AGA Perspectives

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CELIAC DISEASE

Should there be screening for all?

ALBERTO RUBIO-TAPIA, MD; JOSEPH A. MURRAY, MD; and CIARAN KELLY, MD, debate the need for population-wide screening.
CELIAC DISEASE

Should there be screening for all?
The Case for Screening: Detecting Celiac Disease Hidden Below the Waterline

Celiac disease is an emerging public health threat that affects approximately 1 percent of the North American population. The prevalence of celiac disease in the U.S. increased four times in the last 50 years. However, the prevalence of clinically detected celiac disease is much lower than screen-found celiac disease, suggesting that for every patient diagnosed, at least five to 10 individuals remain undiagnosed. Celiac disease epidemiology is like an iceberg where the tip represents few diagnosed cases (often symptomatic), while the vast majority of cases remain undiagnosed below the waterline. Many cases are not diagnosed because of poor awareness of disease, wide spectrum of clinical manifestations or absence of gastrointestinal symptoms. Symptomatic patients may remain undiagnosed for approximately 11 years in the U.S.

Consequences of undiagnosed celiac disease

Undiagnosed celiac disease may increase morbidity, economic burden and mortality. Many people with undiagnosed celiac disease may seek substantial health care before being diagnosed.

The Case Against Screening for Celiac Disease

Screening for celiac disease is not justified because of inadequate information on the possible benefits of diagnosing and treating subclinical or silent celiac disease. In addition, we do not know enough about the natural history of subclinical celiac disease. We do not know the health consequences of identifying and treating silent celiac disease compared to leaving it undiagnosed. Without this information, it is impossible to gauge the theoretical benefits of screening against the all-too-concrete financial and personal costs of diagnosis and treatment.

Before discussing costs and benefits, let me clarify what is meant by screening. Screening means offering testing for celiac disease to individuals with no evident signs or symptoms of the disorder. This may be universal screening where an entire population group is offered testing, or case finding where testing is offered to individuals at higher risk. Screening is very different from early diagnosis, which refers to prompt testing of those with possible symptoms or signs of celiac disease.

The value and wisdom of screening for celiac disease is controversial. Conversely, there is little or no disagreement regarding early diagnosis, which is widely advocated.
correctly diagnosed. Increased mortality risk is a concern and may require further comment. All-cause mortality was increased four-fold among young men with undiagnosed celiac disease than among seronegative referent subjects during 45 years of follow-up. This finding was supported by a European study that demonstrated a two-fold increased mortality risk among middle-aged men and women with positive tissue transglutaminase antibody. However, other studies that either included older individuals and/or had a shorter follow-up failed to confirm these observations. The mortality risk might be influenced by the amount and duration of gluten consumed before and after celiac disease onset. Thus, detection of celiac disease — to be effective — should be started early in life if it will impact survival.

Current strategies for detection

The historical strategy of passive identification of celiac disease cases by testing only individuals with symptoms of malabsorption will detect just a few symptomatic cases. Case finding is a more proactive strategy, effectively increasing detection by testing individuals who belong to clinically identifiable groups at increased risk. These at-risk groups include those with a family history of celiac disease, Hashimoto’s thyroiditis, unexplained anemia, chronic liver disease of unknown etiology, type 1 diabetes, Down’s syndrome and others. The rationale to test most of these conditions is well established and largely accepted. However, most individuals with undiagnosed celiac disease do not belong to at-risk groups or have suggestive symptoms. Thus, although useful and desirable, case finding is not enough and will fail to uncover a large portion of undiagnosed disease. Data from Olmsted County Minnesota suggest that case finding may detect at most 25 percent of cases (unpublished data), leaving the vast majority of cases undiagnosed. Only a minority (approximately 15 percent) of individuals with evidence of celiac disease-specific autoimmunity will be clinically detected by case finding over a period of 10 years. The highest rate of clinical diagnosis of celiac disease in the world was achieved in Finland (point prevalence of 0.35 percent) where doctors have had a low threshold for serological testing.

Population screening can detect a large portion of hidden cases among presumptively healthy individuals that may benefit from early intervention. A good screening strategy must combine both a high sensitivity, so that it does not miss the relatively few cases of celiac disease present among the entire population, with high specificity to avoid overdiagnosis. Sensitivity of immunoglobulin A (IgA) tissue transglutaminase antibody is approximately 95 percent, making this test suitable for initial screening. Thus, the first step of screening will require only a blood test. More invasive evaluation would be recommended to differentiate between true- and false-positive serology results. Although, high IgA tissue transglutaminase titers greater than or equal to five to 10 times the upper limit of normal may have excellent correlation with other markers of celiac disease (e.g., abnormal intestinal biopsy consistent with celiac disease), implying that upper endoscopy with biopsy may not be universally necessary to confirm the diagnosis. A positive IgA endomysial antibody (specificity approximately 99 percent) is a very accurate way of confirming positive IgA tissue transglutaminase antibodies even when celiac disease is not present. Wilson and Jungner set a list of criteria against which a decision to implement a population screening program could be taken. Celiac disease meets several of these criteria while additional clinical research is still needed to obtain some crucial information about others (view table at http://www.gastro.org/rubio-tapia82).

Medical intervention

While the central concept for screening states that the earlier the disease is found, the better the outcome, it has not yet been proven whether active screening and early intervention with a gluten-free diet (GFD) may reduce the development of complications and/or mortality. Adherence to GFD appears to be good in screen-detected cases and can improve nutritional deficiencies and symptoms (when present) even in the elderly. Many screen-found patients, while initially claiming to be asymptomatic, go on to report substantial symptom improvement on a GFD. Dietary treatment is effective in children and adults with positive endomysial antibodies and early non-atrophic intestinal lesions. Population screening and early intervention led to health improvement in 66 percent of children without deterioration of health-related quality of life after 10 years of follow-up.

Areas of uncertainty

Several questions need to be answered before population screening for celiac disease can reach prime time. The best time to screen (and need of re-testing seronegative individuals) remains to be determined. While theoretical modeling suggests that population screening could be cost effective, formal cost-effectiveness analysis based on outcome data is required. Further studies about the natural history of undiagnosed celiac disease (especially symptom-free disease), including estimation of risks and potential benefits, are urgently needed. Finally, a large prospective study to explore the risks and benefits of population screening would be desirable.

Conclusions

In summary, effective methods to detect and treat the majority of hidden cases with celiac disease are needed. Currently, active...
and encouraged. Why this distinction? When a patient presents to a health-care provider, they are seeking help in understanding and managing the symptoms or signs of a possible underlying disease. The onus is on the health-care provider to work with the patient to seek an explanation and determine the best line of treatment. In screening the situation is reversed, as the initiative is taken by the health-care community. Many individuals who are healthy will be approached and tested with the goal of identifying a small number with latent or silent disease. The final result is that most individuals are needlessly inconvenienced and some are “given” a disease. There needs to be a very high degree of certainty of ultimate overall benefit to justify these incursions into the everyday lives of the screened population. Currently there is very little certainty of ultimate overall benefit in the case of screen-detected celiac disease.

There are several potential benefits of screening for silent celiac disease, including improved overall health and well-being, avoidance of nutritional deficiencies and prevention of complications, especially malignancy. However, none of these positive outcomes have been tested rigorously or demonstrated convincingly for screen-detected, silent celiac disease. A substantial improvement in overall health and well-being is difficult, or impossible, to achieve in a group that is without symptoms to begin with. Nutritional deficiencies that are associated with celiac disease can be detected, if and when they arise, during routine medical care and prompt testing for celiac disease performed at that time. In one longitudinal study of more than 11,000 patients with clinically evident celiac disease, 2.3 percent developed a malignancy compared to an expected 1.8 percent in the general population (standardized incidence ratio 1.3). Thus, the increased risk of malignancy in untreated overt celiac disease is real but modest. It seems probable, but not certain, that treatment with a gluten-free diet (GFD) may reduce this risk. However, it is not known whether or not silent celiac disease is also associated with an increased risk for malignancy; the effect, if any, of a GFD on this unknown risk has not been studied. To the contrary, one study found no increased risk for malignancy during almost 20 years of follow-up in individuals found to have a positive celiac serology. The possible benefits of screening for subclinical celiac disease are theoretical rather than evidence based. Not so for the risks and costs of screening.

The most obvious costs are the financial costs of the screening program. Additional financial costs are incurred in further testing of those who yield a positive result on the initial screening test. Testing approaches may vary, but it is likely that many of those who test positive would be offered endoscopy with small intestinal biopsy. This is costly, invasive and carries risk. Many who would undergo biopsy would be found not to have intestinal changes of celiac disease. Thus, the entire workup would prove to be unnecessary. Others would have equivocal or non-specific findings, or at least a difficult-to-interpretable result. Should a GFD be advocated for those individuals or only for those with more advanced pathology, including villous atrophy? If not, should long-term follow-up be offered to those with equivocal histology findings? Even a negative screening result is not without risk; a false negative screening test result may lead to a delay or failure of celiac disease diagnosis due to misplaced trust in the negative findings of the screening assay.

The potential costs and risk for harm in screening for celiac disease is greatest in those who test positive and are confirmed to have silent celiac disease. In addition to the medical costs of diagnosis and long-term management, there is clear and consistent evidence that adherence to a GFD is inconvenient, time-consuming, expensive and can be a social liability. These disadvantages might be considered minor if the duration of treatment was measured in days, but over many years and decades of treatment, the costs become enormous. Some baulk at the dietary and lifestyle changes involved, and resent the intrusion and the restrictions that it imposes. This problem is compounded by the fact that, in screening symptomless individuals, one cannot expect substantial immediate benefit from adhering to the diet. Compliance with dietary therapy for diabetes mellitus and hypercholesterolemia is generally incomplete despite the fact that the benefits are well established and the dietary regimens less challenging than a strict GFD. Therefore, it is probable that many individuals with screen-detected celiac disease will opt not to adhere to the diet. In that instance, the goal of the screening program is not achieved and the individual is left feeling guilty, anxious or both.

There is another line of reasoning against screening for celiac disease that is based on unproven theories: silent celiac disease is not only common and generally carries low morbidity and so can be ignored, but in some circumstances it may even be beneficial. Celiac disease is associated with a reduction in hypertension and hyperlipidemia, whereas treatment with a GFD may lead to increased body mass index and obesity. Given the enormous increases in obesity-related morbidity and mortality, these phenomena have the potential to offset some or all of the unproven risks of undiagnosed silent celiac disease.

The 2004, the NIH Consensus Conference on Celiac Disease considered the question of whether or not to recommend screening for symptomless celiac disease and concluded: “At this time, there are insufficient data to recommend screening of the general population for celiac disease.” In my opinion, their conclusion still holds good today. In order to fill the main gap in our knowledge regarding the potential value of screening for celiac disease, we need to “conduct a cohort
case-finding is becoming accepted to increase detection, but will fail to uncover most cases. General population screening is feasible and will be required if we want to find most patients with celiac disease.

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study to determine the natural history of untreated celiac disease, especially ‘silent’ celiac disease.” On the other hand, I strongly endorse efforts to advance the early diagnosis of celiac disease, as this is a highly feasible and worthwhile goal.

Dr. Kelly is a scientific and clinical consultant for Alba and ImmusanT, and is a scientific advisory board member of Alba, Alvine and ImmusanT. He also received research support from Alba, Alvine, Shire, SQI Diagnostics and ImmusanT.

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