Association of Dietary Habits with Severity of Acute Pancreatitis

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Abstract

Background: The effect of diet on risk of acute pancreatitis (AP) has been suggested by prior studies, but the association of dietary habits with severity of AP has not been previously evaluated.

Objective: The objective of the study was to assess differences in reported dietary habits in patients with severe AP compared with those with mild or moderate AP.

Methods: A prospectively maintained cohort of patients with AP was utilized. A brief questionnaire on dietary habits was implemented. Dietary habits were categorized based on the overall type of diet, fruit/vegetable servings, fat content, dairy consumption, dessert/sweets consumption, and fluid intake. Patients were grouped into mild/moderate and severe AP. Multivariate analysis was used to determine whether dietary habits have an independent association with AP severity.

Results: 407 patients with AP were studied. Mean patient age was 51 y, and 202 (50%) were men. 29% of patients were smokers and 46% actively consumed alcohol. 225 patients had mild AP, 103 moderate AP, and 79 developed severe AP. The 3 groups were comparable in race, body mass index, etiology of AP, and comorbidities. Dietary factors were overall comparable between the groups except for diet type: subjects with severe AP had a higher percentage of consuming a meat-rich diet (84%) than patients with mild AP (72%) and moderate AP (67%) (P = 0.04). Based on multivariable logistic regression, the OR of developing severe AP was 2.5 (95% CI: 1.24–5.32, P = 0.01) between patients who eat a meat-rich diet and those who consume a vegetable-based diet.

Conclusions: A meat-rich diet is independently associated with the development of persistent organ failure (severe disease) in patients with AP. These findings require further evaluation and could be useful for patient counseling, risk stratification, and disease prevention. This study is registered at clinicaltrials.gov as NCT03075605. Curr Dev Nutr 2018;2:nzy075.

Introduction

Acute pancreatitis (AP) is a leading cause of gastrointestinal-related hospital admissions, and its incidence continues to increase (1). The Revised Atlanta Classification (RAC) is an international consensus that stratifies AP based on disease severity into 3 categories: mild (no organ failure and no local complications), moderate (transient organ failure lasting <48 h, and/or local complications), and severe AP (persistent organ failure ≥48 h, with or without local complications) (2). Patients with severe AP tend to require prolonged hospitalization and have significant morbidity and mortality (3). Furthermore, approximately one-fifth of patients...
after an episode of AP can develop recurrent AP, and ∼10% progress over time to chronic pancreatitis (4).

There are multiple etiologies for developing AP including gallstones, hypertriglyceridemia, and certain medications. The effects of 2 major modifiable risk factors, alcohol consumption and cigarettes smoking, have been extensively evaluated as contributing to the development and progression of AP (5, 6). However, another potential important modifiable risk factor for AP that has not been studied as well is diet. A few population-based research studies evaluated the association between certain dietary components and the incidence of AP (7–11). However, some of these studies lacked individual patient data on key clinical variables. In addition, to our knowledge, the association of dietary habits with the severity of AP has not been previously assessed.

Identifying specific dietary habits that could potentially influence the clinical course and severity of AP can have major implications on patient counseling, risk stratification, and disease prevention. The aim of this study was to assess differences in reported dietary habits between patients with severe AP and those with mild or moderate AP, and to identify key dietary variables that could be targeted to develop effective preventative strategies for AP.

Methods

Study population

This research is registered at www.clinicaltrials.gov (NCT03075605). Pancreatitis-associated risk of organ failure is an ongoing prospective observational study conducted at the University of Pittsburgh Medical Center and approved by the institutional review board (protocol ID PRO08010374). Patients who meet ≥2 of 3 criteria for diagnosis of AP and present within 7 d from pain onset are considered eligible for enrollment: presence of abdominal pain characteristic of AP, serum lipase level ≥3 times the upper limit of normal, and/or cross-sectional imaging findings consistent with AP. Patients with imaging and/or clinical findings suggestive of chronic pancreatitis or pancreatic cancer are excluded. After obtaining informed consent, each patient is enrolled into the study following admission or transfer to our center and is prospectively followed until hospital discharge. Enrollment period for this particular study was from August 2008 to December 2015. No specific sample-size calculation was performed, and prospective data were used at the time of statistical analysis.

Pertinent demographic, laboratory, and radiologic data are prospectively recorded. Outside hospital medical records of transferred patients are reviewed. Etiology of AP, duration of organ failure (if any), and development of local complications (if any) are recorded. Details of alcohol consumption and cigarette smoking history are obtained by personally interviewing the patients.

Diet questionnaire

A brief questionnaire of dietary habits is completed in a prospective manner by personally interviewing enrolled patients during their hospitalization. Dietary habits are categorized based on the overall type of diet (meat-rich compared with vegetable-based), fruit/vegetable servings, fat intake (low, average, or high), dairy consumption, dessert/sweets consumption, and fluid intake (Figure 1). We elected to use this basic FFQ to assess the presence of potential associations for the purpose of this study, because there are no validated diet questionnaires for pancreatic disorders, and a detailed food frequency questionnaire was difficult to utilize because patients were interviewed while hospitalized with an acute illness.

Statistical analysis

To compare baseline patient characteristics and clinical factors among patients with AP across the 3 RAC groups, analysis of variance was applied to continuous variables, and Pearson’s chi-square test was applied to categorical variables. For continuous variables whose distribution is far from normally distributed (BMI, Charlson comorbidity index, and fluid intake), the nonparametric Kruskal–Wallis test was used instead. Categorical variables with ≤10 observations in any of the RAC categories were collapsed with an adjacent variable to preserve statistical power. Those variables were race, AP etiology, diet type, dairy consumption, and fruit/vegetable servings. Multivariable logistic regression models were used to study the association between different diet habits and the risk of severe AP (compared with mild and moderate AP). Gender, age, race, BMI, and diet type were adjusted for in the models. Herein, mild and moderate AP patients were grouped together and compared with patients with severe AP, based on the clinical perspective that these patients are managed differently from patients with severe AP. Variables with unadjusted P values ≤0.2 were included in the multivariable analysis. Variables found to be not statistically significant in the multivariable analysis were not subsequently included in the final model with the exception of age, gender, race, BMI, and active alcohol use, which we adjusted for. Possible interactions between gender, age, BMI, and diet type in these regression models were tested via the Wald test. The Gamma statistic was used to assess the strength of concordance among ordinal diet related variables. All tests were 2-tailed, and a P value of ≤0.05 was considered statistically significant. Analyses were performed using R (R Foundation for Statistical Computing, 2017, Version 3.3.3).

Results

A total of 407 patients with AP were studied. The mean patient age was 51 y (SD 18 y), and 202 (49.6%) were men. At baseline, 29% of patients were smokers, and 46% actively consumed alcohol. Per the RAC, 225 patients had mild AP, 103 had moderate AP, and 79 developed severe AP. Table 1 summarizes the characteristics of all AP patients, comparing the clinical characteristics of patients with mild, moderate, and severe disease. Overall, the 3 groups were comparable in race, etiology of AP (biliary compared with other), and Charlson comorbidity index. Descriptive analysis suggested significant age, gender, and BMI differences among the 3 groups.

Table 2 compares the dietary habits among the 3 RAC severity groups of AP. Supplemental Table 1 lists all dietary habits details among the 3 groups before collapsing certain categorical variables as described in the “Statistical Analysis” section. The dietary habits were overall comparable between the 3 groups except for diet type, because patients with severe AP consumed a significantly higher percentage of diet rich in meat (84%) than did patients with mild AP (72%) and moderate AP (67%) (P = 0.04).
Diet and acute pancreatitis

**Diet Questionnaire**

1. Do you consider your diet?
   - [ ] Vegetarian
   - [ ] Mainly vegetarian, occasional meat or poultry
   - [ ] Meat/poultry a few times a week
   - [ ] Daily meat and/or poultry

2. How many servings of fruits or vegetables do you eat per day?
   - [ ] 5 or more
   - [ ] 3 or 4
   - [ ] 1 or 2
   - [ ] I rarely eat fruit and vegetables

3. Do you consider your diet?
   - [ ] Low fat
   - [ ] Average in fat
   - [ ] High in fat

4. How often do you consume dairy products such as milk, cheese, or yogurt?
   - [ ] Many servings each day
   - [ ] At least one serving per day
   - [ ] A few times per week
   - [ ] I rarely consume dairy products

5. How often do you eat dessert or sweets, such as cake, pie, ice cream or candy?
   - [ ] Daily
   - [ ] A few times per week
   - [ ] Once a week
   - [ ] I rarely eat sweets

6. About how much fluid in the form of water, juice, coffee, tea, or milk do you estimate that you drink per day (in ounces)?

**FIGURE 1** Diet questionnaire.

**Association of diet type with severity of AP**

Based on the multivariable logistic regression model (Table 3) and after adjusting for age, gender, race, BMI, and active alcohol use, the odds ratio of developing severe AP was 2.5 (95% CI: 1.24–5.32, \( P = 0.01 \)) between patients who eat a diet rich in meat and those who consume a mainly vegetable-based diet. Diet type was the only variable significantly associated with severity of AP after adjusting for demographics. Importantly, the Gamma statistic among ordinal diet-related variables showed that diet type (meat intake) and diet fat were moderately correlated (\( \gamma = 0.60 \)).

**Discussion**

AP is associated with substantial morbidity, significant mortality, and high healthcare related expenditure in the United States (12). Given the lack of current disease-specific therapy, identifying modifiable risk factors to prevent AP or alter its potential severe clinical course is especially important. The effect of diet on developing AP has been alluded to for years in the medical literature, because it constitutes an appealing modifiable risk factor for this potentially devastating disease. However, the exact impact of habitual dietary intake on the clinical

| TABLE 1  | Demographic and clinical characteristics among patients with mild, moderate, and severe AP¹ |
|-----------|-----------------------------------------------------------|
|           | Mild AP (N = 225) | Moderate AP (N = 103) | Severe AP (N = 79) | Total (N = 407) | \( P \) value |
| Mean age, y | 49.8 ± 17.7 | 50.6 ± 17.8 | 56.5 ± 15.9 | 51.3 ± 17.6 | 0.01 |
| Male, n (%) | 98 (43.6) | 55 (53.4) | 49 (62.0) | 202 (49.6) | 0.01 |
| Caucasian, n (%) | 198 (88.0) | 95 (92.2) | 69 (87.3) | 362 (88.9) | 0.46 |
| BMI ≥30 kg/m², n (%) | 96 (42.7) | 45 (43.7) | 46 (58.2) | 187 (45.9) | 0.05 |
| Active smoker, n (%) | 66 (29.3) | 31 (30.1) | 21 (26.6) | 118 (29.0) | 0.86 |
| Active alcohol use, n (%) | 93 (41.3) | 54 (52.4) | 39 (49.4) | 186 (45.7) | 0.13 |
| Median Charlson comorbidity index² | 0 [0, 1] | 0 [0, 1] | 1 [0, 2] | 0 [0, 1] | 0.31 |
| Biliary etiology of AP, n (%) | 95 (42.2) | 37 (35.9) | 39 (49.4) | 171 (42.0) | 0.19 |
| Recurrent AP, n (%) | 84 (37.3) | 41 (39.8) | 16 (20.3) | 141 (34.6) | 0.01 |
| Transferred from an outside hospital, n (%) | 92 (40.9) | 68 (66) | 67 (84.8) | 227 (55.8) | <0.001 |
| Mortality, n (%) | 0 | 0 | 16 (20.3) | 16 (3.9) | <0.001 |

¹Values are means ± SDs, median [IQRs], or n (column %). AP, acute pancreatitis.
²Analyzed using nonparametric Kruskal–Wallis test.
course of AP and severity of disease has not been previously explored.

A recent population-based prospective analysis of a large multiethnic cohort of AP patients identified saturated fat and cholesterol intake and their food sources, including red meat, to be positively associated with the risk of gallstone-related AP. This study also reported that fiber intake was inversely associated with both gallstone-related AP and nongallstone-related AP (7). These results were consistent with the Iowa Women’s Health Study that showed an increased risk of AP with higher total and saturated fat intake (8). Two other population-based prospective studies reported a protective effect of vegetables and fish on the incidence of nongallstone-related AP (9, 10). Further supporting the effect of diet on pancreatic inflammation, dietary habits have been shown to affect chronic pancreatitis as well. A large cross-sectional study demonstrated that a high-fat diet is associated with a younger age at diagnosis, younger age at onset of symptoms, and higher probability of continued abdominal pain in patients with chronic pancreatitis (13).

To our knowledge, this is the first study to evaluate the differences of reported dietary habits in patients with severe AP compared with those with mild or moderate AP. In our prospectively enrolled cohort of AP patients admitted or transferred to a major tertiary medical center, and after adjusting for demographics and active alcohol use, we report that the OR of developing severe AP is 2.5 (95% CI: 1.24, 5.32) in patients who consume a diet rich in meat compared with patients who mainly consume a vegetable-based diet \( (P = 0.01) \). Importantly, we demonstrate that diet type (meat intake) and dietary fat are moderately correlated \( (\gamma 0.60) \), which indicates that dietary fat itself may also be indirectly associated with severe AP. This is not unexpected, because a diet rich in meat in westernized countries is usually also high in fat content. Avoiding high fat and red meat is recommended as part of AP management, and our results are supportive of this practice. Although our results are in part similar to the findings of a population-based cross-sectional study conducted in China that reported a 2-fold increase in the risk of AP among subjects with a high meat intake \( [OR: 2.85 (95\% CI: 1.20–6.74), P = 0.017] \), the prior study did not evaluate the correlation of diet with the clinical course, i.e., severity of AP (11).

There are multiple hypothesized mechanisms by which a diet rich in meat (and therefore fat) and poor in vegetables can influence the clinic course of AP. First, both meat and fat are highly stimulatory to the pancreas and associated with increased cholecystokinin secretion. Second, certain dietary components can influence the inflammatory cascade by contributing reactive oxygen and nitrogen species that have been implicated in the pathogenesis of AP (14). An imbalance in the antioxidant status partly driven by dietary factors can sensitize the pancreas to oxidative stress and potentiate AP. This hypothesis has been supported by results of a prospective study of a Swedish population-based cohort over 12 year, which reported a significant inverse linear dose–response association between vegetable consumption and risk of nongallstone-related AP, whereby vegetables (rich in antioxidants such as vitamin C and \( \beta \)-carotene) were suggested to provide a redox balance and protect against the development of AP (10). Third, a high-fat diet (which a primarily meat-based diet is) has been shown to induce pancreatic injury in rat models and to worsen alcohol-mediated pancreatic injury (15, 16). Fourth, diet has a significant influence on the composition of gut microbiota (17). It is plausible that diet may be

### TABLE 2
Comparison of dietary intake among patients with mild, moderate, and severe AP

|                        | Mild AP \( N = 225 \) | Moderate AP \( N = 103 \) | Severe AP \( N = 79 \) | Total \( N = 407 \) | \( P \) value |
|------------------------|-----------------------|--------------------------|------------------------|-------------------|-------------|
| Diet type, n (%)       |                       |                          |                        |                   |             |
| Meat at least a few times a week | 156 (71.6) | 64 (67.4) | 59 (84.3) | 279 (72.8) | 0.04        |
| Mainly vegetables      | 62 (28.4)             | 31 (32.6)                | 11 (15.7)              | 104 (27.2)        |             |
| Diet fat, n (%)        |                       |                          |                        |                   |             |
| High fat               | 21 (12.3)             | 11 (15.5)                | 12 (25.0)              | 44 (15.2)         | 0.15        |
| Mean fat               | 88 (51.5)             | 36 (50.7)                | 26 (54.2)              | 150 (51.7)        |             |
| Low fat                | 62 (36.3)             | 24 (33.8)                | 10 (20.8)              | 96 (33.1)         |             |
| Dairy products, n (%)  |                       |                          |                        |                   |             |
| \( \geq 1 \) serving/d | 152 (69.1)            | 73 (77.7)                | 52 (75.4)              | 277 (72.3)        | 0.25        |
| Rarely or a few times a week | 68 (30.9) | 21 (22.3) | 17 (24.6) | 106 (27.7) |             |
| Fruits/vegetables, n (%) |                   |                          |                        |                   |             |
| \( \geq 3 \) serving/d | 74 (33.9)             | 31 (32.6)                | 21 (30.9)              | 126 (33.1)        | 0.89        |
| \( <3 \) serving/d    | 144 (66.1)            | 64 (67.4)                | 47 (69.1)              | 255 (66.9)        |             |
| Dessert, n (%)         |                       |                          |                        |                   |             |
| Daily                  | 52 (23.7)             | 22 (23.7)                | 22 (31.9)              | 96 (25.2)         | 0.66        |
| A few times a week     | 57 (26.0)             | 26 (28.0)                | 18 (26.1)              | 101 (26.5)        |             |
| 1 time/wk             | 49 (22.4)             | 15 (16.1)                | 11 (15.9)              | 75 (19.7)         |             |
| Rarely                 | 61 (27.9)             | 30 (32.3)                | 18 (26.1)              | 109 (28.6)        |             |
| Median fluid intake, \(^2\) oz | 60 [40, 74] | 64 [40, 76] | 58 [35.5, 70] | 60 [40, 72] | 0.77        |

\(^1\)Values are median [IQRs], or n (column %). AP, acute pancreatitis; oz, ounce.

\(^2\)Analyzed using nonparametric Kruskal–Wallis test.

### TABLE 3
Multivariable logistic regression model

|                        | OR (severe AP vs. mild/moderate AP) | 95\% CI | \( P \) value |
|------------------------|-------------------------------------|--------|--------------|
| Age, \( y \)           | 1.03                                | 1.01–1.05 | <0.01        |
| Sex, male              | 1.51                                | 0.87–2.67 | 0.15        |
| BMI, \( \geq 30 \) kg/m\(^2\) | 2.12                                | 1.23–3.72 | 0.01        |
| Race, Caucasian        | 1.41                                | 0.61–3.02 | 0.4        |
| Active alcohol use     | 1.53                                | 0.86–2.74 | 0.15        |
| Diet rich in meat      | 2.47                                | 1.24–5.32 | 0.01        |
acting as a key disease-modifying factor by altering the gut microbiome composition and inducing a proinflammatory state, thus increasing the risk of AP and worsening its clinical course. Tan et al. (18) reported that gut Enterobacteriaceae and Enterococcus populations were higher, and the Bifidobacterium population was lower in patients with AP (both mild and severe) than in healthy subjects. In this study, multorgan failure was more frequent among AP patients with dysbiosis, suggesting a potential influence of gut microbiome on disease severity.

The major strengths of this study are the prospective method of patient enrollment, large sample size, inclusion of all AP patients regardless of disease etiology, the personal interview to obtain the diet questionnaire, and adequate control for confounders.

There are a number of limitations to our study. The study design prohibits determining the mechanistic association between diet and severity of AP. We used a basic frequency questionnaire to assess the presence of potential associations. We understand that most food-frequency surveys do not reliably represent dietary habits and that the ideal diet questionnaire should detail food content and amount on multiple occasions. However, there are no validated diet questionnaires for pancreatic disorders. Furthermore, existing FFQs are time-consuming because they can include ≤70 food/beverage items, and most of these evaluate dietary intake over the prior year and therefore would not have been feasible to administer in our study setting because patients were interviewed while hospitalized with an acute painful illness. Also, data on diet and other risk factors for pancreatitis including alcohol intake and smoking were obtained from the baseline questionnaire only. Diet changes during follow-up are possible, and because AP is a dynamic disease, worse disease severity could be related to variation of exposure to certain dietary items. Further, recall bias and measurement error in diet questionnaires are inevitable and may have led to misclassification of exposure. Finally, the study is conducted in a tertiary referral center with a significant number of transferred patients, and therefore our findings may not be representative of the community setting of all comers with AP.

In summary, our study shows that a diet rich in meat is independently associated with a severe AP course. If these preliminary findings are confirmed in subsequent prospective studies, they can have important implications on patient counseling and risk stratification, and may be used as a basis for further studies on the role of dietary interventions as preventative and therapeutic strategies for AP.

Acknowledgments

The authors’ responsibilities were as follows—MD, AG, and GIP: conceived and designed the study, acquired the data, performed statistical analysis, interpreted the data, and wrote the manuscript; XG, GT, and PG: performed statistical analysis and interpreted the data; PP, BM, and IP: acquired and interpreted the data; CY: interpreted the data and critically reviewed the manuscript for intellectual content; SJDO, DCW, and DY: acquired the data and critically reviewed the manuscript for intellectual content; GIP: had primary responsibility for final content; and all authors: read and approved the final version of the manuscript.

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