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ORIGINAL ARTICLE

Micronutrient Deficiencies Are Common in Contemporary Celiac Disease Despite Lack of Overt Malabsorption Symptoms

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Abstract

Objective: To evaluate micronutrient deficiencies in a contemporary cohort of adult patients with newly diagnosed celiac disease (CD).

Patients and Methods: This is a retrospective study of prospective adults newly diagnosed with CD from January 1, 2000, through October 31, 2014, at Mayo Clinic. Micronutrient data were collected for tissue transglutaminase IgA, zinc, 25-hydroxy vitamin D, ferritin, albumin, copper, vitamin B_{12}, and serum folate. Data were analyzed for absolute number of deficiencies and associations with age, sex, body mass index, presenting symptoms, and tissue transglutaminase IgA; each deficiency was assessed using logistic regression. Deficiencies were compared with age- and sex-matched controls from the National Health and Nutrition Examination Survey.

Results: In total, 309 patients with CD (196 women and 113 men; mean age, 46.1±15.1 years; mean body mass index, 25.9 kg/m^2) were included. Weight loss was seen in only 25.2% (78/309) of patients. Zinc was deficient in 59.4% (126/212) of patients with CD compared with 33.2% (205/618) of controls ($P<.001$). Albumin was low in 19.7% (24/122) compared with 1.1% of controls ($P<.001$). Copper was low in 6.4% (13/204) compared with 2.1% (13/618) of controls ($P=.003$). Vitamin B_{12} was low in 5.3% (13/244) compared with 1.8% (11/618) of controls ($P=.004$). Folate was low in 3.6% (6/159) compared with 0.3% (2/618) of controls ($P=.002$). 25-Hydroxy vitamin D was low in 19.0% (44/213) compared with 18% (111/618) of controls ($P=.72$). Ferritin was low in 30.8% (66/214) of patients; no NHANES controls were available for comparison for ferritin.

Conclusion: Micronutrient deficiencies remain common in adults with CD despite increased nonclassic presentation. This study provides support for micronutrient assessment at the time of CD diagnosis.

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Celiac disease (CD) is a small bowel enteropathy occurring in genetically susceptible patients in response to ingested gluten.[1] Based on recent data from the National Health and Nutrition Examination Survey (NHANES), the weighted prevalence of CD in the United States is 0.7%, with 0.97% for non-Hispanic whites, 0.71% for those 18 years and older, and increased prevalence at higher northern latitudes.[2,3] Furthermore, the prevalence of CD has increased over the past 50 years.[4,5] The change in prevalence seems to be a change in presentation, with fewer contemporary patients presenting with macronutrient malnutrition (weight loss) and diarrhea.[6]

Recent guidelines on the diagnosis and management of CD recommend testing for nutrient deficiencies at the time of new diagnosis, and this assessment should include vitamin D, iron, folic acid, and vitamin B_{12}.[7] These recommendations have been based on previous studies describing micronutrient deficiencies in adults and children with CD. Historically, data on micronutrient assessment have been published in Europe, with less

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data known from the United States. One large study in Italy evaluated more than 1000 adults and children (older than 14 years) and found low ferritin in 50%, low vitamin B_{12} in 6.6%, and low folate in 73.8%, correlating these results with the degree of villous atrophy.[8] Another study of 93 adults with CD in Denmark found 30% of patients anemic, 40% with low iron stores, 17% with low vitamin B_{12}, and 20% with low folate.[9] In a Finnish study of 37 newly diagnosed adults, 32% were anemic, 35% had low ferritin, 16.2% had low vitamin B_{12}, and 37% had low erythrocyte folate.[10] The association with iron deficiency seen previously was confirmed in a case-control study reporting that in white patients presenting with iron deficiency, CD was the cause in 4%. This does not hold true in non-white patients.[11]

Other micronutrients have been evaluated in the past, including low vitamin D seen in 33% of 93 adults with CD[9] and low serum zinc was seen in 51% of adults with newly diagnosed CD[10] and in 67% of adults with CD in another study.[12] Copper deficiency has been reported in patients with CD presenting with neurological symptoms,[13] but 1 study found copper deficiency to be similar to that in controls.[14] McKeon et al[15] evaluated 44 patients with CD and neurological symptoms and attributed symptoms to CD in 9 patients, with 6 being attributed to a combination of folate, copper, and vitamin E deficiencies.

By contrast, micronutrient deficiencies are rare in children in the United States[16] but common in other locations.[17] A New Zealand study of 263 children found iron deficiency in 87 patients, but other micronutrient deficiencies were noted to be rare.[18]

The literature to date suggests that micronutrient deficiencies are common with CD, but the results are heterogeneous. Little is known about deficiencies in adult patients in societies with mild presentation of disease, widespread nutrient fortification, and rampant supplementation. Moreover, there is paucity of data from the United States. This study aims to determine the frequency of serological nutrient deficiencies in adult patients with newly diagnosed CD compared with matched controls and to determine whether presenting symptoms, anthropometric data, or serological studies are associated with serological deficiency.

PATIENTS AND METHODS

Patients and Study Design

This study is a retrospective analysis of adult patients with a new diagnosis of CD from January 1, 2000, and October 31, 2014, and prospectively recruited to the Mayo Clinic Celiac Disease Registry (Rochester, Minnesota). All adult patients with the serological assessment of any of the nutrients studied were included if the samples were completed 1 month before diagnosis to 3 months after diagnosis. Each patient's age at diagnosis, sex, race, and body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared) were collected from the time of diagnosis. Children (younger than 18 years), those without nutrient assessment inside of the aforementioned window, and those without a confident diagnosis of CD were excluded.

Age-matched controls were obtained from the NHANES database, with serological evaluation for each micronutrient studied. Sex was matched whenever feasible. Controls were matched in a 2:1 ratio and were selected from the 2009 to 2012 NHANES cohorts.[19,20] Because not all NHANES controls had all micronutrients evaluated, 2 sets of controls were identified: one set to assess 25-hydroxy vitamin D and another set to assess the remaining micronutrients. The NHANES matching cohort for vitamin D assessment was matched for age, sex, and race given known racial differences in vitamin D[21] and the availability of controls in this cohort with vitamin D assessment. Given that all NHANES controls did not have micronutrient assessment, the control cohort for all nutrients except vitamin D could not be matched for race in all cases.

This project was approved by the Mayo Clinic Institutional Review Board (study no. 14-008597).

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Celiac Disease Diagnosis

Patients included in this study were diagnosed with CD, with a combination of serological, genetic, and histological parameters yielding a confident diagnosis of CD when patients met 1 of 2 clinical scenarios. First, if the patient had positive serology for celiac disease and confirmatory duodenal biopsy, CD was diagnosed. Second, patients without positive serology for celiac disease must have biopsy findings consistent with CD, human leukocyte antigen DQ-2 or DQ-8, and positive response to a gluten-free diet for a diagnosis of CD.

Presenting Symptoms

When patients are included in the Mayo Clinic Celiac Disease Registry, symptom data are collected at the time of diagnosis. These data were grouped into broader categories of stool symptoms (diarrhea and greasy stool), abdominal symptoms (abdominal distension, abdominal cramping, flatus, and nausea), weight symptoms (anorexia, weight loss, height loss, and failure to thrive), or other symptoms at presentation. If a patient was missing presenting symptoms from registry data, additional medical chart review was performed and missing data were extracted from the time of diagnosis.

Laboratory Parameters

Laboratory parameters were included if they were collected 1 month before diagnosis to 3 months after celiac diagnosis. Tissue transglutaminase IgA data were collected to determine whether a positive result was associated with deficiency. Micronutrient data were collected for serum zinc, 25-hydroxy vitamin D, ferritin, albumin, serum copper, serum folate, and vitamin B_{12}. Albumin was assessed, as this can influence serum zinc values and is a predictor of outcome in refractory CD studies.[22]

National Health and Nutrition Examination Survey data for controls were available for serum zinc, 25-hydroxy vitamin D, albumin, serum copper, serum folate, and vitamin B_{12}. The assays used for patients with CD and NHANES controls were the same for zinc, 25-hydroxy vitamin D, albumin, serum copper, and vitamin B_{12}. Ferritin was not available from NHANES cohorts for comparison.

Patients with values below the reference range were considered to be deficient. The lower limit of normal of the specific assay was used to determine deficiency on the basis of NHANES reference ranges. The lower limit of normal was 75 μg/dL (11.48 umol/L) for zinc, 20 ng/mL (49.9 nmol/L) for 25-hydroxy vitamin D, 0.8 μg/mL (12.56 umol/L) for copper in women and 0.7 μg/mL (10.99 umol/L) in men, 3.5 g/dL (35 g/L) for albumin, and 200 ng/L (147.56 nmol/L) for vitamin B_{12}.[23-26] The assay for folate assessment differed between Mayo Clinic and NHANES, but the lower limit of normal was consistent at 4 μg/L (9.06 nmol/L).[27] The assay for ferritin assessment changed over time with variable reference ranges. The lower limit of normal at the time of testing was used for patients with CD, and no NHANES controls were available for comparison for ferritin.

Statistical Analyses

Baseline clinical characteristics were summarized as mean ± SD for continuous variables and as count (percentage) for categorical variables. The association of the cohort of adult patients with newly diagnosed CD and NHANES controls was tested using the chi-square or Fisher exact test, as appropriate. Because BMI distribution was not similar between the cohort of adult patients with CD and NHANES controls, a sensitivity analysis of the association between CD and the presence of a deficiency was performed using a logistic regression model adjusted for age, sex, and BMI. Body mass index was evaluated as a continuous variable. Finally, the median time to micronutrient assessment was compared between deficient and nondeficient patients with CD by using the Kruskal-Wallis test. In the cohort of adult patients with newly diagnosed CD, logistic regression was used to assess the relationship between presenting symptoms and micronutrient deficiencies while controlling for the possible cofounding effects of age and sex. Statistical significance was defined with an α level of .05 without correction for multiple testing. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc.).

TABLE 1. Demographic and Symptom Data on Patients With Newly Diagnosed Celiac Disease and NHANES Age-Matched Controls[a,b]

Characteristic	Patients with celiac disease (n=309)	NHANES controls set 1: vitamin D (n=618)	NHANES controls set 2: remaining micronutrients (n=618)
Age (y)	46.1±15.1	46.1±15.1	46.1±15.1
Sex: female	196 (63.4)	392 (63.4)	332 (53.7)
Race: white	282 (98.6)	600 (97.1)	419 (67.8)
BMI (kg/m^2)	25.9±6.1	28.6±7.3	29.5±7.5
TTG test result positive	236 (86.8)		
Stool symptoms	149 (48.2)		
Abdominal symptoms	194 (62.8)		
Weight symptoms	78 (25.2)		
Other symptoms	219 (70.9)		

[a]BMI = body mass index; NHANES = National Health and Nutrition Examination Survey; TTG = tissue transglutaminase IgA.
[b]Data are presented as mean ± SD or as No. (percentage).

RESULTS

Patients and Demographic Characteristics

A total of 309 patients with newly diagnosed CD (196 women and 113 men) were included for analysis. The mean age at diagnosis was 46.1±15.1 years, and the mean BMI was 25.9±6.1 kg/m^2. Of the 309 patients, 282 (98.6%) were identified as white, 4 were identified as nonwhite, and 23 were unknown. National Health and Nutrition Examination Survey controls for vitamin D assessment had a mean BMI of 28.6±7.3 kg/m^2 ($P<.001$) and 600 (97.1%) were identified as white ($P=.17$) as compared with the CD cohort (Table 1). National Health and Nutrition Examination Survey controls for the remaining micronutrients had a mean BMI of 29.5±7.5 kg/m^2 ($P<.001$) and 419 (67.8%) were white ($P<.001$) as compared with the CD cohort (Table 1).

Nutrient and Laboratory Assessment Results Compared With NHANES Controls

In CD cases, zinc deficiency was seen most frequently at diagnosis, with 126 of 212 (59.4%) having low zinc. This is significantly more frequent than in NHANES controls, with 205 (33.2%) having low zinc ($P<.001$). Albumin was assessed in 122 patients with CD, with 24 (19.7%) having low albumin. This was significantly more frequent than in NHANES controls, with 7 of 618 (1.1%) being deficient ($P<.001$). Copper was assessed in 204 patients with CD, with 13 (6.4%) being serologically deficient. This was different from NHANES controls, with 13 of 618 (2.1%) being deficient ($P=.003$). Vitamin B_{12} was assessed in 244 patients with CD, and 13 patients (5.3%) had low vitamin B_{12}. This was significantly higher than in NHANES controls, with 11

TABLE 2. Nutrient Assessment Results of Patients With Celiac Disease Compared With NHANES Controls[a,b]

Nutrient	Patients with celiac disease: deficient/normal	NHANES controls: deficient/normal	*P* value[c]
Zinc	126/212 (59.4)	205/618 (33.2)	<.01
Albumin	24/122 (19.7)	7/618 (1.1)	<.01
Copper	13/204 (6.4)	13/618 (2.1)	.03
Vitamin B_{12}	13/244 (5.3)	11/618 (1.8)	.04
Serum folate	6/159 (3.6)	2/618 (0.3)	.02
Vitamin D	44/231 (19.0)	111/618 (18.0)	.72
Ferritin	66/214 (30.8)		

[a]NHANES = National Health and Nutrition Examination Survey.
[b]Data are presented as No. (percentage).
[c]*P* values were derived using the χ^2 or Fisher exact test, as appropriate.

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of 618 patients (1.8%) having low vitamin B_{12} (P=.004). Serum folate was low in 6 of 159 patients with CD (3.6%) compared with 2 of 618 controls (0.3%) (P=.002). Of 231 patients with CD and 25-hydroxy vitamin D assessment at diagnosis, 44 (19.0%) had serological deficiency, which is similar to NHANES controls, with 111 of 618 (18%) having deficiency (P=.72) (Table 2).

Among patients with CD, ferritin assessment was performed in 214, revealing that 66 (30.8%) had low ferritin. There were no NHANES comparisons for ferritin. The tissue transglutaminase IgA test result was positive in 236 patients, negative in 36 patients, and missing in 37 patients from the Mayo Clinic Celiac Disease Registry (Table 1).

Because BMI distribution was not similar between the cohort of adult patients with CD and NHANES controls, a sensitivity analysis was performed controlling for sex, age, and BMI. During sensitivity analysis, patients were excluded for each micronutrient due to incomplete data, but CD maintained association with deficiency for zinc (P<.001),

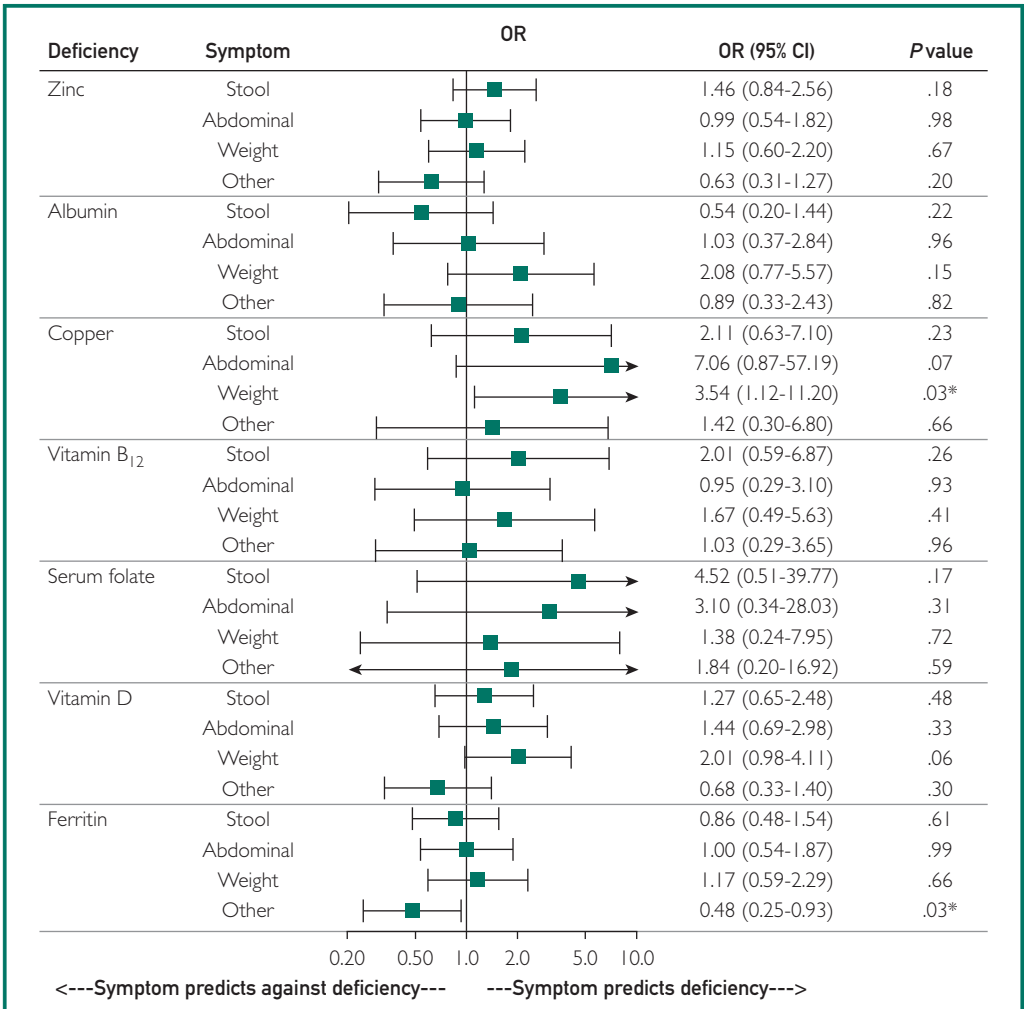

FIGURE 1. Symptom associations with deficiency in the cohort of adult patients with newly diagnosed celiac disease. In patients with celiac disease, the odds ratio (OR) and 95% CI are presented for each category of symptoms. Asterisks indicate significant associations. The logistic regression model was adjusted for age and sex.

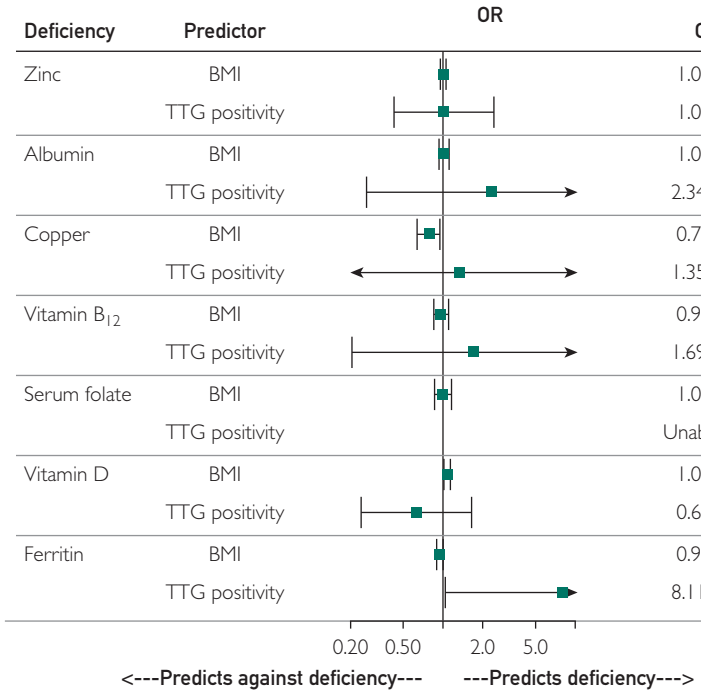

FIGURE 2. Body mass index (BMI) and tissue transglutaminase IgA (TTG) associations with micronutrient deficiency. In patients with celiac disease, the odds ratio (OR) and 95% CI for BMI and TTG are presented for each micronutrient. The OR and 95% CI for TTG positivity in the cohort of patients with folate deficiency were not calculated, as all patients deficient in folate had a positive TTG test result. Asterisks indicate significant associations.

copper (P=.02), albumin (P<.001), and folate (P=.003). Again, no association was seen between CD and low vitamin D (P=.16). However, the association between CD and vitamin B_{12} was lost with this analysis (P=.06), with the caveat that 5 of 13 cases in the cohort of adult patients with CD were excluded given lack of BMI data available. Finally, the time until testing for each micronutrient was compared to evaluate whether there were differences in the time until assessment between deficient and nondeficient patients with CD. There were no statistically significant differences between deficient and nondeficient patients with regard to the time between diagnosis and nutrient assessment.

Symptom Data in the Cohort of Adult Patients With Newly Diagnosed CD

Stool symptoms, including diarrhea and greasy stool, were present in 149 patients (48.2%). Abdominal symptoms, including abdominal distension, cramping, flatus, and nausea, were present in 194 patients (62.8%). Weight symptoms, including anorexia, weight loss, failure to thrive, or height loss, were present in 78 patients (25.2%). Finally, 219 patients (70.9%) noted symptoms not included in the above-mentioned categories (designated as other symptoms) (Table 1).

Certain symptom profiles were associated with micronutrient deficiencies, but these were not consistent between micronutrients (Figure 1). Associations between BMI and tissue transglutaminase IgA are depicted in Figure 2. Older age was associated with lower albumin (adjusted odds ratio, 1.06; 95% CI, 1.02-1.10; P=.001). Finally, low albumin was associated with copper deficiency (P=.006), but not with zinc deficiency (P=.32), suggesting that low zinc is not secondary to low albumin.

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DISCUSSION

This study found micronutrient deficiencies more common in adults in the United States at the time of CD diagnosis than in controls. This was true for zinc, copper, iron, and serum folate. Albumin was frequently low, suggesting a possible component of macronutrient deficiency. There was no difference in vitamin D deficiency between the groups, with nearly one-fifth having low vitamin D. Vitamin B_{12} was associated with CD in our primary analysis, but sensitivity analysis cast some doubt when controlling for BMI. There are anthropometric and symptom profiles associated with deficiencies, but these are not consistent between micronutrients and often weak associations. The frequencies of zinc deficiency and depleted iron stores (ferritin) in this cohort are similar to those seen previously.[8-10,12] Vitamin B_{12} deficiency appears lower in our study than in previous work.[9,10,28,29] This may represent patients presenting with milder disease, earlier diagnosis, or be secondary to the frequent nutrient fortification and supplementation seen in the United States. Similarly, recent data suggest some micronutrient deficiencies to be less common in patients with limited or ultrashort CD,[30] though the extent of bowel involvement was not assessed in our study. Copper deficiency was found in 6.4% of patients in our study and considerably more frequent than in controls. This differs from previous work suggesting similar copper levels in adults with CD and controls.[14] Overall, these data support testing for micronutrient deficiencies at the time of CD diagnosis given the frequency of some micronutrient deficiencies (zinc and iron) and the potential sequelae of those with less frequent but meaningful deficiencies (copper, folate, and vitamin B_{12}).

Several other observations are apparent in this study. First, the patients studied did not routinely exhibit the classic CD presentation of thin patients with diarrhea and weight loss. The mean BMI was 25.9 kg/m^2, and only a quarter had weight loss and half had diarrhea. Body mass index was higher in this study than in several previous European studies in which most patients had a normal or low BMI. Furthermore, abdominal symptoms of distension, cramping, flatus, and nausea were more common. This may suggest a change in the phenotype of CD presentation, milder disease, or earlier diagnosis.

This study has several strengths. First, most symptom data were collected prospectively from patients at the time of diagnosis, with missing data extracted upon chart review. Furthermore, the narrow window of micronutrient assessment around CD diagnosis prevents the results from representing patients already being supplemented after diagnosis or after a gluten-free diet has been prescribed. Finally, comparisons were made to NHANES controls matched for age and sex. There are several limitations to the study. First, deficiencies were serological deficiencies detected on laboratory assessment and patients may not have had clinical manifestations of the deficiency. Second, data are from a single tertiary care referral center, possibly decreasing generalizability. Furthermore, we were not able to match for BMI given insufficient NHANES matched controls meeting all matching criteria. The presented sensitivity analysis controlling for BMI was an effort to evaluate the effect of BMI. Next, there is a possibility of bias, as there has been no standard micronutrient assessment protocol and the included patients may have been selected for evaluation because of a clinical finding. Lastly, although NHANES data are representative of the US population, the US population and the population with CD have different racial profiles, with CD having a predominantly white demographic and the US population having greater racial diversity. This is reflected in the study's results and makes the results of this study most applicable to the US white population with CD.

CONCLUSION

Micronutrient deficiencies remain common in adults with recently diagnosed CD despite the low prevalence of weight loss and average overweight BMI. These data, in conjunction with previous descriptions of

micronutrient deficiencies, suggest value in continued micronutrient assessment of adults at the time of CD diagnosis.

Abbreviations and Acronyms: **BMI** = body mass index; **CD** = celiac disease; **NHANES** = National Health and Nutrition Examination Survey

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