Characteristics and comorbidities of inpatients without celiac disease on a gluten-free diet

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Objectives Despite the increasing popularity of gluten-free diet (GFD), the demographic characteristics and medical features of patients without celiac disease on this diet have not been extensively investigated. We aimed to characterize the medical conditions and demographic backgrounds of hospitalized patients without celiac disease who adhere to a GFD, to further understand their reasons for gluten avoidance.

Materials and methods We performed an observational cohort study on all inpatients at Columbia University Medical Center on a GFD in 2011–2016, excluding those with celiac disease, compared with age-matched and sex-matched inpatients on a regular diet. We determined the odds ratio (OR) of being on a GFD for various comorbidities using conditional logistic regression.

Results Of 769 inpatients on a GFD, most (63.6%) did not have celiac disease. Gluten-avoiding patients were more likely to be non-Hispanic Whites [OR: 2.92; 95% confidence interval (CI): 2.31–3.70]. They had a lower prevalence of hypertension (OR: 0.38; 95% CI: 0.27–0.52) and diabetes (OR: 0.58; 95% CI: 0.32–0.75) and higher prevalence of inflammatory bowel disease (OR: 1.56; 95% CI: 1.02–2.41), irritable bowel syndrome (OR: 6.16; 95% CI: 2.11–10.23), hyperthyroidism (OR: 2.73; 95% CI: 1.22–6.10), hypothyroidism (OR: 2.06; 95% CI: 1.39–3.06), lupus (OR: 2.87; 95% CI: 1.13–7.29), and autism spectrum disorder (OR: 23.42; 95% CI: 5.29–103.73).

Conclusion Nonceliac gluten-avoiding patients have higher prevalences of inflammatory bowel disease, irritable bowel syndrome, thyroid disease, lupus, and autism spectrum disorder, suggesting patients with these disorders have turned to a GFD for perceived benefit, despite a scant evidence basis. Eur J Gastroenterol Hepatol 30:477–483

Introduction

Celiac disease is an immune-mediated enteropathy characterized by a multitude of intestinal and extraintestinal symptoms including diarrhea, weight loss, abdominal pain, anemia, metabolic bone disease, and infertility, triggered by the ingestion of gluten in genetically susceptible individuals [1]. The prevalence of celiac disease in the USA in 2009–2010 was found to be 0.7% in a national screening study [2], and the prevalence has increased 4–5-fold over the past 50 years [3]. In susceptible individuals, ingestion of gluten, a protein derived from wheat, barley, and rye, results in the passage of gluten peptides across the epithelial barrier of the intestine causing an immune response, particularly in the duodenum [4]. Patients with celiac disease mount antibodies to tissue transglutaminase and develop duodenal villous atrophy in response to gluten ingestion, and most have significant symptomatic improvement on a gluten-free diet (GFD).

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Nonceliac gluten sensitivity (NCGS) is a distinct but related phenomenon in which patients who do not meet the criteria for celiac disease nevertheless have symptoms that are relieved by avoiding gluten [5–9]. The presenting symptoms are variable but overlap considerably with celiac disease [6,7]. However, those with NCGS have no duodenal villous atrophy, and there are no established biomarkers.

The GFD has been proposed as a treatment for, or demonstrated to be used by patients with a variety of other medical conditions, including inflammatory bowel disease (IBD) [10,11], irritable bowel syndrome (IBS) [12], and autism spectrum disorders [13,14]. Although studies have shown potential benefit in a GFD for NCGS and IBS [15], there is uncertainty whether some of the improvements of symptoms are because of the overlap between the GFD and a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, agents that can trigger intestinal symptoms [16]. Moreover, evidence for GFD as a treatment for other conditions such as autism and IBD is lacking. For example, although a 2010 single-blinded nonplacebo-controlled randomized trial showed improvement in autism symptom scores for patients on a GFD and casein-free diet [17], a 2016 double-blinded, albeit smaller, study showed no benefit [18].

There is also a growing interest in the general health benefits of avoiding gluten among healthy individuals. A questionnaire study evaluating athletes without celiac disease found that 41% adhered to a GFD over 50% of the time [19]. In fact, most people on a GFD in the USA do not have celiac disease [2], and the prevalence of a GFD among

patients without celiac disease has tripled in the past decade, whereas the prevalence of celiac disease has remained stable [20].

Given the wide variety of reasons patients without celiac disease may choose to avoid gluten, we aimed to characterize the medical and demographic features of hospitalized individuals without celiac disease who maintain a GFD, to better understand their reasons for doing so.

Materials and methods

We performed an observational cohort study analyzing medical and demographic characteristics of inpatients without celiac disease on a GFD admitted to New York Presbyterian/Columbia University Medical Center, an academic medical center in New York City. All data were obtained from the hospital's electronic medical record (EMR).

We identified all inpatients admitted to this hospital between 1 January 2011, and 31 December 2016, whose admission orders included a GFD. To only include patients without celiac disease, patients were excluded if they carried a known diagnosis of celiac disease [identified using the International Classification of Disease (ICD) coding system], had a duodenal biopsy consistent with celiac disease, or had positive celiac disease serologies (antigliadin, antitissue transglutaminase, or antiendomysial antibodies).

Each one of these patients was then matched to two age-matched and sex-matched controls, chosen from hospitalized patients prescribed a regular diet. The control patients were selected by identifying the two inpatients admitted during the same time period on a regular diet who had the closest age at time of admission to the gluten-avoiding patient, also excluding patients who had a diagnosis of celiac disease or positive biopsy or serologies for celiac disease. In this study, the controls were all patients on regular diets without any medical restrictions (such as carbohydrate or sodium restriction), although the regular diets did include cultural/religious restrictions such as a kosher and vegetarian preference.

Demographic characteristics obtained from the EMR were then identified for each patient, including age, sex, race, ethnicity, insurance status/type, and other dietary restrictions. The prevalence of specific medical conditions, including hypertension, diabetes, IBD, IBS, and autism spectrum disorder was then determined for each patient, also using ICD diagnostic code assignments in the EMR. We also recorded a history of depression by the presence of either an ICD code for this condition or one of the following outpatient medications listed on the admission medication reconciliation note: fluoxetine, sertraline, paroxetine, citalopram, escitalopram, mirtazapine, trazodone, bupropion, venlafaxine, duloxetine, amitriptyline, and nortriptyline.

We used the Cochran–Mantel–Haenszel test to compare the prevalence of each comorbidity in the gluten-avoiding patients to matched controls. To identify factors independently associated with gluten avoidance, we performed conditional logistic regression, measuring for the association between gluten avoidance and the diagnosis of each comorbidity, adjusting for race, ethnicity, and insurance status. Statistical analysis was performed with Stata 13.1 (StataCorp., College Station, Texas, USA). All P values are two-sided with an α level of 0.05. The Institutional Review Board at Columbia University Medical Center approved this study.

Results

Of the 769 in patients receiving a GFD order in 2011–2016, most (489, 63.6%) did not have a diagnosis of celiac disease, and these patients served as our study cohort. Of these 489 patients, the mean age at admission was 41.2 years (SD 23.7 years, range 25 days to 96 years), and 68.3% were female. The 978 patients in the control group were matched by age and sex and had the same female predominance (68.3%) and similar mean age (41.2 years for GFD vs. 41.7 years for controls; SD 23.7 years in both groups, Table 1). Twenty percent of all nonceliac GFD orders were for children younger than 18 years.

The percentage of non-Hispanic White patients was significantly higher in the gluten-free group (55.6 vs. 29.7%, $P < 0.001$), whereas the gluten-free group had a lower percentage of Black (3.5 vs. 12.1%, $P < 0.001$) or Hispanic patients (9.4 vs. 20.9%, $P < 0.001$). GFD patients were also more likely to have additional dietary

Table 1. Demographic characteristics of gluten-free patients and controls

Characteristics	Gluten-free ($n = 489$) [n (%)]	Control ($n = 978$) [n (%)]	P value[a]
Age [mean (SD)] (years)	41.2 (23.7)	41.7 (23.7)	0.74
0–17	100 (20.4)	196 (20.0)	0.85
18–29	60 (12.3)	118 (12.1)	
30–39	95 (19.4)	189 (19.3)	
40–49	50 (10.2)	105 (10.7)	
50–59	71 (14.5)	141 (14.4)	
60–69	45 (9.2)	89 (9.1)	
> 70	68 (13.9)	140 (14.3)	
Sex			
Male	155 (31.7)	310 (31.7)	1
Female	334 (68.3)	668 (68.3)	
Race			
Black	17 (3.5)	118 (12.1)	< 0.001
White	299 (61.1)	399 (40.8)	
Other	173 (35.4)	461 (47.1)	
Ethnicity			
Hispanic	46 (9.4)	204 (20.9)	< 0.001
Non-Hispanic	250 (51.1)	393 (40.2)	
Unknown/decline	193 (39.5)	381 (39.0)	
Non-Hispanic White	272 (55.6)	290 (29.7)	< 0.001
Antidepressant use[b]	69 (14.1)	81 (8.3)	0.005
Kosher diet	18 (3.7)	11 (1.1)	0.001
Vegetarian diet	22 (4.5)	6 (0.6)	< 0.001
Length of stay [mean (SD)] (days)	6.7 (11.9)	5.6 (11.7)	0.071
Insurance[c]			
Commercial	425 (86.9)	725 (74.1)	< 0.001
Medicare	111 (22.7)	209 (21.3)	0.41
Medicaid	88 (18.0)	306 (31.3)	< 0.001
Self-pay/none	5 (1.0)	45 (4.6)	< 0.001
Other/unknown	20 (4.1)	60 (6.1)	0.1

[a]Calculated using Student t-test for continuous variables (age and length of stay) and Cochran–Mantel–Haenszel test for categorical data.
[b]Antidepressants included sertraline, paroxetine, citalopram, escitalopram, fluoxetine, mirtazapine, venlafaxine, duloxetine, amitryptiline, nortryptiline, trazodone, and bupropion.
[c]Sum is greater than overall sample size due to certain patients having at least 1 insurance type.

restrictions, such as a kosher diet (3.7 vs. 1.1%) or vegetarian diet (4.5 vs. 0.6%).

The gluten-free patients were more likely than controls to have commercial insurance (86.9 vs. 74.1%). They were less likely to have Medicaid (18.0 vs. 31.3%) or no insurance (1.0 vs. 4.6%). They had similar rates of Medicare enrollment (22.7 vs. 21.3%).

Both the number and proportion of GFDs ordered for inpatients increased annually, except for 2016 (Figs 1 and 2). Each year, most GFD orders were entered for patients without a celiac disease diagnosis (Fig. 2). Starting in 2012, the percentage of GFDs that were ordered for patients without celiac disease increased each year, and in 2016, 68% of GFD orders were for patients without celiac disease.

The medical service to which each patient was admitted is listed in Table 2. The gluten-free patients were less likely to be admitted to the internal medicine service and more likely to be admitted to neurology, orthopedic surgery, and pediatric neurology. They were admitted in similar rates to obstetrics/gynecology, general surgery, and psychiatry.

The various medical diagnoses assigned to each patient in the EMR are listed in Table 3. Patients on a GFD were less likely than controls to be diagnosed with hypertension (18.0 vs. 33.5%, $P<0.001$) or diabetes (6.5 vs. 12.2%, $P<0.001$). They were more likely than controls to be diagnosed with IBS (4.7 vs. 1.2%, $P<0.001$), hypothyroidism (14.7 vs. 7.5%, $P<0.001$), and autism spectrum disorder (5.5 vs. 0.5%, $P<0.001$). Hypertension and diabetes remained less prevalent in the gluten-free group versus the control group after adjusting for race, ethnicity, and insurance status. Diagnoses entered significantly more frequently among gluten-free patients on multivariable analysis included IBS, IBD, autism spectrum disorder, hypothyroidism, hyperthyroidism, and systemic lupus erythematosus.

The prevalence of depression was similar, at 21.7% in the gluten-free group and 20.1% in the control group ($P=0.49$). Patients who avoid gluten were significantly more likely to be prescribed an antidepressant medication. Among the gluten-avoiding patients, 69 (14.1%) patients were taking one of the antidepressants listed in Table 1, compared with 81 (8.3%) of the control group ($P=0.005$). The percentage of patients taking multiple antidepressant medications was higher in the gluten-avoiding group, at 1.6 versus 1.1%, but the difference was not significant ($P=0.42$).

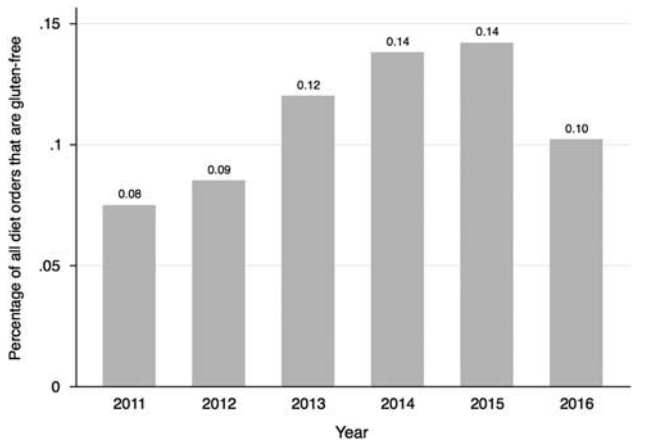

Fig. 1. Percentage of all inpatient diet orders for a gluten-free diet, excluding NPO orders, 2011–2016.

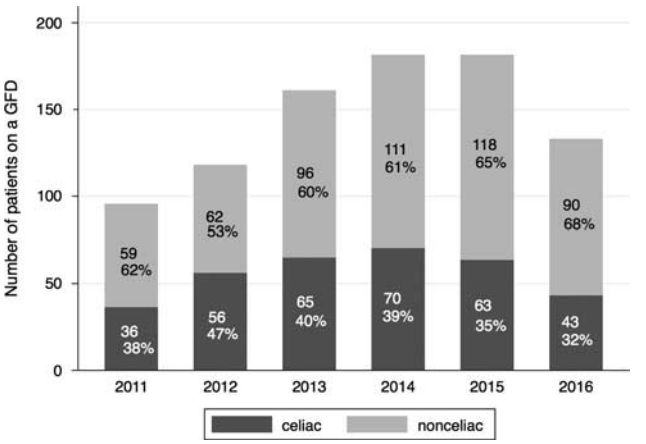

Fig. 2. Gluten-free diet inpatient orders according to celiac disease diagnosis. GFD, gluten-free diet.

Discussion

In this analysis of hospitalized patients, we found that over a 6-year period, most individuals with a GFD order did not have celiac disease. Over the course of this study, the proportion of GFD orders entered for patients without celiac disease has increased. One out of every five GFD orders was entered for a child. Patients without celiac disease on a GFD were more likely to be non-Hispanic Whites with commercial insurance, and to have IBD, IBS, thyroid disease, lupus, and autism spectrum disorders, and be prescribed antidepressant medications compared with patients on a regular diet.

GFDs are increasingly popular among patients without celiac disease [21]. Some patients without celiac disease maintain a GFD owing to NCGS, presenting with a variety of intestinal and extraintestinal symptoms similar to celiac disease, but without the characteristic pathological and serological features [7]. In addition, many patients with other conditions, including IBD, IBS, and autism, also consume a GFD at least part of the time [11,12,22,23]. However, there is a lack of high-quality evidence that GFDs are beneficial in these circumstances. Because of the clinical uncertainty in this area, many patients are self-diagnosed, maintaining a GFD without the recommendation of their physician.

Adhering to a strict GFD is not always benign. GFDs can be deficient in fiber as well as B vitamins [24,25]. There is evidence that patients who avoid gluten are more likely to be anemic and deficient in folate [26]. Low gluten consumption has not been shown to reduce the risk of coronary heart disease, and there is concern that reducing gluten intake could be harmful if whole grain consumption is also reduced [27]. There is additionally concern regarding inadvertent toxin exposure for individuals on a GFD, likely owing to lack of dietary diversity, and studies have shown patients on a GFD have higher blood and urine levels of certain heavy metals including arsenic, mercury, lead, and cadmium [28,29]. The diet can be socially isolating, given the need to avoid many foods

Table 2. Admitting service of gluten-free patients and controls

Specialty	Gluten-free ($n=489$) [n (%)]	Controls ($n=978$) [n (%)]	Odds ratio (95% CI)	P value
Adult services				
Internal medicine	113 (23.1)	299 (30.6)	0.64 (0.48–0.84)	0.0013
Neurology	35 (7.2)	41 (4.2)	1.74 (1.10–2.77)	0.015
Obstetrics/gynecology	67 (13.7)	136 (13.9)	0.98 (0.68–1.40)	0.9
Neurosurgery	29 (5.9)	44 (4.5)	1.35 (0.83–2.20)	0.23
Surgery	57 (11.7)	148 (15.1)	0.72 (0.51–1.01)	0.068
Orthopedic surgery	35 (7.2)	41 (4.2)	1.85 (1.14–3.02)	0.012
Other surgical subspecialty[a]	7 (1.4)	23 (2.4)	0.59 (0.25–1.41)	0.24
Psychiatry	26 (5.3)	35 (3.6)	1.50 (0.90–2.51)	0.12
Pediatric services				
Pediatric medicine	51 (10.4)	107 (10.9)	0.91 (0.57–1.45)	0.69
Pediatric neurology	44 (9.0)	24 (2.5)	5.57 (2.92–10.65)	<0.001
Pediatric psychiatry	1 (0.2)	1 (0.1)	2 (0.13–31.98)	0.62
All pediatric surgery	11 (2.2)	51 (5.2)	0.38 (0.19–0.77)	0.0049
Other[b]	13 (2.7)	28 (2.9)	0.92 (0.47–1.83)	0.82

CI, confidence interval.
[a]Ophthalmology, urology, otolaryngology.
[b]Rehabilitation medicine, hospice, family medicine, anesthesiology, interventional radiology.

Table 3. Comparison of comorbidities of inpatients on gluten-free versus regular diets

Diagnosis	Gluten free ($n=489$) [n (%)]	Control ($n=978$) [n (%)]	Odds ratio (95% CI)	P value	Adjusted[a] odds ratio (95% CI)	P value
Hypertension	88 (18.0)	328 (33.5)	0.34 (0.25–0.47)	<0.001	0.38 (0.27–0.52)	<0.001
Diabetes	32 (6.5)	119 (12.2)	0.49 (0.32–0.75)	<0.001	0.58 (0.37–0.90)	0.015
Inflammatory bowel disease	42 (8.6)	68 (7.0)	1.25 (0.84–1.86)	0.26	1.56 (1.02–2.41)	0.041
Irritable bowel syndrome	23 (4.7)	12 (1.2)	4.4 (2.07–9.33)	<0.001	4.65 (2.11–10.23)	<0.001
Stroke	7 (1.4)	29 (3.0)	0.42 (0.17–1.06)	0.061	0.43 (0.17–1.11)	0.08
Coronary artery disease	22 (4.5)	51 (5.2)	0.84 (0.49–1.44)	0.53	1.06 (0.60–1.87)	0.85
Hyperthyroidism	13 (2.7)	18 (1.8)	1.44 (0.71–2.95)	0.31	2.73 (1.22–6.10)	0.014
Hypothyroidism	72 (14.7)	73 (7.5)	2.25 (1.56–3.23)	<0.001	2.06 (1.39–3.06)	<0.001
Liver disease	0 (0)	7 (0.7)			NC[b]	
Systemic lupus erythematosus	11 (2.2)	10 (1.0)	2.2 (0.93–5.18)	0.064	2.87 (1.13–7.29)	0.027
Autism spectrum disorder	27 (5.5)	5 (0.5)	17.33 (4.44–67.63)	<0.001	23.42 (5.29–103.73)	<0.001
Schizophrenia	6 (1.2)	11 (1.1)	1.09 (0.40–2.95)	0.86	1.12 (0.38–3.24)	0.84
Depression	106 (21.7)	197 (20.1)	1.10 (0.84–1.13)	0.49	1.10 (0.83–1.47)	0.51
Anxiety disorder	26 (5.3)	38 (3.9)	1.44 (0.84–2.46)	0.19	1.56 (0.88–2.76)	0.13
ADHD	10 (2.0)	14 (1.4)	1.46 (0.63–3.39)	0.37	1.39 (0.57–3.41)	0.47

ADHD, attention deficit hyperactivity disorder; CI, confidence interval.
[a]Adjusted for race, ethnicity, and insurance status.
[b]NC, not calculated due to low cell counts.

commonly consumed in restaurants, schools, and other social settings. Gluten-free food products are more expensive and difficult to find compared with wheat-based alternatives [30].

The prevalence of a GFD in the USA among patients without celiac disease was estimated to be 0.5%, based on data from the National Health and Nutrition Examination Survey (NHANES). This was a 2009–2010 sample of 7762 individuals representing the civilian, noninstitutionalized population of the USA, who responded to a questionnaire regarding GFD adherence [31]. In that sample, the prevalence of GFD adherence was higher among females (0.58%) than males (0.37%), although the difference was not significant. Patients on a GFD were older (46.6 vs. 40.5 years, $P=0.005$). The study was limited by low statistical power owing to the small number (49) of individuals reporting adherence to a GFD. The current study differs in that we investigated only hospitalized patients, who would therefore be expected to have higher medical acuity. We also noted that most patients on a GFD were female (68.3%), with a similar mean age of 41.2 years. However, as our matching parameters for identification of controls consisted of age and sex, no comparisons can be drawn for these characteristics against the general inpatient population.

In a recent update of the NHANES data on gluten avoidance, Kim *et al.* [21] found that patients without celiac disease make up more than half of those on a GFD, and that the prevalence of gluten avoidance in the absence of celiac disease has tripled from 2009–2010 (0.52%) to 2013–2014 (1.69%). In our study, we also found that between half and two-thirds of the GFDs each year were ordered for patients without celiac disease (Fig. 2), providing further evidence that most people adhering to a GFD do not have celiac disease.

We found that patients on a GFD were significantly more likely to be non-Hispanic Whites than controls (55.6 vs. 29.7%, $P<0.001$). The prevalence of Blacks was lower in the gluten-avoiding group (3.5 vs. 12.1%). In contrast, another analysis of the 2009–2012 NHANES data found that the prevalence of nonceliac gluten avoidance was significantly higher in Black patients at 1.2% compared with Hispanics (0.5%) and Whites (0.7%) [32]. This is despite the fact that celiac disease was more common among Whites (1.0%) than Blacks (0.2%) or Hispanics (0.3%). However, another recent study analyzing Internet search trends found that GFD searches are significantly more common in areas with a higher proportion of non-Hispanic Whites, and in areas of higher income [33]. The increased interest in the GFD among non-Hispanic Whites

may be because of a belief among these patients that they are at higher risk of celiac disease; the association with income may reflect the higher cost of gluten-free products.

Although the NHANES study found no difference in mean family income or high school graduation status based on GFD adherence, suggesting no detectable difference in socioeconomic status [31], our study used insurance status as a surrogate for socioeconomic status and found that gluten-avoiding patients were more likely to have commercial insurance and less likely to have Medicaid or to be uninsured. The difference may reflect the fact that our patients were drawn from a single academic medical center in New York City, whereas the NHANES study was representative of the entire USA. There may be regional differences in the demographic characteristics of individuals on a GFD. There is evidence, for example, that the prevalence of celiac disease and gluten avoidance are higher in the Northern USA than the Southern USA, independent of race, ethnicity, and socioeconomic status [34]. However, our study also analyzed 10-fold more patients on a GFD compared with the analysis of demographics in NHANES (489 vs. 49), increasing our ability to detect small differences.

The number of GFD orders at our institution increased every year until 2015, when it remained relatively stable, and even decreased in 2016 (Figs 1 and 2). This may indicate that the increasing adoption of the GFD may be slowing, although it is premature to generalize the findings of a single year at one institution to the broader population.

Our study noted a number of differences between the regular diet and gluten-free patients in prevalence rates of other medical conditions, shown in Table 3. Gluten-avoiding patients were significantly less likely to have diabetes and hypertension but had no differences in prevalence of stroke or coronary artery disease. This may suggest that patients already on a restrictive diet, such as a carbohydrate or sodium restricted diet, may be less interested in adopting additional restrictions. However, we found that the gluten-avoiding patients were also more likely to be on kosher and vegetarian diets. It may simply reflect the fact that these patients were more likely to non-Hispanic Whites, who have lower rates of diabetes and hypertension than Hispanic or Black patients [35,36].

Although there was no difference in the prevalence of depression (21.7% in the gluten-free group vs. 20.1% in the control group), a higher proportion of the gluten-free patients had an antidepressant medication listed on their admission note (at 14.1 vs. 8.3%, $P = 0.005$). The reason for this difference in medication use is unknown, though some patients without celiac disease may be using the GFD as a treatment for depressive symptoms [37]. Antidepressants are sometimes used for associated conditions such as IBS [38]. Alternatively, persistent physical ailments may drive both a desire to try various therapies as well as depressive symptoms.

Gluten-avoiding patients were more likely to be admitted to the cardiology service than the patients on a regular diet (3.9% in the gluten-free group vs. 1.8% in controls, $P = 0.017$), despite a lower prevalence of hypertension and diabetes and no difference in prevalence of stroke or coronary artery disease. This could be owing to the fact that few patients on the cardiology service are on a regular diet, with the majority being on fat-restricted and sodium-restricted diets.

Our findings regarding comorbidities in this population expand upon the preliminary studies of this topic. We previously compared outpatients without celiac disease who avoid gluten to patients with celiac disease as well as healthy controls from the NHANES database, regarding comorbidities and biomarkers [26]. In that study, 79% of the gluten-avoiding patients were female, which was somewhat higher than the 68% of the patients in the current study. Compared with controls, the gluten-avoiding patients had lower BMI, hemoglobin, and folate levels. They were significantly less likely to have hypertension, similar to the current study. Interestingly, the previous study noted a higher prevalence of thyroid disease in females who avoid gluten, at 27% compared with 18% of controls, although the difference did not reach significance ($P = 0.07$). Among males, however, there was a lower prevalence of thyroid disease among those who avoided gluten (0 vs. 6%, $P = 0.62$). The present study also found a higher prevalence of hypothyroidism and hyperthyroidism in gluten-avoiding patients, although the difference in hyperthyroidism was only significant on the multivariable analysis. This finding may suggest the possibility that patients with thyroid disease have sought out the GFD as a treatment for their condition owing to the association of autoimmune thyroid disease with celiac disease [39]. Similarly, we noted that the gluten-avoiding patients had a higher prevalence of lupus, which is also seen more commonly in patients with celiac disease [40].

We also noted an increased prevalence of IBS in the gluten-free group, which is unsurprising given that there is some evidence that a GFD may be helpful for these patients. For example, a study by Vasquez-Roque *et al.* [15] looking at the effect of a GFD in diarrhea-predominant IBS patients without celiac disease found a reduction in the frequency of bowel movements in patients randomly assigned to a GFD, compared with controls. In this group, it may be nongluten components eliminated in a GFD such as fermentable oligosaccharides, disaccharides, monosaccharides, and polyols or wheat amylase trypsin inhibitors that lead to resolution of symptoms in individuals diagnosed with IBS as well as NCGS [16,41]. We also observed a higher prevalence of IBD in the gluten-free group. Although to our knowledge there are no randomized trials evaluating the GFD as a treatment for IBD, a questionnaire of 1647 patients with IBD found that 19.1% of respondents had tried a GFD, and 8.2% were currently using one [11]. In that study, 65.6% of patients who had tried a GFD reported improvement in their symptoms, and 38.6% reported fewer or less severe IBD flares, suggesting the popularity, and possibly the effectiveness, of this diet in IBD.

One of the most striking findings in this study was the very high rate of autism spectrum disorders in the gluten-free group compared with controls (5.5 vs. 0.5%, $P < 0.001$). Dietary interventions, in particular GFD and casein-free diet, have been used as a treatment for autism spectrum disorders going back decades. There are anecdotal parental reports of symptomatic improvement in children with autism after adopting a GFD [22,23]. However, in a randomized, double-blinded study of 15 children with autism spectrum disorder, Elder *et al.* [13] found no significant differences in behavioral measures after 3 months between the children on a GFD versus the

placebo diet. Studies in support of a GFD for autism are limited by very small sample sizes, as reported in a systematic review [42]. Given the popularity of a GFD among this patient population, larger, blinded, randomized investigations are needed to determine whether this diet has any efficacy in treating autism spectrum disorder.

One significant limitation to our study is that our analysis was limited to hospitalized patients, who may not be generalizeable to the broader USA population. Patients sick enough to be hospitalized may be more likely to have severe symptoms, for example, prompting them to seek novel or unusual remedies such as a GFD. In addition, hospitalized patients may carry more medical diagnoses, such as neurologic, autoimmune and cardiac disease, than the general population. Additionally, this was a single-center study, which further limits generalize ability, given that the demographic distribution of patients admitted to a quaternary care medical center in Manhattan may not reflect the socioeconomic background of patients elsewhere. Another limitation is that the diagnoses of comorbidities were drawn from ICD codes attached to each patient's electronic medical record by the medical team, and there is a possibility that an accurate diagnosis may not have been entered for all patients. In addition, it is likely that many patients on a GFD captured in this study were not tested for celiac disease before starting this diet. As such, it is possible that some of the patients classified as nonceliac may have undiagnosed celiac disease.

Conclusion

We found that most hospitalized patients on a GFD do not have a diagnosis of celiac disease. Our study also suggests that many of those on a GFD may not have NCGS, but may instead be on a GFD owing a belief that it may provide benefit in a variety of other conditions, ranging from IBS and IBD to lupus and autism. Further research is needed to assess for potential benefits in these conditions, given the difficulties and potential harm of adhering to an unnecessarily restrictive diet.

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This analysis was approved by the Institutional Review Board of Columbia University.

Conflicts of interest

There are no conflicts of interest.

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