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ORIGINAL RESEARCH—CLINICAL

A Comprehensive Analysis of the Impact of Acute Myocardial Infarction in Patients With Celiac Disease

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BACKGROUND AND AIMS: We aimed to study the impact of acute myocardial infarction (AMI) in patients with celiac disease (CD). **METHODS:** We used the National Inpatient Sample 2011–2018 to identify patients aged 18 years and older with a history of CD who presented with AMI using International Classification of Disease Nineth and Tenth Revision codes. Primary outcome of interest was mortality differences in AMI patients with and without CD. Secondary outcomes were in-hospital length of stay, hospital costs, and coronary revascularization. **RESULTS:** A total of 2,287,840 weighted patients were included in this study with a principal diagnosis of AMI. Among this population, 183,027 weighted patients had a history of CD (0.08%), and 2,286,010 weighted patients had AMI without a history of CD (99.92%). Most AMI patients with and without CD were older (69.57 ± 13.21 vs 67.08 ± 13.87 years, respectively) and white (92.55% vs 75.39%, respectively). Patients with AMI and CD were more likely to be female than patients without CD (53.76% vs 38.47%; $P < .05$). In our study, we found that the difference in hospital charges (adjusted mean difference $2644.7) was lower among AMI and CD; however, length of stay was higher among patients with CD (adjusted mean difference 0.36 day) although they were not statistically significant ($P > .05$). Both cohorts had higher number of Medicare recipients and lower number of patients who self-pay. Our study also found that smoking was more prevalent among patients with CD, 12.14%, vs patients without CD, 2.51%. Moreover, patients with CD who developed AMI had a lower adjusted odds of mortality than those without CD (adjusted odds ratio [aOR] 0.41; $P < .05$). Patients with CD and AMI also had lower odds of coronary revascularization (aOR 0.80; $P < .05$). In addition, we found that adults with CD had a lower odds of developing AMI (aOR 0.78; $P < .05$). **CONCLUSION:** CD is a chronic disease leading to chronic inflammation and various nutrition-related problems which can lead to increased morbid conditions. However, we found lower odds of AMI among patients with CD, as well as lower mortality and comorbidities related to AMI, thus contradicting previous assumptions.

Keywords: Celiac Disease; Acute Myocardial Infarction; Chronic Inflammatory State

Introduction

Celiac disease (CD) is an intestinal immune-mediated disease triggered by the ingestion of gluten in genetically susceptible individuals. Previously thought to be a disease of childhood, the prevalence of CD is now estimated to affect 1% of the world's population with increasing prevalence in adults.[1] While intestinal manifestations are common, CD has been associated with a wide range of extraintestinal manifestations including acute myocardial infarction (AMI). Studies have found CD to be associated with significant increases in cardiovascular disease (CVD), such as cardiomyopathies and premature atherosclerosis, compared with the general population.[2] Although previous reports have established that chronic inflammation and autoimmune diseases are associated with accelerated atherosclerosis, few studies have assessed the outcomes between CD and non-CD with AMI.[3] With approximately 2.3 million Americans at risk of cardiac complications,[4] we aim to assess the impact of AMI in patients with CD.

Methods

Data source

Our study is a retrospective cohort study using the combined 2011–2018 National Inpatient Sample (NIS), an initiative provided by the Healthcare Cost and Utilization Project.[5] The

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Abbreviations used in this paper: **aMD, adjusted mean difference; AMI, acute myocardial infarction; aOR, adjusted odds ratio; CD, celiac disease; GFD, gluten-free diet; HLD, hyperlipidemia; ICD-9, International Classification of Diseases, Nineth Revision; ICD-10, International Classification of Diseases, Tenth Revision; LOS, length of stay; NIS, National Inpatient Sample; T2DM, type 2 diabetes mellitus.**

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Table 1. List of ICD-9 and ICD-10 Codes Used in the Study

ICD-9		ICD-10	
410.xx - 410.0 - 410.1 - 410.2 - 410.3 - 410.4 - 410.5 - 410.6 - 410.7 - 410.8 - 410.9	Acute myocardial infarction	I21.xx - I21 - I21.0 - I21.1 - I21.2 - I21.3 - I21.4 - I21.9	Acute myocardial infarction
579.0	Celiac disease	K90.0	Celiac disease

NIS is one of the largest all-payer databases available in the United States and is maintained by the Agency for Healthcare Research and Quality. It comprises records of over 7 million unweighted and over 35 million weighted hospital encounters each year.[5] The data provided in the database are initially unweighted, then using an algorithm provided by Healthcare Cost and Utilization Project, it is converted to weighted data, which allows for estimates on a national level.[5] Institutional review board approval was not required for this study as the NIS includes patient information that has been deidentified and made publicly available.

Study population

The NIS includes a 20% random sample of all inpatient hospitalizations from over 45 states and contains 1 primary diagnosis and up to 39 secondary diagnoses using International Classification of Diseases, Tenth Revision, (ICD-10), as well as 29 secondary diagnoses with the International Classification of Diseases, Nineth Revision, Clinical Modification (ICD-9-CM) codes. ICD codes were used to identify hospitalizations with a principal diagnosis of AMI (ICD-9: 410.xx; ICD-10 code: I21.xx) and a secondary diagnosis of CD (ICD-9 code: 579.0; ICD-10 code: K90.0) (Table 1). All patients included in this study were 18 years of age or older. The primary outcome of interest was mortality differences in admissions. Secondary outcomes were in-hospital length of stay (LOS), hospital costs, and differences in outcomes based on coronary revascularization.

Statistical analysis

The Pearson chi-square test and Student's t-test were utilized for assessing baseline categorical and continuous variables, respectively. After adjusting for characteristics and comorbidities to account for confounding variables such as insurance status, age, gender, race, hospital bed size, Charlson comorbidity index, day of admission, hospital region/teaching status, and median income quartile based on zip code, a 2-step hierarchical multivariate regression model was used to calculate odds ratios of events associated with AMI in CD patients, such as coronary revascularization, developing AMI, and mortality. Furthermore, a multivariate regression model was used to find the difference in LOS and hospital charges (adjusted for inflation over time) in patients presenting with AMI and CD compared to non-CD patients. Stata Version 17 by StataCorp LLC (College Station, TX) was utilized for all statistical analyses.

Results

A total of 2,287,840 weighted patients were included in this study with a principal diagnosis of AMI. Among this population, 183,027 weighted patients had a history of CD (0.08%), and 2,286,010 weighted patients had AMI without a history of CD (99.92%) (Table 2). Most AMI patients with

Table 2. Baseline Characteristics of Patients With Acute Myocardial Infarction With and Without Celiac Disease from 2011 to 2018

Variables	Celiac (N = 183,027)	No celiac (N = 2,286,010)	*P* value
Age (y)	69.57 (±13.21)	67.08 (±13.87)	<.05
Gender, %			<.05
Male	46.24	61.53	
Female	53.76	38.47	
Charlson comorbidity index	2.56 (±1.59)	2.70 (±1.76)	.101
Race, %			<.05
White	92.55	75.39	
Other	7.45	24.61	
Comorbidities, %			
CAD	76.88	79.85	.172
HLD	57.80	64.31	<.05
HTN	55.49	55.06	.871
T2DM	29.19	38.10	<.05
CHF	28.90	31.37	.3336
Anemia	32.08	22.09	<.05
End-stage renal disease	3.18	3.72	.591
Obesity	12.14	16.11	<.05
Acute renal failure	12.72	16.36	.067
Smoking	12.14	2.51	<.05

CAD, coronary artery disease; CHF, congestive heart failure; HTN, hypertension.

Table 3. Outcomes of AMI Hospitalizations With CD vs Without CD

Outcomes	AMI + CD	AMI + no CD	*P* value[a]	Adjusted odds ratio	95% CI (LL-UL)	Adjusted *P* value[b]
All-cause in-hospital mortality	2.31%	4.98%	<.05	0.41	0.19–0.87	<.05
Coronary revascularization	50.29%	55.69%	<.05	0.80	0.65–0.99	<.05
Insurance status						
Medicare	67.05%	57.33%	<.05			
Self-pay	1.45%	5.85%	<.05			
Total hospital charges (mean)[c]	$85,911.30	90,950.00	.355			
Length of stay (d) (mean ± SD)	4.74 ± 5.07	4.54 ± 5.31	.445			

CI, confidence interval; LL, lower level; UL, upper level.
[a]Significant *P* values ≤ .05 at 95% confidence interval indicates statistical significance.
[b]Weighted logistic regressions were performed adjusting for confounders including baseline characteristics such as age at admission, sex, race, hospital characteristics including bed size, location/teaching status, region, type of admission, median household income, payer status, and pre-existing comorbidities.
[c]Adjusted for inflation over time.

and without CD were older (69.57 ± 13.21 vs 67.08 ± 13.87 years, respectively) and white (92.55% vs 75.39%, respectively). However, patients with AMI and CD were more likely to be female than patients without CD (53.76% vs 38.47%; $P < .05$).

The most prevalent comorbidities in the CD cohort were coronary artery disease, hyperlipidemia (HLD), hypertension, type 2 diabetes mellitus (T2DM), congestive heart failure, and anemia (Table 2). Moreover, prevalence of conditions normally associated with risk of AMI such as coronary artery disease, HLD, T2DM, congestive heart failure, and obesity was lower in the CD cohort than in the non-CD cohort (Table 2). Patients with CD and AMI also had lower odds of coronary revascularization (adjusted odds ratio [aOR] 0.80; $P < .05$) (Table 3). In addition, we found that adults with CD had lower odds of developing AMI (aOR 0.78; $P < .05$) (Table 3). Furthermore, patients with CD who developed AMI had lower adjusted odds of mortality than those without CD (aOR 0.41; $P < .05$) (Table 3).

In our study, we found that the difference in hospital charges (adjusted mean difference [aMD] $2644.7) was lower among patients with AMI and CD; however, LOS was higher among patients with CD (aMD 0.36 day) although they were not statistically significant ($P > .05$) (Table 3). Both cohorts had higher number of Medicare recipients and lower number of patients who self-pay (Table 3). Our study also found that smoking was more prevalent among patients with CD, 12.14%, vs patients without CD, 2.51%.

Discussion

CD, previously known as celiac sprue, is a chronic, systemic immune-mediated enteropathy triggered by ingestion of gluten in genetically susceptible individuals.[6] Once considered a disease of childhood, CD is estimated to affect 1% of the population worldwide with increasing prevalence in adults.[1] The disease is associated with human leukocyte antigen, specifically DQ2 and DQ8 haplotypes, a group of genes located on chromosome 6 that are responsible for regulating the immune system.[7]

CD is unique in that its clinical presentation is variable and can include intestinal and/or extraintestinal manifestations. Common gastrointestinal symptoms include abdominal pain from malabsorption due to villous atrophy of the intestinal wall by intraepithelial lymphocytes.[8] An emerging extraintestinal manifestation of CD of particular significance is the presumed increased risk of CVDs such as AMI. The increased risk of CVD is attributed to a combination of chronic inflammation, nutrient deficiencies, and an adaptive immune response.[9] Previous reports have established that the presence of chronic inflammation and autoimmune disease is associated with accelerated atherosclerosis due to endothelial dysfunction.[3] The resultant injury to the endothelium results in compensatory changes leading to procoagulant properties and recruitment of macrophages and T-lymphocytes. This mechanism is similar to that of acute coronary syndrome, a predisposing risk factor for AMI, whereby chronic inflammation leads to loss of the protective function of the endothelium.[6] This in turn leads to an increased propensity for stenosis and infarction of the coronary artery.[6]

Despite these associations, our study revealed lower odds of developing an AMI in patients with CD. There is evidence that suggests that a gluten-free diet (GFD) may be protective against this increased CVD risk.[10] A study carried out by Wei et al demonstrated an increase in CVD events only in patients with CD who had not been given a GFD.[10] Another study by Whorwell et al found a reduction in the incidence and mortality of ischemic heart disease in patients with CD.[11] Their proposed mechanism suggests an apparent protective effect of CD due to malabsorption of dietary lipids.[11] Our data across 8 years strengthen this hypothesis by demonstrating a significant decrease in mortality among patients with CD who have concomitant AMI (Table 2). Our data also showed a significant decrease in the prevalence of

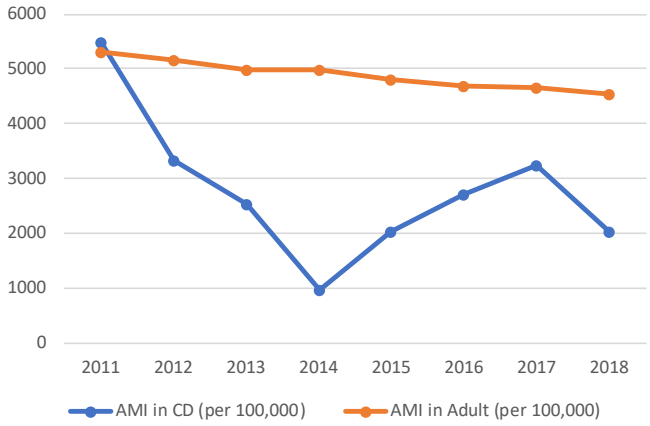

Figure. Mortality in patients with acute myocardial infarction (AMI) with celiac disease (CD) vs without CD.

comorbidities such as T2DM and HLD among patients with CD consistent with previous studies.[12] These comorbidities are all prominent risk factors in the development of AMI.[13]

Dietary management through a GFD is the only therapy for CD that has been shown to help manage symptoms and promote small-intestinal healing.[14] In addition, GFD has been shown to have an impact on the BMI of patients with underweight patients gaining weight and obese/overweight patients losing weight.[15] The link between BMI and a GFD is important as there is an increased risk of mortality associated with increasing BMI.[16] Our data demonstrated a lower prevalence of obese patients among those with CD and AMI.

The results from our current study suggest that patients with CD and AMI had, on average, a longer length of hospital stay and a lower aMD in total hospital charges than patients with AMI alone although it was not statistically significant. Borrelli et al showed a downward trend in hospitalizations as well as LOS for patients with CD over a 19-year period from 1995 to 2014.[17] Similarly, our data showed a downward trend in patients with CD with and without AMI (Figure). There is evidence that shows a correlation between LOS and mean hospital charges whereby a decrease in LOS would result in an expected decrease in hospital costs.[18]

The assessment of whether patients receive coronary revascularization, by percutaneous coronary intervention or coronary artery bypass grafting, takes into account many clinical factors such as age, comorbidities, prior myocardial infarction, and resting electrocardiography abnormalities.[19] Our data demonstrated that patients with AMI and CD had lower odds of receiving revascularization. One study showed that after adjusting for comorbidities and demographic factors, morbidly obese patients had higher rates of coronary artery bypass grafting surgery than those not morbidly obese when presenting with an AMI.[20] The patients in our AMI-with-CD cohort not only were less likely to be obese but also exhibited fewer comorbidities, such as diabetes and HLD, which is consistent with previous data that show higher comorbid risk factors in obese patients.[21]

Cigarette smoking has been proven to have a negative impact on cardiovascular outcomes.[22] It has been linked to increased risk of myocardial infarctions, stroke, and mortality.[22] Our study showed that patients with CD were found to have higher rates of smoking. Although only approximately 12% of the CD patient sample size were cigarette smokers, further studies need to be done to assess this potential confounding variable. A meta-analysis performed in Britain reviewed the association of smoking to CD and found that patients who were smokers were less likely to have CD.[23] However, no concrete studies exist that assess the outcomes of smoking and having CD and associated outcomes.

Although our study contained a large sample size, certain limitations about this study must be addressed. Limitations include the administrative nature of the data set, inability to longitudinally trace patient encounters, and possibility of overcalculation or undercalculation of the disease as it is limited to ICD codes and/or multiple inpatient admissions of the same patient. ICD codes require proper documentation, which may not always be the case. In addition, this study contains data that encompass both ICD-9 and ICD-10 codes, and it is known that ICD-9 codes may not be as specific for CD as ICD-10 codes. Furthermore, it is not possible to specify the cause of death. Moreover, NIS does not provide data on severity of the disease process, and it can be difficult to establish a timeline regarding the disease process or to determine whether the patient's CD is controlled and if they are on a GFD. The data set does not provide pertinent lab values or imaging that can help stratify the disease process and better guide researchers. However, the NIS is one of the largest publicly available databases that highlights outcomes associated with certain diseases, which are CD and AMI in our case.

Conclusion

Our study identified a significant association of AMI in patients with CD. Overall, patients who presented with a history of CD during 2011-2018 had lower odds of developing AMI, indicating a possible protective effect. These patients also had lower rates of comorbidities commonly associated with CVD, lower odds of mortality, and received coronary revascularization. These patients also had a longer LOS, less hospital charges, and decreased mortality compared to patients with AMI and without CD. In addition, we observed a decreasing trend in incidence of AMI in patients with CD and associated mortality from 2011 to 2018. We suspect that the underlying etiology may be due to immune-mediated intestinal damage and resultant malabsorption which may play a protective role in patients with CD.

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James R. Pellegrini Jr, MD (data acquisition, drafting of manuscript, critical revision of the manuscript for important intellectual content, study supervision). Rezwan F. Munshi, MD (data acquisition, drafting of manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis). Kristen Farraj, DO (drafting of manuscript, revision of manuscript). Jose R. Russe-Russe, MD (drafting of manuscript, revision of manuscript). Amr Abdou, BS (drafting of manuscript, revision of manuscript). Kashyap Shah, DO (drafting of manuscript). Madison Lannom, MD (drafting of manuscript). Kaleem Rizvon, MD (revision of manuscript). Paul Mustacchia, MD (critical revision of the manuscript for important intellectual content, study supervision).

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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
All data materials are available publicly through the National (Nationwide) Inpatient Sample (NIS). It is a set of longitudinal hospital inpatient databases included in the Healthcare Cost and Utilization Project (HCUP) family. These databases are created by the Agency for Healthcare Research and Quality through a Federal-State-Industry partnership.