Scientific References from,

"Dietary 'Fueling' and Endotoxin 'Initiating' Neurological Disorders"

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ABSTRACT
Neuromyelitis optica is a clinical syndrome characterised by acute transverse myelitis plus an acute or subacute optic neuritis with or without recovery. Although once believed to be a variant of multiple sclerosis, diagnostic criteria have recently been proposed for neuromyelitis optica, making it a clinically distinct syndrome. The term gluten sensitivity refers to a state of heightened immunological responsiveness to ingested gluten in genetically susceptible individuals, as indicated by circulating antibodies to gliadin. Several neurological complications have been described associated with gluten sensitivity ranging from peripheral neuropathy and cerebellar ataxia to an increased risk of epilepsy. Although myelopathy has been described in some case reports of coeliac disease, neuromyelitis optica has never been described in association with gluten sensitivity. We describe two cases of gluten sensitivity presenting as neuromyelitis optica with no previous history of significant gastrointestinal symptoms. Gluten sensitivity was confirmed by immunological and histological studies.


No Abstract Available

“Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains (including wheat, rye, and barley) in genetically susceptible persons. The disease is associated with HLA-DQ2 in 90 to 95 percent of cases and with HLA-DQ8 in 5 to 10 percent of cases and is self-perpetuating in the continued presence of gluten.1 It is the interplay between genes (both HLA and other types) and environment (i.e., gluten) that leads to the intestinal damage that is typical of the disease.2 Under physiologic circumstances, this interplay is prevented by competent intercellular tight junctions, structures that limit the passage of macromolecules . . .”


ABSTRACT

BACKGROUND:
Reports suggest that gluten sensitivity (GS) exists in the absence of coeliac disease (CD). This clinical entity has been termed noncoeliac gluten sensitivity (NCGS).
OBJECTIVES:
To determine the population prevalence of self-reported GS and referral characteristics to secondary care.

PATIENTS AND METHODS:
A UK population-based questionnaire screened for GS and related symptoms. Diagnostic outcomes were also analyzed in patients referred to secondary care with GS. CD diagnosis entailed a positive coeliac serology (endomysial and/or tissue transglutaminase antibodies) plus Marsh 1-3 on duodenal biopsies. NCGS diagnosis was based on exclusion of CD. Clinical comparisons were made between NCGS and CD.

RESULTS:
A total of 1002 adults in the population (female 55%, mean age 39 years). The self-reported prevalence for GS was 13% (female 79%, mean age 39.5 years, P<0.0001), with 3.7% consuming a gluten-free diet and 0.8% known to have a doctor diagnosis of CD. Individuals with GS had an increased prevalence of fulfilling the Rome III criteria for irritable bowel syndrome, in comparison with those without GS (20 vs. 3.89%, odds ratio 6.23, P<0.0001). In secondary care 200 GS patients (female 84%, mean age 39.6 years) were investigated, in whom 7% were found to have CD and 93% to have NCGS. All CD patients were human leucocyte antigen DQ2 or DQ8 positive compared with 53% of NCGS cases (P=0.0003). Nutritional deficiencies (P≤0.003), autoimmune disorders (23.1 vs. 9.7%, P=0.0001) and a lower mean BMI (23.7 vs. 25.8, P=0.001) were significantly associated with CD compared with NCGS.

CONCLUSION:
GS is commonly self-reported with symptoms suggesting an association with irritable bowel syndrome. The majority of patients have NCGS, an entity which demonstrates clinical and immunologic difference to CD.


ABSTRACT

GOALS:
To characterize the serological pattern of gluten sensitivity (GS) and to compare it with that found in celiac disease.

BACKGROUND:
GS has recently been identified as a new clinical entity included in the spectrum of gluten-related disorders, but it is still lacking of diagnostic markers.

STUDY:
Sera from 78 patients with GS and 80 patients with celiac disease were retrospectively assessed for immunoglobulin (Ig)G/IgA antigliadin antibodies (AGA), IgG deamidated gliadin peptide antibodies (DGP-AGA), IgA tissue transglutaminase antibodies (tTGA), and IgA endomysial antibodies (EmA).
RESULTS:
IgG AGA were positive in 56.4% of GS patients and in 81.2% of celiac patients, with high antibody titers in both groups. IgA AGA were detected in 7.7% of GS patients and in 75% of celiac patients, showing lower enzyme-linked immunosorbent assay activities in GS than those found in celiac disease. Only 1 of the 78 patients with GS was positive for IgG DGP-AGA (detected in 88.7% of patients with celiac disease). IgA tTGA and IgA EmA were negative in all GS patients, whereas their positivity in celiac patients was 98.7% and 95%, respectively. Patients with GS displayed a variegated clinical picture with intestinal and extraintestinal symptoms (abdominal pain, bloating, diarrhea, constipation, foggy mind, tiredness, eczema/skin rash, headache, joint/muscle pain, numbness of legs/arms, depression, and anemia) together with normal or mildly abnormal small intestinal mucosa.

CONCLUSIONS:
The serological pattern of GS is characterized by IgG AGA positivity in more than half of cases associated to IgA AGA in a few patients, but without EmA, tTGA, and DGP-AGA, which are the specific markers of celiac disease.


EXTRACT
From gut to brain
It has taken nearly 2000 years to appreciate that a common dietary protein introduced to the human diet relatively late in evolutionary terms (some 10 000 years ago), can produce human disease not only of the gut but also the skin and the nervous system. The protean neurological manifestations of gluten sensitivity can occur without gut involvement and neurologists must therefore become familiar with the common neurological presentations and means of diagnosis of this disease.

COELIAC DISEASE THROUGH THE AGES: FROM GUT TO SKIN
” . . .the stomach being the digestive organ, labours in digestion, when diarrhoea seizes the patient . . .and if in addition, the patient’s general system be debilitated by atrophy of the body, the coeliac disease of a chronic nature is formed”.
This extract is from the book on chronic diseases by Aretaeus the Cappadocian, one of the most distinguished ancient Greek doctors of the first century AD. This chapter, entitled “on the coeliac diathesis”, was the first description of coeliac disease (from the greek word κυλιακη meaning abdominal). Aretaeus' books were first published in Latin in 1500 and the new Latin word coeliac was used to translate κυλιακη. Coeliac disease (CD) remained obscure until 1887 when Samuel Gee gave a lecture entitled On the coeliac affection2 at the Hospital for Sick Children, Great Ormond Street, London. In it he acknowledged Aretaeus' contribution and went on to give an accurate description of CD based on his own clinical observations.
With clinical manifestations primarily confined to the gastrointestinal tract or attributable to malabsorption, it was logical to assume that the target organ and hence the key to the pathogenesis of this disease was the gut. The first report of neurological manifestations associated with CD was by Carnegie Brown in 1908. In his book entitled Sprue and its treatment.


ABSTRACT  
A 3-year-old girl presented with a hemorrhagic conjunctival lesion in the right eye. The medical history revealed premature cessation of breast feeding, intolerance to the ingestion of baby foods, anorexia, and abdominal distention. Prior to her referral, endoscopic small intestinal biopsy had been carried out under general anesthesia with a possible diagnosis of Celiac Disease (CD). Her parents did not want their child to undergo general anesthesia for the second time for the excisional biopsy. We decided to follow the patient until all systemic investigations were concluded. In evaluation, the case was diagnosed with CD and the conjunctival tumor showed complete regression during gluten-free dietary treatment. The clinical fleshy appearance of the lesion with spider-like vascular extensions and subconjunctival hemorrhagic spots, possible association with an acquired immune system dysfunction due to CD, and spontaneous regression by a gluten-free diet led us to make a presumed diagnosis of conjunctival Kaposi sarcoma.


ABSTRACT  
BACKGROUND:  
Although previous studies have shown increased mortality in patients with coeliac disease and their relatives, no data are available in relation to different patterns of clinical presentation. We assessed mortality in patients with coeliac disease and their first-degree relatives.

METHODS:  
We enrolled, in a prospective cohort study, 1072 adult patients with coeliac disease consecutively diagnosed in 11 gastroenterology units between 1962 and 1994, and their 3384 first-degree relatives. We compared the number of deaths up to 1998 with expected deaths and expressed the comparison as standardised mortality ratio (SMR) and relative survival ratio.
FINDINGS:
53 coeliac patients died compared with 25.9 expected deaths (SMR 2.0 [95% CI 1.5-2.7]). A significant excess of mortality was evident during the first 3 years after diagnosis of coeliac disease and in patients who presented with malabsorption symptoms (2.5 [1.8-3.4]), but not in those diagnosed because of minor symptoms (1.1 [0.5-2.2]) or because of antibody screening (1.2 [0.1-7.0]). SMR increased with increasing delay in diagnosis and for patients with poor compliance with gluten-free diet. Non-Hodgkin lymphoma was the main cause of death. No excess of deaths was recorded in relatives with coeliac disease.

INTERPRETATION:
Prompt and strict dietary treatment decreases mortality in coeliac patients. Prospective studies are needed to clarify the progression of mild or symptomless coeliac disease and its relation to intestinal lymphoma.


ABSTRACT
Celiac disease (CD) is a syndrome characterized by damage of the small intestinal mucosa caused by the gliadin fraction of wheat gluten and similar alcohol-soluble proteins (prolamines) of barley and rye in genetically susceptible subjects. The presence of gluten in these subjects leads to self-perpetuating mucosal damage, whereas elimination of gluten results in full mucosal recovery. The clinical manifestations of CD are protean in nature and vary markedly with the age of the patient, the duration and extent of disease, and the presence of extraintestinal pathologic conditions. In addition to the classical gastrointestinal form, a variety of other clinical manifestations of the disease have been described, including atypical and asymptomatic forms. Therefore, diagnosis of CD is extremely challenging and relies on a sensitive and specific algorithm that allows the identification of different manifestations of the disease. Serologic tests developed in the last decade provide a noninvasive tool to screen both individuals at risk for the disease and the general population. However, the current gold standard for the diagnosis of CD remains histologic confirmation of the intestinal damage in serologically positive individuals. The keystone treatment of CD patients is a lifelong elimination diet in which food products containing gluten are avoided.


ABSTRACT
BACKGROUND:
Patients with celiac disease have an increased risk of death from gastrointestinal malignancies and lymphomas, but little is known about mortality from other causes and few studies have assessed long-term outcomes.
METHODS:
Nationwide data on 10 032 Swedish patients hospitalized from January 1, 1964, through December 31, 1993, with celiac disease and surviving at least 12 months were linked with the national mortality register. Mortality risks were computed as standardized mortality ratios (SMRs), comparing mortality rates of patients with celiac disease with rates in the general Swedish population.

RESULTS:
A total of 828 patients with celiac disease died during the follow-up period (1965-1994). For all causes of death combined, mortality risks were significantly elevated: 2.0-fold (95% confidence interval [CI], 1.8-2.1) among all patients with celiac disease and 1.4-fold (95% CI, 1.2-1.6) among patients with celiac disease with no other discharge diagnoses at initial hospitalization. The overall SMR did not differ by sex or calendar year of initial hospitalization, whereas mortality risk in patients hospitalized with celiac disease before the age of 2 years was significantly lower by 60% (95% CI, 0.2-0.8) compared with the same age group of the general population. Mortality risks were elevated for a wide array of diseases, including non-Hodgkin lymphoma (SMR, 11.4), cancer of the small intestine (SMR, 17.3), autoimmune diseases (including rheumatoid arthritis [SMR, 7.3] and diffuse diseases of connective tissue [SMR, 17.0]), allergic disorders (such as asthma [SMR, 2.8]), inflammatory bowel diseases (including ulcerative colitis and Crohn disease [SMR, 70.9]), diabetes mellitus (SMR, 3.0), disorders of immune deficiency (SMR, 20.9), tuberculosis (SMR, 5.9), pneumonia (SMR, 2.9), and nephritis (SMR, 5.4).

CONCLUSION:
The elevated mortality risk for all causes of death combined reflected, for the most part, disorders characterized by immune dysfunction.


ABSTRACT

BACKGROUND:
Several skin disorders are present in patients affected by coeliac disease (CD) - among them, psoriasis has been described. However, at present the relationship between CD and psoriasis remains controversial since there are few and contrasting data on this topic.

METHOD:
Here we describe a case of psoriasis in a CD patient not responding to specific therapies for psoriasis.

RESULT:
The regression of skin lesions after gluten-free diet (GFD) was evident in a short time.
CONCLUSION:
The present case supports the association between CD and psoriasis and the concept that psoriasis in CD patients can be improved by GFD. Future studies are needed to clarify the possible mechanisms involved in this association.


ABSTRACT

BACKGROUND AND AIM:
Individuals with coeliac disease have increased risk of depression and death from external causes, but conclusive studies on death from suicide are missing. We examined the risk of suicide in coeliac disease and amongst individuals where the small intestinal biopsy showed no villous atrophy.

METHODS:
We collected biopsy data from all 28 clinical pathology departments in Sweden for individuals diagnosed during 1969-2007 with coeliac disease (Marsh 3: villous atrophy; n=29,083 unique individuals), inflammation without villous atrophy (Marsh 1-2; n=13,263) or positive coeliac disease serology but normal mucosa (Marsh 0, n=3719). Through Cox regression we calculated Hazard ratios for suicide as recorded in the Swedish Cause of Death Register.

RESULTS:
The risk for suicide was higher in patients with coeliac disease compared to general population controls (HR=1.55; 95%CI=1.15-2.10; based on 54 completed suicides). Whilst suicide was also more common amongst individuals with inflammation (HR=1.96; 95%CI=1.39-2.77), no such increase was seen amongst individuals with a normal mucosa but positive coeliac disease serology (HR=1.06; 95%CI=0.37-3.02).

CONCLUSIONS:
We found a moderately increased risk of suicide amongst patients with coeliac disease. This merits increased attention amongst physicians treating these patients.


ABSTRACT

INTRODUCTION:
To explore whether the excess mortality in celiac disease is related directly to the disease and duration of gluten exposure before diagnosis we have examined the long-term mortality experience of people with celiac disease diagnosed as children and as adults.
METHODS:
Two hundred eighty-five children and 340 adults diagnosed with celiac disease were followed until death, loss to follow-up, or December 31, 2004. We calculated standardized mortality ratios (SMRs).

RESULTS:
All-cause mortality more than 5 yr after diagnosis was increased threefold in children (SMR 3.32, 95% CI 2.05-5.07) compared with only a 38% increase in adults (SMR 1.38, 95% CI 1.16-1.63). This excess mortality in children was primarily because of an increased risk of death from accidents, suicide, and violence (seven deaths, SMR 3.22, 95% CI 1.29-6.63), cancer (five deaths, SMR 3.72, 95% CI 1.21-8.67), and cerebrovascular disease (two deaths, SMR 10.03, 95% CI 1.21-36.00).

CONCLUSIONS:
Children diagnosed with celiac disease had a threefold increased risk of long-term mortality. This is in marked contrast to the experience of adult celiac disease where the long-term increase of mortality was modest. The increased mortality in children from external causes may reflect behavioral change associated with coping with a chronic disease and its treatment.


ABSTRACT

BACKGROUND & AIMS:
The historical prevalence and long-term outcome of undiagnosed celiac disease (CD) are unknown. We investigated the long-term outcome of undiagnosed CD and whether the prevalence of undiagnosed CD has changed during the past 50 years.

METHODS:
This study included 9133 healthy young adults at Warren Air Force Base (sera were collected between 1948 and 1954) and 12,768 gender-matched subjects from 2 recent cohorts from Olmsted County, Minnesota, with either similar years of birth (n = 5558) or age at sampling (n = 7210) to that of the Air Force cohort. Sera were tested for tissue transglutaminase and, if abnormal, for endomysial antibodies. Survival was measured during a follow-up period of 45 years in the Air Force cohort. The prevalence of undiagnosed CD between the Air Force cohort and recent cohorts was compared.

RESULTS:
Of 9133 persons from the Air Force cohort, 14 (0.2%) had undiagnosed CD. In this cohort, during 45 years of follow-up, all-cause mortality was greater in persons with undiagnosed CD than among those who were seronegative (hazard ratio = 3.9; 95% confidence interval, 2.0-7.5; P < .001). Undiagnosed CD was found in 68 (0.9%) persons with similar age at sampling and 46 (0.8%) persons with similar years of birth. The rate of undiagnosed CD was 4.5-fold and 4-fold greater in the recent cohorts, respectively, than in the Air Force cohort (both P < or = .0001).
CONCLUSIONS:
During 45 years of follow-up, undiagnosed CD was associated with a nearly 4-fold increased risk of death. The prevalence of undiagnosed CD seems to have increased dramatically in the United States during the past 50 years.


ABSTRACT

Context:
Studies of mortality in celiac disease have not taken small-intestinal pathology into account.

Objective:
To examine mortality in celiac disease according to small-intestinal histopathology.

Design, Setting, and Patients:
Retrospective cohort study. We collected data from duodenal/jejunal biopsies taken between July 1969 and February 2008 on celiac disease (Marsh stage 3: villous atrophy; n = 29 096 individuals) and inflammation (Marsh stage 1-2; n = 13 306) from all 28 pathology departments in Sweden. A third cohort consisted of individuals with latent celiac disease from 8 university hospitals (n = 3719). Latent celiac disease was defined as positive celiac disease serology in individuals with normal mucosa (Marsh stage 0). Through linkage with the Swedish Total Population Register, we estimated the risk of death through August 31, 2008, compared with age- and sex-matched controls from the general population.

Main Outcome Measure:
All-cause mortality.

Results:
There were 3049 deaths among patients with celiac disease, 2967 with inflammation, and 183 with latent celiac disease. We found an increased hazard ratio (HR) for death in celiac disease (HR, 1.39; 95% confidence interval [CI], 1.33-1.45; median follow-up, 8.8 years), inflammation (HR, 1.72; 95% CI, 1.64-1.79; median follow-up, 7.2 years), and latent celiac disease (HR, 1.35; 95% CI, 1.14-1.58; median follow-up, 6.7 years). The absolute mortality rate was 10.4 (95% CI, 10.0-10.8) per 1000 person-years in celiac disease, 25.9 (95% CI, 25.0-26.8) in inflammation, and 6.7 (95% CI, 5.7-7.6) in latent celiac disease. Excess mortality was 2.9 per 1000 person-years in celiac disease, 10.8 in inflammation, and 1.7 in latent celiac disease. This risk increase was also seen in children. Excluding the first year of follow-up, HRs decreased somewhat.

Conclusion:
Risk of death among patients with celiac disease, inflammation, or latent celiac disease is modestly increased.
Celiac disease is an immune-mediated disorder that is triggered by gluten exposure in genetically sensitive individuals, occurring in about 1% of the Western population.
With few exceptions, research has shown an increased risk of death in celiac disease and in individuals with positive antiendomysial antibodies (EMA) or either EMA or antigliadin. However, several studies were not population-based or were limited by their focus on inpatients, less than 1000 individuals with celiac disease, or lack of inclusion of children.

The introduction of celiac disease serological markers has allowed screening of individuals with less marked symptoms; it is therefore possible that earlier studies (based on data until 2000) overestimate the risk of death in celiac disease.

While villous atrophy is usually required for the diagnosis of celiac disease, less is known about the long-term consequences of nonspecific small-intestinal inflammation without villous atrophy. Research on other inflammatory disorders suggests that inflammation may be associated with increased mortality, but this has not been investigated for nonspecific inflammation in the small intestine.

Some individuals have positive antibodies but normal small-intestinal mucosa, often referred to as having "latent" celiac disease. Although villous atrophy in small-intestinal biopsy has been the gold standard for a celiac disease diagnosis, it has been argued that small-intestinal biopsy can, under certain circumstances, be replaced by celiac disease serology. Positive celiac disease serology has been linked to increased mortality; however, the predictive value and long-term consequences of celiac disease serology in individuals with normal mucosa are unknown.

We used nationwide histopathology data to examine the overall risk of death in individuals with celiac disease and inflammation. Through regional data linkage, we were also able to examine mortality in latent celiac disease.

RESULTS:
A total of 13,338 people had an endomysial antibody and/or an anti-gliadin antibody test in Northern Ireland between 1993 and 1996. There were 490 patients who tested positive for endomysial antibodies and they were assumed to have coeliac disease. There were 1133 patients who tested positive for anti-gliadin antibodies and they were defined as gluten sensitive. Malignant neoplasms were not significantly associated with coeliac disease; however, all-cause mortality was significantly increased following diagnosis. The standardized incidence and mortality ratios for non-Hodgkin's lymphoma were increased in coeliac disease patients but did not reach statistical significance. Lung and breast cancer incidence were significantly lower and all-cause mortality, mortality from malignant neoplasms, non-Hodgkin's lymphoma and digestive system disorders were significantly higher in gluten sensitive patients compared to the Northern Ireland population.

CONCLUSION:
Patients with coeliac disease or gluten sensitivity had higher mortality rates than the Northern Ireland population. This association persists more than one year after diagnosis in patients testing positive for anti-gliadin antibodies. Breast cancer is significantly reduced in the cohort of patients with gluten sensitivity.


ABSTRACT
A 4-year-old boy presented with a history of tremor for 7 days. He also had recurrent diarrhea for the previous 1 year, and poor weight gain. Magnetic resonance of the brain was suggestive of central pontine myelinolysis. There was no evidence of electrolyte abnormalities. The serum tissue transglutaminase level was markedly elevated, and the duodenal biopsy revealed features of celiac disease. The patient was started on gluten-free diet. The tremor resolved within 3 months. Repeat imaging of the brain done 3 months after starting gluten-free diet showed complete resolution of the lesion. This case highlights the unusual presentation of central pontine myelinosisis as tremor in a malnourished child with celiac disease.


ABSTRACT
BACKGROUND:
The objective of this study was to compare celiac disease (CD)- specific antibody tests to determine if they could replace jejunal biopsy in patients with a high pretest probability of CD.
METHODS:
This retrospective study included sera from 149 CD patients and 119 controls, all with intestinal biopsy. All samples were analyzed for IgA and IgG antibodies against native gliadin (ngli) and deamidated gliadin peptides (dpgli), as well as for IgA antibodies against tissue transglutaminase and endomysium.

RESULTS:
Tests for dpgli were superior to ngli for IgG antibody determination: 68% vs. 92% specificity and 79% vs. 85% sensitivity for ngli and dpgli, respectively. Positive (76% vs. 93%) and negative (72% vs. 83%) predictive values were also higher for dpgli than for ngli. Regarding IgA gliadin antibody determination, sensitivity improved from 61% to 78% with dpgli, while specificity and positive predictive value remained at 97% (P < 0.00001). A combination of four tests (IgA anti-dpgli, IgG anti-dpgli, IgA anti- tissue transglutaminase, and IgA anti-endomysium) yielded positive and negative predictive values of 99% and 100%, respectively and a likelihood ratio positive of 86 with a likelihood ratio negative of 0.00. Omitting the endomysium antibody determination still yielded positive and negative predictive values of 99% and 98%, respectively and a likelihood ratio positive of 87 with a likelihood ratio negative of 0.01.

CONCLUSION:
Antibody tests for dpgli yielded superior results compared with ngli. A combination of three or four antibody tests including IgA anti-tissue transglutaminase and/or IgA anti- endomysium permitted diagnosis or exclusion of CD without intestinal biopsy in a high proportion of patients (78%). Jejunal biopsy would be necessary in patients with discordant antibody results (22%). With this two-step procedure, only patients with no CD-specific antibodies would be missed.


ABSTRACT
Forty five women and 10 men with coeliac disease diagnosed in adult life, who were already on a gluten free diet, had serial bone mineral density measurements at the lumbar spine and femoral neck over 12 months. Osteoporosis, defined as a bone mineral density (BMD) < or = 2 SD below the normal peak bone mass was found in 50% of male and 47% of female coeliac patients. Patients with a BMD < or = 2 SD below age and sex matched normal subjects, had a significantly lower body mass index (21.3 kg.m-2 compared with 25.2 kg.m-2, p < 0.02 Wilcoxon rank sum test) and lower average daily calcium intake (860 mg/day compared with 1054 mg/day, p < 0.05 Wilcoxon rank sum test) than patients with normal bone mineral density. In postmenopausal women with coeliac disease there was a strong correlation between the age at menopause and BMD at both the lumbar spine (r = 0.681, p < 0.01, Spearman's rank correlation) and femoral neck (r = 0.632, p < 0.01). No overall loss of bone was shown over the 12 months of follow up, and relative to the reference population there was a significant improvement in BMD at the lumbar spine in women (p < 0.025, paired t test) and at the femoral neck in men (p < 0.05, paired t test). There was a significant negative correlation between the annual percentage change in BMD at the lumbar spine and the duration of gluten free diet (r = -0.429, p<0.01, Spearman's rank correlation), with the largest gain in BMD in patients with most recently diagnosed coeliac disease. Osteoporosis was
shown in 47% of patients with treated adult coeliac disease. Recognised risk factors for osteoporosis in the general population including low body mass index, dietary calcium intake, and early menopause are particularly important in coeliac disease. Treatment of coeliac disease with a gluten free diet probably protects against further bone loss, and in the early stages is associated with a gain in bone mineral density.


ABSTRACT

BACKGROUND AND OBJECTIVE:
Celiac disease (CD) is believed to be a permanent intolerance to gluten. A number of patients, however, discontinue the gluten-free diet (GFD) without developing symptoms or signs. The aim of our study was to investigate whether CD patients are capable of developing tolerance to gluten.

METHODS:
All 77 adult patients from our hospital known to have biopsy-proven CD for more than 10 years were invited to participate. We investigated symptoms, gluten consumption, antibodies for CD and other autoimmunity, human leukocyte antigen (HLA)-typing, bone mineral density, and performed small bowel biopsies. Tolerance was defined as no immunological or histological signs of CD while consuming gluten.

RESULTS:
Sixty-six patients accepted participation, but after review of the diagnostic biopsies 53 were found to have true CD. Twenty-three percent of patients had a gluten-containing diet, 15% admitted gluten transgression and 62% followed the GFD. Patients on a GFD had significantly more osteoporosis. Normal small bowel mucosa was found in four of eight on gluten-containing diet and in four of four with gluten transgression. Two patients were considered to have developed tolerance to gluten. One of them was HLA-DQ2/DQ8 negative.

CONCLUSION:
Development of tolerance to gluten seems possible in some patients with CD. Further follow-up will show whether this tolerance is permanent or only a long-term return to latency. This feature may be associated with genetic characteristics, especially with HLA genotypes that differ from DQ2 or DQ8. More insight into the mechanisms of the development of gluten tolerance may help to distinguish those CD patients that might not require life-long GFD.
ABSTRACT

BMD is a primary predictor of osteoporotic fracture, and its genetic determination is still unclear. This study showed that the correlation between BMD at different skeletal sites is caused by an underlying genetic structure of common genetic effects. In addition to possible shared (pleiotropic) genetic and environmental effects, each of the BMD variables may also be determined by site-specific genetic factors.

INTRODUCTION:
BMD is a primary predictor of osteoporotic fracture and a key phenotype for the genetic study of osteoporosis. The interindividual variation in BMD measured at a given skeletal site is largely regulated by genetic factors. A strong phenotypic covariation exists for BMD at different skeletal sites. This study tests the hypothesis that the covariation is in fact caused by an underlying genetic structure of common genetic effects and that, in addition to possible shared (pleiotropic) genetic effects, each of the BMD variables may also be determined by site-specific genetic factors.

MATERIALS AND METHODS:
A bivariate complex segregation analysis as implemented in statistical package PAP was conducted to explore various models of pleiotropic genetic and environmental transmission in lumbar spine and femoral neck BMD, as well as in compact and spongious segments of hand phalanges. The BMD was obtained in three ethnically, culturally, and socially heterogeneous samples of white pedigrees, with 2549 individuals between 18 and 100 years of age, from Australia, Europe, and North America.

RESULTS AND CONCLUSIONS:
The genetic correlation between BMD measures ranged between 0.50 +/- 0.09 and 0.79 +/- 0.04 in the three samples. In each sample, the model incorporated a major locus pleiotropic effect, and residual correlation was found to be the most parsimonious model. Estimated parameters from the model indicated a significant pleiotropic major gene effect on both lumbar spine and femoral neck BMD, with the existence of a significant residual correlation (0.51 +/- 0.07 to 0.66 +/- 0.04). These results suggest that the covariation in BMD at different skeletal sites, and between mostly compact versus mostly trabecular bone, was largely determined by common genetic factors that are pleiotropic or in close linkage and linkage disequilibrium, while at the same time, exhibiting considerable evidence of shared environmental effects. The results, for the first time, suggest that the possibility of pleiotropic genetic effect may be controlled by a major genetic locus. Identification of the major locus could open new opportunity to understanding the liability and pathogenic processes in which they are involved in the determination of fracture risk.

ABSTRACT

BACKGROUND:
Non-celiac gluten sensitivity (NCGS) or 'wheat sensitivity' (NCWS) is included in the spectrum of gluten-related disorders. No data are available on the prevalence of low bone mass density (BMD) in NCWS. Our study aims to evaluate the prevalence of low BMD in NCWS patients and search for correlations with other clinical characteristics.

METHODS:
This prospective observation study included 75 NCWS patients (63 women; median age 36 years) with irritable bowel syndrome (IBS)-like symptoms, 65 IBS and 50 celiac controls. Patients were recruited at two Internal Medicine Departments. Elimination diet and double-blind placebo controlled (DBPC) wheat challenge proved the NCWS diagnosis. All subjects underwent BMD assessment by Dual Energy X-Ray Absorptiometry (DXA), duodenal histology, HLA DQ typing, body mass index (BMI) evaluation and assessment for daily calcium intake.

RESULTS:
DBPC cow's milk proteins challenge showed that 30 of the 75 NCWS patients suffered from multiple food sensitivity. Osteopenia and osteoporosis frequency increased from IBS to NCWS and to celiac disease (CD) (P <0.0001). Thirty-five NCWS patients (46.6%) showed osteopenia or osteoporosis. Low BMD was related to low BMI and multiple food sensitivity. Values of daily dietary calcium intake in NCWS patients were significantly lower than in IBS controls.

CONCLUSIONS:
An elevated frequency of bone mass loss in NCWS patients was found; this was related to low BMI and was more frequent in patients with NCWS associated with other food sensitivity. A low daily intake of dietary calcium was observed in patients with NCWS.


ABSTRACT

Background:
There is an increased prevalence of osteoporosis among patients with celiac disease. However, the relative prevalence of celiac disease among osteoporotic and nonosteoporotic populations is not known, and the benefit of screening the osteoporotic population for celiac disease remains controversial.

Methods:
We evaluated 840 individuals, 266 with and 574 without osteoporosis, from the Washington University Bone Clinic by serologic screening for celiac disease. Individuals with positive serologic test results for antitissue transglutaminase or antiendomysial antibody were offered endoscopic intestinal biopsy to confirm the diagnosis of celiac disease. Individuals with biopsy-proven celiac disease were treated with a gluten-free diet and followed up for improvement in bone mineral density.

Results:
Twelve (4.5%) of 266 patients with osteoporosis and 6 (1.0%) of 574 patients without osteoporosis tested positive by serologic screening for celiac disease. All but 2 serologically positive individuals underwent intestinal biopsy. Nine osteoporotic patients and 1 nonosteoporotic patient had positive biopsy results. The prevalence of biopsy-proven celiac disease was 3.4% among the osteoporotic population and 0.2% among the nonosteoporotic population. All biopsy-positive individuals tested positive by antitissue transglutaminase and antiendomysial antibody. The antitissue transglutaminase levels correlated with the severity of osteoporosis as measured by T score, demonstrating that the more severe the celiac disease the more severe the resulting osteoporosis. Treatment of the patients with celiac disease with a gluten-free diet resulted in marked improvement in T scores.

Conclusions:
The prevalence of celiac disease among osteoporotic individuals (3.4%) is much higher than that among nonosteoporotic individuals (0.2%). The prevalence of celiac disease in osteoporosis is high enough to justify a recommendation for serologic screening of all patients with osteoporosis for celiac disease.

Celiac disease is an antigen-driven enteropathy of the small intestine, resulting from an inappropriate immune response to dietary gliadin, a component of wheat proteins.1 Celiac disease can have a varied clinical presentation, with most symptoms being attributed to malabsorption.2,3 The discovery of tissue transglutaminase as the predominant autoantigen of celiac disease allowed for the development of standardized and quantitative serologic screening tests.4 These tests have facilitated the widespread screening of asymptomatic individuals and have altered our perception of the incidence of celiac disease. However, despite the observation that celiac disease is much more common than previously appreciated, and despite the availability of serologic tests for screening, we still do not know which groups of individuals will most benefit from screening for celiac disease.

Adults with newly diagnosed celiac disease have a low bone mineral density (BMD), and treatment of these individuals with a gluten-free diet increases their BMD.5- 8 However, studies9- 12 screening asymptomatic osteoporotic individuals for the presence of celiac disease have yielded conflicting results. Given these results, current practice for the workup of postmenopausal women presenting with osteoporosis does not include serologic screening for the presence of celiac disease. In an attempt to resolve these issues, we performed a large prospective screening trial for the presence of celiac disease in osteoporotic and nonosteoporotic individuals.

ABSTRACT

OBJECTIVES:
In patients with celiac disease, enteropathy is caused by the entry of gluten peptides into the lamina propria of the intestine, in which their immunogenicity is potentiated by tissue transglutaminase (tTG) and T-helper type 1-mediated immune responses are triggered. Tight junction disassembly and paracellular permeability are believed to have an important role in the transport of gluten peptides to the lamina propria. Larazotide acetate is a tight-junction regulator peptide that, in vitro, prevents the opening of intestinal epithelial tight junctions. The aim of this study was to evaluate the efficacy and tolerability of larazotide acetate in protecting against gluten-induced intestinal permeability and gastrointestinal symptom severity in patients with celiac disease.

METHODS:
In this dose-ranging, placebo-controlled study, 86 patients with celiac disease controlled through diet were randomly assigned to larazotide acetate (0.25, 1, 4, or 8 mg) or placebo three times per day with or without gluten challenge (2.4 g/day) for 14 days. The primary efficacy outcome was the urinary lactulose/mannitol (LAMA) fractional excretion ratio. Secondary endpoints included gastrointestinal symptom severity, quality-of-life measures, and antibodies to tTG.

RESULTS:
LAMA measurements were highly variable in the outpatient setting. The increase in LAMA ratio associated with the gluten challenge was not statistically significantly greater than the increase in the gluten-free control. Among patients receiving the gluten challenge, the difference in the LAMA ratios for the larazotide acetate and placebo groups was not statistically significant. However, larazotide acetate appeared to limit gluten-induced worsening of gastrointestinal symptom severity as measured by the Gastrointestinal Symptom Rating Scale at some lower doses but not at the higher dose. Symptoms worsened significantly in the gluten challenge-placebo arm compared with the placebo-placebo arm, suggesting that 2.4 g of gluten per day is sufficient to induce reproducible gluten toxicity. Larazotide acetate was generally well tolerated. No serious adverse events were observed. The most common adverse events were headache and urinary tract infection.

CONCLUSIONS:
LAMA variability in the outpatient setting precluded accurate assessment of the effect of larazotide acetate on intestinal permeability. However, some lower doses of larazotide acetate appeared to prevent the increase in gastrointestinal symptom severity induced by gluten challenge.


ABSTRACT

OBJECTIVES:
In celiac disease, complete histological normalization of the small-intestinal mucosa occurs in only 8-20% of adult patients after commencing a gluten-free diet. Intraepithelial lymphocytosis may
persist for years while villous morphology normalizes. Factors contributing to this and the clinical relevance of persistent intraepithelial lymphocytosis were here investigated.

METHODS:
Altogether 177 adult celiac disease patients adhering to a long-term strict gluten-free diet were enrolled. Co-morbidities, ongoing medications, and consumption of oats and wheat-starch were recorded. Small-bowel morphology and intraepithelial lymphocyte count as well as laboratory parameters of malabsorption were evaluated. Gastrointestinal symptoms and psychological well-being were measured by structured questionnaires.

RESULTS:
In all, 170 (96%) out of the 177 patients evinced normal villous architecture and 7 (4%) villous atrophy. Among patients with normal villous structure, 96 (56%) had persistent intraepithelial lymphocytosis and 74 (44%) completely normal small-intestinal mucosa. Consumption of oats was the only factor contributing to the persistent intraepithelial lymphocytosis. Co-morbidities, Helicobacter pylori gastritis, drugs, or wheat-starch in the diet had no effect. The clinical outcome of the patients with persistent intraepithelial lymphocytosis was good, since no signs of malabsorption, excess malignancies, increase in gastrointestinal symptoms, or impaired quality of life were associated with it when compared to subjects with completely normal mucosa. The only outcome found in this study was a significantly lower, although normal villous height-crypt depth ratio among the patients with persistent intraepithelial lymphocytosis as compared to those with completely normal mucosa.

CONCLUSIONS:
Despite excellent villous recovery in this study, persistent intraepithelial lymphocytosis was still common among celiac disease patients on a long-term strict gluten-free diet. Consumption of oats was associated with persistent duodenal lymphocytosis and this calls for further investigations. The prognosis of patients with persistent intraepithelial lymphocytosis seems to be good while adhering to a gluten-free diet for a mean of 11 years.


ABSTRACT

BACKGROUND:
Expected benefits of gluten-free diet (GFD) in coeliac patients include healing of small intestinal mucosa, but it remains unclear to what extent this benefit is achieved in adults.

AIM:
To assess factors affecting histological outcome of GFD in a large cohort of adult coeliac patients.

METHODS:
We extracted information on 465 consecutive coeliac patients studied before and during GFD.
RESULTS:
Duodenal biopsies at diagnosis were classified as Marsh I in 11, II in 25 and III in 429 cases. After a median 16 months GFD, 38 (8%) patients had histological 'normalization', 300 (65%) had 'remission' with persistent intraepithelial lymphocytosis, 121(26%) had 'no change' and 6 (1%) had 'deterioration'. Coeliac disease related serology was negative in 83% of patients with Marsh III lesion during GFD. Male gender and adherence to GFD were independently associated with histological 'normalization' and 'remission'. Persistence of intraepithelial lymphocytosis was not associated with human lymphocyte antigen gene dose or with Helicobacter pylori infection.

CONCLUSIONS:
Complete normalization of duodenal lesions is exceptionally rare in adult coeliac patients despite adherence to GFD, symptoms disappearance and negative CD related serology. Control biopsies are mandatory to identify lack of response to gluten-free diet.


ABSTRACT
The author examined 41 children, suffering from celiac disease with psychiatric methods and EEG. The children, aged 7-17 y., were many years on gluten-free diets. Various psychiatric symptoms were found in 48.8%, and EEG abnormalities in 70.7%. Only 9 children (21.9%) were free from any psychiatric disorders and EEG abnormalities.


ABSTRACT
OBJECTIVES:
To estimate the rate of celiac disease diagnosis and evaluate the economic benefits of diagnosis by analyzing retrospective cohorts from a national managed-care-population database.

METHODS:
We identified patients who received a new diagnosis of celiac disease. We also identified 3 control groups, persons without a diagnosis of celiac disease but who exhibited 1, 2, or 3 or more symptoms associated with the disease. Using claims, encounter, and eligibility data of approximately 10.2 million managed care members across the United States between January 1999 and December 2003, we measured and compared direct standardized relative value based (RVU) medical costs and utilization of selected health care services among the 4 study cohorts.
RESULTS:
The rate of new diagnosis for celiac disease more than doubled over the 4-year period. The celiac disease cohort had a significant trend reduction in direct standardized medical costs relative to the three control groups. RVU-based medical costs in the celiac cohort were 24%, 33%, and 27% lower than cohort 1 (p<0.05), 29.0%, 38%, and 24% lower than cohort 2 (p<0.05), and 38%, 33%, and 31% lower than cohort 3 (p<0.01) for the 12-month, 24-month and 36-month post-diagnosis periods, respectively. The reductions in costs were attributable to decreasing trends in utilization of office visits, lab, diagnostic, imaging, and endoscopy procedures relative to the 3 comparative cohorts over the 3-year follow-up period.

CONCLUSIONS:
There was an increase in the rate of celiac disease diagnosis, which was associated with significant reduction in direct standardized RVU-based medical costs and utilization of selected health care services over time.


No ABSTRACT Available

“SOMETHING YOU’RE EATING may be killing you, and you probably don’t even know it! If you eat cheeseburgers or French fries all the time or drink six sodas a day, you likely know you are shortening your life. But eating a nice dark, crunchy slice of whole wheat bread—how could that be bad for you? Well, bread contains gluten, a protein found in wheat, barley, rye, spelt, kamut, and oats. It is hidden in pizza, pasta, bread, wraps, rolls, and most processed foods. Clearly, gluten is a staple of the American diet. What most people don’t know is that gluten can cause serious health complications for many. You may be at risk even if you don’t have full blown celiac disease. I want to reveal the truth about gluten, explain the dangers, and provide you with a simple system that will help you determine whether or not gluten is a problem for you…”


ABSTRACT
A large national investigation into the extent of gluten cross-contamination of naturally gluten-free ingredients (flours and starches) sold in Canada was performed. Samples (n = 640) were purchased from eight Canadian cities and via the internet during the period 2010-2012 and analysed for gluten contamination. The results showed that 61 of the 640 (9.5%) samples were contaminated above the Codex-recommended maximum level for gluten-free products (20 mg kg⁻¹) with a range of 5-7995 mg kg⁻¹. For the ingredients that were labelled gluten-free the contamination range (5-141 mg kg⁻¹) and number of samples were lower (3 of 268). This picture was consistent over time, with approximately the same percentage of samples above 20 mg kg⁻¹ in both the initial set and
the subsequent lot. Looking at the total mean (composite) contamination for specific ingredients the largest and most consistent contaminations come from higher fibre ingredients such as soy (902 mg kg\(^{-1}\)), millet (272 mg kg\(^{-1}\)) and buckwheat (153 mg kg\(^{-1}\)). Of the naturally gluten-free flours and starches tested that do not contain a gluten-free label, the higher fibre ingredients would constitute the greatest probability of being contaminated with gluten above 20 mg kg\(^{-1}\).


ABSTRACT

Many gluten-free (GF) food choices are now available in supermarkets. However, the unintentional presence of gluten in these foods poses a serious health risk to wheat-allergic and celiac patients. Different GF labelled foods (275) and non-GF labelled foods, without wheat/rye/barley on the ingredient label (186), were analysed for gluten content by two different enzyme linked immunosorbent assay (ELISA) kits. Considering the gluten threshold of 20ppm, GF labelled foods had 98.9% GF labelling compliance with 1.1% (3 out of 275) of foods being mislabelled/misbranded. Among the non-GF labelled foods, 19.4% (36 out of 186) of foods had >20ppm of gluten, as measured by at least one ELISA kit, of which 19 foods had >100ppm of gluten. The presence of oats in non-GF labelled foods was strongly correlated with a positive ELISA result. Gluten was also found in a significant number of foods with gluten/wheat-related advisory warnings.


ABSTRACT]

BACKGROUND:
Celiac disease is an enteropathy triggered by dietary gluten found in wheat, barley, and rye. The current treatment is a strict gluten-free diet. Quinoa is a highly nutritive plant from the Andes, with low concentrations of prolamins, that has been recommended as part of a gluten-free diet; however, few experimental data support this recommendation.

OBJECTIVE:
We aimed to determine the amount of celiac-toxic prolamin epitopes in quinoa cultivars from different regions of the Andes and the ability of these epitopes to activate immune responses in patients with celiac disease.

DESIGN:
The concentration of celiac-toxic epitopes was measured by using murine monoclonal antibodies against gliadin and high-molecular-weight glutenin subunits. Immune response was assessed by
proliferation assays of celiac small intestinal T cells/interferon-γ (IFN-γ) and production of IFN-γ/IL-15 after organ culture of celiac duodenal biopsy samples.

RESULTS:
Fifteen quinoa cultivars were tested: 4 cultivars had quantifiable concentrations of celiac-toxic epitopes, but they were below the maximum permitted for a gluten-free food. Cultivars Ayacuchana and Pasankalla stimulated T cell lines at levels similar to those for gliadin and caused secretion of cytokines from cultured biopsy samples at levels comparable with those for gliadin.

CONCLUSIONS:
Most quinoa cultivars do not possess quantifiable amounts of celiac-toxic epitopes. However, 2 cultivars had celiac-toxic epitopes that could activate the adaptive and innate immune responses in some patients with celiac disease. These findings require further investigation in the form of in vivo studies, because quinoa is an important source of nutrients for patients with celiac disease.


ABSTRACT

BACKGROUND AND AIMS:
Patients with rheumatoid arthritis (RA) often feel there is an association between food intake and rheumatoid disease severity. To investigate a putative immunological link between gut immunity and RA, food antibodies were measured in serum and perfusion fluid from the jejunum of RA patients and healthy controls to determine the systemic and mucosal immune response.

METHODS:
IgG, IgA, and IgM antibodies to dietary antigens were measured in serum and jejunal perfusion fluid from 14 RA patients and 20 healthy subjects. The antigens originated from cow's milk (alpha-lactalbumin, beta-lactoglobulin, casein), cereals, hen's egg (ovalbumin), cod fish, and pork meat.

RESULTS:
In intestinal fluid of many RA patients, all three immunoglobulin classes showed increased food specific activities. Except for IgM activity against beta-lactoglobulin, all other IgM activities were significantly increased irrespective of the total IgM level. The RA associated serum IgM antibody responses were relatively much less pronounced. Compared with IgM, the intestinal IgA activities were less consistently raised, with no significant increase against gliadin and casein. Considerable cross reactivity of IgM and IgA antibodies was documented by absorption tests. Although intestinal IgG activity to food was quite low, it was nevertheless significantly increased against many antigens in RA patients. Three of the five RA patients treated with sulfasalazine for 16 weeks had initially raised levels of intestinal food antibodies; these became normalised after treatment, but clinical improvement was better reflected in a reduced erythrocyte sedimentation rate.
CONCLUSIONS:
The production of cross reactive antibodies is strikingly increased in the gut of many RA patients. Their food related problems might reflect an adverse additive effect of multiple modest hypersensitivity reactions mediated, for instance, by immune complexes promoting autoimmune reactions in the joints.


ABSTRACT
Celiac Sprue, a widely prevalent autoimmune disease of the small intestine, is induced in genetically susceptible individuals by exposure to dietary gluten. A 33-mer peptide was identified that has several characteristics suggesting it is the primary initiator of the inflammatory response to gluten in Celiac Sprue patients. In vitro and in vivo studies in rats and humans demonstrated that it is stable toward breakdown by all gastric, pancreatic, and intestinal brush-border membrane proteases. The peptide reacted with tissue transglutaminase, the major autoantigen in Celiac Sprue, with substantially greater selectivity than known natural substrates of this extracellular enzyme. It was a potent inducer of gut-derived human T cell lines from 14 of 14 Celiac Sprue patients. Homologs of this peptide were found in all food grains that are toxic to Celiac Sprue patients but are absent from all nontoxic food grains. The peptide could be detoxified in in vitro and in vivo assays by exposure to a bacterial prolyl endopeptidase, suggesting a strategy for oral peptidase supplement therapy for Celiac Sprue.


ABSTRACT
BACKGROUND:
Gliadin amino acid sequence(s) responsible for toxicity in susceptible individuals have not been fully elucidated. Previous in vitro studies have suggested the presence of active sequences in the NH(2)-terminal part of the A-gliadin molecule. In this paper the in vitro activity of A-gliadin synthetic peptides 31-55, 31-43, and 44-55 has been investigated.

METHODS:
Organ culture of jejunal mucosa from untreated and treated coeliac patients was used. In the first system enterocyte height was used as a measure of peptide toxicity; in the second system evidence of activated mucosal cell-mediated immune response was sought.

RESULTS:
Peptides 31-55 and 31-43 were active on untreated coeliac mucosa at a concentration of 0.5 mg/ml and peptide 44-55 only at a concentration of 3 mg/ml. In in vitro-cultured treated coeliac mucosa peptides 31-55 and 31-43 at 1 mg/ml and peptide 44-55 at 3 mg/ml were able to induce enhanced epithelial expression of HLA-DR and 4F2 molecules and the appearance of CD25 positive cells.

CONCLUSIONS:
Our results suggest that 31-43 and 44-55 A-gliadin peptides are both active, even if to different extents. In vitro systems remain essential tools to screen material to be subsequently tested in vivo.

35. Lammer K, et al. “Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3.” Gastroenterology 2008; 135:194-204

ABSTRACT

BACKGROUND & AIMS:
Celiac disease is an immune-mediated enteropathy triggered by gliadin, a component of the grain protein gluten. Gliadin induces an MyD88-dependent zonulin release that leads to increased intestinal permeability, a postulated early element in the pathogenesis of celiac disease. We aimed to establish the molecular basis of gliadin interaction with intestinal mucosa leading to intestinal barrier impairment.

METHODS:
Alpha-gliadin affinity column was loaded with intestinal mucosal membrane lysates to identify the putative gliadin-binding moiety. In vitro experiments with chemokine receptor CXCR3 transfectants were performed to confirm binding of gliadin and/or 26 overlapping 20mer alpha-gliadin synthetic peptides to the receptor. CXCR3 protein and gene expression were studied in intestinal epithelial cell lines and human biopsy specimens. Gliadin-CXCR3 interaction was further analyzed by immunofluorescence microscopy, laser capture microscopy, real-time reverse-transcription polymerase chain reaction, and immunoprecipitation/Western blot analysis. Ex vivo experiments were performed using C57BL/6 wild-type and CXCR3(-/-) mouse small intestines to measure intestinal permeability and zonulin release.

RESULTS:
Affinity column and colocalization experiments showed that gliadin binds to CXCR3 and that at least 2 alpha-gliadin 20mer synthetic peptides are involved in this binding. CXCR3 is expressed in mouse and human intestinal epithelia and lamina propria. Mucosal CXCR3 expression was elevated in active celiac disease but returned to baseline levels following implementation of a gluten-free diet. Gliadin induced physical association between CXCR3 and MyD88 in enterocytes. Gliadin increased zonulin release and intestinal permeability in wild-type but not CXCR3(-/-) mouse small intestine.
CONCLUSIONS:
Gliadin binds to CXCR3 and leads to MyD88-dependent zonulin release and increased intestinal permeability.


ABSTRACT
CD is an autoimmune-mediated disorder of the gastrointestinal tract. Initial symptom presentation is variable and can include neurologic manifestations that may comprise ataxia, neuropathy, dizziness, epilepsy, and cortical calcifications rather than gastrointestinal-hindering diagnosis and management. We present a case of a young man with progressive neurologic symptoms and brain MR imaging findings worrisome for ALS. During the diagnostic work-up, endomysium antibodies were discovered, and CD was confirmed by upper gastrointestinal endoscopy with duodenal biopsies. MR imaging findings suggestive of ALS improved after gluten-free diet institution.


ABSTRACT
One of the most important and overlooked functions of the gastrointestinal tract is to provide a dynamic barrier to tightly controlled antigen trafficking through both the transcellular and paracellular pathways. Intercellular tight junctions (TJ) are the key structures regulating paracellular trafficking of macromolecules. Although steady progress has been made in understanding TJ ultrastructure, relatively little is known about their pathophysiological regulation. Our discovery of zonulin, the only known physiological modulator of intercellular TJ described so far, increased understanding of the intricate mechanisms that regulate gut permeability and led us to appreciate that its up-regulation in genetically susceptible individuals may lead to immune-mediated diseases. This information has translational implications, because the zonulin pathway is currently exploited to develop both diagnostic and therapeutic applications pertinent to a variety of immune-mediated diseases.
ABSTRACT

Over the past decades evidence has been accumulating that intestinal barrier integrity loss plays a key role in the development and perpetuation of a variety of disease states including inflammatory bowel disease and celiac disease, and is a key player in the onset of sepsis and multiple organ failure in situations of intestinal hypoperfusion, including trauma and major surgery. Insight into gut barrier integrity and function loss is important to improve our knowledge on disease etiology and pathophysiology and contributes to early detection and/or secondary prevention of disease. A variety of tests have been developed to assess intestinal epithelial cell damage, intestinal tight junction status and consequences of intestinal barrier integrity loss, i.e. increased intestinal permeability. This review discusses currently available methods for evaluating loss of human intestinal barrier integrity and function.

ABSTRACT

Chronic fatigue syndrome (CFS) is complex illness of unknown etiology. Among the broad range of symptoms, many patients report disturbances in the emotional realm, the most frequent of which is anxiety. Research shows that patients with CFS and other so-called functional somatic disorders have alterations in the intestinal microbial flora. Emerging studies have suggested that pathogenic and non-pathogenic gut bacteria might influence mood-related symptoms and even behavior in animals and humans. In this pilot study, 39 CFS patients were randomized to receive either 24 billion colony forming units of Lactobacillus casei strain Shirota (LcS) or a placebo daily for two months. Patients provided stool samples and completed the Beck Depression and Beck Anxiety Inventories before and after the intervention. We found a significant rise in both Lactobacillus and Bifidobacteria in those taking the LcS, and there was also a significant decrease in anxiety symptoms among those taking the probiotic vs controls (p = 0.01). These results lend further support to the presence of a gut-brain interface, one that may be mediated by microbes that reside or pass through the intestinal tract.
Immune factors are implicated in normal brain development and in brain disorder pathogenesis. Pathogen infection and food antigen penetration across gastrointestinal barriers are means by which environmental factors might affect immune-related neurodevelopment. Here, we test if gastrointestinal inflammation is associated with schizophrenia and therefore, might contribute to bloodstream entry of potentially neurotropic milk and gluten exorphins and/or immune activation by food antigens. IgG antibodies to Saccharomyces cerevisiae (ASCA, a marker of intestinal inflammation), bovine milk casein, wheat-derived gluten, and 6 infectious agents were assayed. Cohort 1 included 193 with non-recent onset schizophrenia, 67 with recent onset schizophrenia and 207 non-psychiatric controls. Cohort 2 included 103 with first episode schizophrenia, 40 of whom were antipsychotic-naïve. ASCA markers were significantly elevated and correlated with food antigen antibodies in recent onset and non-recent onset schizophrenia compared to controls (p≤0.00001-0.004) and in unmedicated individuals with first episode schizophrenia compared to those receiving antipsychotics (p≤0.05-0.01). Elevated ASCA levels were especially evident in non-recent onset females (p≤0.009), recent onset males (p≤0.01) and in antipsychotic-naïve males (p≤0.03). Anti-food antigen antibodies were correlated to antibodies against Toxoplasma gondii, an intestinally-infectious pathogen, particularly in males with recent onset schizophrenia (p≤0.002). In conclusion, gastrointestinal inflammation is a relevant pathology in schizophrenia, appears to occur in the absence of but may be modified by antipsychotics, and may link food antigen sensitivity and microbial infection as sources of immune activation in mental illness.

There is now evidence that major depression (MDD) is accompanied by an activation of the inflammatory response system (IRS) and that pro-inflammatory cytokines and lipopolysaccharide (LPS) may induce depressive symptoms. The aim of the present study was to examine whether an
increased gastrointestinal permeability with an increased translocation of LPS from gram negative bacteria may play a role in the pathophysiology of MDD. Toward this end, the present study examines the serum concentrations of IgM and IgA against LPS of the gram-negative enterobacteria, Hafnia Alvei, Pseudomonas Aeruginosa, Morganella Morganii, Pseudomonas Putida, Citrobacter Koseri, and Klebsielle Pneumoniae in MDD patients and normal controls. We found that the prevalences and median values for serum IgM and IgA against LPS of enterobacteria are significantly greater in patients with MDD than in normal volunteers. These differences are significant to the extent that a significant diagnostic performance is obtained, i.e. the area under the ROC curve is 90.1%. The symptom profiles of increased IgM and IgA levels are fatigue, autonomic and gastro-intestinal symptoms and a subjective feeling of infection. The results show that intestinal mucosal dysfunction characterized by an increased translocation of gram-negative bacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. It is suggested that the increased LPS translocation may mount an immune response and thus IRS activation in some patients with MDD and may induce specific "sickness behaviour" symptoms. It is suggested that patients with MDD should be checked for leaky gut by means of the IgM and IgA panel used in the present study and accordingly should be treated for leaky gut.


ABSTRACT

Pigtail macaques (PTMs) rapidly progress to AIDS after simian immunodeficiency virus (SIV) infection. Given the strong association between human immunodeficiency virus (HIV) and SIV disease progression and microbial translocation and immune activation, we assessed whether high basal levels of immune activation and microbial translocation exist in PTMs. We found that before SIV infection, PTMs had high levels of microbial translocation that correlated with significant damage to the structural barrier of the gastrointestinal tract. Moreover, this increased microbial translocation correlated with high levels of immune activation and was associated with high frequencies of interleukin-17-producing T cells. These data highlight the relationship among mucosal damage, microbial translocation and systemic immune activation in the absence of SIV replication, and underscore the importance of microbial translocation in the rapid course of disease progression in SIV-infected PTMs. Furthermore, these data suggest that PTM may be an ideal model to study therapeutic interventions aimed at decreasing microbial translocation-induced immune activation.
ABSTRACT

OBJECTIVE:
Little is known about the interaction of gliadin with intestinal epithelial cells and the mechanism(s) through which gliadin crosses the intestinal epithelial barrier. We investigated whether gliadin has any immediate effect on zonulin release and signaling.

MATERIAL AND METHODS:
Both ex vivo human small intestines and intestinal cell monolayers were exposed to gliadin, and zonulin release and changes in paracellular permeability were monitored in the presence and absence of zonulin antagonism. Zonulin binding, cytoskeletal rearrangement, and zonula occludens-1 (ZO-1) redistribution were evaluated by immunofluorescence microscopy. Tight junction occludin and ZO-1 gene expression was evaluated by real-time polymerase chain reaction (PCR).

RESULTS:
When exposed to gliadin, zonulin receptor-positive IEC6 and Caco2 cells released zonulin in the cell medium with subsequent zonulin binding to the cell surface, rearrangement of the cell cytoskeleton, loss of occludin-ZO1 protein-protein interaction, and increased monolayer permeability. Pretreatment with the zonulin antagonist FZI/0 blocked these changes without affecting zonulin release. When exposed to luminal gliadin, intestinal biopsies from celiac patients in remission expressed a sustained luminal zonulin release and increase in intestinal permeability that was blocked by FZI/0 pretreatment. Conversely, biopsies from non-celiac patients demonstrated a limited, transient zonulin release which was paralleled by an increase in intestinal permeability that never reached the level of permeability seen in celiac disease (CD) tissues. Chronic gliadin exposure caused down-regulation of both ZO-1 and occludin gene expression.

CONCLUSIONS:
Based on our results, we concluded that gliadin activates zonulin signaling irrespective of the genetic expression of autoimmunity, leading to increased intestinal permeability to macromolecules.

ABSTRACT

The intestinal epithelium is faced with the complex task of providing a barrier while also allowing nutrient and water absorption. The frequency with which these processes are disrupted in disease can be taken as evidence of their importance. It is therefore of interest to define the mechanisms of altered intestinal barrier and transport function and develop means to correct disease-associated defects. Over the past 10 years, some of the molecular events underlying physiological
epithelial barrier regulation have been described. Remarkably, recent advances have shown that activation of the same mechanisms is central to barrier dysfunction in both in vitro and in vivo models of disease. Although the contribution of barrier dysfunction to pathogenesis of chronic disease remains incompletely understood, it is now clear that cytoskeletal regulation of barrier function is both an important pathogenic process and that targeted inhibition of myosin light chain kinase, which affects this cytoskeleton-dependent tight junction dysfunction, is an attractive candidate for therapeutic intervention.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2886850/

ABSTRACT

Autoimmune diseases are characterized by tissue damage and loss of function due to an immune response that is directed against specific organs. This review is focused on celiac disease (CD), an autoimmune enteropathy, and type 1 diabetes (T1D), a hyperglycosaeamia caused by a destructive autoimmune process targeting the insulin-producing pancreatic islet cells. Even if environmental factors and genetic susceptibility are clearly involved in the pathogenesis of autoimmunity, for most autoimmune disorders there is no or little knowledge about the causing agent or genetic makeup underlying the disease. In this respect, CD represents a unique autoimmune disorder because a close genetic association with HLA-DQ2 or HLA-DQ8 haplotypes and, more importantly, the environmental trigger (the gliadin fraction of gluten-containing grains wheat, barley, and rye) are known. Conversely, the trigger for autoimmune destruction of pancreatic Î² cells in T1D is unclear. Interestingly, recent data suggest that gliadin is also involved in the pathogenesis of T1D. There is growing evidence that increased intestinal permeability plays a pathogenic role in various autoimmune diseases including CD and T1D. Therefore, we hypothesize that besides genetic and environmental factors, loss of intestinal barrier function is necessary to develop autoimmunity. In this review, each of these components will be briefly reviewed.


ABSTRACT

OBJECTIVE: The only treatment for celiac disease is lifelong adherence to a gluten-free diet, yet adherence is limited and factors influencing adherence are poorly understood. The purpose of this study was to determine factors influencing gluten-free diet adherence in adults with celiac disease.
METHODS:
A questionnaire was developed and administered to 154 adults with celiac disease who then underwent a standardized gluten-free diet evaluation by an experienced nutritionist. Multivariate analysis was conducted to determine factors associated with adherence level.

RESULTS:
Thirteen factors hypothesized to contribute to gluten-free diet adherence were found to be significantly associated with improved adherence including: understanding of the gluten-free diet, membership of a celiac disease advocacy group, and perceived ability to maintain adherence despite travel or changes in mood or stress (P < 0.001).

CONCLUSIONS:
This study identified specific factors correlated with gluten-free diet adherence. These results provide a foundation for the design of educational interventions to improve adherence.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1116331/

No ABSTRACT Available

“Coeliac disease is an inflammatory disease of the upper small intestine and results from gluten ingestion in genetically susceptible individuals.1,2 Inflammation may lead to the malabsorption of several important nutrients. Clinical and mucosal recovery after institution of a gluten free diet is objective evidence that the enteropathy is gluten induced. In 1950, Dicke observed the central role of gluten in the pathogenesis of coeliac disease.3 Coeliac disease is closely related to dermatitis herpetiformis.4 In dermatitis herpetiformis, skin rash and a similar small intestinal enteropathy to that of coeliac disease are typically present, and both respond to withdrawal of gluten.”

Summary points

In coeliac disease, dietary gluten causes inflammation of the small intestine, which may affect absorption of important nutrients including iron, folic acid, calcium, and fat soluble vitamins.
Studies show coeliac disease to be a common disorder, possibly affecting 1 in 200 of the general population, the majority of patients being diagnosed in adulthood
Many patients have minimal symptoms, and gastrointestinal symptoms are frequently absent.
Coeliac disease should be considered in a wide range of clinical situations including anaemia or osteoporosis and in patients with a range of associated disorders such as type 1 diabetes.
The diagnosis and screening for coeliac disease has been facilitated by testing for endomysial autoantibodies.
Treatment consists of permanent withdrawal of gluten from the diet, which results in complete remission.
Celiac disease (CD) is a chronic disease causing inflammation of the proximal small intestine that occurs in genetically predisposed individuals when they eat gluten, which is the storage protein in wheat, barley, and rye. The disease injury usually resolves when gluten is excluded from the diet. Although the injury will heal, the reaction to gluten is permanent and will recur with the reintroduction of gluten. The condition is surprisingly common, affecting as many as 1% of white populations. The consequences of the disease are predominantly those of malnutrition due to maldigestion and malabsorption, such as diarrhea, weight loss, and anemia. Symptoms caused by inflammation of the small intestine are also common. CD, although it is common and its pathophysiology is well understood, frequently goes undiagnosed, probably because of the nonspecific or vague nature of many of the symptoms that occur. The cornerstone of treatment for CD is elimination of gluten from the diet. In most patients diagnosed with CD, a strict gluten-free diet (GFD) alone should result in complete symptomatic and histologic resolution of the disease and reduce risk of complications. Noncompliance with diet is the leading cause of failure to respond in patients with CD. For these reasons, thorough assessment and counseling at the time of diagnosis and ongoing care are crucial. In this article, we address briefly what is known about the pathogenesis and diagnosis of CD and address its treatment in detail.

BACKGROUND:
Psychiatric symptoms, common in untreated coeliac disease patients, may improve after gluten withdrawal.

AIMS:
To estimate the incidence of psychiatric disorders in coeliac disease patients on gluten withdrawal and to evaluate: (1) the psychological weight of a chronic disease that involves a restrictive diet and a limited life style; (2) the acceptance of the disease; (3) the effects of both disease and diet on behaviour and quality of life.

PATIENTS AND METHODS:
Three groups of 100 patients (coeliac disease patients, diabetic patients and healthy controls, respectively) were assessed by means of a professional semi-structured diagnostic interview based on DSM-IV criteria. This interview, together with specific psychiatric questionnaires, ruled out axis I or II psychopathological disturbances.
RESULTS:
The modified Self-rating Depression Scale and State and Trait Anxiety Inventory Y2 scores were significantly higher in both coeliac and diabetic patients than in healthy controls. The duration of gluten restriction was related to significantly higher modified Self-rating Depression Scale scores in patients with a more recent diagnosis. Quality of life was poorer in both coeliac and diabetic patients than in healthy controls and significantly correlated with anxiety. The Illness Behaviour Questionnaire showed a high psychological and somatic perception of illness in both coeliac and diabetic patients. Its subscale scores correlated significantly with anxiety and depression symptoms.

CONCLUSIONS:
In coeliac disease, affective disorders should be ascribed to difficulties in adjusting to the chronic nature of the disease rather than directly to the disease itself, thus giving an indication for preventive liaison psychiatric interventions.


ABSTRACT
Several extraintestinal clinical manifestations have been reported in celiac disease (CD). Among them, growing evidence suggests the association between CD and affective and psychiatric disorders. In this review the most frequent affective and psychiatric disorders associated with CD and the possible mechanisms involved in these associations were analyzed. The available data suggest that screening for CD in patients with affective and/or psychiatric symptoms may be useful since these disorders could be the expression of an organic disease rather than primary psychiatric illnesses.


ABSTRACT
BACKGROUND AND AIM:
Individuals with coeliac disease have increased risk of depression and death from external causes, but conclusive studies on death from suicide are missing. We examined the risk of suicide in coeliac disease and amongst individuals where the small intestinal biopsy showed no villous atrophy.
METHODS:
We collected biopsy data from all 28 clinical pathology departments in Sweden for individuals diagnosed during 1969-2007 with coeliac disease (Marsh 3: villous atrophy; n=29,083 unique individuals), inflammation without villous atrophy (Marsh 1-2; n=13,263) or positive coeliac disease serology but normal mucosa (Marsh 0, n=3719). Through Cox regression we calculated Hazard ratios for suicide as recorded in the Swedish Cause of Death Register.

RESULTS:
The risk for suicide was higher in patients with coeliac disease compared to general population controls (HR=1.55; 95%CI=1.15-2.10; based on 54 completed suicides). Whilst suicide was also more common amongst individuals with inflammation (HR=1.96; 95%CI=1.39-2.77), no such increase was seen amongst individuals with a normal mucosa but positive coeliac disease serology (HR=1.06; 95%CI=0.37-3.02).

CONCLUSIONS:
We found a moderately increased risk of suicide amongst patients with coeliac disease. This merits increased attention amongst physicians treating these patients.
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Dr. Tom O’Bryan is an internationally recognized speaker and workshop leader specializing in the complications of Non-Celiac Gluten Sensitivity and Celiac Disease as they occur inside and outside of the intestines. He is the founder of www.theDr.com. He recently hosted the paradigm-shifting ‘The Gluten Summit – A Grain of Truth,’ bringing together 29 of the world’s experts on Celiac Disease and Non-Celiac Gluten Sensitivity at www.theglutensummit.com.