Dig Dis Sci (2014) 59:1255–1261
DOI 10.1007/s10620-013-2981-6

ORIGINAL ARTICLE

Characteristics of Patients Who Avoid Wheat and/or Gluten in the Absence of Celiac Disease

Anna Tavakkoli · Suzanne K. Lewis · Christina A. Tennyson · Benjamin Lebwohl · Peter H. R. Green

Received: 30 September 2013 / Accepted: 28 November 2013 / Published online: 28 December 2013

Abstract
Background Gastrointestinal symptoms that respond to the removal of wheat and/or gluten are becoming more common. Patients who avoid wheat and/or gluten (PWAWG) are a heterogeneous group and predominantly self-diagnosed prior to presenting for clinical evaluation.
Specific aim We characterized PWAWGs seen at a tertiary care referral center and compared them to patients with celiac disease (CD) and subjects in the National Health and Nutrition examination survey (NHANES).
Methods This was a cross-sectional study evaluating patients seen by four gastroenterologists at a CD referral center. Baseline characteristics, laboratory values, and medical comorbidities were compared to CD patients who presented at the same center and subjects enrolled in NHANES.
Results Eighty-four PWAWGs were identified and compared to 585 CD patients and 2,686 NHANES patients. Thirty-two alternative diagnoses were made in 25 (30 %) PWAWGs, including small intestinal bacterial overgrowth and fructose/lactose intolerance. When compared to patients with CD, PWAWGs had similar body mass index (BMI, 23.1 vs. 23.5, $p = 0.54$) and mean hemoglobin value (13.4 vs. 13.3, $p = 0.6$). When compared to male and female patients in NHANES, BMI, folate, and mean hemoglobin values were lower in PWAWGs. Both male and female PWAWGs had a lower prevalence of hypertension.
Conclusion While there are similarities between CD and PWAWGs that could possibly be due to shared HLA haplotypes or an effect of the gluten-free diet, alternative diagnoses are common in these patients. PWAWGs have a similar cardiovascular profile as CD patients in terms of lower BMI and lower prevalence of hypertension.

Keywords Patients who avoid wheat and/or gluten · Celiac disease · Gluten-free diet · Alternative diagnoses

Introduction

The popularity and availability of the gluten free diet (GFD) has been increasing across the United States with a recent study finding that about 0.6 % of the US population are on a GFD [1]. A number of patients with chronic gastrointestinal symptoms, such as abdominal pain, bloating, or diarrhea, often start a GFD on their own with subsequent relief of their symptoms [2–6]. Patients who avoid wheat and/or gluten (PWAWG) are a heterogeneous group and are predominantly self-diagnosed by the patient prior to presenting to a physician's office. Due to the heterogeneity and diversity of these patients, there are no formal diagnostic criteria to characterize them once celiac disease (CD) has been ruled out through a combination of serological and endoscopic studies [2–7].

There have been several studies linking the relief of symptoms from irritable bowel syndrome (IBS) with the exclusion of gluten from the diet [8–13]. Since its description in 1981, studies have found that gluten worsens many functional symptoms when reintroduced into

A. Tavakkoli · S. K. Lewis · C. A. Tennyson · B. Lebwohl · P. H. R. Green (✉)
Department of Medicine, Celiac Disease Center, Columbia University, 180 Fort Washington Avenue, Suite 936, New York, NY 10032, USA
e-mail: pg11@columbia.edu

B. Lebwohl
Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

patients' diets [8–14]. However, a recent placebo controlled gluten challenge study found that these patients fail to develop symptoms due to gluten ingestion when placed on a dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates [fermentable, olio-, di-, monosaccharides and polyols (FODMAPs)]. In addition, a lack of increased psychiatric comorbidity was noted despite increased symptoms after a gluten challenge [10, 12]. The current data supports the notion that patients who self-avoid wheat and/or gluten are a complex and heterogeneous group that needs further characterization.

The clinical features of PWAWGs and alternative diagnoses made in these patients have not been described in the United States. We aimed to characterize self-identified PWAWGs that present to a CD referral center and to compare them to patients with CD and also to subjects who participated in the National Health and Nutrition Examination Survey (NHANES).

Methods

Study Sample

This was a cross-sectional study evaluating patients seen by four gastroenterologists at a CD referral center. Patients seen in the years spanning 2009–2012 were identified via a review of the electronic medical record using the *International Classification of Diseases*, *ninth edition* (ICD-9) code 995.7. The ICD-9 code 995.7 is defined as "adverse food reactions not elsewhere defined" and was used by the physicians at our referral center to identify those patients who self-identified themselves as having symptoms responsive to gluten withdrawal. The four clinicians investigated patients' symptoms based on their clinical assessment and without a formal protocol for investigation. The Institutional Review Board at the study center approved the study.

CD was excluded as a diagnosis in all patients through a combination of serological testing (anti-tissue transglutaminase, total IgA levels, and/or deamidated gliadin IgA and IgG peptide), the absence of HLA-DQ2 or HLA-DQ8 haplotype, or a normal duodenal biopsy with preserved villous architecture performed at the time of endoscopy. A total of 67.9 % ($n = 57$) of patients received an endoscopy, which was negative for any evidence of celiac disease by biopsy. Of the patients who did not receive an endoscopy ($n = 27$), 52 % ($n = 14$) were DQ2/DQ8 negative, 19 % ($n = 5$) were DQ8 positive, 7 % ($n = 2$) were DQ2 positive, and 11 % ($n = 3$) were positive for the DQ2 heterodimer. Only three patients who did not undergo endoscopy were lacking genetic testing for HLA DQ2/DQ8 haplotype. All patients included in the study were negative for celiac disease based on serological testing, including anti-tissue transglutaminase and deamidated gliadin IgA and IgG antibodies.

Patients were excluded from the study if they were subsequently diagnosed with CD or there was a high clinical suspicion for CD, had inflammatory bowel disease (ulcerative colitis and/or Crohn's disease), or were under the age of 18. Patients were not individually evaluated for IBS using the Rome III criteria.

Control Groups

PWAWGs were compared to patients with CD seen in the same center and to healthy controls from the NHANES database. Patients with CD were identified through a prospectively maintained database at the Celiac Disease Center at Columbia University. Information compiled from the database and used in our study included gender, date of birth, mean age at diagnosis, body mass index, mean hemoglobin value, and medical comorbidities. Patients were excluded if there was no hemoglobin level or data to calculate the body mass index. All patients evaluated with CD were Caucasian.

PWAWGs were also compared to healthy controls from the Continuous National Health and Nutrition Examination Survey (NHANES). This survey is a health related nationally representative survey of civilian, non-institutionalized people that is conducted via questionnaire, physical examination, and laboratory assessments. The 2009–2010 database was utilized for this study, which enrolled a total of 10,537 subjects. Subjects were excluded from the NHANES database if they were younger than 18 years of age ($n = 4{,}010$), were of a non-Caucasian ethnicity ($n = 3{,}448$), had a positive, weakly positive, or no available laboratory value for anti-tissue transglutaminase antibody (tTG) or endomysial antibody (EMA) ($n = 75$), had answered "yes" to being on a GFD ($n = 19$) or ever being told that they had CD ($n = 3$). After including only those patients with a hemoglobin level and body mass index (BMI) values, a total of 2,686 patients were included in this analysis.

Laboratory Biomarkers

PWAWGs and patients with CD who were seen in our CD center received a physical examination in addition to laboratory assessments, including complete blood count (CBC), C-reactive protein (CRP), lipid panel (including HDL and LDL level), folate level, B12 level, TSH, iron, and ferritin level. The normal range from the hospital laboratory was used as a reference.

Among patients from the NHANES group, laboratory values were obtained through SAS 9.2 software and normal

values were pre-defined from their laboratory. Anti-tTG or anti-EMA antibodies were defined as "positive," "weakly positive," or "negative." Laboratory values, such as CBC, CRP, lipid panel, and folate levels were issued as absolute values. Comorbidities, such as thyroid disease or hypertension, were defined by "yes/no" questions.

Statistical Analysis

The primary aim of the study was to compare physical characteristics, laboratory values, and medical comorbidities among PWAWGs as compared to both patients with CD and healthy controls in the NHANES database. Quantitative data was analyzed using the Student's t test and categorical variables were analysed through the chi-square test. Because PWAWGs differed from the NHANES population with regard to age, we calculated age-adjusted p values for these comparisons using linear and logistic regression for continuous and categorical variables respectively. All p values were two-sided.

Results

Demographics and Medical Comorbidities of PWAWGs and Patients with CD

PWAWGs ($n = 84$) were identified and compared to 585 patients with CD seen at our center that had a hemoglobin level and BMI value on record from a clinic visit. Among PWAWGs, 79 % of patients were female as compared to 72 % of patients with CD ($p = 0.08$). The mean age at the time of diagnosis among PWAWGs was 42.9 versus 44.5 years among patients with CD ($p = 0.39$). PWAWGs had similar body mass index (BMI), mean hemoglobin value, and prevalence of type 1 diabetes as compared to CD patients (Table 1). Furthermore, PWAWGs had high rates of thyroid disease (21 %) compared to CD patients (13 %, $p = 0.07$).

Table 1 Demographics of patients who avoid wheat and/or gluten (PWAWGs) in comparison to patients of celiac disease (CD)

	Celiac disease ($n = 585$)	PWAWGs ($n = 84$)	p value
Demographics			
Male	162 (28 %)	18 (21 %)	0.08
Female	423 (72 %)	66 (79 %)	
Mean age at diagnosis	44.5	42.9	0.39
Mean BMI	23.1	23.5	0.54
Mean hemoglobin	13.4	13.3	0.60
Comorbidities			
Type 1 diabetes	8 (1 %)	1 (1 %)	1.0
Thyroid disease	78 (13 %)	18 (21 %)	0.07

BMI body mass index

Symptoms and Characteristics of Gluten-Free Diet

The most common presenting symptoms among PWAWGs were bloating (61 %), abdominal pain (60 %), fatigue (51 %), and diarrhea (43 %). A total of 87 % ($n = 73$) of PWAWGs were on a GFD at the time of their first visit. This diet was self-prescribed in 82 % ($n = 69$, Table 2). The median length of time on a GFD was 2.3 years. In addition, 50 % of patients ($n = 42$) had undergone a gluten challenge, defined as reintroducing gluten-containing products into their diet, and the vast majority of patients (98 %) had undergone this challenge on their own without the supervision of a physician. Furthermore, gluten was not the only food avoidance in these patients; 52 % of PWAWGs had additional food avoidances including dairy (59 %) and soy products (25 %).

Alternative Diagnoses and Genetic Testing Results

Thirty-two alternative diagnoses were made in 25 (30 %) patients who avoided wheat and/or gluten. Of the 25 patients, 16 (50 %) had small intestinal bacterial overgrowth (SIBO), five had fructose intolerance, and three had lactose intolerance with some patients having more than one alternative diagnosis (Table 3). Furthermore, patients were additionally diagnosed with other food intolerances ($n = 3$), microscopic colitis ($n = 3$), gastroparesis ($n = 1$), and pelvic floor dysfunction ($n = 1$, Table 3). We found no

Table 2 Characteristics of gluten free diet in patients who avoid wheat and/or gluten (PWAWGs)

Characteristics	Total number
Gluten free diet characteristics	
Number of patients on a gluten free diet at the time of presentation to the CD center	73 (87 %)
Patients who started a gluten-free diet prior to consulting with a physician	69 (82 %)
Mean/median length of time on gluten free diet at presentation	2.3 years
Patients who underwent a gluten challenge	42 (50 %)
Patients who underwent a gluten challenge without physician recommendations	41/42 (98 %)
Gluten challenge prescribed by provider at the CD center	9/42 (14 %)
Patients with other food avoidances	44 (52 %)
Dairy	26/44 (59 %)
Soy	11/44 (25 %)

CD celiac disease

Table 3 Food avoidances and breath test results among patients who avoid wheat and/or gluten (PWAWGs)

Characteristics	Total number (%)
Alternative diagnoses	32
Small intestinal bacterial overgrowth	16 (50 %)
Fructose intolerance	5 (16 %)
Lactose intolerance	3 (9 %)
Food intolerances	3 (9 %)
Microscopic colitis	3 (9 %)
Gastroparesis	1 (3 %)
Pelvic floor dysfunction	1 (3 %)
Genetic evaluation	Number tested
DQ2/DQ8 negative	28 (39 %)
DQ2 heterodimer	20 (28 %)
DQ8 positive	13 (18 %)
DQ2 positive	7 (10 %)
DQ2/DQ8 positive	3 (4 %)

differences in the characteristics of those with alternative diagnoses as compared to those without. Lastly, of the patients tested for the presence of HLA-DQ2 or DQ8, 61 % were positive for these celiac-related genetic markers (Table 3).

Endoscopy Data

Esophagogastroduodenoscopy (EGD) was performed in 57 (67.9 %) of the patients at some point in their evaluation (Table 4). Twenty eight (49 %) were on a gluten-free diet at the time of endoscopy for a median period of 1 year, and 29 (51 %) patients were on a gluten-containing diet at the time of EGD. Among the 29 patients on a gluten-containing diet at time of EGD, nine had undergone a gluten challenge as prescribed by their physician, as opposed to 20 who had incorporated gluten back into their diet on their own.

Among those patients who underwent EGD, the majority (54/57, 95 %) had no significant histologic abnormalities. Two patients were noted to have intraepithelial lymphocytosis, Marsh 1 and one patient was noted to have chronic duodenitis. All three of these patients were on a gluten-containing diet at the time of endoscopy.

NHANES and PWAWGs

Among the NHANES population, there were 1,396 females and 1,290 men who met the inclusion criteria. Among females, the mean age of PWAWGs was 42.8 years as compared to 50.4 years in the NHANES control group (Table 5, $p = 0.0002$). The BMI was lower among PWAWGs as compared to the NHANES cohort (23.5 vs. 28.5, $p < 0.0001$). The mean hemoglobin, LDL, and folate were lower among PWAWGs (Table 5). In addition, the HDL and CRP levels were higher in PWAWGs when compared to patients in NHANES (Table 5). Furthermore, only 9 % of PWAWGs had a history of hypertension as compared to 32 % of patients in NHANES ($p < 0.0001$). After adjusting for age, the differences between PWAWGs and NHANES participants with regard to BMI, hemoglobin, HDL, CRP, folate level, and prevalence of hypertension and thyroid disease all remained significant (see Table 5).

Among males, the mean age of PWAWGs was 49.9 years as compared to 51.4 years in the NHANES control group (Table 5, $p = 0.7$). Men who avoided wheat and/or gluten had a mean BMI of 23.4 as compared to a BMI of 28.6 among men in the NHANES cohort ($p < 0.0001$). The mean hemoglobin and folate levels were lower among male PWAWGs (Table 5). While the mean HDL and CRP levels were higher among men who avoided wheat and/or gluten, these differences were not statistically significant. Furthermore, 11 % of men who avoided wheat and/or gluten had hypertension versus 36 % of men in the NHANES cohort ($p = 0.04$). After adjustment for age, the differences between male PWAWGs and participants of NHANES with regard to BMI, hemoglobin, and HDL remained significant (Table 5).

When patients with alternative diagnoses were excluded from the analysis, the findings described above in terms of BMI, hemoglobin, HDL, CRP, folate levels and prevalence of hypertension and thyroid disease remained the same except for the difference in LDL values observed among female NHANES and PWAWGs. While the mean value was actually lower among female PWAWGs (115.7 NHANES F vs. 99.5 PWAWG F, $p = 0.08$), the number of female PWAWGs was lower and underpowered to show a statistically significant difference.

Discussion

In this study, patients who avoided wheat and/or gluten were compared to both patients with CD and healthy controls. We found that PWAWGs are similar to patients with CD in regard to comorbidities, mean BMI, and mean hemoglobin levels. However, when PWAWGs are compared to participants in NHANES, whom are considered to be representative of the population of the United States, both male and female patients had a lower BMI, mean hemoglobin values, and folate values. Furthermore, both male and female PWAWGs were less likely to have hypertension as compared to those in the NHANES study. Lastly, we found that 30 % of patients who avoided wheat and/or gluten had alternative diagnoses.

Table 4 Endoscopy data

Endoscopy data	Total number
Number of patients who received endoscopy	57 (67.9 %)
Gluten free diet (GFD) and endoscopy	
Number of patients on GFD at time of endoscopy	28
Median time on GFD at the time of EGD	1 year
<1 month	5
1–2.99 months	1
3–6 months	3
>6 months	16
Number of patients on gluten-containing diet at time of endoscopy	29
Gluten challenge prescribed by MD	9
Regular gluten-containing diet	20
Duodenal biopsy results	
Chronic duodenitis	1
Increased IEL/Marsh 1	2

Current literature supports the notion that patients with CD have a lower BMI, a decreased risk of metabolic syndrome, hypertension, and, as a result, an improved cardiovascular profile as compared to healthy controls [15–17]. In addition, patients with CD are more likely to have iron-deficiency anemia and lower folate levels [18–27]. While data regarding CD, its pathogenesis, and implications of the disease/diet are well known, little is known regarding its related clinical counterpart.

PWAWGs appear to share several objective clinical criteria with CD, including anemia and weight loss [7, 11, 28]. This finding was confirmed in our study in which patients with CD and PWAWGs shared a similar hemoglobin level and BMI. While these findings may be a direct consequence of the GFD, several studies have implicated a possible role of the immune system in its pathogenesis. While different arms of the immune system may be activated in both diseases [29], a shared immunological pathway could also potentially explain these similarities, considering that 60 % of the PWAWGs in this study were positive for a HLA-DQ2/DQ8 haplotype. A predominance of this celiac related HLA type appears consistent in patients who self-restrict gluten-containing items [8, 13, 28, 30]. Our data also showed that both men and women PWAWGs were less likely to have hypertension when compared to patients in NHANES. A recent study found that patients with CD have a lower prevalence of metabolic syndrome as compared to patients with NHANES, even after controlling for BMI [16]. However, the mechanism behind this effect is unclear. Gluten has been shown to have a beneficial effect on high blood pressure; therefore, a GFD is not a potential explanation for these findings [31–34]. Rather, there might be a unifying reason that both patients with CD and PWAWGs have lower prevalence of hypertension, such as a shared link to activating the immune system.

In addition, our study showed that 30 % of patients were diagnosed with other gastrointestinal syndromes through breath testing and endoscopy. While the presence of food intolerances in patients with IBS has been well documented in the literature, to our knowledge, this is the first study evaluating alternative diagnoses in patients who avoid wheat and/or gluten. The relatively high number of patients diagnosed with SIBO and other food intolerances suggests that patients who avoid wheat and/or gluten could be symptomatic due to other elements in their diet. Furthermore, perhaps these patients can be relieved of the strict GFD and the inherently unhealthy elements of this diet through further, non-invasive, diagnostic testing at the time of clinical presentation.

The results of our study are in contrast to those published earlier by our group evaluating characteristics of patients on a GFD in the NHANES survey. While some of our results were similar, such as higher HDL levels among patients on a GFD and lower body mass index, not all of them were congruent. Our study did find that patients who avoid wheat and/or gluten have a lower hemoglobin level and were of a younger age compared to patients in NHANES. Several differences in study design and patient population could explain the differences in these results. First of all, all patients who avoided wheat and/or gluten in our study were self-referred to a tertiary care center, increasing the likelihood that they would present earlier in their disease course versus patients chosen at random for survey in the NHANES study. Second of all, patients evaluated in this study had alternative diagnoses and other food avoidances that could have further driven the differences seen in values such as the hemoglobin and iron level. Third, only patients of Caucasian descent were evaluated in the NHANES survey due to the lack of minority groups in both our PWAWG and CD population, which could have contributed to the differences seen between these two studies. Finally, the predominance of the celiac-related HLA type in patients who restricted wheat and/or gluten could have further driven the favorable cardiovascular profile seen in our study.

Our study has several limitations. This is a retrospective analysis and the number of PWAWGs is small ($n = 84$), though greater than those in the national NHANES study [27]; the number of men ($n = 18$) is even smaller, making the study underpowered to detect gender-specific differences both among CD patients and NHANES participants. A large percentage of patients were already on a gluten-free diet at the time of initial evaluation and were not receptive to a gluten challenge. A total of 30 % in this

Table 5 Demographics and laboratory comparisons among PWAWGs and NHANES cohort

Demographics and laboratory data	PWAWGs	NHANES	Unadjusted *p* value	Age-adjusted *p* value
Female patients				
Age (years)	42.8 ($n = 66$)	50.4 ($n = 1,396$)	0.0002	–
BMI	23.5 ($n = 53$)	28.5 ($n = 1,396$)	<0.0001	<0.0001
Hemoglobin	13.0 ($n = 63$)	13.6 ($n = 1,396$)	<0.0001	0.0257
HDL	68.5 ($n = 26$)	57.6 ($n = 1,396$)	0.002	0.0027
LDL	101.5 ($n = 26$)	115.7 ($n = 677$)	0.05	0.1390
Ferritin	54.3 ($n = 58$)	60.4 ($n = 710$)	0.4	0.3599
CRP	1.37 ($n = 35$)	0.41 ($n = 1,396$)	0.012	<0.0001
Folate	13.57 ($n = 45$)	22.58 ($n = 1,396$)	<0.0001	0.0095
Iron	84.08 ($n = 25$)	81.65 ($n = 1,395$)	0.64	0.3859
Comorbidities				
Hypertension	6 (9 %)	451 (32 %)	<0.0001	0.0016
Thyroid disease	18 (27 %)	246 (18 %)	0.073	0.0107
Male patients				
Age (years)	49.9 ($n = 18$)	51.4 ($n = 1,290$)	0.704	–
BMI	23.4 ($n = 14$)	28.6 ($n = 1,290$)	<0.0001	0.0007
Hemoglobin	14.5 ($n = 18$)	15.1 ($n = 1,290$)	0.04	<0.0001
HDL	56.1 ($n = 7$)	47.6 ($n = 1,290$)	0.098	0.0434
LDL	117.1 ($n = 7$)	113.3 ($n = 569$)	0.800	0.6536
CRP	1.603 ($n = 10$)	0.34 ($n = 1,290$)	0.15	0.4531
Folate	12.57 ($n = 10$)	19.20 ($n = 1,290$)	0.0009	0.2880
Iron	91.4 ($n = 5$)	94.57 ($n = 1,290$)	0.81	0.1221
Comorbidities				
Hypertension	2 (11 %)	458 (36 %)	0.043	0.2714
Thyroid disease	0 (0 %)	73 (6 %)	0.62	0.9841

PWAWGs patients who avoid wheat and/or gluten, *NHANES* National Health and Nutrition examination survey, BMI body mass index

cohort had alternative diagnoses, which included small intestinal bacterial overgrowth, fructose or lactose intolerance, microscopic colitis, gastroparesis, and pelvic floor dysfunction. Other food allergies were not excluded in this population of patients. Due to the risk of increased intestinal permeability with food allergies, this is a potential area to study in a prospective analysis [35]. Furthermore, patients who self-restricted gluten were not evaluated for IBS using Rome III criteria. In addition, not every PWAWG and patient with CD received similar laboratory studies, such as a lipid panel or iron studies, limiting the power to detect a statistically significant difference among both men and women PWAWGs. Finally, there is a potential that unmeasured confounding factors, such as underlying medical issues or medications, could possibly have influenced the results. However, our finding that a significant number of PWAWGs had alternative diagnoses reinforces that this entity is heterogeneous, complex, and is most oftentimes self-diagnosed by patients. Furthermore, the recent study demonstrating that these patients respond to FODMAP exclusion additionally reinforces that we need to keep an open mind as to this disorder and attempt to explore the etiology of the patients' symptoms [12].

In conclusion, our data demonstrates that PWAWGs have lower BMI, lower hemoglobin levels, and lower prevalence of hypertension as compared to controls. In addition, our data argues for a potential similarity between CD and PWAWGs of which the mechanism has not yet been delineated but could possibly be related to shared HLA haplotypes. Since PWAWG are a heterogeneous population, more research is needed to characterize these patients [36].

Conflict of interest None.

References

1. Rubio-Tapia A, Ludvigsson JF, Brantner TL, et al. The prevalence of celiac disease in the United States. *Am J Gastroenterol*. 2012;107:1538–1544.
2. Ferch CC, Chey WD. Irritable bowel syndrome and gluten sensitivity without celiac disease: separating the wheat from the chaff. *Gastroenterology*. 2012;142:664–673.

3. Ludvigsson JF, Leffler DA, et al. The Oslo definitions for coeliac disease and related terms. *Gut*. 2013;62:43–52.
4. Di Sabatino A, Corazza GR. Nonceliac gluten sensitivity: sense or sensibility? *Ann Intern Med*. 2012;156:309–311.
5. Troncone R, Jabri B. Coeliac disease and gluten sensitivity. *J Intern Med*. 2011;269:582–590.
6. Sapone A, Bai JC, Ciacci C, et al. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med.* 2012;10:13.
7. Lundin KE, Alaedini A. Non-celiac gluten sensitivity. *Gastrointest Endosc Clin N Am*. 2012;22:723–734.
8. Wahnschaffe U, Schulzke JD, Zeitz M, Ullrich R. Predictors of clinical response to gluten-free diet in patients diagnosed with diarrhea-predominant irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2007;5:844–850.
9. Biesiekierski JR, Newnham ED, Irving PM, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol*. 2011;106:508–514.
10. Brottveit M, Vandvik PO, Wojniusz S, et al. Absence of somatization in non-coeliac gluten sensitivity. *Scand J Gastroenterol*. 2012;47:770–777.
11. Carroccio A, Mansueto P, Iacono G, et al. Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. *Am J Gastroenterol.* 2012;107:1898–1906.
12. Biesiekierski JR, Peters SL, Newnham ED, et al. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. *Gastroenterology*. 2013;145:320.e3–328.e3. doi:10.1053/j.gastro.2013.04.051.
13. Vazquez-Roque MI, Camilleri M, Smyrk T, et al. A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. *Gastroeneterology*. 2013;144:903–911.
14. Cooper BT, Holmes GK, Ferguson R, et al. Gluten-sensitive diarrhea without evidence of celiac disease. *Gastroenterology*. 1981;81:192–194.
15. Brar P, Kwon GY, Holleran S, et al. Change in lipid profile in celiac disease: beneficial effect of gluten-free diet. *Am J Med*. 2006;119:786–790.
16. Kabbani TA, Kelly CP, Betensky RA, et al. Patients with celiac disease have a lower prevalence of non-insulin-dependent diabetes mellitus and metabolic syndrome. *Gastroenterology*. 2013;144:912.e1–917.e1. doi:10.1053/j.gastro.2013.01.033.
17. Cheng J, Brar PS, Lee AR, Green PH. Body mass index in celiac disease: beneficial effect of a gluten-free diet. *J Clin Gastroenterol*. 2010;44:267–271.
18. Mubarak A, Wolters VM, Gerritsen SA, Gmelig-Meyling FH, Ten Kate FJ, Houwen RH. A biopsy is not always necessary to diagnose celiac disease. *J Pediatr Gastroenterol Nutr*. 2011;52:554.
19. Thompson T, Dennis M, Higgins LA, Lee AR, Sharrett MK. Gluten-free diet survey: are Americans with coeliac disease consuming recommended amounts of fibre, iron, calcium and grain foods? *J Hum Nutr Diet*. 2005;18:163–169.
20. Hallert C, Grant C, Grehn S, et al. Evidence of poor vitamin status in coeliac patients on a gluten-free diet for 10 years. *Aliment Pharmacol Ther*. 2002;16:1333–1339.
21. Hallert C, Svensson M, Tholstrup J, Hultberg B. Clinical trial: B vitamins improve health in patients with coeliac disease living on a gluten-free diet. *Aliment Pharmacol Ther*. 2009;29:811–816.
22. Howard MR, Turnbull AJ, Morley P, Hollier P, Webb R, Clarke A. A prospective study of the prevalence of undiagnosed coeliac disease in laboratory defined iron and folate deficiency. *J Clin Pathol*. 2002;55:754–757.
23. Ohlund K, Olsson C, Hernell O, Ohlund I. Dietary shortcomings in children on a gluten-free diet. *J Hum Nutr Diet*. 2010;23:294–300.
24. Wild D, Robins GG, Burley VJ, Howdle PD. Evidence of high sugar intake, and low fibre and mineral intake, in the gluten-free diet. *Aliment Pharmacol Ther*. 2010;32:573–581.
25. Rampertab SD, Pooran N, Brar P, Singh P, Green PH. Trends in the presentation of celiac disease. *Am J Med.* 2006;119:355e9–355e14.
26. Hernandez L, Green PH. Extraintestinal manifestations of celiac disease. *Curr Gastroenterol Rep*. 2006;8:383–389.
27. DiGiacomo DV, Tennyson CA, Green PH, Demmer RT. Prevalence of gluten-free diet adherence among individuals without celiac disease in the USA: results from the Continuous National Health and Nutrition Examination Survey 2009–2010. *Scand J Gastro*. 2013;48:921–925. doi:10.3109/00365521.2013.809598.
28. Coburn JA, Vande Voort JL, Lahr BD, et al. Human leukocyte antigen genetics and clinical features of self-treated patients on a gluten-free diet. *J Clin Gastroenterol*. 2013;47:828–833. doi:10.1097/MCG.0b013e31828f531c.
29. Green PH, Jabri B. Coeliac disease. *Lancet*. 2003;362:383–391.
30. Brottveit M, Raki M, Bergseng E, et al. Assessing possible celiac disease by an HLA-DQ2-gliadin tetramer test. *Am J Gastroenterol*. 2011;106:1318–1324.
31. Thewissen BG, Pauly A, Calus I, et al. Inhibition of angiotensin I-converting enzyme by wheat gliadin hydrolysates. *Food Chem*. 2011;127:1653–1658.
32. Behall KM, Scholfield DJ, Hallfrisch J. Whole-grain diets reduce blood pressure in mildly hypercholesterolemic men and women. *J Am Diet Assoc*. 2006;106:1445–1449.
33. Tighe P, Duthie G, Vaughan N, et al. Effect of increased consumption of whole-grain foods on blood pressure and other cardiovascular risk markers in healthy middle-aged persons: a randomized controlled trial. *Am J Clin Nutr*. 2010;92:733–740.
34. Gaesser GA, Siddhartha AS. Gluten-free diet: imprudent dietary advice for the general population? *J Acad Nutr Diet*. 2012;112:1330–1333.
35. Perrier C, Corthesy B. Gut permeability and food allergies. *Clin Exp Allergy*. 2011;41:20–28.
36. Vanga R, Leffler D. Gluten sensitivity: not celiac and not certain. *Gastroenterology*. 2013;145(2):276–279. doi:10.1053/j.gastro.2013.06.027.