Gastroenterology and Hepatology From Bed to Bench.

Second Gluten and Food Related Disorders Conference. Worcester, UK. December 6-7 2012

Guest Editor

Geoffrey Holmes
Emeritus Consultant Gastroenterologist, Royal Derby Hospital, Derby, UK

This two day conference was organised by Kamran Rostami who lined up a number of experts to bring us up to date on some important topics related to coeliac disease (CD) and other food related disorders. He opened the proceedings and pointed out that the clinical manifestations of CD are protean and making the diagnosis is particularly challenging in those with so-called atypical symptoms and only mild abnormalities in the small intestinal mucosa although the advent of accurate serological tests has made the task somewhat easier. He introduced non-CD gluten sensitivity, characterised by negative antibodies and near normal small bowel biopsies, an entity that is receiving increasing attention. David Sanders continued on the theme of gluten sensitivity in the absence of CD regarding this as a non-allergic, non-autoimmune disorder in which the consumption of gluten leads to symptoms similar to those seen in CD. The small intestinal mucosa is grossly normal, CD antibodies are negative and improvement occurs on a gluten free diet (GFD). The number of patients with this condition is increasing at an astonishing rate generating an enormous market in gluten free foods running into billions of dollars in the USA. Whether all those on this diet really need it or benefit from it in the long term is another question. Marios Hajivassiliou who has done so much to define gluten sensitive neurological disorders, pointed out that gluten ataxia is the best characterised entity within this group that results from cerebellar degeneration. Recently introduced techniques have allowed identification of patients with a "hyper-excitable" brain which generates myoclonus. Of great interest, evidence is accruing that some conditions may be stabilised or even be improved by strict adherence to GFD.

Isabel Skypala pointed out that IgE-mediated food allergy affects 1-4% of adults, the diagnosis can be challenging and avoidance of trigger foods is the mainstay of management. Importantly, exclusion diets can be nutritionally inadequate and measures need to be taken to avoid this pitfall. Functional gut disorders are common and among these Irritable bowel syndrome (IBS) is the most common. Yvonne McKenzie discussed the role of the low FODMAP diet (restriction of fermentable short-chain carbohydrates) in the management of IBS that can improve the symptoms in about two thirds of patients with diarrhoea and/or bloating. Sulphite sensitivity was explored by Justine Bold and can manifest as asthma and anaphylaxis. Sulphite preservatives are commonly encountered in foods and drinks but only further studies will determine the proportion of the population that experience adverse reactions.

It may come as a surprise to many who associate CD with malabsorption and poor appetite that adults and children can present with obesity and this aspect of the disorder was discussed by David Aldulaimi. Many will be aware that following a GFD patients gain weight. So the messages from this interesting paper are that even in an

overweight patient the diagnosis of CD may still need to be considered and that calorie restriction on a GFD is likely to be required in many instances to avoid excess weight gain.

Can CD be prevented? In an exciting European Multicentre study, this is being addressed and Gemma Castillejo gave some preliminary results although the final outcome, which is eagerly awaited, will not be known until the last child enrolled is three years old. From a Swedish population study it does appear that the time of introduction of gluten in infant feeding is important and that gradual introduction of gluten at four months with continued breast feeding is better than introduction at six months with regard to lowering the frequency of CD.

Carlo Catassi discussed the epidemiological aspects of gluten related disorders and noted that there are indications that the prevalence of CD is increasing and as the diet in many parts of the developing world becomes more "westernized" CD will be seen much more frequently in these locations. The prevalence of non-CD gluten sensitivity is currently unknown but the frequency has been placed between 2 and 6% making it more common than CD at 1%. Such high numbers will challenge health care systems and providers of gluten free products in many parts of the globe.

In recent years there has been a resurgence of interest in the role of intestinal permeability as a factor in the causation of some diseases. For example, with regard to CD, gluten can only cause immune disturbance if it can gain access to the immune system through a "leaky" intestinal mucosa. Ali Keshavarzian discussed gut leakiness and how it is affected by upsets of the circadian rhythms which are governed by sophisticated molecular clockwork mechanisms. Circadian rhythms can be disrupted by altering the times of exposure to light and dark which can affect intestinal permeability. This simulates shift work patterns which are such a feature of modern life. How this might impact on CD is still to be determined and is an interesting line of research.

One of the commonest and sometimes the only manifestation of CD is iron deficiency anaemia and has been investigated in some detail by Naveen Sharma who has postulated that TNF alpha produced by intraepithelial lymphocytes in CD could have an inhibitory effect on iron absorption and so contribute to iron deficiency. In addition, ferritin is inappropriately elevated in some CD patients with iron deficiency which might result in iron being trapped in enterocytes. It is tempting to speculate that a GFD might reverse these abnormalities.

Type 1 diabetes mellitus (type 1 DM) is the most common and best researched autoimmune disorder associated with CD. Sabine Hogg-Kollars reviewed this association pointing out that in about 90% of patient's type 1 DM is diagnosed first. Making the diagnosis either of CD or diabetes can be challenging and the problems are compounded by the fact that some patients with diabetes may not have CD antibodies present early in their diagnosis. Whether type 1 DM is associated with non-gluten sensitivity and what the impact of GFD might be will have to await further research.

This was an enjoyable, informative two days. Knowledge is accruing at an ever increasing rate so it will not be too long before planning for a third conference needs to be underway.

Gluten related disorders, pitfalls in screening

Kamran Rostami

Department of Gastroenterology, Luton and Dunstable NHS Foundation Trust, UK

It is increasingly evident that undiagnosed gluten related disorders presenting with a multitude of symptoms and complications inside and outside small bowel are highly prevalent. While

environmental factors associated with complex genetics lead to destruction of the small intestinal villi resulting in malabsorption syndrome in celiac disease (CD), gluten sensitivity (GS) is characterised by negative antibodies and grossly normal histology (1). The association between celiac disease and other disorders has been clearly established and there have been many reports of numerous intestinal and extra intestinal coexistent disorders with CD. Celiac disease is an auto-immune disorder generated in genetically susceptible subjects via the ingestion of gluten containing grains such as wheat, rye and barley. The immune response to these grains leads to progressive damage in the small intestine and to the production of serum antibodies directed against tTGA.

Despite the availability of specific and sensitive serological tests diagnosis of atypical forms of CD can be very challenging. Intestinal biopsy is still considered a useful diagnostic tool for detection of CD in different stages of development. Histology also permits evaluation of the response to gluten-free diet, should there be any doubt about the diagnosis.

The sensitivity of the serological tests available is correlated with the degree of mucosal abnormalities and according to many studies a negative serological test does not exclude the diagnosis of CD. The mucosal lesions in CD can be patchy, and if sampling is insufficient, the risk of missing the diagnosis increases. Low degrees of mucosal abnormalities like microscopic enteritis in small intestinal specimens are not specific for CD, but a combination of clinical, serological and genetic evaluation may help to confirm the diagnosis. If possible, it would be more desirable to avoid endoscopy completely. Indeed, endoscopy may be unnecessary in the small sub group of patients who have classic symptoms and positive serology, but taking a biopsy appears essential in the majority of cases. A normal endoscopic appearance lacks sufficient sensitivity to exclude CD. As mucosal abnormalities in CD are patchy and the orientation of biopsies are variable, multiple biopsies (4-6 biopsies) from the duodenal bulb and descending duodenum are usually recommended as indicated by most studies as the standard method for CD evaluation.

1. Anonymous, Rostami K, Hogg-Kollars S. Non-coeliac gluten sensitivity. BMJ. 2012 Nov 30;345:e7982. doi: 10.1136/bmj.e7982. PubMed PMID: 23204003

The rise and fall of gluten

David Sanders

Department of Gastroenterology, Royal Hallamshire Hospital and University of Sheffield Room P39, Glossop Road, Sheffield S10 2JF

Coeliac disease is a chronic inflammatory disorder of the small bowel which affects 1% of the population (1). The condition can be defined as a state of heightened immunological responsiveness to ingested gluten (from wheat, barley or rye) in genetically susceptible individuals (2). The gold standard diagnosis of coeliac disease is the demonstration of villous atrophy on duodenal biopsies, with coeliac serology (endomysial [EMA] and/or tissue transglutaminase [TTG] antibodies) playing a supportive role (2, 3). The cornerstone of treatment for coeliac disease is lifelong adherence to a strict gluten-free diet, which in the majority leads to an improved clinical outcome, psychological well-being and quality of life (2).

An increasing observation noted is that the number of patients consuming a gluten-free diet seems greatly out of proportion to the projected number of coeliac disease patients. Marketers have estimated that 15-25% of American consumers want gluten free foods (4, 5). This is now ‘big business’ with Reuters projecting an increased revenue in the gluten free market from $1.31

billion in the United States alone for the year 2011 to $1.68 billion by the year 2015 (6). In tandem with these findings, a growing problem encountered in clinical practice is the diagnosis and management of patients complaining of gluten related symptoms yet in the absence of diagnostic markers for coeliac disease, such as negative coeliac serology and normal duodenal biopsies. These patients pose a clinical dilemma to gastroenterologists, general practitioners and dietitians alike and in the past have been described as belonging to a "no man's land" due to the diagnostic uncertainty (7).

Observational data exists of patients reporting gluten-related symptoms but without evidence of coeliac disease (8,9). For instance a prospective series of 94 adults reported that a positive history of abdominal symptoms after cereal ingestion appeared to be a poor predictor of coeliac disease or cereal allergy, as 63% of study subjects did not have either disease.

Despite this these individuals symptomatically benefitted from a gluten-free diet, although the diet was not tested in a separate group of 30 controls (10). Historically, it has also been noted that there seems to be an increased prevalence of antigliadin antibodies in those complaining of gluten related symptoms (40%) (11) and in irritable bowel syndrome (IBS) patients (17%) (11) by comparison to healthy controls (12%)1, despite the exclusion of coeliac disease through normal duodenal biopsies and negative TTG/EMA.

A large double blind wheat-placebo controlled crossover study has recently demonstrated the existence of wheat sensitivity in patients without coeliac disease: 920 IBS patients commenced a standard four week elimination diet (wheat, cow's milk, eggs, tomato, chocolate plus any other known food hypersensitivities) prior to undergoing a two week crossover challenge with a one week washout period. A third of patients (n 276) demonstrated clinical and statistically significant sensitivity to wheat and not placebo, with worsening abdominal pain, bloating and stool consistency (12).

The evidence therefore suggests that, even in the absence of coeliac disease, gluten based products can induce abdominal symptoms which may present as IBS.

Non-coeliac gluten sensitivity is an umbrella term and has been proposed as incorporating a wide range of possible clinical features (13). Data from the Maryland clinic (n 347) (13) and an evaluation of 78 Italian patients (14) with non-coeliac gluten sensitivity has found subjects attributing gluten ingestion to cause intestinal symptoms (including those consistent with IBS) such as abdominal discomfort, bloating, pain or diarrhoea or it may present with a variety of extra-intestinal symptoms which may include headaches, foggy mind, depression, fatigue, musculoskeletal pains and skin rash.

Other investigators have suggested that whereas patients with coeliac disease demonstrate both an innate (non-specific) and adaptive (specific: T-cell mediated and antibodies) immune response to gluten exposure, those with non-coeliac gluten sensitivity only seem to trigger an innate response (15, 16).

In summary, for patients who report "wheat intolerance or gluten sensitivity", exclude coeliac disease (with TTG/EMA and duodenal biopsies on a gluten containing diet) and wheat allergy (IgE serum assays and/or skin prick test to wheat). Those patients with negative TTG/EMA and normal to near normal duodenal biopsies should be diagnosed as non-coeliac gluten sensitivity - these patients symptomatically benefit from a gluten-free diet. It should be emphasised to patients with non-coeliac gluten sensitivity that this is a newly recognised clinical entity for which we do not yet fully understand the natural history or indeed the pathophysiology.

References

1. Sanders DS, Patel D, Stephenson TJ, et al. A primary care cross-sectional study of undiagnosed adult coeliac disease. Eur J Gastroenterol Hepatol 2003;15(4):407-13.
2. Hopper AD, Hadjivassiliou M, Butt S, Sanders DS. Adult coeliac disease. BMJ 2007;335(7619):558-62.
3. Hopper AD, Cross SS, Hurlstone DP, et al. Pre-endoscopy serological testing for coeliac disease: evaluation of a clinical decision tool. BMJ 2007;334(7596):729.
4. Painter, K. Gluten-free diets gaining in popularity. USA Today 17 August 2008.
5. Di Sabatino A, Corazza GR. Nonceliac gluten sensitivity: sense or sensibility? Ann Intern Med 2012;156(4):309-11.
6. Ferch CC, Chey WD. Irritable bowel syndrome and gluten sensitivity without celiac disease: separating the wheat from the chaff. Gastroenterology 2012;142(3):664-6.
7. Verdu EF, Armstrong D, Murray JA. Between celiac disease and irritable bowel syndrome: the "no man's land" of gluten sensitivity. Am J Gastroenterol 2009;104(6):1587-94.
8. Ellis A, Linaker BD. Non-coeliac gluten sensitivity? Lancet 1978;1(8078):1358-9.
9. Cooper BT, Holmes GK, Ferguson R, Thompson RA, Allan RN, Cooke WT. Gluten-sensitive diarrhea without evidence of celiac disease. Gastroenterology 1980;79(5 Pt 1):801-6.
10. Kaukinen K, Turjanmaa K, Mäki M, et al. Intolerance to cereals is not specific for coeliac disease. Scand J Gastroenterol 2000;35(9):942-6.
11. Sanders DS, Carter MJ, Hurlstone DP, et al. Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling ROME II criteria referred to secondary care. Lancet 2001;358(9292):1504-8.
12. Carroccio A, Mansueto P, Iacono G, et al. Non-Celiac Wheat Sensitivity Diagnosed by Double-Blind Placebo-Controlled Challenge: Exploring a New Clinical Entity. Am J Gastroenterol 2012.
13. Sapone A, Bai JC, Ciacci C, et al. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. BMC Med 2012;10:13.
14. Volta U, Tovoli F, Cicola R, et al. Serological Tests in Gluten Sensitivity (Nonceliac Gluten Intolerance). J Clin Gastroenterol 2011.
15. Sapone A, Lammers KM, Mazzarella G, et al. Differential mucosal IL-17 expression in two gliadin-induced disorders: gluten sensitivity and the autoimmune enteropathy celiac disease. Int Arch Allergy Immunol 2010;152(1):75-80.
16. Sapone A, Lammers KM, Casolaro V, et al. Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. BMC Med 2011;9:23.

Neurological manifestations of gluten related disorders

Marios Hadjivassiliou

Department of Neurology. Royal Hallamshire Hospital, Sheffield

The term gluten-related disorders have recently been proposed to reflect the spectrum of diverse manifestations seen in the context of sensitivity to gluten. Neurological manifestations can be the presenting feature of CD and the last 18 years have seen significant advances in the clinical characterisation of patients with such manifestations.

Gluten ataxia remains the best characterised entity within this group. The term refers to cerebellar degeneration causing loss of balance. The condition remains progressive unless diagnosis and treatment with strict gluten-free diet is instigated. The selective susceptibility of particular cells (eg Purkinje cells) within the nervous system is of particular interest to the pathogenesis of this disease. Whilst the cerebellum is often a prime target the rest of the brain can also be involved as illustrated by myoclonic ataxia in the context of celiac disease. Whilst this combination was originally described as far back as 1986, better clinical and neurophysiological characterisation has only just been possible. Such patients tend to have a “hyper-excitable” brain which generates the myoclonus that at times resembles epilepsia partialis continua (focal epilepsy that is continuous). What is of more interest is the fact that this neurological manifestation is strongly associated with refractory CD type 1 and it requires treatment with immunosupression.

Other common manifestations include peripheral neuropathy. We now know what particular types of peripheral neuropathy are common in the context of CD and these include length-dependant axonal sensorimotor neuropathy and sensory ganglionopathy. Sensory ganglionopathy is of particular interest in that it is a result of selective damage of the dorsal root ganglia. Such damage tends to be seen in some other immune mediated diseases such as Sjogrens syndrome and paraneoplastic neurological syndromes.

Headache is a common manifestation in the context of coeliac disease. A subgroup of such patients also has abnormal MRI scan showing extensive white matter abnormalities. Gluten free diet results in resolution of the headaches and arrest of the MRI abnormalities. This entity is called gluten encephalopathy.

An important question on the subject relates to the prevalence in patients with CD who present to a gastroenterologist vs those who present primarily with neurological manifestations to a neurologist. Data from Sheffield suggest that for every 7 patients with CD presenting to the gastrointestinal clinics there are 2 patients presenting to the neurologist. Cross sectional studies in patients with established CD and those with newly diagnosed CD have demonstrated that neurological dysfunction (based on clinical examination and brain MR imaging is very common and underdiagnosed.

The diagnosis of neurological dysfunction remains problematic. TG6 antibodies, however are emerging as a specific marker of neurological dysfunction and may need to be added to the battery of antibody testing aiding the diagnosis of gluten-related disorders.

Anxiety and depression are often overrepresented in patients with CD. A recent study suggested that patients with established CD and neurological symptoms have significantly reduced grey matter volume not just of the cerebellum but also in other brain regions. Such regions include the gyrus rectus and anterior cingulated gyrus. These are regions associated with executive and psychomotor symptoms including depression. It is therefore possible that the depression seen in patients with CD is not just secondary to the burden of living with a chronic disease but a result of structural abnormalities affecting the central nervous system.

It is essential for all clinicians working in the field to be aware of the diverse manifestations of gluten related disorders in order to be able to diagnose and treat them. The evidence so far suggests that for adult patients with CD, structural abnormalities may be permanent but that there is evidence of clinical improvement after the introduction of a strict gluten-free diet.

Atopic Food Allergy in Adults

Isabel Skypala

Royal Brompton & Harefield NHS Foundation Trust, Sydney Street, London SW3 6NP

Adverse reactions to foods are classified according to the presence or absence of involvement of the immune system, which may or may not include the production of IgE antibodies. Reported reactions to foods are often believed to be manifestations of a food allergy; however IgE-mediated food allergy only affects 1-4% of adults, with seafood, tree nuts, peanuts, fruits and vegetables being the most common triggers. Diagnosis is challenging and most commonly achieved through careful evaluation of the clinical history followed by elimination and re-introduction or challenge with the suspected offending food. With acute-onset allergic reactions, estimation of food-specific IgE antibodies is frequently used to confirm or refute the diagnosis. Recent developments, such as single allergen assays enhance the diagnosis of IgE-mediated food allergy but the gold standard

remains oral food challenge. Despite recent advances in the management of food allergy, including the promotion of oral tolerance, the mainstay of management is still the avoidance of food triggers. Dietary management can be compromised by nutritional inadequacy, accidental exposure, food labeling and quality of life or adherence issues. It is essential that adults with confirmed food allergy receive optimal nutritional and dietetic support to enable them to manage their condition.

The Low FODMAP Diet as Treatment for Functional Gut Disorders

Yvonne McKenzie

Specialist Dietitian in Gastrointestinal Nutrition, IBS Clinical Lead for the Gastroenterology Specialist Group of the British Dietetic Association

Functional gut disorders (FGD) or medically unexplained gut symptoms impact on one in five of us. The most common is irritable bowel syndrome (IBS); others include functional bloating and functional diarrhoea. They are chronic conditions that can lead to a substantial reduction in quality of life with high health-care and economic costs. Treatment options, either singly or in combination, include dietary, pharmacological and behavioural interventions.

Dietetic management aims to improve the severity and frequency of IBS symptoms and quality of life through dietary and lifestyle modification whilst supporting dietary adequacy in line with general healthy eating guidelines. The British Dietetic Association's evidence based practice guidelines, stemming from 5 systematic reviews relating to IBS symptom improvement and the role of milk/lactose, dietary fibre, fermentable carbohydrates, probiotics and empirical and elimination diets includes an IBS algorithm for dietitians to use in the UK healthcare setting (McKenzie *et al*, 2012). Fermentable carbohydrate restriction is given as second-line advanced dietetic intervention to treat IBS symptoms.

FODMAPs (Fermentable, Oligo-, Di- and Mono-saccharides and Polyols) are fermentable short-chain carbohydrates. The mechanisms underlying the low FODMAP dietary approach to improve FGD symptoms are described. High FODMAP foods are widespread in our diets e.g. onion, wheat-based staples, legumes, stone fruits, and common sources along with alternative foods low in FODMAPs are shown. A recent randomised controlled trial demonstrates that a low FODMAP diet is effective in inducing global symptom satisfaction in 68% of IBS patients with diarrhoea and/or bloating (Staudacher et al., 2012). Other levels of evidence for its efficacy in treating FGD are described, as are the clinical dietetic requirements for the successful management of FGD.

References

1. McKenzie YA, Alder A, Anderson W, Wills A, Goddard L, Gulia P, Jankovich E, Mutch P, Reeves LB, Singer A, Lomer MCE. On behalf of Gastroenterology Specialist Group of the British Dietetic Association. British Dietetic Association evidence-based practice guidelines for the dietary management of irritable bowel syndrome in adults. J. Hum. Nutr. Diet. 2012; 25: 260–274.

2. Staudacher HM et al. Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. J Nutr. 2012; 142(8):1510-8.

Sulphite sensitivity

Justine Bold

Senior Lecturer, University of Worcester, UK

Sulphite preservatives are widely used in foods, drinks, cosmetics and pharmaceuticals. They can cause asthma, anaphylaxis and are acknowledged

to have caused a number of deaths. This presentation is a summary of research and data concerning sulphite sensitivity (including anaphylaxis and asthma), as well as an exploration of the mechanisms that cause sensitivity. Tests used to diagnose sensitivity, treatment options and estimates of prevalence are reviewed with factors affecting the nutritional management of a sulphite sensitive individual. The true prevalence of sulphite sensitivity in the general population is not known. Figures of prevalence in the asthmatic population vary. There are several reported mechanisms; the most common appears to be sulphur dioxide inhalation and irritation of the airways (as this commonly affects asthmatics). However, IgE involvement has been demonstrated in some subjects. Studies have also demonstrated that there is a genetic factor (associated with an IgE mechanism) and that a deficiency of the enzyme sulphite oxidase or its dietary co-factors is also possible. Additionally, interference with glutathione S-transferase and depletion of glutathione is also another possible mechanism. The impact of sulphites on nitric oxide and its function as a neurotransmitter is also implicated in toxicity. Sulphite sensitivity is an extremely complex area and further studies are required to fully understand the multiple mechanisms and establish the number of people vulnerable to adverse reactions.

Celiac disease and Obesity

David Aldulaimi

Department of Gastroenterology, Alexandra Hospital, Redditch, UK

Celiac disease (CD) is classically associated with mal-absorption, weight loss and failure to thrive. Increasingly, it has been recognised that patients diagnosed with CD are frequently obese. This presentation will review recent studies that have investigated the prevalence of obesity among patients diagnosed with CD and the effect of a GFD (gluten free diet) upon BMI (body mass index) in adult and paediatric populations.

The high prevalence of obesity among patients diagnosed with CD reflects the high prevalence of obesity among the general population. It also reflects advances in non-invasive testing and national guidelines suggesting that patients with iron deficiency anaemia and the irritable bowel syndrome are screened for CD.

In 1998 Dickey et al published a series of 50 patients with uncomplicated CD, from a single centre in Northern Ireland. 11 patients were underweight, 17 patients were overweight. In 2006, the same centre published a series of 371 patients; 5% of patients were underweight and 13% of patients were obese. Patients with a low BMI were more likely to be female, have a history of diarrhoea, be anaemic, have reduced bone mineral density and have more severe villus atrophy than patients with a normal or raised BMI. Furthermore adherence to a GFD was associated with weight gain in the majority of patients, including those with a raised BMI (1,2). These findings were supported by studies published by Cheng et al, and Kobbani et al from centres in North America and Tucker et al from England (3-5).

Few studies have been published regarding obesity in children with CD. Valletta published a case series from a single centre. At diagnosis 11% of patients were overweight and 3% were obese. Furthermore, the proportion of overweight patients increased after GFD (6).

These studies suggest that obesity is common in both adult and paediatric patients with CD. Furthermore, they suggest that a GFD may lead to weight gain. Clinicians need to consider a diagnosis of CD, even if patients are obese and careful dietetic advice is required given the likely effect of a GFD.

References

1. Dickey W, Bodkin S. Prospective study of body mass index in patients with coeliac disease. BMJ. 1998; 317(7168):1290.
2. Dickey W, Kearney N.Overweight in celiac disease: prevalence, clinical characteristics, and effect of a gluten-free diet. Am J Gastroenterol. 2006; 101:2356-9.
3. Cheng J, Brar PS, Lee AR, Green PH. Body mass index in celiac disease: beneficial effect of a gluten-free diet. J Clin Gastroenterol 2010; 44(4):267-71.
4. Kabbani TA, Goldberg A, Kelly CP, Pallav K, Tariq S, Peer A, et al. Body mass index and the risk of obesity in coeliac disease treated with the gluten-free diet. Aliment Pharmacol Ther 2012; 35(6):723-9.
5. Tucker E, Rostami K, Prabhakaran S, Al Dulaimi D. Patients with coeliac disease are increasingly overweight or obese on presentation. J Gastrointestin Liver Dis. 2012; 21(1):11-5.
6. Valletta E, Fornaro M, Cipolli M, Conte S, Bissolo F, Danchielli C. Celiac disease and obesity: need for nutritional follow-up after diagnosis. Eur J Clin Nutr. 2010; 64(11):1371-2.

Prelimminary results of the EU PREVENTCD PROJECT: Influence of the dietary history on the prevention of CD: possibilities of induction of tolerance for gluten in genetic predisposed children

Gemma Castillejo
On behalf of PreventCD (www.preventcd.com)

The PreventCD study (www.preventcd.com) European multicentre study comprising 17 partners in 11 countries: Belgium, Croatia, Germany, Hungary, Italy, Israel, The Netherlands, Norway, Poland, Spain and Sweden. PreventCD involves 13 clinical centres and/or universities, three industrial companies and the Association of European Coeliac Disease (CD) Societies. It is supervised by the Leiden University Medical Center (LUMC) in Leiden, The Netherlands. PreventCD has been funded by a grant from the European Commission (FP6-2005-FOOD-4B-36383 – PREVENTCD).

To investigate the influence of infant feeding on the risk of developing CD. The hypothesis is that by exposing infants to small quantities of gluten while they are still being breast-fed, it is possible to induce tolerance to gluten thus reducing the risk for CD in genetically susceptible individuals. The study examines the complex interactions between the various factors in CD development: The role of HLA and non-HLA risk alleles, the early immune response to gluten introduction and the role of infant feeding with respect to gluten introduction and breast-feeding.

Two different populations are encompassed in the project with a different study design for each:

1) Family intervention study: Multicentre, prospective, double-blind, randomized gluten/placebo dietary-intervention in infants from high-risk CD families, which repeated CD screening up to 3 years of age.

2) The other study population takes advantage of the Swedish epidemic. It is a Swedish population-based CD screening study among 12 year olds in two birth cohorts that differ with respect to dietary exposures during infancy

Prelimminary results:

1) PreventCD has recruited 1343 children from families with a first degree relative with CD. The proband was a sibling, the mother or the father in 42%, 47% and 11% of the cases, respectively. 78% of the children were HLA-DQ2 and/or -DQ8 positive and 946 entered the randomization protocol. As far as breast feeding is concerned, at the end of the intervention (6 months) 66% of the infants were still breast fed and 41% of them were exclusively breast fed. The preliminary (coded) results show that 66 infants with high levels of CD antibodies and/or with symptoms of CD underwent 68 small bowel biopsies, resulting in the identification of 49 cases of CD and 17 non-CD. All the children with CD (median age 28

months, range 13-48) had high IgA tissue transglutaminase antibodies (TG2).
2) The total prevalence of CD in the 1993 cohort of 12-year-old children born during the CD epidemic shows the highest frequency of CD in Europe, 3% (95% CI 2.5-3.3), with 2/3 undiagnosed prior to the screening. The comparison with the total prevalence of CD in the 1997 cohort born after the epidemic (21/1000) shows a significant lower in frequency of CD with an odds ratio of 0.75 (0.60-0.93).
For the family double blind intervention study, at present is not possible to obtain any conclusion about the efficacy of the intervention and tolerance induction as the code will not be broken till the last child enrolled is three years old.
For the Swedish population study, the results suggest that gluten introduced in infant feeding affects the risk of developing CD, at least up to 12 years of age and that a gradual introduction of gluten from 4 months of age seems favorable compared to an abrupt introduction at 6 months of age, more often without on-going breastfeeding.

Epidemiology of gluten-related disorders

Carlo Catassi
Department of Pediatrics, Universita' Politecnica delle Marche, Ancona, Italy

Celiac disease (CD), also known as genetic gluten intolerance, is the most known gluten-related disorder. CD is one of the most common diseases in countries predominantly populated by people of European origin (for example, North and South America, Australia) affecting approximately 1% of the general population. Interestingly, recent studies indicate a trend toward a rising prevalence of CD during the last several decades for reasons that are currently unclear. Epidemiological studies have provided evidence that this disorder is also common in other parts of the world, including North Africa, the Middle East and parts of the Asian continent. CD frequency is likely to increase in many developing countries, due to the progressing 'Westernization' of the diet.
CD is more common in females than in males, and in at-risk groups, e.g. patients with other autoimmune disease (e.g. type 1 diabetes, thyroid disorders), selective IgA deficiency, Down and Turner syndromes.
As far as wheat allergy (WA) is concerned, in adults in the United States, a list-assisted random-digit-dial survey by the US Food and Drug Administration found a 0.4% prevalence of initially self-reported and later on doctor-diagnosed WA. In a systematic review, two population-based studies from the UK and one from Germany reported positive wheat challenge tests in children, with a prevalence as high as 0.5%.
The overall prevalence of non-celiac gluten sensitivity (GS) in the general population is currently unknown. Anecdotal observations indicate that GS could be more common than CD, with an estimated frequency of 2-6%. In adults with irritable bowel syndrome, one of the commonest disorders in the general population, the frequency of GS documented by a double-blind, placebo-controlled challenge was 28%.

Circadian disruption: susceptibility factor for gut leakiness

Keshavarzian A, Voigt RM, Summa KC, Forsyth CB, Shaikh M, Tang Y, Vitaterna M, Turek F
Rush University Medical Centre, Chicago, USA

Intestinal hyperpermeability (i.e. gut leakiness) is a feature common to many gastrointestinal disorders such as celiac disease, inflammatory bowel disease, alcoholic liver disease, and non-

alcoholic steatohepatitis that promotes local (i.e. mucosal) and systemic inflammation that can have clinically relevant pathological consequences impacting health. One factor that may promote intestinal permeability is circadian rhythm disruption. Circadian rhythms are generated and governed by a sophisticated molecular clockwork that exerts temporal organization over physiological processes and behavior, enabling optimal physiological efficiency in the context of external stimuli, such as cycles of light and darkness. Circadian regulation is achieved at the level of cells, tissues, and systems throughout the body through transcriptional, biochemical, molecular, and behavioral rhythms, as well as endocrine and neural signals. The intestine exhibits circadian rhythms at the organ level and intestinal cells express circadian clock genes. Importantly, disruption of circadian rhythmicity both in vitro and in vivo significantly impacts intestinal epithelial barrier function and increases susceptibility of the intestinal mucosa to injury.

Using alcohol as a tool to induce intestinal hyperpermeability, we have demonstrated that: (1) Knocking down circadian clock gene expression in intestinal epithelial cells (i.e. Caco-2) in vitro prevents alcohol-induced hyperpermeability (2) Environmental disruption of circadian rhythms via chronic light/dark cycle shifting promotes intestinal hyperpermeability in vivo, an effect that synergizes with alcohol; and (3) Whole animal genetic disruption of the circadian clock promotes intestinal hyperpermeability, leading to dramatic exacerbations of alcohol-induced effects. An increasing number of animal and human studies demonstrate that disrupted circadian rhythmicity is associated with numerous pathologies. Indeed, we have previously demonstrated that circadian rhythm disruption makes the intestine more susceptible to injury in an animal model of ulcerative colitis wherein exposure to chronic light/dark cycle shifting in mice, a model of shift work, leads to increased morbidity and mortality, as well as greater pathological damage and inflammation, to DSS- induced colitis.

Circadian rhythm disruption is a pervasive feature of modern day society and, given the obvious pathological consequences and clinical relevance, further investigation into the roles and mechanisms of circadian disruption on the intestine in diseases associated with gut leakiness, such as celiac disease and neurological disorders like Parkinson disease, is warranted.

Iron Absorption and Metabolism in Coeliac Disease

Naveen Sharma

Department of Gastroenterology, Heartlands Hospital, Birmingham, UK

Coeliac disease is found in approximately 1% of the Western Caucasian population (1-3). The main clinical features at presentation relate to nutrient malabsorption. These typically comprise weight loss, diarrhoea, folate deficiency and vitamin D deficiency (4). However, the most common feature at presentation is iron deficiency anaemia (5). Iron deficiency anaemia is observed in approximately 65% of patients with newly diagnosed CD and may be the only presenting feature (6, 7).

The majority of the body's iron requirement is absorbed from the lumen of the proximal small intestine and so it seems logical that CD would have a deleterious effect on iron absorption (8). Historically the iron deficiency observed in CD has been ascribed to a reduced absorptive surface area in the proximal small intestine as a result of villous atrophy. However, a number of questions remain unanswered. Firstly, only 10% of dietary iron is absorbed to meet body iron requirements (9). Given this redundancy in absorptive capacity, it would seem that simply reducing the available surface area may not be sufficient to explain the observed iron deficiency. Secondly, although iron

deficiency appears to be prevalent in CD a significant proportion of individuals remain iron replete despite the disease. We are unaware of any work to date that has identified potential reasons for this disparity.

As there is no physiological excretion of iron, its absorption from the small intestine must be tightly regulated, and the small bowel is therefore a vital site in the regulation of iron metabolism. Ferrous iron is taken up into the enterocyte by the multi-ion divalent metal transporter 1 (DMT-1) which is located on the apical villous membrane of the duodenum and proximal jejunum (10). Once in the enterocyte, iron has two possible fates: it may be stored bound to ferritin, or is exported from the enterocyte by the basal transporter ferroportin (11). During systemic iron deficiency the enterocyte expression of DMT-1 and ferroportin is increased whilst ferritin expression is low (12). The converse occurs during systemic iron excess.

In previous work we have shown that the pro-inflammatory cytokine TNF alpha is able to inhibit iron absorption across the enterocyte by altering the expression and/or cellular localisation of the main iron transport proteins described above (13;14). It has also been shown that TNF alpha is abundant in intra-epithelial lymphocytes (IEL) from patients with coeliac disease compared to normal subjects (15). We therefore postulated that TNF alpha produced by activated IEL in CD could also have an inhibitory effect on iron absorption and so contribute to iron deficiency.

In a further study presented here we described the mRNA and protein expression of the main iron transport proteins in duodenal samples from coeliac patients with and without iron deficiency anaemia (16). In addition, we describe the cellular localisation of these proteins and the observed effect on intracellular iron levels. The study goes onto to determine the effects of co-culturing activated IEL and intestinal cells on iron transport.

The results of these experiments suggest ferritin expression is innapropriately increased in the face of iron deficiency in some coeliac patients and may contibute to differential iron status in these patients by means of iron trapping within duodenal enterocytes. The results of the cell co-culture model suggest that iron transport is TNF alpha dependant and these effects can be blocked my means of a TNFR2 antibody. It is interesting to speculate that there may be differences in TNF alpha responsive elements in the ferritin promoter which determine iron staus in coeliac patients.

References

1. Maki M, Mustalahti K, Kokkonen J, Kulmala P, Haapalahti M, Karttunen T, et al. Prevalence of Celiac disease among children in Finland. N Engl J Med 2003; 348:2517-24.

2. West J, Logan RF, Hill PG, Lloyd A, Lewis S, Hubbard R, Reader R, Holmes GK, Khaw KT. Seroprevalence, correlates, and characteristics of undetected coeliac disease in England. Gut 2003;52:960-65.

3. Logan RF, Tucker G, Rifkind EA, Heading RC, Ferguson A. Changes in clinical features of coeliac disease in adults in Edinburgh and the Lothians 1960-79. Br Med J (Clin Res Ed) 1983;286:95-97.

4. Green PH. The many faces of celiac disease: clinical presentation of celiac disease in the adult population. Gastroenterology 2005;128:S74-S78.

5. Ciclitira PJ, King AL, Fraser JS. AGA technical review on Celiac Sprue. American Gastroenterological Association. Gastroenterology 2001;120:1526- 1540.

6. Jones S, D'Souza C, Haboubi NY. Patterns of clinical presentation of adult coeliac disease in a rural setting. Nutr J 2006;5:24.

7. Sanders DS, Hurlstone DP, Stokes RO, Rashid F, Milford-Ward A, Hadjivassiliou M, et al. Changing face of adult coeliac disease: experience of a single university hospital in South Yorkshire. Postgrad Med J 2002;78:31-33.

8. Sharma N, Butterworth J, Cooper BT, Tselepis C, Iqbal TH. The emerging role of the liver in iron metabolism. Am J Gastroenterol 2005;100:201-206.

9. Andrews NC, Schmidt PJ. Iron homeostasis. Annu Rev Physiol 2007;69:69-85.

10. Gunshin H, Mackenzie B, Berger UV, Gunshin Y, Romero MF, Boron WF, Nussberger S, Gollan JL,

Hediger MA. Cloning and characterization of a mammalian proton-coupled metal-ion transporter. Nature 1997;388:482-488.
11. Donovan A, Brownlie A, Zhou Y, Shepard J, Pratt SJ, Moynihan J, et al. Positional cloning of zebrafish ferroportin1 identifies a conserved vertebrate iron exporter. Nature 2000;403:776-781.
12. Morgan EH, Oates PS. Mechanisms and regulation of intestinal iron absorption. Blood Cells Mol Dis 2002; 29:384-399.
13. Sharma N, Laftah AH, Brookes MJ, Cooper B, Iqbal T, Tselepis C. A role for tumour necrosis factor alpha in human small bowel iron transport. Biochem J 2005; 390:437-446.
14. Laftah AH, Sharma N, Brookes MJ, McKie AT, Simpson RJ, Iqbal TH,
Tselepis C. Tumour necrosis factor alpha causes hypoferraemia and reduced intestinal iron absorption in mice. Biochem J 2006; 397:61-67.
15. O'Keeffe J, Lynch S, Whelan A, Jackson J, Kennedy NP, Weir DG, et al. Flow cytometric measurement of intracellular migration inhibition factor and tumour necrosis factor alpha in the mucosa of patients with coeliac disease. Clin Exp Immunol 2001;125:376-382.
16. Sharma N, Begum J, Eksteen B, Elagib A, Brookes M, Cooper BT, Tselepis C, Iqbal TH. Differential ferritin expression is associated with iron deficiency in coeliac disease. Eur J Gastroenterol Hepatol. 2009; 21(7):794-804.

Gluten and Diabetes Mellitus

Sabine Hogg-Kollars
MSc, Dip NT, PhD student at the University of Birmingham & college lecturer for the Irish Institute of Nutrition and Health

Objective of this presentation was to investigate the relationship between the gluten induced disorders coeliac disease (CD)/ non coeliac gluten sensitivity (NCGS) and type 1 diabetes mellitus (T1DM).

CD is an autoimmune condition caused by a reaction to gluten, a protein constituent found in wheat, rye, barley and to a lesser degree also in oats. The toxic effects of gluten on the intestinal cells in sensitive subjects include inflammation through toxic gluten oligopeptides, the reduction of the F-actin component and rearrangement of the cytoskeleton, the inhibition of cellular growth, induction of apoptosis and villous atrophy.

While CD affects 1% of the general population, its prevalence is up to 10 times higher in populations with T1DM. Like CD type 1 diabetes mellitus is an autoimmune condition. It affects 0.4% of persons of European origin and is associated with a great number of complications.

Both conditions are found in people who show a variation of the HLA-DQB1 gene. As part of the HLA family, this gene helps the immune system distinguish the body's own proteins from those made by foreign invaders such as bacteria and viruses.

Due to the high prevalence of CD in T1DM, it is recommended that diabetes subjects should be screened for CD. While in most cases CD is present at onset of T1DM, in 90% of patients diabetes is diagnosed before CD. Suffering from CD also increases the risk of developing conditions such as osteoporosis, small bowel cancer or lymphoma. Furthermore living with more than two long-term conditions such as T1DM and CD has been shown to severely compromise life quality.

The diagnosis of CD can be challenging. Although IgA tissue transglutaminase antibodies (tTGA) and endomysial antibodies (EMA) are the primary diagnostic markers in CD, negative test results do not 100% rule out the condition. Some people with T1DM may not have positive antibody results for CD early in their diagnosis; they may become antibody positive later on. If antibodies are positive or CD is suspected an intestinal biopsy is recommended.

A gluten free diet may improve diabetes control, diabetes symptoms and reduce the frequency of hypoglycaemia and insulin requirements. Nutrient

status and the life quality of patients may also be improved.

NCGS is a gluten-induced disorder characterised by the absence of allergic or autoimmune mechanisms. It presents with symptoms resembling those seen in CD. How far diabetes might also be associated with GS and what might be the impact of a gluten-free diet in these patients will only be determined by future research.