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# High Dietary Intake of Specific Fatty Acids Increases Risk of Flares in Patients with Ulcerative Colitis in Remission During Treatment With Aminosalicylates

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## Abstract

**Background & Aims—**Dietary factors may have a significant role in relapse of disease among patients with ulcerative colitis (UC). However, the relationship between diet and UC is inadequately understood. We analyzed data from the diet's role in exacerbations of mesalamine maintenance study to determine whether dietary factors affect risk of disease flares in patients with UC.

**Methods—**We performed a prospective, multi-center, observational study of 412 patients, from 25 sites, with UC in remission during monotherapy with an aminosalicylate. Patients completed a validated food frequency questionnaire at enrollment and were followed for 12 months. We analyzed the relationship between diet and disease remission or flare for groups of macro- and micro-nutrients, as well as food groups previously associated with an increased risk of flare.

**Results—**Forty-five patients (11%) had a UC relapse within 1 year of study enrollment. When analyzed in tertiles, increasing intake of multiple fatty acids was associated with increasing odds of relapse. In multivariable logistic regression analysis, only myristic acid (Odds Ratio 3.01, 95% CI 1.17 – 7.74) maintained this dose-response relationship. Other foods previously implicated in flares of UC, such as processed meat, alcohol, and foods high in sulfur, were not associated with an increased risk of flare.

**Conclusions—**In a prospective study of more than 400 patients with UC undergoing treatment with aminosalicylates, we associated high dietary intake of specific fatty acids, including myristic

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acid (commonly found in palm oil, coconut oil and dairy fats) with an increased risk of flare. These findings can help design interventional studies to evaluate dietary factors in UC.

**Keywords**

DREAM study; IBD; risk factor; disease progression

## Introduction

Diet is considered an important environmental risk factor in both the development of Inflammatory Bowel Disease (IBD) and the clinical course after diagnosis, although the exact relationship has been difficult to determine. As the incidence of both ulcerative colitis (UC) and Crohn's Disease (CD) has risen in areas such as Asia where IBD was previously thought to be uncommon,[1] more focus has been placed on the potential role that the adoption of a "Western diet" may play in these epidemiologic trends. The increasing focus on nutrition and its impact on health has also augmented interest in the role of diet as a potential therapy in IBD.

Diet may influence gut inflammation through multiple mechanisms, including changes to the gut microbiota, direct effects of dietary antigens, changes in gut permeability after dietary exposure, immune influences and alteration of gene expression.[2] However, the particular substances in a diet which may be protective or harmful remain uncertain. The characteristics of a Western diet, where protein and fat contents are high while fruit and vegetable intake is low, have been proposed as a potential explanation for the increasing incidence of IBD.[3] In addition, the unbalanced ratio of polyunsaturated fatty acids (PUFAs) in the Western diet has been suggested as a potential mechanism for increasing the risk of IBD.[4]

The identification of nutritional risks can be challenging, as dietary studies at disease onset may already be biased by changes due to symptoms. Although associations between dietary factors and UC have been reported,[3,5–7] many of these studies have utilized a retrospective design.[2] In large prospective studies such as the Nurses' Health Study, due to 4 year survey intervals there may be a significant lag between questionnaire completion and the time of diagnosis of IBD.[7,8] When the relationship between fats and risk of development of UC was examined in prospective cohorts from the UK, dietary arachidonic acid was associated with an increased risk of development of a UC, while total dietary n-3 PUFAs, oleic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were associated with a decreased risk of development of UC.[9,10]

An alternate approach is to study individuals in remission, which provides the opportunity to identify factors associated with flares prospectively. Using this approach, Jowett et al, identified that increased meat consumption, processed meats in particular and sulfur intake more generally, and alcohol were associated with a higher risk of relapse in patients with UC.[11] Despite an overall high rate of relapse in a somewhat heterogenous population, the potential association between high sulfur compounds and risk of relapse was a novel and interesting association prompting further interest.

To understand better the relationship between diet and risk of disease relapse among patients with UC, we performed a prospective study evaluating dietary patterns among a homogeneous population utilizing the same medications for treatment of UC and with similar risks of flare. Our primary aim was to compare patterns of macro and micronutrient intake among those patients who experienced a flare of UC to the dietary patterns of those patients who remained in clinical remission throughout the study period.

## Methods and Materials

### Patients

Participants were recruited from a consortium of academic and community gastroenterology practices, including some subjects that had previously been recruited for a separate study.[12] We enrolled patients from 25 sites in the United States, between August 2007 and March 2014.

We included male and female patients with a documented history of UC, age 18 years or older. UC must have been successfully maintained in remission, as documented by a Simple Clinical Colitis Activity Index (SCCAI)[13] < 2, for at least 3 months prior to study entry. Patients were required to be utilizing a stable dose of mesalamine, sulfasalazine, or balsalazide for at least 3 months prior to enrollment, and only this class of medications could be utilized as maintenance therapy for UC. Patients with any extent of colitis were eligible for inclusion. All eligible patients were required to have at least one documented flare within the 18 months prior to enrollment, with flares defined by the individual provider.

Patients were excluded if they had a history of allergy to salicylates, aminosalicylates, or any component of the mesalamine tablet. Additional exclusion criteria included the use of aspirin (except for cardioprotective reasons up to a maximum dose of 325 mg per day) or nonsteroidal anti-inflammatory drugs (NSAIDs) within 1 week prior to baseline visit, or use of antibiotics (other than topical application), anti-diarrheals and/or anti-spasmodics within 1 month of the baseline visit. Patients were excluded if they had been treated with an immunosuppressive, biologic, or any oral, intravenous, intramuscular, or rectally administered corticosteroid therapy (excluding budesonide) in the 90 days prior to enrollment, including but not limited to therapy with mercaptopurine, azathioprine, cyclosporine, methotrexate, infliximab, adalimumab, certolizumab, or other biologic therapy for UC. Additional exclusion criteria are detailed in Supplement 1.

### Study Procedures

Basic demographics were collected along with clinical history including duration of disease, extent of colonic involvement, date of last flare, and smoking history. At enrollment, patients completed a validated food frequency questionnaire (FFQ)[14] in the provider's office. Patients were contacted via phone every 3 months, through month 12 or until a flare occurred. Flares were defined as a SCCAI ≥ 5 or a change in disease activity requiring a change in medication. If a patient had an office visit scheduled for the two weeks before or after a scheduled study phone call, the study follow up could be conducted at the time of the office visit. If a patient presented for an office visit or was hospitalized because of a flare, no

further follow up was necessary. Patients lost to follow up were not included in our final analysis (n=34). This study was approved by the Partners Healthcare Institutional Review Board and the Institutional Review Boards of participating sites prior to inception. All authors had access to the study data, reviewed, and approved the final manuscript.

## Measurement and Validation of Nutritional Intake

Dietary intake of and macro and micronutrients was assessed using a previously validated FFQ.[14,15] Patients were questioned regarding habitual dietary habits, and exposure to different food groups including dairy, fruits, vegetables, eggs, meat, fish, cereals, breads, and starches, as well as beverage intake and exposure to sweets and baked goods.

A serving size was provided for the majority of the food items, with patients asked to indicate how often, on average, they had consumed each food over the past year. Patients were asked to choose from nine potential responses, ranging from “never or less than once per month” to “six or more times per day.” Calculation of nutrient values was based on United States Department of Agriculture publications.[15] Nutrient intake was calculated using a technique where the portion size specified for each food was multiplied by a weight assigned to the frequency of intake.[15]

## Statistical Analysis

Continuous variables are reported as means with standard deviations (SD) and were compared using the student t test. Categorical variables are reported as raw numbers with corresponding percentages and were compared using the Chi Square Test. Dietary intake was analyzed in tertiles, in a manner similar to prior nutritional analyses.[11] Comparisons were performed between those patients who remained in clinical remission and those who experienced a flare, using univariate analysis to identify predictors of flare. Due to concerns about multiple comparisons, we limited our analyses to those nutrients and food groups that had previously been suggested as potentially increasing an individual’s risk of flare. Additionally, we used the Benjamini and Hochberg method to correct for false discovery rate,[16] with a false discovery rate (FDR) of 5% used in those analyses where multiple comparisons were a concern. We also evaluated for potential dose-response effects by analyzing trends across median intake by tertile for each nutrient or group. Collinearity among potential predictors of flare was assessed prior to inclusion in any logistic regression model. Backwards selection was used to create a final multivariable logistic regression model, evaluating all significant dietary and non-dietary variables from univariate analysis for potential inclusion.

Given the prior association between risk of flare and increased intake of meats, alcohol, protein, and sulfur,[11] we chose to evaluate these particular groups a priori. Prior versions of the FFQ did not assess sulfur intake, and thus the data collection process was augmented to allow for analysis of sulfur. As prior studies suggested a significant role for fatty acid intake in the risk of development of UC,[9,10] we chose to evaluate individual and grouped fatty acid intake to determine the risk of flare among patients with established UC.

## Results

A total of 412 patients were enrolled, of which 45 (11%) experienced a flare of disease within the 12 month study period. The mean time to flare was 247.5 days (SD 111 days). A comparison of baseline demographic and clinical characteristics among those patients who experienced a flare and those who remained in remission is seen in Table 1. The only significant difference noted was the mean number of flares in the 18 months prior to study entry, which was higher among patients who experienced a flare during the study period (2.37 vs. 1.75, p=0.003). The mean intake of specific nutrients and food groups is seen in Table 2. There were no differences in mean nutrient intake among those patients who experienced a flare within the 6 months preceding study enrollment and those patients who experienced a flare between 6 and 18 months prior to study enrollment.

In univariate analysis, an apparent dose-response relationship was noted across multiple fatty acids, where the highest intake was associated with increased odds of experiencing a flare of disease (Table 3). When the trend across tertiles was assessed by evaluating median intake by tertile, significant trends were noted for myristic acid (p=0.007), total omega-3-fatty acid without supplementation (p=0.011), oleic acid (p=0.022), monounsaturated fat (p=0.022), saturated fat (p=0.033), eicosenoic acid (p=0.029), and palmitelaidic acid (p=0.036). While the intake of these fatty acids was significant ($p<0.05$) on univariate analysis and assessment of trend across tertiles, they did not meet the rigorous statistical thresholds of adjustment for multiple comparisons with the Benjamini-Hochberg method (FDR 0.05).

In multivariable analysis, higher intake of myristic acid (OR 3.01, 95% CI 1.17 – 7.74) and alpha linolenic acid (OR 5.50, 95% CI 1.56 – 19.34) were associated with increased risk of relapse, though a dose-response relationship was retained only for myristic acid intake (Table 4). The four nutrient or food groups presented were the only four that met criteria for inclusion in the final multivariable model. In both univariate and multivariable analysis, there was no significant increase in odds of flare related to intake of sulfur, alcohol, protein and meat intake (Table 3).

## Discussion

In our prospective study, we evaluated dietary elements associated with disease flares. We demonstrated a dose-response effect across multiple fatty acids in univariate analysis, although these findings were not significant after adjustment for multiple comparisons. In multivariable analysis, only myristic acid continued to show this dose-response effect. Although ALA is an n-3 PUFA and thus we could have expected a decreased odds of flare, there was a significant risk of flare among patients in the medium intake tertile.

Our finding of a dose-response effect between higher intake of myristic acid and increased odds of flare of UC within 12 months is a novel finding. Myristic acid, which is commonly found in coconut oil, palm oil and dairy products, has been associated with increased inflammation in other disease processes such as obesity.[17] Correlations between elevated myristic acid and higher levels of IL-6 have been demonstrated in other populations;[18]

however, there has been no prior link between myristic acid and a worsening risk profile among patients with UC.

One of the critical questions regarding the potential role of fatty acids in the development of IBD is whether these effects are due to a single fatty acid or an imbalance in the ratio of fatty acids.[4] In contrast to the proinflammatory actions of n-6 PUFAs, n-3 PUFAs seem to act in a regulatory manner with regards to inflammation.[19] While some studies have demonstrated beneficial effects of high intake of n-3 PUFAs,[20,21] in a meta-analysis, there was no difference in relapse rate between those patients with IBD using omega-3-fatty acids and the control group.[22] The association between ALA and increased risk of flare was surprising, given that ALA is a precursor for long chain n-3 PUFAs such as DHA and EPA.

Despite pre-specified analyses, we did not replicate the findings of the only other prospective study evaluating dietary risk factors for flare among patients with UC in remission, as we were unable to associate increased odds of flare with higher intake of processed meat, protein, alcohol, or sulfur. In the study by Jowett et al,[11] 52% of patients relapsed within one year of follow up, which is higher than the reported rates of relapse in other studies of patients with UC,[12,23] raising questions about non-dietary factors that may have led to an increased risk of flare. While all patients were required to be in remission at the start of the study, only 74% were on medical therapy with a 5-ASA medication. Use of other medications was not detailed. We designed this study to evaluate a homogenous group of patients in clinical remission on aminosalicylates at enrollment.

Despite a large number of studies evaluating the relationship between nutrient intake and development of UC,[6,9,10,24–30] due to heterogeneity, pooling this data is difficult. The Nurses' Health Study cohorts have yielded several large prospective evaluations of dietary influences on the risk of development of UC among women.[7,8,30] Noteworthy patterns have been revealed in these large cohorts, including a reduced risk of UC among patients reporting higher intake of long chain n-3 PUFAs.[30] Other findings have been limited to a risk of development of CD only, such as long term intake of fiber[7] or adolescent dietary patterns.[8] When the role of dietary interventions as a therapy in patients with UC has been evaluated, the results have also been inconclusive.[22,31–33]

The inability to identify multiple specific dietary risk factors that were predictive of flare of UC may indicate that the primary factors associated with risk of flare are much more powerful than the intake of specific nutrients or food groups. As the role of dietary factors in the disease course of patients with UC may be relatively modest, a much larger dataset may be required to thoroughly evaluate this relationship.

Our study does have inherent limitations. As patients were treated with a variety of aminosalicylate compounds, there was no standardized dose administered. Although a higher dose of medication may have reduced the chance of flare among some patients, we would presume that those patients who experienced a flare did so due to differences in dietary intake and not underlying dose of aminosalicylate. Additionally, the requirement for monotherapy with an aminosalicylate may limit the generalizability of our results. While we did not have information regarding endoscopic activity to confirm relapse of disease, the

SCCAI has been validated[13] and has been utilized in prior dietary studies in UC.[21] Although our study utilized a prospective design, it remains an observational cohort. The potential remains that the intake of multiple fatty acids could be related to intake of similar foods that were not specifically evaluated. Although we assessed for collinearity among the nutrients and food groups, there may also be unmeasured confounders that contribute to an individual's risk of flare.

While we would assume that the patients in this study had relatively mild colitis based on their use of aminosalicylate monotherapy, the limited number of patients with pancolitis was an unexpected finding. Although the percentage of patients experiencing a flare within 12 months was similar to that reported in other studies of patients with UC treated with mesalamine,[12,23] the total number of patients experiencing a flare was relatively small. This limits the number of predictors included our final multivariable model, and may limit our ability to identify weak associations.

In conclusion, in our evaluation of a uniform group of patients with UC treated with aminosalicylates, we identified multiple nutritional factors associated with increased odds of disease relapse, particularly intake of myristic acid. We did not associate an increased risk of flare with intake of protein, meats, alcohol, or sulfur. Our broader goal is to determine how alterations in diet can improve the care of people with IBD. These findings can help design interventional dietary studies to determine if supplementation or avoidance of certain compounds identified here might reduce the risk of a flare for patients with UC in remission.

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## Abbreviations

| | |
|---|---|
| **ALA** | alpha linolenic acid |
| **CD** | Crohn’s Disease |
| **DHA** | docosahexaenoic acid |
| **DREAM** | Diet’s Role in Exacerbations of Mesalamine Maintenance |
| **EPA** | eicosapentaenoic acid |
| **FFQ** | food frequency questionnaire |
| **IBD** | Inflammatory Bowel Disease |
| **NSAIDs** | nonsteroidal anti-inflammatory drugs |
| **PUFA** | polyunsaturated fatty acids |
| **SCCAI** | Simple Clinical Colitis Activity Index |
| **UC** | Ulcerative Colitis |

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## Table 1

Comparison of baseline demographics among patients with Ulcerative Colitis who experienced a flare and those who did not experience a flare within the 12 month study period

| | Patients who did not experience a flare (n=367) | Patients who experienced a flare (n=45) | p-value |
|---|---|---|---|
| **Age**[a,b] | 48.66 (14.71) | 44.61 (12.64) | 0.06 |
| **Race**[a] | | | 0.11 |
| White | 331 (89.7%) | 30 (81.1%) | |
| Non-White | 38 (10.3%) | 7 (18.9%) | |
| **Gender**[a] | | | 0.48 |
| Male | 207 (56.7) | 28 (62.2) | |
| Female | 158 (43.3) | 17 (37.8) | |
| **Smoking History**[a] | | | 0.42 |
| Never | 181 (50.3%) | 27 (62.8) | |
| Previously | 123 (34.2%) | 11 (25.6) | |
| Currently | 55 (15.3%) | 5 (11.6) | |
| **UC Location**[c] | | | 0.66 |
| Proctitis | 79 (41.8%) | 13 (43.3%) | |
| Left-sided colitis | 66 (34.9%) | 8 (26.7%) | |
| Pancolitis | 5 (2.7%) | 0 (0%) | |
| **Time since last flare (months)**[a,b] | 8.55 (4.33) | 7.59 (4.05) | 0.10 |
| **Number of UC flares in the past 18 months**[b,c] | 1.75 (2.35) | 2.37 (1.92) | **0.003** |

[a] All 412 patients were evaluated for this variable

[b] Continuous variables reported as means (Standard Deviation)

[c] 219 patients were evaluated for this variable

## Table 2

Comparison of mean intake of nutrient and food groups among all enrolled patients, patients who experienced a flare, and patients who did not experience a flare

| | All enrolled patients (n=412) | Patients who did not experience a flare (n=367) | Patients who experienced a flare (n=45) |
|---|---|---|---|
| **Myristic Acid (g/day)** | 1.83 (1.31) | 1.79 (1.30) | 2.21 (1.31) |
| **Alpha Linolenic Acid (g/day)** | 1.40 (0.95) | 1.37 (0.91) | 1.66 (1.24) |
| **Oleic Acid (g/day)** | 24.8 (14.3) | 24.4 (14.1) | 28.7 (15.3) |
| **Eicosenoic Acid (g/day)** | 0.25 (0.22) | 0.25 (0.23) | 0.28 (0.16) |
| **Palmitelaidic Acid (g/day)** | 0.09 (0.07) | 0.09 (0.07) | 0.10 (0.06) |
| **Total Trans Lineoleic Acid (g/day)** | 0.33 (0.23) | 0.33 (0.24) | 0.38 (0.21) |
| **Saturated Fat (g/day)** | 24.0 (14.6) | 23.5 (14.6) | 27.7 (14.6) |
| **Monounsaturated Fat (g/day)** | 26.5 (15.2) | 26.0 (15.1) | 30.6 (16.1) |
| **Total Omega-3 Fatty Acid without supplementation (g/day)** | 1.57 (1.11) | 1.54 (1.09) | 1.87 (1.21) |
| **Total Protein (g/day)** | 85.4 (53.4) | 84.7 (55.0) | 91.7 (37.7) |
| **Processed Meat (g/day)** | 4.48 (3.94) | 4.47 (3.86) | 4.58 (4.61) |
| **Alcohol (g/day)** | 3.28 (4.76) | 3.29 (4.77) | 3.18 (4.77) |
| **Sulfur (mg/day)** | 1038.8 (530.4) | 1035.9 (542.7) | 1065.0 (413.8) |

Results expressed as mean (SD)

No significant differences noted when comparing patients who experienced a flare to those who did not experience a flare, using Benjamini and Hochberg method with false discovery rate 0.05

## Table 3

Comparison of medium and high intake of nutrient and food groups to low intake and the relationship to odds of disease relapse among patients with Ulcerative Colitis

| | Categorical analysis (comparing medium and high tertiles to tertile of lowest dietary intake)[a] | | | |
|---|---|---|---|---|
| | **Tertile 2 Medium Intake** | **Benjamini-Hochberg q-value** | **Tertile 3 High Intake** | **Benjamini-Hochberg q-value** |
| **Myristic Acid** | 1.52 (0.63, 3.67) | 0.899 | 2.87 (1.28, 6.45) | 0.055 |
| **Alpha Linolenic Acid** | 2.94 (1.19, 7.25) | 0.705 | 2.94 (1.19, 7.25) | 0.159 |
| **Oleic Acid** | 1.73 (0.73, 4.11) | 0.899 | 2.58 (1.13, 5.85) | 0.069 |
| **Eicosenoic Acid** | 1.47 (0.63, 3.43) | 0.899 | 2.36 (1.07, 5.21) | 0.069 |
| **Palmitelaidic Acid** | 1.46 (0.62, 3.43) | 0.899 | 2.34 (1.02, 5.37) | 0.069 |
| **Total Trans Lineoleic Acid** | 2.03 (0.87, 4.73) | 0.899 | 2.31 (1.01, 5.30) | 0.069 |
| **Saturated Fat** | 1.43 (0.61, 3.35) | 0.899 | 2.30 (1.04, 5.09) | 0.069 |
| **Monounsaturated Fat** | 1.73 (0.73, 4.11) | 0.899 | 2.58 (1.13, 5.85) | 0.069 |
| **Total Omega-3 Fatty Acid without supplementation** | 1.00 (0.42, 2.39) | 0.705 | 2.35 (1.10, 5.03) | 0.055 |
| **Total Protein** | 0.79 (0.21, 3.00) | 0.899 | 1.21 (0.36, 4.06) | 0.097 |
| **Processed Meat** | 0.30 (0.13, 0.74) | 0.085 | 0.94 (0.47, 1.87) | 0.926 |
| **Alcohol** | 0.50 (0.21, 1.23) | 0.705 | 1.01 (0.51, 2.01) | 0.715 |
| **Sulfur** | 0.57 (0.13, 2.50) | 0.705 | 1.42 (0.43, 4.70) | 0.860 |

[a]Significance for trends across tertiles assessed with the Benjamni-Hochberg method, with false discovery rate 0.05 Results expressed as OR (95% CI) Tertile 2 and Tertile 3 compared to Reference, Tertile 1, Low Intake

**Table 4**

Odds of disease relapse among patients with Ulcerative Colitis analyzed by multivariable analysis comparing medium and high intake of nutrient/food groups to low intake

| | Tertile 2 Medium Intake | p-value | Tertile 3 High Intake | p-value |
|---|---|---|---|---|
| Myristic Acid | 1.65 (0.64, 4.28) | 0.894 | 3.01 (1.17, 7.74) | 0.023 |
| Alpha Linolenic Acid | 5.50 (1.56, 19.34) | 0.001 | 1.34 (0.26, 7.00) | 0.393 |
| Total Omega-3-Fatty Acid without supplementation | 0.31 (0.09, 1.02) | 0.005 | 1.58 (0.38, 6.61) | 0.084 |
| Processed Meats | 0.22 (0.09, 0.56) | 0.007 | 0.53 (0.24, 1.15) | 0.734 |

Note: Results expressed as OR (95% CI)

Tertile 2 and Tertile 3 compared to Reference, Tertile 1, Low Intake