Cross-Sectional Analysis of Overall Dietary Intake and Mediterranean Dietary Pattern in Patient's with Crohn's Disease

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ABSTRACT

The purpose of this study was to (a) compare macro- and micronutrient intakes between male and female CD patients (b) compare micronutrient intakes of CD patients to a representative population of healthy individuals, and; (c) describe Mediterranean diet scores (P-MDS) of male and female CD patients in remission recruited from an IBD clinic in Calgary, AB.

Consecutive patients with ileal and/or colonic CD in endoscopic remission were recruited for participation in this cross-sectional study.

Sixty-seven patients were enrolled, with a mean age of 45, and a BMI $\geq$ 25. Compared with the healthy population, patients with CD had similar energy, protein, carbohydrate and total fat intake. However, PUFA, omega-6 and 3 and MUFA were lower in CD patients and dietary fibre intake was higher. Vitamins C, D, thiamin, niacin, magnesium, phosphorus, zinc and potassium were all significantly lower in all CD patients compared to a healthy population. Few patients with CD met P-MDS criteria for olive oil, vegetable, legumes, and fish intake or consuming Sofrito sauce (mean 4.5, SD=1.1 in males and 4.7, SD=1.8 in females). Patients with CD in remission have suboptimal dietary intakes and patterns and targeted dietary interventions may be beneficial in this population to improve intake.

Keywords: Crohn's disease, dietary intake, malnutrition, Mediterranean diet

INTRODUCTION

There is a compelling argument for environmental factors, such as diet, to play a role in the course of inflammatory bowel disease (IBD) [1]. Given mounting evidence for the role of diet and gut microbial composition and function in IBD development and exacerbation, a richer understanding of the role of diet in disease pathogenesis is warranted. Perturbations related to dietary intake are thought to relate to consumption of a dietary pattern that negatively alters gut microbiota composition [2,3] leading to functional changes in SCFA profiles affecting the inflammation process [4] and stimulating an inappropriate immune activation of the gut mucosa.

There are limited published data describing dietary patterns and macro- and micronutrient intakes in patients with Crohn's disease (CD); particularly differences between males and females Nearly 50% of CD patients perceive diet to be an initiating factor in their disease, and over half of patients report diet exacerbates disease severity [5]. In IBD, deficiencies of micro- and macronutrients are observed and arise through multifactorial etiologies, including disruptions in digestion, malabsorption, and disease activity, resulting in increased energy and nutrient requirements, anorexia, consumption of a nondiversified diet with food avoidance due to symptoms, and cachexia arising as a consequence of pro-inflammatory cytokines [6]. The reported prevalence of malnutrition is variable (12-85%) [7-9] and depends on disease activity and definitions used to define malnutrition. Nutrient deficiencies usually develop over time and are linked to duration of illness. Macronutrient deficiencies leading to protein-energy

malnutrition are less common in the biologic era, however, still of significant prevalence in patients admitted to hospital. Overt malnutrition may lead to complications such as frequent infections, poor immunity and increased hospitalizations [10]. Micronutrient deficiencies occur for multiple reasons including: chronic blood loss leading to iron deficiency; chronic diarrhea resulting in hypomagnesemia or zinc deficiency; malabsorption leading to B12, folate, and vitamin D deficiencies, and; other deficiencies such as antioxidants [11,12]. No previous study has reported the prevalence of macro- and micronutrient deficiencies in Canadian CD patients compared to a representative population.

While single nutrients may play a role in the natural history of IBD [13,14], single nutrients are rarely consumed in isolation. Specific to IBD, epidemiological studies described associations of increased risk of IBD and high dietary intake of refined sugar, grains, calories, animal fat from meat and dairy, and regular intake of processed foods, while a diet high in fruit, vegetables and dietary fiber decreases risk [15,16]. A recent meta-analysis showed an inverse association between intake of vegetables and fruit and CD respectively (pooled odds ratio for the highest versus lowest consumption of fruit 0.57 (95% CI 0.44-0.74) [17]. Patients consuming a pro-inflammatory diet (e.g., high in animal protein, low in fruits and vegetables) have demonstrated a higher risk of ulcerative colitis [18]. Recently the association between food intake and course of disease in patients with IBD was explored using fecal calprotectin and a protective role of legumes and potato, and detrimental influence of meat in maintaining clinical remission in IBD was identified [19].

There is a large body of evidence showing Mediterranean dietary patterns regulate inflammation in chronic disease [20-22]. A Mediterranean dietary pattern is high in extra-virgin olive oil, vegetables, fruit, legumes, nuts and seeds with moderate consumption of fish, poultry and milk products and low in processed foods, baked goods and red and processed meat. This dietary pattern is high

in monounsaturated fats (MUFA), omega-3 polyunsaturated fats (PUFA), fermentable fibers and polyphenols, and adherence to a

Mediterranean dietary pattern is associated with lower levels of biomarkers of inflammation. A Mediterranean dietary pattern has

shown positive effects in chronic disease [23], although it may impact men and women differently [24], and has been understudied in

IBD.

The purpose of this study was to (a) compare macro- and micronutrient intakes between male and female CD patients (b)

compare micronutrient intakes of CD patients to a representative population of healthy individuals, and; (c) describe Mediterranean

diet scores (P-MDS) of male and female CD patients in a Canadian academic ambulatory care setting.

METHODS

Study Design and Recruitment

A single center cross-sectional study was undertaken at the University of Calgary, Foothills Medical Center, in Calgary,

Alberta, Canada. Eligible patients were recruited consecutively from ambulatory gastrointestinal clinics at this site.

Eligibility Criteria

To be eligible for the study patients were required to: (a) be $\geq$ 18 years of age, (b) have a documented diagnosis of ileal

and/or colonic CD based on clinical, radiological and endoscopic criteria, (c) be in clinical and endoscopic remission, defined by a

Harvey Bradshaw Index (HBI) < 5 with evidence of mucosal healing by endoscopy defined by no large ulcers, inflammation or

strictures, within 3 months of recruitment, (d) been in steroid-free remission for 3 months prior to study entry, (e) achieved induction

of remission either through anti-TNF agents or corticosteroids (f) provide informed consent. Patients were excluded if (a) HBI > 5, (b)

had evidence of active endoscopic mucosal disease, (c) used corticosteroids within the preceding 3 months, (d) had >1 bowel resection, (d) presence of ostomy (e) used laxatives in the past 3 months, (f) used prebiotic fiber supplements in past 3 months, (f) used probiotic supplements in the past 3 months, and (g) used antibiotics in the past 6 months.

Ethics and Consent

The study protocol was approved by the University of Calgary Conjoint Health Research Ethics Board REB15-1805. All participants provided informed written consent prior to participating in the study.

Data Collection

Patient characteristics, medications and symptoms were extracted from the patients' medical record and confirmed with the patient during the first study visit. The following data were collected: age, sex, HBI, recent endoscopic findings, current medication, previous IBD surgery, last use of antibiotics and/or probiotics, corticosteroids and laxative use.

Dietary intake was collected using prospective 3-day weighed food records. Eligible patients met with the study coordinator to receive training on how to record an accurate 3-day weighed food record. Patients were instructed to document dietary intake on 2 representative weekdays, and 1 weekend day. The food records were then reviewed by the study dietitian (RD) with the patient to identify any missing food or drink items. While there are limitations to the use of the 3-day food record to capture dietary intake, this validated tool has been used extensively to measure food intake in a variety of populations.

Three-day dietary intake data were subsequently entered and analyzed using ESHA Food Analysis Software [25]. Intake data was reviewed for acceptable ranges of macro- and micronutrients. Adherence to a Mediterranean diet was measured using the 13-item PREDIMED Mediterranean Diet Score (P-MDS) [26], however points were not given for red wine consumption considering the impact alcohol consumption may have on symptoms related to IBD. Each item in the P-MDS received a score of 0 or 1, and items are evenly weighted. Total P-MDS scores ranged from 0-13.

Macro- and micronutrient intakes of CD patients were compared to population usual nutrient intakes from the Canadian Community Health Survey (CCHS; Cycle 2.2) [27]. The CCHS used interviews to collect 24-hour recall data with a subsample of respondents completing a second recall. To transfer daily intake into usual intake a measurement error model was used to reduce the effect of within-individual variance and measure between-individual variance [27]. Data were compared for the following parameters: (a) total energy intake in kilocalories (kcal), (b) protein, carbohydrate, fibre, total fat, PUFA including omega-6 and 3, MUFA and saturated fat (SFA) as proportions of total energy intake (c) select micronutrients (vitamins and minerals) reported as percentage of daily recommended intakes (DRI) and mean daily/usual intakes.

Statistical Analysis

Statistical analysis was carried out using SPSS 25.0 (IBM, 2017). Data are expressed as means with standard deviation or standard errors where it facilitates comparison with normative population data. Median and interquartile ranges (IQR) are presented for P-MDS due to the variability of the data. Comparisons were done using independent sample *t*-tests to identify mean differences between males and females and between CD patients' and population usual intakes. Chi-squared tests were conducted to identify

gender differences in P-MDS for categorical variables and independent sample t-tests were used for mean P-MDS scores. Statistical

significance was established at *p* < 0.05.

RESULTS

Demographic and Health

Sixty-seven patients were enrolled, had a mean age of 45, and a mean BMI characterized as overweight (Table 1). Most

patients (female = 88%, male =73%) were receiving anti-TNF maintenance therapy. Patients who were not receiving anti-TNF

therapies were not on other IBD specific therapies, including dietary therapies. Less than half of the study participants received

immunomodulators. Close to one quarter of patients had one previous small bowel resection, none had colonic resections, and no

patient had an ileostomy.

Table 1: Patient Demographics and Health Information

	Female N=34	Male N=33
Age in years (mean, SD)	44.7 (14.4)	49.7 (12.7)
BMI (kg/m^2; mean, SD)	27.8 (6.1)	26.7 (3.9)
Anti-TNF n, (%)	30 (88.2%)	24 (72.7%)
IMM n, (%)	15 (44.1%)	14 (42.4%)
Previous bowel surgery n, (%)	7 (20.6%)	11 (33.3%)

Abbreviations: BMI: body mass index, Anti-TNF: Anti-tumor necrosis factor, IMM: Receiving immunomodulators.

Macronutrient Intake

Compared with the healthy population, male and female patients with CD had similar energy, protein, carbohydrate and total fat intake (Table 2). However, fat intake from PUFA, omega-6, omega-3 in females only, and MUFA was significantly lower in patients with CD compared to healthy Albertans (Table 2). Dietary fibre intake was significantly higher in patients with CD compared to healthy Albertans.

Table 2. Macronutrient composition compared to current guidelines

Macronutrient	DRI Acceptable Macronutrient Distribution Range (AMDR) and Adequate Intake (AI)[1]	Academy of Nutrition and Dietetics[2]	Crohn's Patients (N=67; Mean±SE)		Healthy Population (N=1547; Mean±SE)[27]	
			M (n=33)	F (n=34)	M (n=721)	F (n=826)
Total energy intake (kcal/d)	Men = 662 - (9.53 x age [y]) + PA x {(15.91 x weight [kg]) + (539.6 x height [m])} Women = 354 - (6.91 x age [y]) + PA x {(9.36 x weight [kg]) + (726 x height [m])}		2358(95.3)	1881(86.5)	2346(61)	1730(42)
Protein (% total energy)	10-35% total energy		18.3(1.0)	18.0(0.7)	17.0(0.4)	16.8(0.3)
Carbohydrate (% total energy)	45-65% total energy		47.1(1.5)	48.1(1.1)	48.7(0.9)	48.5(0.6)
Fibre (g/day)^	M: 30-38 F: 21-25		22.8(1.4)*	20.9(1.6)*	19.2(0.6)	13.9(0.5)
Total fat (% total energy)	20-35% total energy		33.7(1.2)	34.3(1.0)	31.0(0.8)	32.4(0.6)
PUFA (% total energy)	5-10% total energy	3-10% total energy	4.5(0.4)*	3.9(0.3)*	5.6(0.2)	5.6(0.1)
Omega-6 (linoleic)	5-10% total energy	3-10% total energy	3.3(0.4)*	2.8(0.2)*	4.5 (0.1)	4.5 (0.2)
Omega-3 (α-linolenic)	0.6-1.2% total energy	0.6-1.2% total energy	0.6(0.15)	0.5(0.09)*	0.8(0.04)	0.8(0.02)
MUFA (% total energy)	No AI level	15-20% total energy	8.2(0.6)*	7.1(0.5)*	12.6(0.4)	12.8(0.2)
SFA (% total energy)	As low as possible	7-10% of total energy <7% to reduce CVD risk 5-6% to lower lipids	10.7(0.4)	11.1(0.5)	9.8 (0.2)	10.7(0.3)
TransFA (% total energy)	As low as possible	<1% total energy	0.4(0.1)	0.3(0.1)	unavailable	

Abbreviations: Dietary reference intakes (DRI), Males (M), Females (F), Polyunsaturated fatty acids (PUFA), Monounsaturated fatty acids (MUFA), Saturated Fatty Acids (SFA), Cardiovascular disease (CVD), Males (M), Females (F)

* Indicates significant differences between patients with Crohn's compared to Albertan population, results are gender specific ($p<0.05$).

^Higher values are for adults 19-50 years.

Vitamin Intake

Vitamin comparisons are all listed in Table 3. Compared to the healthy population, vitamins C, D, thiamin and niacin were significantly lower in male and female patients with CD, whereas lower intake of riboflavin and pyridoxine was observed only in female patients with CD, and lower folate intake was noted only in males with CD. Males compared to female patients with CD had significantly lower intake of vitamin K, and higher thiamin, niacin, pyridoxine and biotin intakes. Compared to the DRIs, both male and female patients had inadequate intakes of vitamins A, D, E, pantothenic acid, biotin, folate and choline; although there was a high level of variation around the mean scores. Healthy population level data for some vitamins (E, K, pantothenic acid, biotin, choline) and minerals (chromium, copper, manganese, selenium) were not available for comparison.

Table 3. Vitamin intake compared to a healthy representative population

Vitamins	DRI Adequate Intake/day (AI)[1]		Crohn's Patients (N=67)				Healthy Population (N=1547)[27]	
	Males	Females	M (n=33) % of DRI (M±SD)	F (n=34) % of DRI (M±SD)	M (n=33) Daily intake (M±SE)	F (n=34) Daily intake (M±SE)	M (n=721) Usual intake[2] (M±SE)	F (n=826) Usual intake[2] (M±SE)
Vitamin A RAE μg	900	700	69 (55)%	97 (162)%	609 (86)	682 (195)	667 (33)	577 (28)
Vitamin D μg@	15-20		21 (20)%	16 (17)%	3 (0.5)**	2.5 (0.4)**	5.9 (0.3)	5.0 (0.3)
Vitamin E α-tocopherol mg	15		48 (59)%	32 (28)%	5 (1.5)	7.1 (0.7)	n/a	n/a
Vitamin K μg	120	90	52 (46)%*	106 (101)%*	61 (9.7)	97 (15.7)	n/a	n/a
Viatmin C mg (N=1484) Vitamin C smokers mg (N=679)	90 125	75 110	121 (78)%	108 (84)%	106 (12)**	82 (11)**	143 (8) 92 (7)	113 (4) 102 (8)
Thiamin, B1 mg	1.2	1.1	115 (60)%*	82 (41)%*	1.4 (0.12)**	0.9 (0.08)**	2.0 (0.07)	1.4 (0.04)
Riboflavin, B2 mg	1.3	1.1	141 (67)%	113 (52)%	1.8 (0.15)	1.3 (0.10)**	2.1 (0.07)	1.6 (0.05)
Niacin, B3 NE	16	14	212 (113)%*	161 (76)%*	34 (2)**	23 (2)**	46 (2)	32 (1)
Pantothenic Acid, B5 mg	5		87 (46)%	68 (35)%	4.4 (0.4)	3.4 (0.3)	n/a	n/a
Pyridoxine, B6 mg[t]	1.3-1.7	1.3-1.5	119 (64)%*	86 (45)%*	1.8 (1.0)	1.2 (0.7)**	2.1 (0.1)	1.6 (0.1)
Biotin, B7 mg	30		47 (42)%*	25 (19)%*	14 (2.2)	8 (1.0)	n/a	n/a
Folate, B9 DFE μg	400		72 (32)%	61 (59)%	287 (34)**	244 (33)	488 (15)	325 (41)
Cobalamin, B12 μg	2.4		177 (123)%	130 (109)%	4.2 (0.5)	3.1 (0.5)	4.9 (0.3)	3.5 (0.2)
Choline mg^	550	425	43 (26)%	39 (23)%	229 (25)	165 (17)	n/a	n/a

Abbreviations: Retinol Activity Equivalents (RAE), Dietary Folate Equivalents (DFE), Not available (n/a)
@Higher values for greater than 70 years. Does not include values for children or pregnant females.
[t] Higher values for 51 years and older.
^Choline requirements may be met by endogenous production and food sources may not be required.
*Indicates a significant difference in %DRI between males and females (p<0.05).
**Indicates a significant difference between patients with Crohn's and Albertan usual intakes, specific to gender(p<0.05).

Mineral Intake

Compared to the healthy population, intakes of magnesium, phosphorus, zinc and potassium was lower for both male and female CD patients, whereas sodium intake was higher in female patients (Table 4). Compared to male patients with CD, female patients had lower intakes of iron, phosphorus and sodium. Both male and female patients with CD did not meet DRI adequacy for calcium, chromium, magnesium, zinc or potassium.

Table 4: Mineral intake compared to a healthy representative population

Minerals	DRI Adequate Intake/day (AI)[1]		Crohn's Patients, (N=67)				Healthy Population (N=1547)[27]	
	Males	Females	M (n=33) % of DRI (M±SD)	F (n=34) % of DRI (M±SD)	M (n=33) Daily intake (M±SE)	F (n=34) Daily intake (M±SE)	M (n=721) Usual intake[2] (M±SE)	F (n=826) Usual intake[2] (M±SE)
Calcium mg/d[@]	1000-1200		87(49)%	73 (42)%	906 (97)	785 (76)	890 (38)	799 (35)
Chromium µg/d[t]	35-30	25-20	18 (50)%	8 (6)%	5.8 (3.1)	1.7 (0.3)	n/a	n/a
Copper µg/d	900		110 (63)%	93 (69)%	989 (99)	837 (106)	n/a	n/a
Iron mg/d^	8	8-18	187(102)%*	118 (86)%*	17 (1.6)	13 (1.1)	16 (0.5)	11 (0.3)
Magnesium mg/d[#]	400-420	310-320	63 (33)%	60 (34)%	256 (23)**	191 (19)**	352 (9)	274 (7)
Manganese mg/d	2.3	1.8	197 (306)%	114 (64)%	4.5 (1.2)	2.1 (0.2)	n/a	n/a
Phosphorus mg/d	700		144 (68)%*	111(54)%*	1030 (79)**	777 (65)**	1500 (44)	1152 (33)
Selenium µg/d	55		151 (81)%	134(78)%	83 (7.8)	74 (7.4)	n/a	n/a
Zinc mg/d	11	8	83 (38)%	72% (34)	9 (0.7)**	6 (0.5)**	13 (0.5)	10 (0.3)
Potassium mg/d	4700		54 (30)%	44 (31)%	2532 (246)**	1880 (157)**	3355 (103)	2657 (62)
Sodium mg/d	1200-1500+		169 (74)%*	135 (51)%*	3880 (296)	3101 (203)**	3543 (120)	2550 (75)

Abbreviations: Not available (n/a)
*Indicates a significant difference between males and females (p<0.05).

**Indicates a significant difference between Crohn's patients and the Albertan population, gender specific ($p < 0.05$).
@Higher values for greater than 70 years. Does not include values for children or pregnant females.
^{t} Higher values for 51 years and older.
^Higher values are for menstruating females.
#Higher values for 31 years and older.
+Lower values for 51 years and older.

P-MDS Adherence

Few patients with CD met P-MDS criteria for olive oil, vegetable, legume intake or consuming sofrito sauce, a sauce made from olive oil, onions, garlic and tomatoes similar to spaghetti sauce (Table 5). One quarter of male patients and one fifth of female patients met P-MDS criteria for fruit servings, while 36% of males and 24% of females met P-MDS criteria for nuts. Fish and/or shellfish intake had a median intake of 0 per week and 21% of males and 32% of females ate more than 3 or more servings a week. Over 70% of patients met serving recommendations for limiting butter, sugar sweetened beverages and red or processed meat and approximately half of patients limited baked goods and sweets to less than 3 times a week. Although patients reported limiting red meat according to P-MDS criteria (<6 oz or 175 g/day), few chose poultry over red meat on a regular basis.

Table 5. Predimed Mediterranean Diet (P-MDS) Adherence Scores

P-MDS Adherence Criteria[26]	Canada Food Guide 1-serving size and P-MDS answers	Canada Food Guide Servings (Median ± IQR)		Percent meeting P-MDS criteria, n (%)	
		Male	**Female**	**Male**	**Female**
Olive oil as main culinary fat	• Yes, No answer	n/a	n/a	2 (6)	0 (0)
≥ 4 tbsp olive oil per day	• 1 Tbsp (15 mL)	n/a	n/a	0 (0)	0 (0)
≥ 5 servings vegetables with ≥ 2 servings as raw leafy vegetables per day	• ½ cup (125 mL) fresh, frozen, canned vegetables • 1 medium vegetable • 1 cup (250 mL) raw or leafy vegetables	total 1.0 (0.4-1.7) leafy 0.0 (0.0-0.5)	total 1.9 (1.0-3.0) leafy 0.5 (0-1.0)	0 (0)	1 (3)
≥ 3 servings fruit and unsweetened fruit juice per day	• ½ cup (125 mL) fresh, frozen, canned fruit • 1 medium fruit • ½ cup (125 mL) unsweetened fruit juice	1.8 (1.3-3.3)	1.4 (0.9-2.6)	9 (27)	7 (21)
<2 servings of red meat, hamburger, or processed meat such as ham, sausage, etc. per day	• 85 grams (3 oz) meat • ½ cup (125 mL)	1.7 (1.0-2.0)	0.7 (0.3-1.5)	23 (70)	28 (82)
<1 serving of butter, hydrogenated margarine or cream per day	• 1 Tbsp (15 mL)	n/a	n/a	27 (82)	27 (79)
<1 sugar sweetened beverage per day	• Yes, No answer	n/a	n/a	31 (94)	27 (79)
≥ 3 servings beans, peas, lentils per week	• ¾ cup (175 mL)	0.0 (0.0-0.0)	0.0 (0.0-0.2)	3 (9)	3 (9)
≥ 3 servings fish and/or shellfish per week	• CFG = 85 g (3 oz.) • 100 grams (3.5 oz) fish • 200 grams (7.0 oz) shellfish	fish 0.0 (0.0-0.0) seafood 0.0 (0.0-0.0)	fish 0.0 (0.0-3.1) seafood 0.0 (0.0-0.0)	7 (21)	11 (32)
Eat <3 times a week baked goods, sweets, pastries or candy	• Yes, No answer	n/a	n/a	19 (58)	19 (56)
≥ 3 servings nuts per week	• ¼ cup nuts or whole large seeds (30 g) • 2 Tbsp (30 mL) nut and seed butters or small/ground seeds	0.0 (0.0-5.4)	0.4 (0.0-2.6)	12 (36)	8 (24)

Choose chicken, turkey or rabbit more often than veal, pork, hamburger or sausage	• Yes, No answer	n/a	n/a	12 (36)	18 (53)
Consume sofrito sauce ≥ 2 times per week	• Yes, No answer	n/a	n/a	4 (12)	11 (32)
Total mean MDS Score (possible score out of 13)				4.5 (1.1)	4.7 (1.8)

Abbreviations: interquartile range (IQR)

No significant differences in P-MDS criteria were evident using chi-square tests between males and females for categorical variables and independent sample t-tests for mean MDS score ($p<0.05$)

DISCUSSION

The present study is a comprehensive analysis of dietary patterns and food intake adequacy in adult patients in remission with CD. To our knowledge, this is the first study to report on P-MDS in an adult cohort of patients with CD, and to examine gender and population data differences in nutrient intakes. Major study findings identified significantly different (a) micronutrient intakes between male and female CD patients; (b) micronutrient intakes between CD patients and a representative population of healthy individuals; and, (c) dietary patterns compared to P-MDS recommendations.

Few published studies have identified dietary predictors of relapse. One such study in 103 CD and ulcerative colitis (UC) patients, used a cross-sectional design to evaluate the association between food intake and course of disease; half with active disease [19]. Intake of legumes and potato were inversely associated with the risk of active disease, defined as fecal calprotectin > 150, with close to 80% of the highest quartile consumers of legumes at lower risk of active disease (adjusted OR 0.21, 95% CI 0.57-0.81). Similarly patients consuming the highest intake of meat coincided with a higher risk of active disease (unadjusted OR 3.6). In the Tasson study [19], significant effects for fruits and vegetables on disease relapse were not identified. The duration of active inflammation before data collection prevented the authors from inferring causality of diet determinants of relapse. It is compelling to observe that in our current study, only three males and females consumed 3 or more servings of legumes, and 30% of male patients demonstrated meat overconsumption.

Similar to our study, significant micronutrient deficits were observed, including suboptimal intake of vitamins A, E, C, folate and zinc. Vitamins C and E are antioxidants, and supplementation has previously been shown to result in reduction of oxidative

stress [28]. Zinc plays a pivotal role in wound repair, tissue regeneration and the immune system; zinc deficiency in IBD has been associated with an increased risk of hospitalizations, surgeries and disease related complications. Normalization of zinc was associated with improvement of these adverse clinical outcomes [29]. Limited dietary diversity, including avoidance of food groups, may offer one possible explanation for the deficiency in micronutrient intake. Optimizing dietary diversity through focused nutrition counseling may lead toward improvement in micronutrient intake.

Gender differences in micronutrient intakes were observed; although there was a large degree of variability in the sample. Females consumed lower thiamin compared to males, however, still met 80% of DRI . Given the adequacy of intake, the clinical relevance of this finding is likely not significant. Males only consumed half of recommended potassium intake, and were lower than female intake. Both males and females had low intakes of biotin compared to DRI recommendations; however, females were significantly lower than males at 25%. The consequence and etiology for these findings are not readily apparent, although likely result from the extremely low intakes of legumes, fruit and vegetables and nuts and seeds. Although both males and females exceeded the DRI recommendation for sodium, males had a significantly greater intake, possibly a surrogate for greater intake of processed foods. Both males and females exceeded DRIs for sodium in the healthy population, however, to a lesser extent than our sample of patients with CD. While the dietary intake of sodium is under-reported in IBD, there are signals that show a diet enriched in sodium chloride enhances inflammatory cytokine production and exacerbates colitis in animal models [30].

Compared to a healthy population, dietary MUFA intake from foods like olive and canola oils, avocado and nuts were low in patients with CD. One recently published study showed that dietary lipid and overall energy intake in a mixed IBD sample was higher than healthy control subjects, however, no differences were observed in protein and carbohydrate intake [31]. Dietary lipid

composition, unfortunately, was not reported in this study, rendering the proportion of MUFA and PUFA unknown. An older study in patients stratified by disease severity using the CD Activity Index threshold of 150, showed mean energy and macronutrient intakes were close to recommended levels in both patients with active disease and in remission, and reported MUFA intakes of 12% [32]. The MUFA intakes in our CD patients were significantly lower than this. In Rheumatoid Arthritis, high intake of MUFAs, was recently demonstrated to be an independent predictor of remission [33].

The dietary composition in our patient sample differed from P-MDS criteria. Olive oil was seldom used as the primary culinary fat of choice, few patients in our sample met P-MDS criteria for intake of vegetables or legumes and fruit including fruit juice, and median intakes were 50% below the recommended three or more fruit servings a day. For fruit and vegetable intake, P-MDS criteria are similar to North American dietary recommendations. Thirty percent of males exceeded recommendations for red or processed meats per P-MDS criteria. Over 80% of patients reported inadequate intake of fish and nuts.

Data evaluating the relationship between Mediterranean diets (MD) and disease characteristics (severity and relapse) in IBD are limited. Drawing from the cardiovascular literature, the incidence of major cardiovascular events was lower among participants assigned to an energy-unrestricted MD, and MD supplemented with extra-virgin olive oil or nuts, compared to those assigned to a reduced-fat diet [23]. A subsequent study identified significant reductions in plasma concentrations of high-sensitivity C-reactive protein, interleukin-6 and tumor necrosis factor in patients following a MD supplemented with extra-virgin olive oil or nuts compared to a low fat diet, identifying anti-inflammatory signals to explain the observed clinical findings [34]. Recently, Arpon et al. identified specific components of the MD, particularly nuts and extra virgin olive oil were able to induce methylation changes in several peripheral white blood cells, showing a role for specific fatty acids on epigenetic modulation [35]. To our knowledge, studies

assessing the gut microbiome composition in long term MD consumers compared to habitual diet in humans have not yet been completed. However, a very recent study identified significant microbiome differences in non-human primates consuming MD compared to a Western Diet [36].

The results of our study provoke further curiosity into the relationships between dietary patterns, nutrition adequacy and disease pathogenesis in IBD. Protective mechanistic roles for MD patterns in IBD are plausible, mediated through anti-oxidant effects, microbiome changes, and anti-inflammatory effects. Interventional studies are required to test the efficacy of MD patterns on disease severity. Promising effects on disease activity have been observed with elimination diets such as the specific carbohydrate diet [37], and the autoimmune protocol diet [38], among other test diets, in the recent literature, highlighting the growing interest in undertaking intervention studies in this population of patients.

The P-MDS was useful in identifying low intakes of foods rich in the deficient micronutrients like olive oil, legumes, nuts and fruits and vegetables. In patients with suboptimal intakes of these foods early referral to effective nutrition intervention programs and/or supplementation should be considered. At the present time, in our center, patients are not routinely referred for dietary assessment and counseling, nor do they receive nutrition risk screening. Gastroenterologists and nurse practioners providing care to patients with IBD at our site generally refrain from offering diet-focused therapies as a solution for disease management in the absence of overt malnutrition. We recognize the lack of dietary focus as therapy may differ from other centers. We also recognize that the patients with IBD assessed at our center are interested in dietary therapies although the source for nutrition education is not readily apparent. Patients with IBD had higher dietary fibre intake compared to the healthy population, and 70% met serving recommendations to limit

butter, sugar sweetened beverages and processed meat.

There are study limitations that should be noted. This study was conducted in a single Canadian center, and therefore generalizability of study findings may be limited. Deficient dietary intake may not be synonymous with deficient total body stores of micronutrients. The current study design is unable to infer a relationship between intake and body stores. In addition, the healthy population data did not report on several micronutrients, so comparisons between patients with IBD and a healthy representative population were not possible for all micronutrients. As well, the small numbers in this cross-sectional study produced point estimates with a large degree of variability and results should be interpreted with caution. More studies with larger numbers would be beneficial to confirm this study's conclusions. Finally, we acknowledge using 3-day weighed food records to measure intake may result in biased estimates of intake due to underreporting or changes in normal dietary patterns. Future directions include well-designed randomized controlled trials testing the efficacy of promoting a MD pattern on disease related outcomes, including flares and surgical interventions.

Conclusions

Differences in dietary quality and micronutrient intakes were observed between male and female patients with CD and a healthy population. Compared with a MD pattern that has been shown to have anti-inflammatory properties, patients with CD report significant gaps in food choices that promote a wide nutrient intake. Patients with CD should be screened for nutrient deficiencies and poor dietary patterns. Using a simple tool such as the P-MDS may be a practical and effective way to identify pro-inflammatory dietary patterns at an individual level. Further investigation into the efficacy of nutrition interventions to improve diet quality and effect on clinical outcomes and nutrient deficiency is warranted.

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Conflicts of Interest:

None of the authors have conflicts of interests to report.