Morbidity and Mortality Among Older Individuals With Undiagnosed Celiac Disease

JONATHAN D. GODFREY,* TRICIA L. BRANTNER,‡ WALEED BRINJIKJI,§ KEVIN N. CHRISTENSEN,§ DEANNA L. BROGAN,‡ CAROL T. VAN DYKE,‡ BRIAN D. LAHR,¶ JOSEPH J. LARSON,¶ ALBERTO RUBIO–TAPIA,‡ L. JOSEPH MELTON III,¶ ALAN R. ZINSMEISTER,* ROBERT A. KYLE,¶ and JOSEPH A. MURRAY‡

AQ: BACKGROUND & AIMS: Outcomes of undiagnosed celiac disease (CD) are unclear. We evaluated the morbidity and mortality of undiagnosed CD in a population-based sample of individuals 50 years of age and older.

METHODS: Stored sera from a population-based sample of 16,886 Olmsted County, Minnesota, residents 50 years of age and older were tested for CD based on analysis of tissue transglutaminase and endomysial antibodies. A nested case-control study compared serologically defined subjects with CD with age- and sex-matched, seronegative controls. Medical records were reviewed for comorbid conditions.

RESULTS: We identified 129 (0.8%) subjects with undiagnosed CD in a cohort of 16,847 older adults. A total of 127 undiagnosed cases (49% men; median age, 63.0 y) and 254 matched controls were included in a systematic evaluation for more than 100 potentially coexisting conditions. Subjects with undiagnosed CD had increased rates of osteoporosis and hypothyroidism, as well as lower body mass index and levels of cholesterol and ferritin. Overall survival was not associated with CD status. During a median follow-up period of 10.3 years after serum samples were collected, 20 cases but no controls were diagnosed with CD (15.2% Kaplan–Meier estimate at 10 years).

CONCLUSIONS: With the exception of reduced bone health, older adults with undiagnosed CD had limited comorbidity and no increase in mortality compared with controls. Some subjects were diagnosed with CD within a decade of serum collection, indicating that although most cases of undiagnosed CD are clinically silent, some result in symptoms. Undiagnosed CD can confer benefits and liabilities to older individuals.

Keywords: Prevalence; Epidemiology; Autoantibodies; Outcomes of Undiagnosed Celiac Disease.

Celiac disease (CD) is one of the most common chronic inflammatory conditions of the digestive system. Once thought to be rare, CD affects approximately 1% of the population1–3 and appears to be associated with increased mortality4–6 along with substantial morbidity,7,8 much of which is preventable or reversible with the gluten-free diet.9,10 Well recognized are the gastrointestinal consequences of severe malabsorption with weight loss or growth failure, macronutrient and micronutrient deficiencies, and a host of extraintestinal manifestations varying from autoimmune disorders to arthralgia to neurologic problems.11–15 Historically considered a childhood disease, it now has become apparent that the diagnosis of CD may be delayed for many years and the condition often remains unrecognized.16–19 Although there is no doubt that symptomatic CD can be a devastating illness, it is not clear if this outcome applies to all patients or just the small proportion that become clinically obvious.

Newer serologic tests20–27 including tissue transglutaminase (tTGA) and endomysial antibodies (EMAs) now make CD readily detectable, but most screen- found patients tend to have few or no gastrointestinal symptoms at the time of detection.19,28 Prior investigation has shown that the submerged part of the CD “iceberg” may be associated with certain comorbid conditions including metabolic bone disorders,29 type 1 diabetes mellitus,15 and iron-deficiency anemia.28,30 A recent study that included young adults (median age, 20.5 y) showed that undiagnosed CD was associated with a nearly 4-fold increased risk of death during 45 years of follow-up evaluation.31,32 However, a recent study from Finland in adults with a mean age of 50 suggested the prognosis of adults with unrecognized CD appeared to be good, except for a significantly increased risk for lymphoma and esophageal carcinoma.33 Consequently, it is of crucial importance to know the impact that undetected, and hence untreated, CD has in older adults. This information could have profound implications for public health decisions and could help answer questions regarding the prognosis for patients in whom CD is detected in the absence of substantial gastrointestinal symptoms or

Abbreviations used in this paper: CD, celiac disease; CI, confidence interval; EMA, endomysial antibody; Ig, immunoglobulin; tTGA, tissue transglutaminase.
other consequences of the disease. Thus, the aim of this study was to evaluate the morbidity and mortality of undiagnosed CD in a population-based sample of subjects age 50 and older.

Materials and Methods

Setting

Population-based epidemiologic research can be conducted in Olmsted County (2000 population, ~124,000) because medical care is virtually self-contained within the community and there are relatively few providers. The 2 major medical care providers (Mayo Clinic and Olmsted Medical Center) each use a dossier (or unit record) system whereby all medical information for each individual is accumulated in a single life-long record. These clinical data are accessible because Mayo Clinic has maintained the original records as well as an extensive index of clinical and histologic diagnoses and surgical procedures since 1910. The medical records linkage system was developed further by the Rochester Epidemiology Project by indexing the records of the other providers into the same system used at Mayo.

Participants

As part of a prior study of monoclonal gammopathy of undetermined significance, serum samples of 24,727 Olmsted County residents age 50 and older were obtained between the years 1995 and 2001 and stored. During that time, study consent was granted for research of these specimens by 18,774 (75.9%) individuals. Thirty-four (0.2%) patients with known CD diagnosed before serum draw were excluded from the present study, leaving 18,738 subjects whose disease status was unknown at that time. Among these, 16,886 (90.1%) specimens still had sufficient volume for testing and hence were screened for CD.

Laboratory Testing

Serum was screened for CD using a sequential testing paradigm with tTGA immunoglobulin (IgA enzyme-linked immunosorbent assay as the initial screen. The enzyme-linked immunosorbent assay procedure was performed on the Thermolab DSX enzyme-linked immunosorbent assay automated system (INOVA Diagnostics, Inc, San Diego, CA), and automated pipetting techniques were used to preserve sample volume. Each run had both positive and negative controls and calibrators. Those with positive screens were tested further with an EMA immunofluorescence assay (Beckman Coulter, Inc, Brea, CA) for confirmation. The sensitivity and specificity of these tests have been described previously. Un-diagnosed CD was defined by the presence of a tTGA level greater than 2.0 U/mL with a positive EMA test. A tTGA level less than 2.0 U/mL was considered negative and no EMA test was performed. Samples also were considered negative if the tTGA level was between 2.0 and 4.0 U/mL and the EMA test was negative. Tests were considered indeterminate if the tTGA level was greater than 4.0 U/mL and the EMA test was negative. The technologist reading the EMA assay was unaware of the tTGA status and nature of the research study.

Data Collection

Upon completion of the serology testing, a nested, matched, case-control design was proposed to compare serologically defined undiagnosed CD subjects with seronegative controls based on 2:1 matching of age and sex. Patients without general research authorization for use of their medical records were excluded from institutional review board-approved review, including 2 seropositive patients and 278 potential controls. Complete medical records before and after the date of serum draw were reviewed by individuals unaware of serum status. These records included inpatient, outpatient, and emergency room documentation. Diagnosis lists, clinical notes, hospital notes, and laboratory results were used to obtain information pertaining to known comorbid conditions related to CD along with information regarding mortality. Comorbid conditions present before the serum draw date were included in the association analysis. For review of laboratory testing, values obtained closest to the date of serum draw were used.

Statistical Analysis

Descriptive statistics summarizing the data included percentages for categorical data and medians and ranges for continuous data. To ensure adequate follow-up evaluation for each of the 2 controls within a matched set, the follow-up time of each subject was stopped at the latest recorded medical follow-up evaluation within that set. We assessed the risk of having various comorbid conditions before and after the serum draw date in undiagnosed CD cases relative to controls using conditional logistic regression, or unconditional logistic regression if extensive amounts of data were missing (eg, certain laboratory parameters). Odds ratios (with 95% confidence intervals [CIs]) were used to measure the strength of association between comorbidity and serology status. In addition, the Kaplan-Meier method was used to estimate overall survival and survival free of subsequent clinically diagnosed CD. Cox proportional hazards regression, stratified on a matched set, was used to test for an association between positive serology and overall survival. In all models, the matching variables (age and sex) were included as covariates to control for any residual confounding not prevented by the matching itself. Given that more than 100 potential conditions, diseases, and laboratory findings were evaluated, these analyses are considered hypothesis-generating and results are considered significant at an α level of .05 and should be interpreted cautiously. All analyses were performed
Results

Among subjects whose disease status was unknown, 16,886 Olmsted County, Minnesota, residents age 50 and older who had consented to use of their serum for research were screened for CD. In total, 163 (1.0%) individuals tested positive for tTGA and underwent confirmatory EMA testing, whereas 143 had borderline tTGA levels (2.0–4.0 U/mL) and also were EMA tested. Based on a combined serology status of both the tTGA and EMA result, 39 subjects were considered equivocal and were excluded from subsequent analyses (final denominator, 16,847). None of the 39 subjects subsequently were diagnosed with CD (10-year Kaplan–Meier rate, 15.2%; 95% CI, 8.2%–22.1%) after a median of 10.3 years (range, 0.0–12.9 years) of follow-up evaluation. Of note, no controls have yet to be diagnosed subsequently with CD.

Undiagnosed CD was associated with decreased lumbar spine T-scores when compared with controls (−1.7 vs −0.9; odds ratio, 0.64; 95% CI, 0.48–0.85) (Figure 1) and an increased risk of osteoporosis (Figure 2). These patients also showed higher rates of hypothyroidism. Conversely, undiagnosed CD patients had lower weight and body mass index values (median value, 26.4 vs 27.4) and, although not statistically significant, a reduced rate of glucose intolerance. Laboratory evaluation showed undiagnosed CD was associated with reduced levels of cholesterol (median value, 200.0 vs 213.0) and ferritin (25.0 vs 33.0) (Table 2).

Diagnosed and symptomatic CD is known to be associated with an increased risk of cancer. Upon review of the medical records, there was not a significantly increased risk of cancer detected in the undiagnosed CD patients compared with controls. The total number of cases (51% women; median age, 63.0 years; range, 51.7–87.7 years), 254 matched controls were selected for comparison (Table 1). Upon review, 20 seropositive patients subsequently were diagnosed (clinically) with CD (10-year Kaplan–Meier rate, 15.2%; 95% CI, 8.2%–22.1%) after a median of 10.3 years (range, 0.0–12.9 years) of follow-up evaluation. Of note, no controls have yet to be diagnosed subsequently with CD.

Table 1. Demographics of Study Participants

<table>
<thead>
<tr>
<th></th>
<th>Serology negative (n = 254)</th>
<th>Serology positive (n = 127)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at serum draw, y</td>
<td>62.9 (51.9–87.7)</td>
<td>63.0 (51.7–87.7)</td>
<td>1.19 (0.80–1.78)</td>
</tr>
<tr>
<td>Female</td>
<td>132 (52.0%)</td>
<td>65 (51.2%)</td>
<td>0.64 (0.38–1.34)</td>
</tr>
<tr>
<td>Weight, kg²</td>
<td>78.0 (38.9–142.0) (n = 247)</td>
<td>74.8 (44.0–120.6) (n = 125)</td>
<td>0.98 (0.67–1.43)</td>
</tr>
<tr>
<td>Height, cm²</td>
<td>1.66.4 (144.3–189.7) (n = 242)</td>
<td>167.6 (124.0–203.2) (n = 123)</td>
<td>1.01 (0.69–1.46)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.4 (17.5–55.5) (n = 242)</td>
<td>26.4 (17.2–42.9) (n = 123)</td>
<td>0.94 (0.60–1.49)</td>
</tr>
</tbody>
</table>

*Descriptive statistics based on marginal distributions of seronegatives and seropositives do not take matching into account.
*Odds ratio (95% CI) from conditional logistic regression, which retains the matching.
*Obtained from recorded weight and height closest to the date of serum draw.

Using the SAS statistical software package (version 9.1; SAS Institute, Cary, NC).

Figure 1. Impact of undiagnosed CD on lumbar spine T-score. Serology negative, 82; serology positive, 51. The age of the serology-negative vs serology-positive patients was 62.2 vs 63.7 years (P = .22). The percentage of women in the serology-negative vs serology-positive group was 85.4% vs 82.4% (P = .64).

Figure 2. Summary of outcomes of undiagnosed celiac disease cases compared with serology-negative controls. *Odds ratio (95% CI) from conditional logistic regression, which retains the matching.
cases identified as having cancer was 31 (24.4%) in the undiagnosed group compared with 51 (20.1%) in the control group (odds ratio, 1.29; 95% CI, 0.77–2.15). Two patients in the seropositive group were found to have a CD-associated malignancy (both small-bowel lymphoma), as did 2 patients in the seronegative group (both esophageal cancer). Of the 2 undiagnosed CD patients with small-bowel lymphoma, 1 patient was found to have a T-cell lymphoma.

Patient status (undiagnosed CD vs controls) was not found to be associated with potential CD symptoms (Table 3). In particular, there was no difference in the proportion reported as having irritable bowel syndrome (10.4% vs 12.6%) or experiencing weight loss (11.2% vs 7.8%) around the time of serum draw. Furthermore, diarrhea was actually less prevalent, albeit not significantly, in undiagnosed cases than controls (21.4% vs 26.2%). Overall, 5 seropositive subjects and none of the controls had a prior diagnosis of dermatitis herpetiformis.

In addition, undiagnosed CD was not found to be associated with an increased rate of all-cause mortality (hazard ratio, 0.80; 95% CI, 0.45–1.41) or cancer-related mortality (Table 4). In particular, undiagnosed CD cases did not show a higher rate of mortality that was caused by any cancer, visceral types of cancer, or CD-associated types of cancer.

Of the 20 seropositive patients who subsequently were diagnosed with CD, iron deficiency (n = 9; 45%) was the most common presenting symptom (Table 5). Three patients were diagnosed with CD after having been diagnosed with dermatitis herpetiformis first. Interestingly, only 3 of the 20 (15%) CD patients had presented with classic symptoms of diarrhea, malabsorption, and weight loss at the time of diagnosis. Other presenting symptoms included family history (n = 3), nausea (n = 1), and small-bowel lymphoma (n = 1). Sex was associated significantly with subsequent CD diagnosis, with 15 (75%) of these 20 patients being women in contrast to the nearly equally divided gender distribution (47% women) in seropositive patients without a subsequent CD diagnosis (P = .02, chi-square test).

### Table 2. Laboratory Evaluation of Patients With Undiagnosed CD Compared With Serology-Negative Controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Serology negative (n = 254)</th>
<th>Serology positive (n = 127)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol mg/dL</td>
<td>213.0 (99.0–461.0) (n = 242)</td>
<td>200.0 (122.0–314.0) (n = 120)</td>
<td>0.91 (0.85–0.98)</td>
</tr>
<tr>
<td>Ferritin ug/L</td>
<td>78.5 (5.0–1688.0) (n = 86)</td>
<td>25.0 (4.1–443.0) (n = 52)</td>
<td>0.48 (0.32–0.71)</td>
</tr>
<tr>
<td>Iron level, ug/dL</td>
<td>74.0 (16.0–433.0) (n = 65)</td>
<td>64.0 (4.0–173.0) (n = 39)</td>
<td>0.65 (0.43–1.00)</td>
</tr>
<tr>
<td>Hemoglobin g/dL</td>
<td>14.0 (6.9–17.0) (n = 252)</td>
<td>13.6 (8.8–17.1) (n = 125)</td>
<td>0.87 (0.73–1.05)</td>
</tr>
<tr>
<td>B12 level, ng/L</td>
<td>387.5 (84.9–1318.0) (n = 94)</td>
<td>405.5 (33.0–2000.0) (n = 50)</td>
<td>0.83 (0.58–1.18)</td>
</tr>
<tr>
<td>Folate level, ug/L</td>
<td>16.1 (3.7–586.0) (n = 74)</td>
<td>13.8 (4.0–24.0) (n = 44)</td>
<td>0.71 (0.45–1.10)</td>
</tr>
<tr>
<td>Albumin level, g/dL</td>
<td>4.2 (1.3–9.2) (n = 213)</td>
<td>4.1 (2.3–4.9) (n = 106)</td>
<td>0.80 (0.45–1.40)</td>
</tr>
</tbody>
</table>

*Odds ratio (95% CI) expressed per 10-mg/dL change in cholesterol level.

### Table 3. Classic CD Symptoms in Undiagnosed CD Cases Compared With Serology-Negative Controls

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Serology negative (n = 254)</th>
<th>Serology positive (n = 127)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>65 (26.2%)</td>
<td>27 (21.4%)</td>
<td>0.77 (0.46–1.31)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>19 (7.8%)</td>
<td>14 (11.2%)</td>
<td>1.67 (0.79–3.51)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>92 (37.2%)</td>
<td>46 (36.2%)</td>
<td>0.96 (0.62–1.51)</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>0 (0.0%)</td>
<td>5 (4.0%)</td>
<td>—</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>31 (12.6%)</td>
<td>13 (10.4%)</td>
<td>0.79 (0.40–1.54)</td>
</tr>
<tr>
<td>Deficient hemoglobin</td>
<td>33 (13.1%)</td>
<td>23 (18.4%)</td>
<td>1.63 (0.86–3.08)</td>
</tr>
</tbody>
</table>

*Descriptive statistics based on marginal distributions of seronegatives and seropositives do not take matching into account.

### Table 4. Association Between Undiagnosed CD and Mortality

<table>
<thead>
<tr>
<th>Type of mortality</th>
<th>Hazard ratio 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.80 0.45–1.41</td>
<td>.44</td>
</tr>
<tr>
<td>Cancer-related mortality</td>
<td>0.63 0.16–2.48</td>
<td>.51</td>
</tr>
<tr>
<td>Visceral cancer-related mortality</td>
<td>0.79 0.25–2.50</td>
<td>.68</td>
</tr>
<tr>
<td>CD-associated cancer mortality</td>
<td>1.01 0.14–7.00</td>
<td>.99</td>
</tr>
</tbody>
</table>

NOTE. Results obtained from Cox PH regression stratified on matched set.

*Hazard ratio (95% CI) corresponds to risk in undiagnosed CD cases compared with serology-negative controls.
Table 5. Presenting Diagnosis of the 20 Seropositive Patients Subsequently Diagnosed Clinically With CD

<table>
<thead>
<tr>
<th>Symptom</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Diarrhea, weight loss</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Screened because of family history</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Small-bowel lymphoma</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

rope. This is in contrast to a recent study by Rubio-Tapia et al, who found a 4-fold increased risk of death for undiagnosed CD among a younger cohort (age, 18–24 years at the time of blood draw) with follow-up evaluation for more than 45 years. Possible explanations for this difference exist. Accumulated excess mortality in the Rubio-Tapia et al cohort did not occur until 25 years after the serum sample collection date, suggesting that if one got CD later in life, longer follow-up evaluation may be required to determine if excess mortality exists. In addition, in our study, 15% of the initial undiagnosed CD cases were clinically detected and treated with a gluten-free diet, although it is unlikely that any of those in the younger cohort were diagnosed with CD and treated. It also is possible that some subjects in the older group with undiagnosed CD died before the age of sampling and are not represented in this cohort. Finally, a recent study suggested that loss of tolerance in CD may occur late in life. Thus, because of the cross-sectional design of the serologic testing in our study, we cannot exclude that late-onset CD may explain the lack of morbidity and mortality in some of our patients with undiagnosed CD.

Although there is no difference in mortality among older patients with undiagnosed CD, it is evident that these patients do have some excess morbidity related to CD. Significant results include a lower bone mineral density score and lower ferritin levels, findings consistent with what is found in clinically detected CD. This suggests that, although without an increase in symptoms from a gastrointestinal standpoint, undiagnosed CD is not entirely without nutritional consequences. On the other hand, undiagnosed CD patients did appear to have some theoretically protective characteristics that could be considered beneficial in a population in which excess weight is the norm, such as a lower body mass index and lower average cholesterol levels. Undiagnosed CD patients in our study also showed a trend toward less arthritis and less glucose intolerance, which could be related directly to a lower body mass index.

Of the 129 undiagnosed patients originally found to have a positive IgA tTG and EMA tests, a significant minority subsequently were diagnosed with CD. Patients were most likely to be diagnosed with CD after a work-up of iron-deficiency anemia and only 6 (30%) patients in this subgroup suffered from gastrointestinal symptoms. One patient was diagnosed with celiac disease only after being diagnosed first with small-bowel lymphoma. What is interesting when comparing this group with the undiagnosed group is that 75% were women compared with 47% in the undiagnosed group, suggesting that women are more likely to be clinically diagnosed. Prior studies looking at CD in Olmsted County residents found a similar female predominance of diagnosed CD.

The use of mass screening of the general population for CD has been the topic of much discussion in the recent past. Those in favor of screening point out that CD is associated with an increase in mortality and morbidity, including certain cancers such as small-bowel lymphoma and gastrointestinal cancers, many of which are diagnosed before or at the time of the diagnosis of CD. Also, treatment by virtue of a gluten-free diet is readily available. This, along with the development of improved screening tests for CD, including IgA tTG and EMA immunofluorescence, make screening for the disease a possibility. The question still remains, however, whether the general population should be screened. As found in our study of middle-aged subjects, undiagnosed CD is not associated with an increased risk of mortality. Moreover, it has been suggested that those with undiagnosed CD who remain asymptomatic may be less likely to comply with the gluten-free diet, so benefits may be limited. Screening older populations for CD will find many individuals with undiagnosed or asymptomatic disease. Furthermore, a substantial minority of these patients will be clinically diagnosed with CD. It is possible that early identification of these patients may affect the ultimate outcome, but whether this will have a significant impact on quality of life and prevention of morbidity and mortality is not known.

There were several limitations to this study. Because the diagnosis of CD was not verified by small-bowel biopsy, we relied on the accuracy of serologic testing to make the diagnosis. We used IgA tTG as an initial screening test. This test has been found to have a sensitivity approaching 91%–98%, and it is readily available. This, along with the development of improved screening tests for CD, including IgA tTG and EMA immunofluorescence, make screening for the disease a possibility. The question still remains, however, whether the general population should be screened. As found in our study of middle-aged subjects, undiagnosed CD is not associated with an increased risk of mortality. Moreover, it has been suggested that those with undiagnosed CD who remain asymptomatic may be less likely to comply with the gluten-free diet, so benefits may be limited. Screening older populations for CD will find many individuals with undiagnosed or asymptomatic disease. Furthermore, a substantial minority of these patients will be clinically diagnosed with CD. It is possible that early identification of these patients may affect the ultimate outcome, but whether this will have a significant impact on quality of life and prevention of morbidity and mortality is not known.

There were several limitations to this study. Because the diagnosis of CD was not verified by small-bowel biopsy, we relied on the accuracy of serologic testing to make the diagnosis. We used IgA tTG as an initial screening test. This test has been found to have a sensitivity approaching 91%–98%, and it is readily available. This, along with the development of improved screening tests for CD, including IgA tTG and EMA immunofluorescence, make screening for the disease a possibility. The question still remains, however, whether the general population should be screened. As found in our study of middle-aged subjects, undiagnosed CD is not associated with an increased risk of mortality. Moreover, it has been suggested that those with undiagnosed CD who remain asymptomatic may be less likely to comply with the gluten-free diet, so benefits may be limited. Screening older populations for CD will find many individuals with undiagnosed or asymptomatic disease. Furthermore, a substantial minority of these patients will be clinically diagnosed with CD. It is possible that early identification of these patients may affect the ultimate outcome, but whether this will have a significant impact on quality of life and prevention of morbidity and mortality is not known.

There were several limitations to this study. Because the diagnosis of CD was not verified by small-bowel biopsy, we relied on the accuracy of serologic testing to make the diagnosis. We used IgA tTG as an initial screening test. This test has been found to have a sensitivity approaching 91%–98%, and it is readily available. This, along with the development of improved screening tests for CD, including IgA tTG and EMA immunofluorescence, make screening for the disease a possibility. The question still remains, however, whether the general population should be screened. As found in our study of middle-aged subjects, undiagnosed CD is not associated with an increased risk of mortality. Moreover, it has been suggested that those with undiagnosed CD who remain asymptomatic may be less likely to comply with the gluten-free diet, so benefits may be limited. Screening older populations for CD will find many individuals with undiagnosed or asymptomatic disease. Furthermore, a substantial minority of these patients will be clinically diagnosed with CD. It is possible that early identification of these patients may affect the ultimate outcome, but whether this will have a significant impact on quality of life and prevention of morbidity and mortality is not known.

There were several limitations to this study. Because the diagnosis of CD was not verified by small-bowel biopsy, we relied on the accuracy of serologic testing to make the diagnosis. We used IgA tTG as an initial screening test. This test has been found to have a sensitivity approaching 91%–98%, and it is readily available. This, along with the development of improved screening tests for CD, including IgA tTG and EMA immunofluorescence, make screening for the disease a possibility. The question still remains, however, whether the general population should be screened. As found in our study of middle-aged subjects, undiagnosed CD is not associated with an increased risk of mortality. Moreover, it has been suggested that those with undiagnosed CD who remain asymptomatic may be less likely to comply with the gluten-free diet, so benefits may be limited. Screening older populations for CD will find many individuals with undiagnosed or asymptomatic disease. Furthermore, a substantial minority of these patients will be clinically diagnosed with CD. It is possible that early identification of these patients may affect the ultimate outcome, but whether this will have a significant impact on quality of life and prevention of morbidity and mortality is not known.

There were several limitations to this study. Because the diagnosis of CD was not verified by small-bowel biopsy, we relied on the accuracy of serologic testing to make the diagnosis. We used IgA tTG as an initial screening test. This test has been found to have a sensitivity approaching 91%–98%, and it is readily available. This, along with the development of improved screening tests for CD, including IgA tTG and EMA immunofluorescence, make screening for the disease a possibility. The question still remains, however, whether the general population should be screened. As found in our study of middle-aged subjects, undiagnosed CD is not associated with an increased risk of mortality. Moreover, it has been suggested that those with undiagnosed CD who remain asymptomatic may be less likely to comply with the gluten-free diet, so benefits may be limited. Screening older populations for CD will find many individuals with undiagnosed or asymptomatic disease. Furthermore, a substantial minority of these patients will be clinically diagnosed with CD. It is possible that early identification of these patients may affect the ultimate outcome, but whether this will have a significant impact on quality of life and prevention of morbidity and mortality is not known.

There were several limitations to this study. Because the diagnosis of CD was not verified by small-bowel biopsy, we relied on the accuracy of serologic testing to make the diagnosis. We used IgA tTG as an initial screening test. This test has been found to have a sensitivity approaching 91%–98%, and it is readily available. This, along with the development of improved screening tests for CD, including IgA tTG and EMA immunofluorescence, make screening for the disease a possibility. The question still remains, however, whether the general population should be screened. As found in our study of middle-aged subjects, undiagnosed CD is not associated with an increased risk of mortality. Moreover, it has been suggested that those with undiagnosed CD who remain asymptomatic may be less likely to comply with the gluten-free diet, so benefits may be limited. Screening older populations for CD will find many individuals with undiagnosed or asymptomatic disease. Furthermore, a substantial minority of these patients will be clinically diagnosed with CD. It is possible that early identification of these patients may affect the ultimate outcome, but whether this will have a significant impact on quality of life and prevention of morbidity and mortality is not known.
from CD, or, more commonly, have undiagnosed CD.\textsuperscript{1–3} Undiagnosed CD in older adults is not associated with an increase in mortality but is associated with impaired bone density and lower ferritin levels. Furthermore, a minority of subjects with undiagnosed CD, especially women, eventually will be clinically diagnosed with CD. As advances are made in testing for CD, based on the results of this study it is not clear that a net benefit for detection of undiagnosed CD or at least CD that remains truly asymptomatic has been proven. Longer follow-up evaluations and studies in other populations would be necessary. Detection of the majority of patients with undiagnosed CD, even in this medically well-served population, is unlikely to be achieved, even using an augmented case-finding approach. If undiagnosed CD has a net negative effect on morbidity or mortality, this strategy likely will leave the vast majority of patients undiagnosed.

References


Received December 4, 2009. Accepted May 10, 2010.

Reprint requests
Address requests for reprints to: Joseph A. Murray, MD, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905. e-mail: murray.joseph@mayo.edu; fax: (507) 255-6318.

Conflicts of interest
The authors disclose no conflicts.

Funding
This work was supported by research grants R01-DK57892, P01 CA62242, R01-AR30582, and T-32 Al07047 (A.R.-T.) from the National Institutes of Health, U.S. Public Health Service. The project described was supported by grant number 1 UL1 RR024150 from the National Center for Research Resources, a component of the National Institutes of Health, and the National Institutes of Health Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the National Center for Research Resources or the National Institutes of Health. Information on the National Center for Research Resources is available at http://www.ncrr.nih.gov/.

Information on Reengineering the Clinical Research Enterprise can be obtained from http://nihroadmap.nih.gov.