unit of the Fundeni Clinical Institute and Centre Hospitalier Universitaire de Liege during October 2017 were selected, with a total number of 76 and 53 subjects, respectively. The inclusion criteria for these groups were age over 18 years and disease duration over 6 months (from IBD diagnosis). The exclusion criteria were concurrent *Clostridium difficile* or CMV colitis, total suppression of oral intake and exclusive parenteral/enteral nutrition.

Control groups

The control groups included 35 Romanian and 21 Belgian healthy subjects, 50 % were recruited from hospital employees and 50 % were referred by general practitioners near the hospital. The control group was similar to the individuals from the case group in terms of age and sex distribution. All subjects were interviewed and asked to fill in a questionnaire regarding current and past diet preferences (diet before disease onset was recorded) (Fig. 1). A member of our team oversaw the process and the informed consent was signed by all subjects before enrollment.

Variables

Figure 1 shows the data recorded for every subject: age, sex, type of disease (ulcerative colitis/Crohn's disease), disease classification according to Montreal classification and disease severity (i.e. severity of the first flare, the most severe flare and the actual score of severity). The CDAI score was used for Crohn's disease and the Mayo score for ulcerative colitis.

Variables regarding diet before disease onset were registered as follows: number of daily portions of vegetables, fruits and high grain cereals, number of weekly portions of fish, processed meat, seeds and nuts. The frequency of intake of the following foods was noted from daily to rare: cheese, yogurt, fruit yogurt, butter, high fat meat, margarine, fried foods, commercial ice-cream, mayonnaise and chips/nachos/other snacks. Sugar-sweetened beverage consumption was reported from less than 1 liter /day to more than 1 liter/day while sweets consumption was rated as rare, occasional or frequent (daily).

Statistical analysis

Data analysis was performed using the SPSS statistical software (20.0 version from IBM Corporation, Armonk, NY, USA). The quantitative variables with a non-parametric distribution were summarized as the median with minimum and maximum values and were compared using the Mann-Whitney U test. Categorical variables were summarized as percentages and compared using the Fisher's exact test. Two-sided hypothesis testing was used and a p value of less than 0.05 was considered as statistically significant. A logistic regression model was built with the presence of inflammatory bowel disease as a dependent variable and risk factors associated with a $p < 0.10$ according to the bivariate analysis as independent variables. The regression analysis was performed in a stepwise forward manner, due to the relatively small sample compared to the number of variables.

The sample size was calculated for an alpha error of 5 % and a statistical power of 80 % to detect an odds ratio of at least 3. This considered the risk factor with the closest prevalence to 50 % in the general population, which was 62 % (daily sugar consumption from the Romanian National Institute of Public Health) (10). The estimated sample size was 116 patients in the study group and 58 in the control group, calculated with WinPepi 11.65 (11).

The Ethics Committees of the institutions involved approved the study and a grant offered by the Romanian Executive Unity for Financing and Supporting of Higher Education (UEFISCDI): 112 BM supported the study.

QUESTIONNAIRE
The analysis of diet in patient with non-specific inflammatory bowel disese

1. General information about the patient

Name and surname-initials ..... Age .....

Sex: M ☐ / F ☐ Address: urban ☐ / rural ☐

2. Medical information about the patient

Disease diagnosis (according to Monreal classification – including extraintestinal manifestations .....

.....

The year of diagnosis.....

First flare severity: – Crohn´s disease (CDAI) ..... points

– Ulcerative colitis (Mayo score) ..... points

Severity score of the most severe flare .....

Actual score of severity .....

3. Information regarding patients lifestyle before IBD. Nutrition

Type of food	Number of portions / day		Observations
Vegetables-fruits	> 4 portions	< 4 portions	
Fish consumption	> 2 portions/week	< 2 portions/week	
Salt consumption	Very low	High/moderate	
Sweets and sweetened beverages	< 11 sweetened beverages with sugars Occasional	> 11 sweetened beverages with sugars Daily	
High grain cereals	> 3 portions/day (3 slices of bread)	< 3 portions/day (3 slices of bread)	
Seeds and nuts consumption 1 portion = a handful	> 4 portions/week	< 4 portions/week	
Processed meat	< 2 portions/week	> 2 portions/week	
Cheese (cottage cheese, semi-hard yellow cheese)	Daily	Rare	
Yogurt	Daily	Rare	
Fruit yogurt	Daily	Rare	
Butter	Daily	Rare	
High fat meat pork, beef, chicken with skins	Daily	Rare	
Margarine	Daily	Rare	
Fried foods	Daily	Rare	
Icecream	Daily	Rare	
Mayonnaise or bought from shop dressings	Daily	Rare	
Chips/nachos/other snacks	Daily	Rare	

*1 portion of vegetables = 1 cup of chopped raw vegetables or ½ of cup of boiled vegetables + 1 small tomatoes + 1 small cucumber.
**1 portion of fruits = 1 small apple, 1 peach, 1 small orange, one kiwi, a handful of strawberries or cherries.

Fig. 1. *Questionnaire. Environmental factors in patients with inflammatory bowel disease.*

RESULTS

Description of the case-control groups

Romanian IBD group

Males were more frequent in this group (52.6 %), the median age was 41 years, CD was more predominant (60.5 %) and the median IBD duration was 5 years. CD patients had a median age of 42, a slight predominance of female sex and a median disease duration of 3 years. Age at onset was more frequent between 17 and 40 years, the ileocolonic location and the B1 phenotype was the most prevalent; 13 % had perianal disease (Table 1). Romanian UC patients had a median age of 41, with a slight male predominance (66.7 %), a median disease duration of 6 years and the left colonic location was more frequent (53.3 %) (Table 1).

Belgian IBD group

The median age in this group was 42 years, females were predominant (approx. 70 %), CD was more frequent (cca. 80 %) and the median disease duration was 11 years. Belgian CD patients had a median age of 42 years, were predominantly female (approx. 70 %), with a median extent of disease of 10 years. The A1 phenotype was more prevalent (according to Montreal classification), while the ileocolonic location (L1) and B1 phenotype were the most frequent. 40 % of the patients had perianal disease. The median age of Belgian UC cases was 43.5 years, 80 % were female and 78 % had left colonic disease extension.

Comparison between study groups and control groups

IBD patients in both the Romanian and Belgian populations were matched by age and gender with the control cohort. Belgian subjects had a median age of 42 years and a female predominance in both groups. In the Romanian population, the median age was 42 years in the IBD group and 49 years in the control group, with a similar and relatively equal sex distribution (52.6 % men *vs.* 47.6 %, p = 0.7).

Analysis of dietary factors

Comparison between the Romanian IBD cohort and control group

Concerning diet composition, several differences were noted in the Romanian IBD group. In the IBD group, there was a significantly higher consumption of salt (89.5 % *vs.* 52.4 %, p < 0.001), sweets and sweetened beverages (50 % *vs.* 14.30 %, p < 0.001), processed meat (63.2 % *vs.* 28.6 %, p < 0.001), high fat meat (52.6 % *vs.* 19 %, p < 0.001) and fried foods (60.5 % *vs.* 4.8 %, p < 0.001) compared to the control group. Conversely, there was a significantly lower intake of seeds and nuts and yogurt in the Romanian IBD patients compared to the healthy subjects (15.8 % *vs.* 52.4 %, p < 0.001; 26.3 % *vs.* 47.6 %, p = 0.026). The results were at the limit of statistical significance for fruit yogurt (0 % vs.4.8 %, p = 0.056). There were no statistically significant differences between the two analyzed groups in terms of the consumption of vegetables-fruits, fish, high grain cereals, cheese, butter, margarine, commercial ice cream, commercial mayonnaise and chips/nachos/other snacks (Fig. 2).

Comparison between the Belgian IBD cohort and control group

In the Belgian cohort, the results indicated a significantly lower percentage of subjects who consumed vegetables and fruits in the IBD group compared to the control group (30.2 % *vs.* 59.1 %, p = 0.019). Although, a higher percentage was obtained in the case of margarine consumption (45.3 % *vs.* 13.6 %, p = 0.009). Regarding other foods, the consumption did not differ significantly in the IBD and control group in terms of fish, salt, sweets and sweetened

Table 1. *A comparison between Romanian and Belgian patients: general characteristics*

Variable	Romanian CD patients (n = 46)	Belgian CD patients (n = 43)	p
Males (%)	43.5 %	32.6%	0.383
Median age (min. ÷ max.)	42 years (19 ÷ 67 years)	42 years (19 ÷ 73 years)	0.183
Median disease duration	3 years (0.5 ÷ 14 years)	10 years (1 ÷ 42 years)	*< 0.001*
A1/A2/A3	0/73.9/26.1 %	15/75/10 %	*0.005*
L1/L2/L3	26.1/34.8/39.1 %	30/12.5/57.5 %	0.335
B1/B2/B3	45.4/27.3/27.3 %	60/20/20 %	0.208
Upper GI tract location (L4)	4.3 %	11.4 %	0.231
Perianal disease	13 %	40 %	*0.006*
Variable	**Romanian UC patients (n = 30)**	**Belgian UC patients (n = 10)**	**p**
Males (%)	66.7 %	20 %	*0.025*
Median age (min. ÷ max.)	41 years (28 ÷ 74 years)	43.5 years (26 ÷ 64 years)	0.569
Median disease duration	6 years (0.5 ÷ 15 years)	11.5 years (1 ÷ 16 years)	0.158
E1/E2/E3	6.7/53.3/40 %	0/77.8/22.2 %	0.588

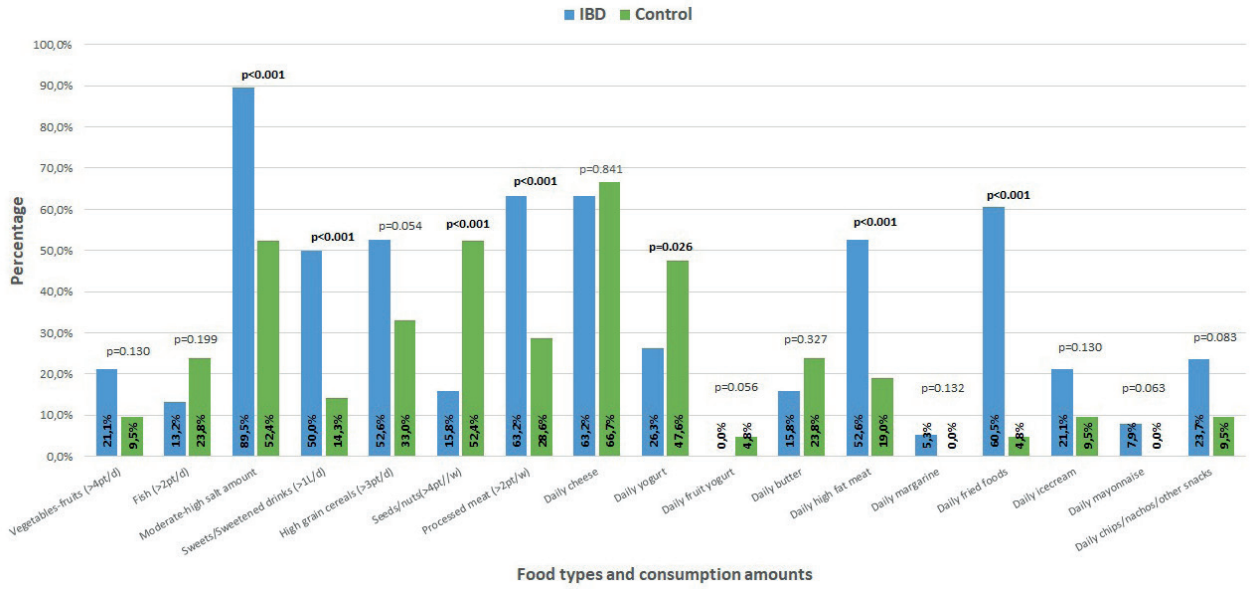

Fig. 2. *Food types and consumption levels in Romanian patients with IBD prior to disease onset versus healthy controls (according to questionnaires) (IBD: inflammatory bowel disease; pt: portion; d: day; w: week).*

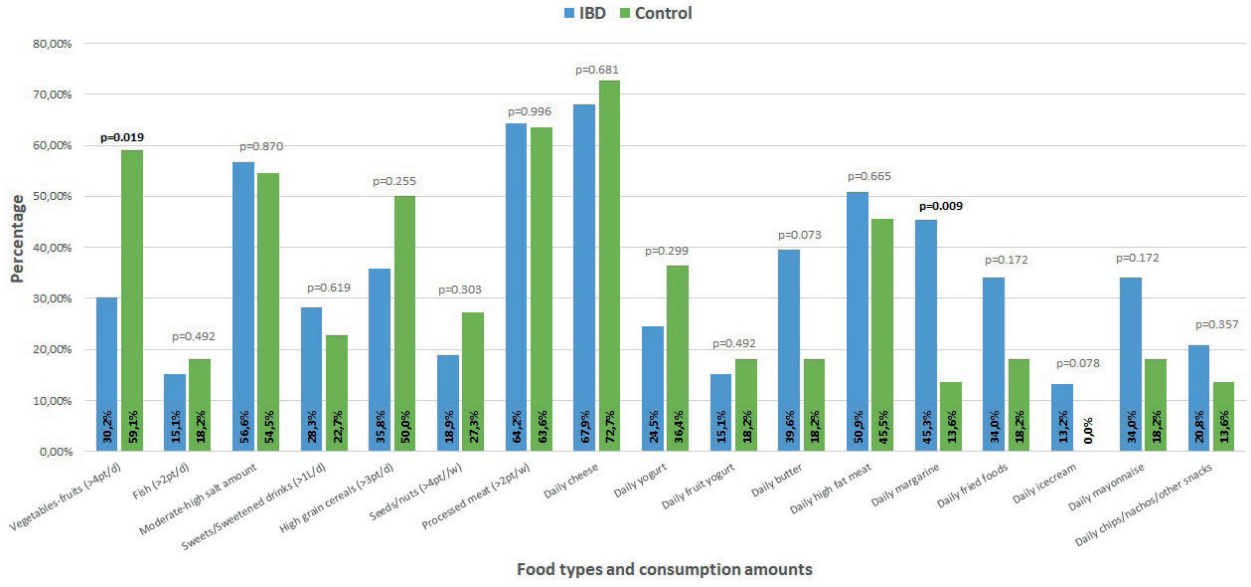

Fig. 3. *Food types and consumption levels in Belgian patients with IBD prior to disease onset versus healthy controls (according to questionnaires) (IBD: inflammatory bowel disease; pt: portion; d: day; w: week).*

beverages, high grain cereals, seeds and nuts, processed meat, cheese, yogurt, fruit yoghurt, butter, high fat meat, fried foods, ice cream, mayonnaise and chips/nachos/other snacks. (Fig. 3).

Comparison between the IBD cohort (Romanian + Belgian) and control group

Table 2 shows the results of the bivariate analysis concerning the impact of different dietary factors in patients with inflammatory bowel diseases. Daily fried foods were the most potent factors associated with IBD, followed by excessive consumption of sweets, margarine, processed meat, commercial ice cream, mayonnaise or dressings and increased salt intake. An adequate amount of seeds and nuts and yogurt consumption were important dietary protective factors.

All dietary variables were introduced in the logistic regression model that were associated with IBD ($p < 0.10$). Two variables remained in the model as independently associated with IBD (Table 3); excessive salt consumption and processed meat. All other variables which were significantly associated with IBD in the bivariate analysis (Table 2) were not maintained in the regression model.

Table 2. *A comparison of diet composition in IBD patients (Romanian and Belgian) and the control group (bivariate analysis)*

Variable	IBD patients (n = 129)	Control group (n = 56)	p	OR (95 % CI)
Moderate-high salt amount	76 %	53.1 %	*0.002*	**2.8 [1.5. 5.3]**
Sweets/sweetened drinks > 1 L/day	41.1 %	17.2 %	*0.001*	**3.36 [1.6. 7]**
Seeds/nuts (> 4 pt/week)	17.1 %	43.8 %	*< 0.001*	**0.26 [0.14.0.52]**
Processed meat (> 2 pt/week)	63.3 %	40.6 %	*0.003*	**2.5 [1.4. 4.7]**
Daily high fat meat	51.9 %	28.1 %	*0.002*	**2.76 [1.45. 5.26]**
Daily yogurt	25.6 %	43.8 %	*0.014*	**0.44 [0.23. 0.83]**
Daily margarine	21.7 %	4.7 %	*0.002*	**5.63 [1.64. 19.33]**
Daily fried foods	49.6 %	9.4 %	*< 0.001*	**9.5 [3.8. 23.6]**
Daily ice-cream	17.8 %	6.2 %	*0.029*	**3.25 [1.1. 9.8]**
Daily mayonnaise	18.6 %	6.2 %	*0.028*	**3.49 [1.1. 10.3]**
Daily chips/nachos/other snacks	22.5 %	10.9 %	*0.053*	**2.3 [0.97. 5.73]**

Table 3. *Multivariable analysis (logistic regression) with IBD as dependent variable*

Variable	Coefficient	p	OR (95 % CI)
Moderate-high salt amount	1.516	0.010	4.55 [1.44, 14.4]
Processed meat (> 2 pt/week)	2.117	< 0.001	8.3 [2.6, 26.7]

DISCUSSION

The rising incidence of IBD in Eastern Europe is thought to be a result of westernized living Therefore, this study aimed to perform a diet analysis between a Romanian and a Belgian IBD population.

An essential environmental factor identified in our study was in relation to vegetable and fruit consumption, which was higher in the Belgian control group compared to the IBD group. 59.1 % of healthy subjects reported consuming at least 4 servings per week, while this was 30.2 % in IBD patients. Many other studies have also shown that eating vegetables and fruits, which are high fiber foods, can be a protective factor for the development of IBD (12-14). A similar study to this one performed in a western population (Denmark) has shown that the daily intake of vegetables was associated with a low risk of developing both Crohn's disease and ulcerative colitis (OR = 0.41, 95 % CI: 0.24-0.71 and OR = 0.51, 95 % CI: 0.31-0.84, respectively) (13).

High grain cereal consumption did not differ between IBD and control groups in either of the populations; Romanian and Belgian was 53.8 % *vs.* 50 % and 52.6 % *vs.* 33 %, respectively. Interestingly, a high consumption of seeds and nuts in the Romanian IBD group was approximately three times lower than that of the control group. Other studies have shown significant beneficial effects of fiber consumption only for ulcerative colitis (15,16). These results for ulcerative colitis are maintained in one pediatric population in a Danish study (OR = 0.3, CI: 0.1-0.8) (17).

The EpiCom cohort was a population-based, prospective inception cohort of 1182 IBD patients from 31 European countries (444 CD, 627 UC, 111 IBD unclassified). Patients were asked to complete an 87-item questionnaire at diagnosis about environmental factors. Sugar intake was higher in CD and UC patients from Eastern Europe than in Western Europe, whereas fiber intake was lower ($p < 0.01$). Daily consumption of fast food was more frequent in Eastern European than in Western European UC patients ($p < 0.01$) (19). These results are consistent with the findings obtained in the Romanian cohort and also with the results of a bivariate analysis performed of the entire group of IBD patients (Romanian + Belgian).

With regard to dairy products, Romanian healthy subjects had a higher yogurt consumption compared to those with IBD. The 47.6 % of patients in the control group ate yogurt daily compared to 26.3 % in the IBD group and there were no differences in the consumption of either cheese or butter. The two groups were similar in the Belgian cohort with respect to this food category. The potential protective effect of yogurt against the onset of IBD was highlighted in our study by the results of bivariate analysis that included both Romanian and Belgian patients (OR 0.44 [95 % CI: 0.23, 0.83, $p = 0.014$]). Yogurt could have beneficial effects in IBD due to its probiotic content, causing an increase in the number of probiotic bacteria in the colon on one hand and balancing an excess of anti-inflammatory molecules from detrimental to pro-inflammatory ones on the other hand (20-24). Dairy consumption (milk, cheese, yoghurt) was also analyzed in the EPIC study. The results showed that individ-

uals who consumed milk have a lower risk of developing Crohn's disease (not ulcerative colitis) than those who do not consume any (OR: 0.3, 95 % CI: 0.13-0.65), there were no significant correlations for the other products (25).

Our study also indicates that the consumption of high-fat meat was higher in the Romanian IBD group compared to the control group (52.6 % *vs.* 19 %), but not in the Belgian cohort (50.9 % *vs.* 45.5 %). This finding was confirmed via the bivariate analysis performed in the whole group (OR 2.76 [1.45, 5.26] (p = 0.002)). Red meat is associated with the risk of IBD due to the metabolism of linoleic acid content that leads to the generation of leukotrienes and prostaglandins (pro-inflammatory mediators) (12,18,26). A meta-analysis of nine studies published in 2015, reported a significantly higher risk of IBD for meat consumers than those who did not consume meat at all or in small amounts (pooled RR: 1.5, 95 % CI: 1.15-1.95) (27).

If the consumption of high fat meat was higher in the Romanian IBD group and in the entire group of IBD patients, no differences were found in any of the cohorts (Romanian and Belgian) in terms of fish consumption. However, as indicated by two recently published systematic reviews, there are numerous studies that found fish consumption to be a protective factor for the development of IBD, including pediatric populations (12,28). These results contradict the initial findings and could be explained by the increased content of ω-6 PUFA with pro-inflammatory effects in red meat and ω-3 PUFA with anti-inflammatory effects in fish. Although this mechanism has not been fully demonstrated (12,28,29).

Furthermore, there was a significantly higher consumption of processed meat in the IBD group in the Romanian cohort compared to the control group (89.5 % *vs.* 52.4 %). This finding was confirmed in the bivariate analysis (OR 2.5 [1.4, 4.7]; p = 0.003) and the multivariable analysis (OR 8.3 [2.6, 26.7]; p < 0.001). Processed meat is rich in food additives, such as detergent-like molecules. This can interfere with barrier function in the gut and also modify intestinal microbiota, which consequently promotes inflammation (30,31). Besides processed meats, other foods such as margarine, commercial mayonnaise, ice cream, chips and related products are known for their content of food additives. In our study, there were significant differences reported in the Belgian cohort and in the entire IBD cohort (Romanians + Belgians). The 43.5 % of Belgian IBD patients used to consume margarine daily compared to 13.6 % of individuals from the control group, 21.7 % in the entire IBD group *versus* 4.7 % in the entire healthy control group (OR 5.63 [95 % CI 1.64, 19.33]). Similarly, Maconni et al. showed a significantly higher risk of UC for a moderate consumption (OR: 11.8, CI: 1.51-91.99) compared to a high consumption (OR: 21.37, CI: 2.32-196.6) of margarine, which was not statistically significant for CD (24).

The literature suggests that monosaccharide and sweets intake have a negative effect on IBD. Our study also confirmed a higher consumption of sweets and sweetened beverages by Romanian IBD patients before disease onset compared to the healthy people. The bivariate analysis was performed on the entire cohort of patients with IBD *versus* healthy volunteers and showed an OR of 3.36 ([95 % CI 1.6, 7], p = 0.001) (13,32). Supporting our findings, the EPIC prospective study demonstrated a positive association between sweeteners and soft drinks and ulcerative colitis. The risk was even higher when associated with a lower vegetables consumption (33). A recent meta-analysis of 1361 IBD cases did not find an association between the high dietary total carbohydrate intake and UC or CD (OR 1.167 (0.777-1.752) and 1.010 (0.630-1.618), respectively). However, this meta-analysis included only studies from Europe and Asia, with a substantial heterogeneity (34).

In the Romanian cohort and in the entire IBD cohort, the consumption of fried food and salt was significantly higher in the IBD group compared to the control group (OR 9.5 and 2.8, respectively). This was also confirmed in the multivariate analysis of a moderate-high diet salt level. Both the above-mentioned foods and fried foods have an increased content of trans-unsaturated fatty acids, which appear to be associated with the occurrence of UC in cases of long-term intake (35).

The focal point of this original study is the use two cohorts from Eastern and Western Europe and a parallel analysis of diet via a detailed questionnaire that thoroughly assessed the alimentary habits of each subject. One limitation of this study was the relatively low number of subjects included; 111 in the Romanian cohort and 74 in the Belgian cohort. Even though statistical power was reached with our data. Another limitation of the study is control group composition, which was partially selected from healthy hospital employees and 50 % were referred by general practitioners near to the hospital. However, this may not represent the general population and further studies should be performed in multinational cohorts.

CONCLUSION

The results obtained in this study reflect significant differences in dietary patterns of people with IBD *versus* the healthy population. The consumption of sweets and sweetened beverages, processed and high fat meat, fried food, salt, bought from shop ice cream and mayonnaise was higher in the entire IBD cohort than in the healthy control group. Whereas seeds, nuts and yoghurt consumption was lower. These differences in diet may provide a clue to the possible environmental factors involved in the development of intestinal inflammatory diseases.

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