Mortality in Patients with Celiac Disease

Celiac disease is an autoimmune disorder triggered by ingestion of gluten-containing foods. Epidemiologic studies dating from the 1950s established its association with gastrointestinal malignancies, particularly small bowel lymphoma. Corrao et al. recently demonstrated that patients with celiac disease are at increased risk of mortality. Further, this risk is directly related to compliance with a gluten-free diet. Continued research is needed regarding the development of malignant complications related to celiac disease.

Key Words: celiac disease, autoimmune disorder, gluten, small-bowel lymphoma

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Celiac disease is an autoimmune enteropathy characterized by damage of the small bowel mucosa as a result of ingestion of gluten-containing foods. From its first report by Arataeus in the second century to the discovery of antiendomysial antibodies in the twenty-first century, much has been learned. The prevalence of celiac disease in the European population is estimated to be as high as 1:130–300. However, there may be a large subpopulation of patients with asymptomatic celiac disease who go unrecognized. Richard Logan suggested an iceberg model in 1991 to further conceptualize the prevalence of celiac disease. Most epidemiologic studies to date have only included the top of this iceberg with a vast number of patients remaining undiagnosed. These patients with silent celiac disease are important because of the association of celiac disease with gastrointestinal malignancies, particularly small bowel lymphoma. With the advent of reliable serologic tests in diagnosing celiac disease, further study regarding mortality in this population is needed. A recent study published in August 2001 by Corrao et al. followed patients with symptomatic and asymptomatic celiac disease.

In their study, Corrao et al. enrolled 1072 patients with biopsy-proven celiac disease between 1962 and 1994. In addition, both parents and siblings of patients with celiac disease were followed in a second arm of the study. Patients with celiac disease were subsequently categorized as severe, mild, or asymptomatic according to clinical presentation. Of note patients with mild or asymptomatic celiac disease accounted for 45% of the population. Data were collected over an accumulated 6444 patient-years of follow-up with mean follow-up of 6 years. Initial data included age at diagnosis, year of presentation, diagnostic delay, and pattern of presentation. Subsequent follow-up data of 862 patients included adherence to a gluten-free diet and vital status or date of death of first-degree relatives. For those patients who had died, date and cause of death were recorded. The authors then calculated the number of deaths expected in each patient cohort using the 5-year age group, sex, and calendar year, and multiplying by the corresponding death rate. They subsequently compared the observed death rate in each subgroup with the expected death rate and calculated a standardized mortality ratio (SMR).

Three important points follow from this study. First, this study confirms a twofold increase in overall mortality of all adult patients with celiac disease. There was a significant excess of deaths from malignant diseases, specifically small bowel lymphoma. Other causes of death included respiratory and digestive diseases. The reductions in relative survival ratios were noted within the first 3 years of diagnosis. Second, patients diagnosed with mild symptoms or by antibody screening did not show any statistically significant difference in mortality from the general population. This becomes important when screening for celiac disease. Finally, patients who did not report strict adherence to a gluten-free diet had a significant increase in mortality. This was noted in patients with both symptomatic and asymptomatic disease.

Corrao et al. found a statistically significant excess of death from malignant diseases; this is also echoed in other studies. Early series dating from 1937 identified an association of malignant diseases and celiac disease. Pricolo et al. in 1990 reviewed 82 patients with celiac disease complicated by malignancy. Lymphoma of the small intestine was the most commonly diagnosed neoplasm accounting for 72% of neoplasms. Adenocarcinoma of the small intestine was present in 14.6% of patients. Finally, squamous cell carcinoma of the esoph-
agus was present in 6.1% of patients. Gastrointestinal malignancies occurred in 67% of patients with prior diagnosis of celiac disease. Likewise, 33% of patients presented with concurrent diagnosis of celiac disease and malignancy.

Swinson et al. reviewed 235 patients with histologically proven celiac disease and associated malignancy. Of the confirmed 259 histologic malignancies, 51.4% were lymphoma. The majority of lymphomas, 79.8%, presented in the small intestine. Other malignancies included invasive small bowel adenocarcinoma and squamous carcinoma of the esophagus. Carcinoma in-situ affecting skin, cervix, and esophagus were also described. When compared with the general population, an excess of malignancies arose from the gastrointestinal tract (51.7% compared with expected 25%). These authors found the diagnosis of celiac disease preceded that of malignancy in 66.4% of cases. The mean interval between celiac disease and malignancy was 7.3 years.

Logan et al. reviewed 653 patients diagnosed with celiac disease in Edinburgh. Similar to the Corrao et al. study, they also found overall mortality to be 1.9 times that of the general population. Patients in this study were enrolled following histologic diagnosis of celiac disease. When a subject in the study died, the authors were notified as to cause of death. Mean follow-up was 13.5 years with a cumulative 8823 patient-years. Unlike the study by Corrao et al., this study included childhood diagnosis of celiac disease. Deaths from malignant disease accounted for 44 (38%) of observed deaths and were more common than expected with an SMR of 3.0. Lymphoproliferative disease and esophageal cancer accounted for the majority of these deaths. Forty-seven percent of deaths occurred within 5 years of diagnosis.

Nielsen et al. registered 100 patients with celiac disease in Denmark. Patients with histologic diagnosis of celiac disease were followed for 18 years. The 5-year survival rate was 88% and the 10-year survival rate was 68.5%. Their data demonstrated an SMR of 3.4 with 23 deaths occurring during this study. Four deaths were attributed to malignancy and nine were from causes unrelated to intestinal disease. Further, four additional patients developed a malignant complication by the time of analysis. The median time from diagnosis of celiac disease to development of malignant complications was 8.5 years.

Cottone et al. evaluated mortality and cause of death in southern Europe. A total of 228 patients were enrolled between 1980 and 1997. The mean follow-up was 73 months. Their data demonstrated an SMR of 3.8 with 12 deaths occurring during the study. The causes of death from malignancy included four intestinal lymphomas, one duodenal adenocarcinoma, and one case of histiocytic reticulosis. Six other patients had malignant diseases and were alive at the time of analysis. The 6-year survival curve was 94%. Again the increased mortality was mainly observed within 4 years of diagnosis.

As evidenced above, celiac disease is associated with an increased mortality risk, but does a gluten-free diet (GFD) decrease the risk of malignancies? Holmes et al. followed 210 patients with celiac disease and monitored their compliance with a GFD. They published two studies, one in 1976 and a follow-up in 1989. In their first study they found no evidence that compliance with a GFD is associated with a decreased risk of malignant complications. The same series was kept under surveillance after 11 years of further follow-up to assess the role of a GFD. Patients were divided into three groups based on compliance with a GFD. One hundred eight patients classified as having strict compliance reported following a GFD for at least 5 years. Those who reported less than 5-year compliance or none at all were grouped together for statistical analysis. Overall the risk of developing non-Hodgkin’s lymphoma, or cancer of the mouth, pharynx, and esophagus was twice that of the general population. The risk of cancer of all sites was not statistically increased for the strict compliance group. This risk was significantly increased in those taking a normal diet or reduced-gluten diet. Of these patients, excess cancers of the mouth, pharynx, and esophagus, as well as an excess of lymphoma were found. These results appear to support a protective role for a GFD with regard to celiac disease complicated by malignancy.

Finally, is celiac disease a premalignant condition? Cellier et al. studied patients with “refractory celiac disease” between 1974 and 1998 to further understand this question. Their findings suggest that abnormal intraepithelial lymphocytes (IEL) may be found in up to 75% of patients with symptoms of refractory celiac disease. Further, these IEL express intracellular CD3 but not CD8 and are associated with clonal rearrangements of the TCR [gamma] gene. The authors suggest that abnormal IEL may disseminate and progress to an overt malignant disorder secondary to a self-sustained inflammatory process. This process is likely due to repeated antigenic (gluten) intestinal stimulation. The cumulative evidence points to a continuum of autoimmune enteropathy progressing to a monoclonal malignant disorder. However, further research into this complex relationship is warranted.

It appears the recent study by Corrao et al. is consistent with previous literature. Celiac disease is associated with an overall increase in mortality. Compliance with a GFD appears to decrease this risk of malignant complications. In addition, Corrao et al. studied those patients with asymptomatic celiac disease and found them at no increased risk of malignant complications. Continued study is needed to determine the role of
Can Vitamin D Supplementation in Infancy Prevent Type 1 Diabetes?

Several recent European studies suggested that supplementing infants with vitamin D during their first year might prevent type 1 diabetes. A dose of 50 μg/day was associated with decreased diabetes risk in Finland, but the effectiveness of lower doses was not examined. The recommended dietary intake of vitamin D for U.S. infants is 5 μg/day and the tolerable upper level is 25 μg/day. There is no evidence that intakes between 5 and 25 μg/day would reduce diabetes incidence, but it would seem prudent to ensure that infants reach at least the lower end of this range.

Key Words: vitamin D, type 1 diabetes, infants

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Vitamin D is produced endogenously when the skin is exposed to sunlight and can be obtained exogenously from foods and supplements. Endogenous vitamin D production depends on the length of time spent outside, clothing and sunscreen, season of the year, and especially important, latitude. In northern areas including New England, Canada, and Northern Europe, little or no vitamin D is produced in the skin during winter months. This is not simply a result of reduced sunlight exposure, but of the different, less effective angle at which sunlight penetrates the atmosphere in the winter. Thus, although sunlight exposure is the principal source of vitamin D in free-living populations, it may not provide sufficient vitamin D, especially in winter, to prevent disease. Researchers have long known that vitamin D deficiency causes rickets in children and osteomalacia in adults. More recently, less pronounced vitamin D deficits have been associated with increased rates of bone loss and fracture; more limited evidence suggests that they may be associated with such diverse chronic conditions as hypertension, certain cancers, type 2 diabetes, and autoimmune disorders, including multiple sclerosis.

Because breast milk contains little vitamin D, infants are dependent on sunlight exposure and dietary or supplemental vitamin D to maintain adequate vitamin D stores. Infant formulas are fortified with vitamin D, but most of the other foods that contain vitamin D, notably fortified cows milk, fortified cereals, and some fish, are

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