Abstracts/Poster Abstracts Falk Symposium 193

Celiac Disease and Other Small Bowel Disorders

September 5 – 6, 2014
Beurs van Berlage
Amsterdam,
The Netherlands

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Falk Symposium 193

CELIAC DISEASE AND OTHER SMALL BOWEL DISORDERS

Amsterdam (The Netherlands)
September 5 – 6, 2014

Scientific Organization:
C.J.J. Mulder, Amsterdam (The Netherlands)
D. Schuppan, Mainz (Germany)
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* = Posters of Distinction
Session I

Immunology of Celiac Disease and the Small Intestine
Small bowel, celiac disease and adaptive immunity

Centre for Immune Regulation, Department of Immunology, University of Oslo and Oslo University Hospital – Rikshospitalet, 0372 Oslo, Norway

Genetic evidence suggests that adaptive immunity is important in the pathogenesis of celiac disease. MHC is by far the single most important genetic factor of the disease. A large number of non-MHC genes of which the majority have functions related to T cells and B cells also contribute to the genetic predisposition, but each of them has modest effect. The primary MHC association is with HLA-DQ2 and HLA-DQ8. These HLA molecules present gluten epitopes to CD4⁺ T cells which can be considered to be the master regulators of the immune reactions that lead to the disease. The epitopes the T cells recognize are usually deamidated, and this deamidation is mediated by the enzyme transglutaminase 2 (TG2). Celiac disease patients have disease-specific antibodies. In addition to antibodies to gluten, these include antibodies to TG2. Antibodies to deamidated gluten are as specific for celiac disease as the anti-TG2 antibodies. Both types of antibodies appear only to be produced in subjects who are HLA-DQ2 or HLA-DQ8 when they are consuming gluten. It is hardly coincidental that TG2 is implicated in T-cell epitope formation and at the same time is a target for autoantibodies. Understanding this connection is one of the major challenges for obtaining a complete understanding of how gluten causes tissue destruction and remodelling of the mucosa in the small bowel.
Interleukin 15, a master piece in the immunological puzzle of celiac disease

Nadine Cerf-Bensussan
Université Paris Descartes, Medical School, INSERM U989, Paris, France

The immune response causing coeliac disease depends on the activation of intestinal CD4⁺ T cells by gluten-derived peptides presented by HLA-DQ2 or HLA-DQ8, the main genetic risk factor. Yet it is now clear that gluten presentation to CD4⁺ T cells is necessary but not sufficient and that other factors are necessary to impair immune tolerance to dietary gluten, stimulate the activation of CD8⁺ T intraepithelial lymphocytes and to induce intestinal damage. We will discuss in situ and ex vivo data in humans that point out to the role of Interleukin 15 (IL-15) in the expansion and activation of intraepithelial lymphocytes, and in impairing responses of effector T cells, notably CD8⁺ to regulatory T cells. Using a mouse model we will show that IL-15 produced in excess in the intestine can cooperate with CD4⁺ T cells specific of a dietary antigen to trigger a celiac-like enteropathy. In this model, CD4⁺ T cells activated by the dietary antigen secreted interleukin 2 which, along with IL-15, stimulated the expansion of non-cognate intestinal cytotoxic CD8⁺ T cells containing large amounts of granzyme B. In the presence of IL-15, the latter cells did not respond to regulatory T cells, and accumulated in the intestine close to epithelial damage. We will further discuss the central role of IL-15 in refractory celiac disease and provide evidence that IL-15 is a meaningful target in this rare but severe complication of CD.
Cellular basis of tolerance and immunity in the intestine

Allan Mcl Mowat
Centre for Immunobiology, Institute of Infection, Immunity and Inflammation, University of Glasgow, Scotland

The immune system in the intestine is the largest and hardest working compartment of the immune system. It is constantly challenged by a wide variety of antigens and other environmental materials, some of which are potentially harmful, while others like dietary components and commensal microbes are beneficial to the host. Strong protective immune responses have to be generated against pathogens, but similar reactions to harmless materials would be wasteful and in fact lead to disorders like coeliac disease and Crohn’s disease. A number of factors contribute to preventing such inflammatory disorders, in which effector CD4\(^+\) T cell responses are generated inappropriately against dietary gluten and commensal bacteria respectively. The first layer of regulation consists of specialised subsets of CD103\(^+\) dendritic cells (DC) found in the normal intestinal mucosa which take up soluble protein antigens from the lumen. These migrate to meet naïve T cells in the draining mesenteric lymph node and drive the generation of regulatory T cells that home back to the mucosa, where they maintain immunological tolerance by preventing the induction of effector T cells. The largest population of these “tolerogenic” DC is unique to the intestine and their effects on T cell differentiation are due to their ability to produce retinoic acid from dietary vitamin A. Although not yet proven, it seems likely that the breakdown in tolerance which leads to pathogenic T cell responses in coeliac disease results from changes in the behaviour of the local DC populations, perhaps driven by the innate immune responses generated by the pro-inflammatory components of gliadin. Whether this involves changes in the same DC that normally induce tolerance, or requires a different subset of DC is an important topic for research. Within the mucosa itself, there are also other mechanisms that help prevent inflammatory responses. The most important of these are the resident macrophages which produce high levels of the cytokine IL10. This not only inhibits local inflammatory responses and maintains DC in a quiescent state, but also maintains the survival of regulatory T cells that have made their way to the mucosa. During inflammation, an influx of potentially inflammatory monocytes changes the local environment, increasing the risk of chronic inflammation and tissue damage. Elucidating how these intestine specific regulatory mechanisms are normally maintained and how they are dysregulated in disease will be important for understanding the pathogenesis of coeliac disease and other conditions.
Host-microbiota interactions in the intestine

Charles O. Elson, M.D.
University of Alabama at Birmingham, Birmingham, AL, USA

Humans and other mammals have co-evolved with a variety of bacterial species, termed “microbiota”, in a complex fashion that affects both innate and adaptive immunity. Multiple host innate mechanisms contribute to intestinal homeostasis, including epithelial production of protective mucin layers maintaining spatial segregation in the intestine and epithelial cell secretion of a range of antimicrobial peptides. Epithelial cells use autophagy to contain and eliminate invading bacteria; interestingly, genetic variants in certain autophagy genes are linked to Crohn’s disease. Innate lymphoid cells, which rapidly respond to cytokine and microbial signals, have emerged as important regulators of the intestinal immune response to the microbiota. In regard to adaptive immunity, specific microbial species stimulate induction of regulatory T cells and others induce effector T cells within the gut. Such stimulation is subject to dysregulation during inflammation and disease. An abnormal composition of the microbiota, termed “dysbiosis”, has now been associated with a variety of immune-mediated inflammatory disorders, including Celiac disease. The microbiota communicates with the immune system and vice versa, thus an abnormal microbiota composition likely translates into an altered host immune response, but the details of such are not yet clear. IgA plays an important role in limiting bacterial access to the host and in maintaining mutualism with the microbiota. Perturbation of the mucosal barrier via infection or other means can induce effector T cells reactive to the intestinal microbiota, which can persist as memory cells for extended periods of time, and potentially serve as pathogenic effector cells upon re-encounter with antigen. Health is associated with a diverse microbiota that appears to maintain the balance between T effector and T regulatory cells in the intestine. Whether dysbiosis can be reversed in immune-mediated disease, thus restoring health is a question of intense interest that is as yet unanswered.
Session II

Celiac Disease: Clinical Perspective
Clinical manifestations of celiac disease

Peter H.R. Green
Celiac Disease center, Columbia University, New York, NY, USA

The clinical presentation of celiac disease has changed. Originally described as a disease of childhood characterized by malabsorption and steatorrhea, silent presentations now predominate. The change can be attributed to both a changing nature of the disease as well as the availability of serological screening tests. The rate of diagnosis however is low with < 20% of those with celiac disease in the United States aware that they have the disease. The modes of presentations vary with age. Children present mainly with recurrent abdominal pain, growth issues or through screening of at risk groups (family members, Down syndrome or autoimmune diseases). Malabsorption and diarrhea occurs in < 10% of children. Adults present with predominantly with diarrhea; anemia, osteoporosis, incidentally at endoscopy and through screening of at risk groups accounts for other main modes of presentation. Many have had a previous diagnosis of IBS. Females are diagnosed more frequently than males (~2:1), however, presentations in the different genders vary with age. Males are diagnosed predominantly in childhood and as elderly. The rate of diagnosis in young adult males is especially low. There may be important geographic variations in the presentation of celiac disease between males and females. While the majority of those with celiac disease have a normal BMI both children and adults can have a low BMI or be obese. In a large cohort we noted adult males with celiac disease to be shorter than men in the general population in the United States while women were slightly taller than their peers. Clinical presentation does not correlate with the degree of villous atrophy in duodenal biopsies.
World perspective and celiac epidemiology

Carlo Cata
Department of Pediatrics, Università Politecnica delle Marche, Ancona, Italy

CD is a common disorder in many parts of the world. In countries mostly populated by people of European origin (Europe, Americas, Australia and New Zealand) the mean prevalence of CD in the general population is around 1%, with a large inter-country variability. For instance, the prevalence of CD is as high as 2–3% in Finland and Sweden, while it is only 0.2% in Germany, for reasons that are currently unclear. CD is a common disorder in North Africa and Middle East countries, whereas there are only anecdotal reports of CD in Sub-Saharan African countries. The frequency of CD in India seems to be higher in the Northern part of the country, so called “celiac belt”, a finding that is at least partially explained by the wheat-rice shift from the North to the South. Both CD-causing factors, i.e. gluten consumption and HLA predisposing genotypes DQ2 and DQ8 are present in China. Nevertheless the evidence of the existence of CD in the Chinese population has been poor so far. CD is likely to be rare in Japan, Indonesia, Korea, the Philippines and many smaller Pacific islands because of low wheat consumption and a low frequency of HLA-DQ2.

Although the incidence of clinically diagnosed CD cases is increasing, still the larger part of the “celiac iceberg” remains undetected, mostly related to paucity of symptoms and poor disease awareness. In Europe and North America the ratio between known and undetected cases usually ranges between 1:3 and 1:10. In India only a few thousand cases of CD have been detected out of the estimated 5–10,000,000 affected individuals. The overall prevalence of CD is on the raise as well. A recent US study showed that CD prevalence was only 0.2% in the year 1975, and increased five-fold during the following 25 years. The reasons for this change are unclear, but have to do with the environmental components of CD.

As far as policies of disease detection, the debate on mass screening versus case-finding is still open. The major limitations of mass serological screening are (1) difficulty in establishing the proper screening age, due to variability in the natural history of loss of gluten tolerance, and (2) ethical issues in treating subjects with clinically silent CD, due to incomplete knowledge of risks of complications. Conversely, the efficacy of the celiac case-finding (serological testing of at-risk individuals) is poor, with more than 50% cases remaining undiagnosed.
How to diagnose extra-intestinal celiacs?

Julio C. Bai
Professor, Gastroenterology Chair, Universidad del Salvador, Dr. Carlos Bonorino Udaondo Gastroenterology Hospital, Av. Caseros 2061, (1264) Buenos Aires, Argentina, E-Mail: jbai@intramed.net

The “Oslo consensus” has recently defined celiac disease (CD) as a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals. Typically, CD is characterized by gastrointestinal symptoms.

Both, the increased awareness of complications of CD in combination with the advent of highly sensitive and specific serological tests have dramatically increased the identification of patients among subjects having a higher risk for the disorder. Case finding is now becoming more and more common and is conducted in a wide range of clinical situations ranging from the presence of gastrointestinal symptoms (diarrhoea, abdominal pain and distension), failure to thrive in children, prolonged fatigue, unexpected weight loss, anemia, through the presence of associated conditions (autoimmune thyroid disease, dermatitis herpetiformis, irritable bowel syndrome, or type 1 diabetes), to patients with unexplained neuropsychiatric disorders and to first degree relatives of celiacs. This aggressive active case finding, introduced in the last decades, has dramatically changed the clinical characteristics of newly diagnosed patients. In such context, increasing numbers of CD patients are now diagnosed because of an extra-intestinal phenotype with a diversity of symptoms affecting many different systems. On the bases of a high risk for complications, current recommendations confirm that patients with extra-intestinal symptoms due to CD deserve diagnosis and treatment. Furthermore, such aggressive approach has been considered as cost-effective for high risk groups, while it is recognized that many patients with CD will still be missed by this strategy. Diagnosis of CD among patients with extra-intestinal symptoms requires a high degree of awareness about clinical conditions that carry a high risk for underlying CD and the correct use of specific serology and duodenal histology. Both procedures combined are able to confirm diagnosis in the vast majority of cases. However, in certain circumstances, serology and even duodenal histology cannot confirm or rule out CD. A common cause of negative IgA serology is IgA deficiency. For such eventuality, IgG-based serological tests can help confirm the diagnosis. Importantly, some histologically diagnosed cases still remain seronegative despite exclusion of IgA deficiency. On the other hand, duodenal histology may be normal despite the presence of CD specific antibodies and an active disorder. This has been clearly demonstrated in some cases of untreated dermatitis herpetiformis, but may also be due to patchy disease, or lesions that are not adequately recognized by non-expert endoscopists and/or pathologists. In conclusion, a widespread alert and a high status of knowledge are essential for diagnosing extra-intestinal CD.

The gluten-free diet is an effective treatment for symptomatic CD and the benefits are well established decreasing clinical symptoms as well as risk of complications. However, the effectiveness of this diet depends on the clinical end point addressed. A good example is the outcome of malabsorption-induced extra-intestinal manifestations such as the bone loss. While the fracture risk normalizes after the first year of
dietary treatment, bone parameters measured by densitometry may not be normalized in the long term follow-up. Moreover, it is still unclear how far an early gluten free diet may positively affect associated autoimmune diseases like type 1 diabetes and autoimmune thyroiditis.
Celiac disease and associated endocrine autoimmunity

George J. Kahaly and Detlef Schuppan*
Department of Medicine I and *Institute of Translational Immunology, Johannes Gutenberg University Medical Center, Mainz, Germany

Autoimmune endocrine diseases (AED) may cluster with several autoimmune disorders. We prospectively evaluated the close relationship between celiac disease (CD) and AED. In an academic referral center for autoimmune diseases with a joint thyroid-gastrointestinal outpatient clinic, demographic and clinical data were obtained from a large collective of consecutive patients with CD and their first-degree relatives. Serological, endocrine and genetic investigations were performed in all subjects. Also, three internationally validated psychometric tests were applied. Endocrine autoimmune diseases, i.e. type 1 diabetes, autoimmune thyroid diseases, Addison’s disease and the polyglandular failure syndrome, were present in approximately two-third and one third of CD patients and their relatives, respectively. Hashimoto’s thyroiditis was the most prevalent AED in patients with CD and their relatives. The following HLA-haplotypes were prevalent in the CD patients: DQ2.5 heterozygous, DQ2.5 homozygous, DQ2.5/DQ2.2, and DQ2.5/DQ8. AED were mostly present in the DQ2.5/DQ8 and heterozygous DQ2.5 carriers, respectively. Nearly all relatives with the DQ2.5/DQ8 had endocrine autoimmune diseases. The psychometric tests showed markedly impaired quality of life scores and significantly higher fatigue in CD patients with AED. In conclusion, this prospective controlled study highlights the close relationship between celiac disease and endocrine autoimmunity and recommends immune genetic, endocrine and serological screening for patients with CD and their relatives. Early detection of autoantibodies and latent organ-specific dysfunction is advocated to alert physicians to take appropriate action in order to prevent full-blown disease.
Session III

Celiac Disease
Celiac disease: Prevention in children

M. Luisa Mearin
Department of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands

Celiac disease is an autoimmune disorder caused by ingestion of gluten in genetically predisposed individuals. In the last years, several studies suggested a protective role of breast feeding and/or the timing and quantity of gluten introduction in the subsequent development of celiac disease. Especially, prolonged breast feeding during the introduction of gluten-containing feeding has been associated with a reduced risk of developing celiac disease in infancy.

Much knowledge about gluten introduction and CD has been obtained from the Swedish epidemic of symptomatic CD during the mid-1980s. The start of the epidemic was related to new dietary recommendations, delaying the introduction of all gluten-containing food to infants until 6 months of ages. The incidence of CD diminished when earlier introduction of gluten (> 4 months) was reintroduced in Sweden. In contrast, another study in Sweden failed to show any association between timing of gluten introduction and risk of CD.

Besides the main role of timing of gluten introduction, the Swedish epidemic suggests that the amount of gluten introduced to young children plays a role in the development of CD. This CD epidemic with regard to gluten exposure was characterized by higher amounts of gluten in infant feeding. Later analysis revealed that especially in children under the age of 2 years, the CD risk was greater when gluten was introduced in large amounts than when introduced in small or medium amounts.

During the first months of life, breast feeding is the optimal feeding for infants. The question is whether breast feeding can protect against the development of CD. Several studies evaluated the role of breast feeding beyond gluten introduction and the risk of CD. A systemic review and meta-analysis, including all studies published on this topic between 1966 and 2004, found that children being breast fed compared to those who were not breast fed at the time of gluten introduction had a 52% risk reduction of developing CD. However, till recently all studies investigating early nutrition and CD had been observational and retrospective. The prospective, observational study by Norris et al. showed that both early (< 3 months) and late (> 7 months) introduction of gluten was associated with an increased development of CD autoimmunity in children with an increased risk of CD and type 1 diabetes mellitus. However, this study did not quantify the amount of gluten ingested and did not confirm the diagnosis of CD with small bowel biopsies. The mentioned results suggest the existence of a "window of opportunity" between 4–6 months of age in which gluten can be introduced in small amounts. Therefore, the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommends that complementary feeding should not be introduced before 17 weeks and not later than 26 weeks and that it is prudent to avoid gluten introduction before the age of 4 months and after the age of 7 months and gluten should be preferably introduced during on-going breast feeding. However, the influence of breast feeding in the development of CD is not well understood, since some studies report prevention and others not and the studies reporting a protective effect of breast feeding do not make
clear if it concerns prevention of the disease or delays the onset of symptoms. For these reasons more prospective studies are needed to fully understand the relationship between breast feeding in particular and for early nutrition in general concerning the development and possible prevention of CD. In order to investigate this, a prospective European multicentre CD research project, Prevent Coeliac Disease (PreventCD), was initiated. The hypothesis of PreventCD (www.preventcd.com) is that it may be possible to induce tolerance to gluten by exposing genetically predisposed infants to small quantities of gluten, preferably while they are still being breast-fed. The optimal method to investigate the influence of early feeding on the development of CD is a prospective, randomised, placebo-controlled intervention study in newborns with long-term follow up. The above-mentioned PreventCD family study is such a multicentre study among infants with a first degree family member with CD and carrying HLA-DQ2 and/or -DQ8(2). From 2007–2010, soon after birth, and after parental informed consent, the children were randomized to a double-blind dietary intervention with 100 mg of gluten daily or placebo, between the age of 4–6 months. The children are repeatedly screened for CD. Breast feeding for at least 6 months was explicitly encouraged. The gluten intake is quantified and the breast feeding is analysed. All included children are already 3 years old, and the first analyses are being prepared (http://www.trialregister.nl).
Celiac disease in Southern and East Asia

Govind K. Makharia, MD, DM, DNB, MNAMS
Professor, Department of Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, New Delhi, India

Once thought to be rare elsewhere and occurred mainly in the Western Europe, celiac disease (CD) is now a common disease affecting approximately 1% of the world’s population. After Europe, America (both North and South) and the Middle East, it is now being increasingly recognized in some Eastern and Southern Asian countries. The Asian region is currently at the crossroads of the frontier of knowledge and awareness of CD. In many Asian nations, CD is still considered to be either non-existent or very rare. A notable exception is India, where CD has been well recognized, especially in the Northern part and a population based study has revealed a prevalence of 1.04%, similar to that in Europe and North America. A few small case series from China predicts that CD exists in China. In Japan, CD-specific antibodies were present in 18% of patients with inflammatory bowel disease compared with the healthy control population of 1.6%. There are no formal reports on CD from Malaysia, Indonesia, Korea, Taiwan, Philippines, and many other nations in this region. On the basis of the current limited data, one can estimate that as many as 5–8 million people in India and perhaps a good number in other parts of Asia have CD. Once diagnosed the real number of patients with CD in Asia may outnumber the numbers present in the Europe and North America.

At present the level of awareness about CD amongst health care professionals and general population is low. Although absolute number of patients with CD at present is not very large, this number is expected to increase over the next few years or decades. It is thus appropriate that medical community across the Asia define extent of problem and get prepared to handle impending epidemic of CD. In recognition of such heterogeneity of knowledge and awareness in Asia, the World Gastroenterology Organization and Asian Pacific Association of Gastroenterology commissioned a Working Party and highlighted the issues specific to CD in Asia-Pacific region. Some of the efforts which, are required to be made include determination of prevalence of CD across the region, spreading of awareness among physicians and patients, training of dieticians for proper counseling and supervision of patients, creation of gluten-free food infrastructure in the food supply and creation of patient advocacy organizations.
Celiac disease and the gluten-free diet: Consequences and recommendations for improvement

Thimmaiah Theethira and Melinda Dennis
Celiac Center, Beth Israel Deaconess Medical Center, Boston, MA, USA

Background: Celiac disease [CD] is a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically susceptible individuals. CD related enteropathy leads to multiple nutritional deficiencies involving macro and micronutrients. Currently, medical nutrition therapy consisting of the gluten-free diet [GFD] is the only accepted treatment for CD.

Key messages: The GFD is the cornerstone of treatment for celiac disease. Prior published studies have concluded that maintenance of the GFD results in improvement of the majority of nutritional deficiencies. In the past, counseling for CD focused mainly on the elimination of gluten in the diet. However, the GFD is not without its inadequacies; compliance to the GFD may result in certain deficiencies such as fiber, B vitamins, iron, and trace minerals.

Paucity of fortified gluten-free foods may be responsible for certain deficiencies which develop on the GFD. Weight gain and obesity have been added to the list of nutritional consequences while on the GFD and have been partially attributed to hypercaloric content of commercially available gluten-free foods. Follow-up of patients diagnosed with CD after starting the GFD has been reported to be irregular and, hence, less than ideal.

Conclusions: Monitoring of the nutritional status using blood tests and use of appropriate gluten-free supplementation are integral components in the management of CD. The ideal GFD should be nutrient-dense with naturally gluten-free foods, balanced with macro and micro-nutrients, reasonably priced, and easily accessible. Rotation of the pseudo-cereals provides a good source of complex carbohydrates, protein, fiber, fatty acids, vitamins and minerals. Fortification/enrichment of commonly consumed gluten-free commercial grain products should be encouraged. Dietitians specializing in CD play a critical role in the education and maintenance of the GFD for patients with CD.
Eosinophilic enteritis

G. Pineton de Chambrun
Gastroenterology Department, Lille University Hospital, North of France University, Lille, France

Eosinophilic enteritis also known as eosinophilic gastroenteritis is a rare primary gastrointestinal disorder of unknown etiology characterized by the presence of an intense eosinophilic infiltrate on histopathology of one or multiple segments from the esophagus to the rectum. It is part of the primary Eosinophil-associated Gastrointestinal Disorders (EGIDs) that also include eosinophilic esophagitis and allergic eosinophilic colitis. EGIDs are characterized by an eosinophil-rich inflammation of the gastrointestinal tract in the absence of known causes for eosinophilia (eg, drug reactions, parasitic infections, and malignancy). The etiology of eosinophilic enteritis and gastroenteritis remains obscure. There is growing evidence to support the role of aeroallergens and food allergens in the pathogenesis of these disorders as children and adults with EGIDs often have positive skin testing to food allergens and a familial history of allergic diseases. Moreover, significant progress has been made in elucidating that eosinophilic gastrointestinal disorders involve mechanisms that fall between pure IgE-mediated and delayed TH2-type responses. Preclinical studies have identified a contributory role for the cytokine IL-5 and the eotaxin chemokines, providing a rationale for specific disease therapy. Eosinophilic gastroenteritis causes a wide array of gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, vomiting, bloating or ascites and its diagnosis requires a high degree of clinical likelihood, given the nonspecific presentation and physical examination findings. The Klein classification arbitrarily divided patients with eosinophilic gastroenteritis into those with predominantly mucosal, muscle layer or subserosal disease relying on the concept that clinical presentation is dependent on the predominant involved layer of the gastrointestinal tract. Since its first description by Kaijser in 1937, less than 300 cases have been reported, most of them as single case reports or rather small case series. Main therapeutic options are represented by oral corticosteroids for a short period with a good efficacy. Antihistaminic drugs and sodium chromoglycate have also been used to treat patients with eosinophilic gastroenteritis. Eosinophilic gastroenteritis is generally considered as a benign disease with no relapse but half of patients may present a more complex natural history characterized by unpredictable relapses and a chronic course.
Whipple’s disease and other rare infections

T. Marth
Innere Medizin, Krankenhaus Maria Hilf, Daun, Germany

The availability of molecular diagnostic tools such as polymerase chain reaction (PCR), immunohistochemistry, and bacterial culture have brought forward the understanding of the clinical spectrum and natural course of *Tropheryma whipplei* infection and of Whipple’s disease (WD).

WD affects in its classical form preferentially middle-aged white men, who may present with weight loss, arthralgia, diarrhea, and abdominal pain. In addition, WD disease may be localized, i.e. without gastrointestinal involvement. Individuals with isolated heart valve involvement may present as culture-negative endocarditis, or patients with affection of the central nervous system with a variety of neurological symptoms. The clinical course of WD may be influenced by immunosuppressive treatment, which is instituted in patients with unclear arthropathy, prior to the diagnosis of WD. An acute and transient infection with *T. whipplei* has been observed in children with fever, cough and diarrhea. Asymptomatic carriers of *T. whipplei* in different frequencies have been described (4% healthy individuals, 20% sewage plant workers, 38% family members).

The diagnosis of WD often is established by small bowel biopsy, which is characterized by periodic acid-Schiff (PAS)-positive inclusions representing the causative bacteria. *T. whipplei* can be detected by specific PCR, immunohistochemistry, or electron microscopy, and has been cultured. PCR can be performed on different biopsy samples and many body fluids.

The hallmark of WD is the invasion of the intestinal mucosa with macrophages incompetent to degrade *T. whipplei*. Several studies show that an immunologic defect in the pathogenesis of WD is evident and includes macrophages, T cells and an impaired humoral immune response, which may predispose individuals with a certain HLA type to a clinical manifestation of *T. whipplei* infection.

Most WD patients respond well to prolonged antibiotic treatment with ceftriaxone and cotrimoxazole. Other, alternative treatment regimens will be discussed. Some patients may develop an immune reconstitution inflammatory syndrome (IRIS) which may be successfully treated by corticosteroids. In few WD patients with relapsing disease or with CNS manifestations prognosis may be poor.

In the differential diagnosis to WD, several other infectious disorders have to be considered. For example, there is a quite frequent association of WD with giardiasis. Mucosal immunity plays an essential role in the susceptibility to infection with Giardia lamblia. Similarly, complicated strongyloidiasis occurs when host immunity is impaired. The clinical features and pathogenesis of postinfectious tropical malabsorption, i.e., tropical sprue, are discussed as well.
Motility disorders in celiac disease versus non-celiac gluten sensitivity

Elena F. Verdu
Farncombe Family Digestive Health Research Institute McMaster University, Hamilton, Ontario, Canada

Regulation of gut motility is complex involving neuromuscular, immune and environmental mechanisms. It is well established that patients with celiac disease (CD) often display gut dysmotility. Studies have shown the presence of disturbed esophageal motility, altered gastric emptying, and dysmotility of the small intestine, gallbladder, and colon in untreated CD. Most of these motility abnormalities resolve after a strict gluten-free diet suggesting that mechanisms related to the inflammatory condition and disease process are responsible for the motor dysfunction. Motility abnormalities are also a hallmark of functional bowel disorders such as irritable bowel syndrome (IBS), where it has been proposed as underlying mechanism for symptom generation (diarrhea, constipation, bloating). Non-celiac gluten sensitivity (NCGS) is a poorly defined entity, mostly self-diagnosed, and that presents clinically with IBS symptoms in the absence of specific celiac markers. Patients with NCGS are believed to react symptomatically to wheat components, and some studies have proposed the presence of low-grade inflammation in these patients. There is little information regarding the functional characterization of these patients before and after a gluten free diet. A study suggested the presence of altered gastrointestinal transit in NCGS patients who also have a high prevalence of non-specific anti-gliadin antibodies. Results of an ongoing clinical study in NCGS patients with positive anti-gliadin antibodies before and after a GFD will be discussed. Elucidating the mechanisms for symptom generation in NCGS patients is important to find new therapeutic alternatives to the burden of imposing a strict GFD in patients who do not have celiac disease.

G. Bouma
Vrije Universiteit, Medisch Centrum, Afd. MDL, Amsterdam, The Netherlands

Microscopic colitis is the common denominator for lymphocytic and collagenous colitis. Patients with microscopic colitis report watery, non-bloody diarrhea that may follow a chronic, intermittent or chronic recurrent course. Patients are typically middle-aged women but disease may occur at every age. Endoscopic and radiologic analyses usually do not reveal abnormalities. Colonic biopsies show in both collagenous and lymphocytic colitis an increased mononuclear infiltration of the lamina propria, whereas lymphocytic colitis is characterized by increased number of intraepithelial lymphocytes and collagenous colitis by a thickened subepithelial collagen deposition. The pathogenesis of microscopic colitis is largely unknown, and may relate to autoimmunity, adverse reactions to drugs or (bacterial) toxins, and abnormal collagen metabolism in the case of collagenous colitis. Treatment options include budesonide, mesalamine, cholestyramine, and thiopurines, although well-designed randomized clinical trials are limited. Budesonide is beneficial in the induction and maintenance of remission, which is of relevance considering the high relapse rate after cessation of treatment. The long-term prognosis of microscopic colitis is good; it does not appear to predispose to malignancies and can be self-limiting. Future research and randomized clinical trials are required to expand our understanding of the pathogenesis of microscopic colitis and on the available therapy for induction and especially maintenance of remission.
Drug-induced celiac-like lesions

Eric Marietta$^{1,2,3}$, Ashley Nadeau$^3$, Amanda Cartee$^3$, Alberto Rubio-Tapia$^3$, and Joseph Murray$^{1,3}$

$^1$Department of Immunology, Mayo Clinic College of Medicine, Rochester, MN, USA
$^2$Department of Dermatology, Mayo Clinic College of Medicine, Rochester, MN, USA
$^3$Department of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN, USA

Background: Olmesartan Associated Enteropathy (OAE) is characterized by abdominal pain, nausea, diarrhea, weight loss, and severe sprue-like enteropathy. Discontinuation of olmesartan medoxomil by OAE patients results in the resolution of all of these symptoms and healing of the enteropathy. Olmesartan is a potent non-competitive irreversible angiotensin type 2 receptor blocker (ARB). Many other ARBs exist, including losartan, telmisartan, and valsartan. Thus far, more than 50 cases of olmesartan associated enteropathy have been identified worldwide, and we have identified one case of Valsartan associated enteropathy.

Objective: To examine the cell types associated with intestinal injury of OAE patients and to determine if mechanistic pathways present in celiac sprue also exist in OAE.

Methods: Paired duodenal biopsies were extracted from OAE patients when first diagnosed (on olmesartan) and after discontinuation of olmesartan (off olmesartan). These biopsies were then formalin-fixed, paraffin-embedded and stained with anti CD8, CD4, granzyme B, FoxP3, and psmad2/3. Caco-2 cells, a colonic epithelial cell line, were directly stimulated with olmesartan medoxomil (Benicar), Losartan, or Telmisartan. Immunofluorescent analysis with confocal laser microscopy was done for the expression/distribution of ZO-1 by Caco2 cells treated with olmesartan, losartan, or telmisartan.

Results: The stomach and large intestine were also found to be affected by olmesartan. Of 35 OAE patients evaluated at the Mayo Clinic, at least 8 of the 35 also had gastritis. In addition, 3 had Crohn’s disease, and 12 had microscopic colitis. Histological analysis of the small intestine of OAE patients revealed a significant increase in the number of CD8$^+$ cells present in the duodenal biopsies of OAE patients on olmesartan. Granzyme B$^+$ and Foxp3$^+$ cells were also increased while on olmesartan. In contrast, the numbers of CD4$^+$ cells found in the duodenum did not change with the administration of olmesartan. ZO-1 tight junction proteins were disrupted after treating Caco2 cells with olmesartan but not with losartan or telmisartan.

Conclusions: OAE has many similarities with celiac disease. These include similar clinical symptoms as well as increased numbers of CTLs and enteropathy. Further, ZO-1, a tight junction protein, is disrupted by olmesartan treatment of the Caco-2 cell line, again similar to celiac disease. Taken together, olmesartan medoxomil exerts a response by intestinal epithelial and non-epithelial cells that is similar to that induced by gluten and may explain why OAE and celiac disease are similar in both presentation of clinical symptoms and histopathological events in the intestinal epithelium.
Session V

Refractory Celiac Disease
Origin of aberrant lymphocytes in RCD

Frederike Schmitz¹, Yvonne Kooy-Winkelaar¹, Anna-Sophia Wiekmeijer¹, Martijn H. Brugman¹, M. Luisa Mearin², Chris Mulder³, Susana Chuva de Sousa Lopes⁴, Christine L. Mummery⁴, Frank J.T. Staal¹, Jeroen van Bergen¹*, Frits Koning¹*
¹Immunohematology and Blood Transfusion, ²Pediatrics, ⁴Anatomy and Embryology, Leiden University Medical Center, Leiden, and ³Gastroenterology, Free University Medical Center, Amsterdam, The Netherlands
*equal contribution

Active celiac disease (CD) is characterized by an oligoclonal expansion of intraepithelial T cells (T-IEL), whereas refractory celiac disease type II (RCDII), a severe complication of CD, is defined by the clonal expansion of Lineage-negative (Lin⁻) IEL that can transform into overt lymphoma. Previously we demonstrated that CD3-negative IEL could be divided into 4 phenotypically distinct subsets based on the expression of CD56 and CD127. To gain insight into their function and relationship we here determined the phenotype, composition and differentiation potential of this innate IEL compartment in non-celiac controls as well as in patients with CD and RCDII. Unsupervised hierarchical clustering analysis of the expression of 14 NK and T cell surface markers demonstrated that the innate IEL subsets cluster together and separate from T-IEL. Moreover, co-expression of the IL7R, IL21R and IL15Rα was a hallmark of CD127⁺ innate IEL while CD127⁻ innate IEL expressed IL2/15Rβ. Age and disease dependent alterations in both the T-IEL and innate IEL compartments were observed, in particular a significant increase in the proportion of Lin⁻CD127⁺IEL and Lin⁻CD127⁺IEL expressing intracellular CD3ε and CD3γ in patients with RCD. In vitro, in the presence of IL-15, Lin⁻CD127⁺IEL from controls and patients with CD, but not from RCDII patients, gave rise to cultures containing both NK and T cells, the latter largely dependent on notch-signalling. Together our data reveal complexity and plasticity of the innate IEL compartment that is influenced by age and disease and provide evidence that innate IEL have the ability to give rise to NK and T cells. This developmental plasticity may allow rapid responses to local cues in health and disease.
Epidemiology and manifestations of refractory celiac disease

Prof Christophe Cellier 1,2,3
French Celiac Disease Center, Paris; 1Université Paris Descartes-Sorbonne Paris Centre; 2Gastroenterology Department, Hôpital Européen Georges Pompidou APHP, Paris; 3Inserm U989; Hôpital Européen Georges Pompidou APHP Paris, France
E-Mail: christophe.cellier@egp.aphp.fr

RCD is defined by persisting malabsorption and villous atrophy after one year of strict GFD assessed by a dietician, since that less than 50% of patients are compliant to the GFD. Diagnosis of RCD is made after exclusion of other causes of intestinal villous atrophy such as autoimmune enteropathy [8], tropical sprue [9] or common variable immunodeficiency (CVID) [10]. RCD has been subdivided into two subgroups according to the normal (RCDI) or abnormal phenotype of intraepithelial lymphocytes (RCDII). Whereas RCDI is hardly distinguishable from active CD, RCDII has a severe clinical presentation and a very poor prognosis and frequently progress to overt lymphoma (EATL).

Epidemiology: Frequency of RCDI and RCDII remains unknown. RCD could have been overestimated in the past because of confusion between non-responsive CD and RCD. In fact epidemiological studies remain very rare. The Derby cohort reports around 0.7% of RCDI patients in series of 713 celiac patients but diagnosis of RCDII patients was only based on aspect of ulcerative jejunitis causing possible errors leading to underestimate RCDII and over estimate RCDI. A single North American referral centre study suggests a cumulative incidence of 1.5% for both RCDI and RCDII among CD patients initially diagnosed in this centre. A higher frequency of cases of RCDI than of RCDII was also observed in two other studies from the US and from Germany. In contrast, we and other reported a higher frequency of RCDII over RCDI in two referral centers in France and Netherlands.

Manifestations: Mean age at diagnosis of RCD is around 50 years. Patients with RCDI and RCDII are primary refractory to a GFD in roughly one third and half cases, respectively. Whatever its type, RCD occurs two to three times more in women than men. RCDII has commonly a severe clinical presentation associated with endoscopic ulcerative jejunitis responsible of severe protein loss enteropathy. Symptoms are notably less severe in RCDI and clinical features are similar to those found in active CD.

Diagnosis relies on endoscopic assessment of upper gastrointestinal tract with intestinal biopsy. Double balloon enteroscopy is required in suspicion of RCDII for a better assessment of ulcers particularly for evidence of ulcerative jejunitis found in roughly 70% of patients [6, 14]. Enteroscopy allows realization of proximal small bowel biopsy necessary for definitive diagnosis and classification of RCD. In RCDI, histological examination is similar to that found in active celiac disease with villous atrophy and increased normal IEL. Not other diagnostic criteria have been yet defined for RCDI. In contrast, the hallmark abnormal population, detected by 3 combined techniques, makes the diagnosis of RCDII more specific: over 25% of the CD103+ or CD45+ IEL lacking surface CD3-T cell receptor complexes on flow cytometry or more than 50% IEL expressing intracellular CD3ε but no CD8 in formol fixed sections and/or the presence of a detectable clonal rearrangement of the
gamma-chain of the T cell receptor (TCR) in duodenal biopsies. Extension of the disease is assessed by capsule endoscopy. It requires preliminary radiological imaging of the small bowel in order to rule out stricturing disease frequently observed in RCDII. In this later condition, MRI small bowel follow-through and computed tomography scan (CT-scan) also frequently detect enlarged mesenteric lymph nodes frequently involved by abnormal cells. Besides the diagnosis of persisting villous atrophy, capsule endoscopy allows the visualization of ulcers all along the intestinal tract possibly found in RCDII patients. In conclusion, upper endoscopy, capsule endoscopy and abdominal imaging are currently three complementary exams essential for diagnosis and assessment of RCD.

In summary, concept of RCD has recently emerged and refers to two distinct entities sustained by two different pathogenic mechanisms. Diagnosis requires small bowel investigations (enteroscopy, videcapsule endoscopy) and very specialized techniques of IEL analyses (immunohistochemistry, molecular biology, flow cytometry) since the risk to progression to overt lymphoma is high. No clear cut treatment strategy is available and European Networking is mandatory on this field.
Therapy in RCD; 2014 and beyond

Vrije Universiteit, Medisch Centrum, Amsterdam, The Netherlands

Refractory coeliac disease type II (RCDII) is characterized by a continuous gluten-independent duodenal immune-activation with an extreme high risk of malignant transformation and is therefore considered as low-grade-no-mass lymphoma. RCDII is characterized by the presence of villous atrophy (MARSH IIIa–c) in combination with an aberrant intra-epithelial lymphocyte (IEL) population consisting of > 20% sCD3-CD7+iCD3+ IEL. The sCD3-CD7+iCD3+ IEL are a lineage negative (LIN-) cell population that show both intra- and extracellular heterogeneity; some IEL show CD127 and IL15Rα expression whereas others are CD127 negative and show variable IL15Rβ. Furthermore, sCD3-CD127- IEL express either an intracellular CD3ε, iCD3εγ+ or iCD3εγ- phenotype. Together with the observation that some patients express an aberrant (monoclonal) TCR-gamma-delta phenotype, this confirms the heterogeneity of the aberrant IEL population in RCDII. It is tempting to speculate that the heterogeneity of aberrant IEL found in RCDII might reflect the fact that proliferation and (pre-) malignant transformation of these IEL could take place at different time points of cellular development. Although cladribine with or without autologous stem-cell transplantation are both effective in the treatment of signs and symptoms of RCDII and improve survival as compared to symptomatic topical steroid therapy, cladribine-failures still bear a high risk of malignant transformation and the rate of EATL development in this subgroup is extremely high. It might be hypothesized that a small percentage, of phenotypical ‘different’ aberrant IEL, might be cladribine/fludarabine resistant in some patients and that those IEL evolve into EATL over time. Therefore, we hypothesize that the heterogenous nature of aberrant T-cells as described above, and the high risk of malignant transformation, requires heterogenic treatment strategies based on the phenotype of patients’ IEL evaluated using flow-cytometry. RCDII should be seen more in the light of a low-grade-no-mass lymphoma and therefore up-front personalized treatment-strategies consisting of combination therapy with cladribine/fludarabine and a receptor-specific biological might be required.
Enteropathy associated T-cell lymphoma – Treatment today and tomorrow

P. Nijeboer, G. Malamut, CJ. Mulder, G. Bouma, C. Cellier, O. Hermine, O. Visser*
VU University Medical Center Amsterdam, Amsterdam, The Netherlands
*presentation

Enteropathy-associated T-cell lymphoma (EATL) is a rare and usually rapidly fatal intestinal T-cell non-Hodgkin lymphoma that arises from intraepithelial lymphocytes and has a high association with coeliac disease. Based on clinical presentation EATL can be divided into two subgroups; EATL can arise in patients without a preceding history of coeliac disease (primary EATL) or EATL manifests in adult patients with previously diagnosed (refractory) coeliac disease who clinically deteriorate (secondary EATL). The high mortality of EATL is associated not only with the very aggressive and often chemotherapy-refractory nature of the T-cell lymphoma itself, but also the poor condition of patients due to prolonged and severe malnutrition of the patients, which severely compromises the ability to deliver high dose chemotherapy. Currently, there are no standardized treatment protocols and the optimal therapy for patients with EATL remains unclear. The first step of treatment consists of local debulking, preferably as early as possible after EATL diagnosis since morbidity and mortality seems to rise with advanced stages of disease due to tumour-size progression, worse nutritional status and a higher risk of surgery in the acute-setting. The next step in EATL-therapy is preferably resumed between 2–5 weeks post-debulking (depending on e.g. clinical condition, wound healing) and consist of antracycline-based chemotherapy. Up-front high dose chemotherapy followed by consolidation with autologous stem cell transplantation have been associated with better outcomes although this treatment strategy has only been applied in patients eligible for this aggressive regimen and the promising results might reflect selection-bias. Unfortunately, prognosis of EATL remains poor; five-year survival varies from 8 to 50% depending on the ability of the patients’ condition to receive additional steps of EATL-therapy. New treatment strategies are urgently needed for a better prognosis of this lethal complication of coeliac disease. Brentuximab – vedotin [anti-CD30] could be very promising added to conventional chemotherapy in upfront treatment.

Keywords: T-cell non-Hodgkin lymphoma, enteropathy associated T-cell lymphoma, EATL, coeliac disease, refractory coeliac disease, stem cell transplantation
Session VI

Serology and Imaging
Celiac disease (CD) is an autoimmune disease of the small bowel induced by ingestion of wheat, rye and barley. Current guidelines indicate histological analysis on at least four duodenal biopsies as the standard way to diagnosing CD.

These indications are based on the conception of the inability of white-light endoscopy to truly diagnose CD and/or to target biopsy sampling. Over the last years, endoscopic technology has greatly improved. The accuracy of macroscopic evaluation of duodenal villous pattern has steadily increased. This was achieved mainly due to the introduction of high definition endoscopy and virtual as well as standard chromoendoscopy.

In my talk I will review the value and the technique of virtual chromoendoscopy, standard chromoendoscopy, endocytoscopy as well as endomicroscopy.

Endomicroscopy enables in vivo histology during ongoing endoscopy at 1000 magnification. This provides subcellular resolution. Thus, histological diagnosis can be made and ease the diagnosis of CD.

Furthermore, functional imaging becomes possible and allows observing the reaction of the small bowel against different antigens. Ultimately, molecular imaging might help to better define subgroups of the diseases.

Selected references:


Serum markers: Standards and novel developments

Daniel A. Leffler, M.D., M.S.
Associate Professor of Medicine, Harvard Medical School, Research Director Celiac Center, Beth Israel Deaconess Medical Center, Boston, MA, USA

The advent of highly reliable non-invasive celiac diagnostic tests has transformed the field of celiac disease, from diagnosis, to epidemiology, to clinical and translational research. Serologic tests in their modern forms are highly sensitive and specific for diagnosis, allowing for consideration of avoidance of diagnostic intestinal biopsy in some settings.

On the other hand, as predictors of intestinal inflammation and for use in monitoring, currently available non-invasive tests have been disappointing. Serologic tests, while a measure of disease activity, do not correlate well with histology or symptomatology and it is unclear if they predict long term risk. Additionally, while the many clinically available tests have improved accessibility, tests can have widely different cut-off levels and overall performance, making comparison of levels in individual patients over time and across populations quite difficult.

In the future, we can expect to see improvement in the currently available serologic tests including tTG and DGP with expansion of the dynamic range of the tests and the celiac community should push for standardization of assays which would simplify research and patient care. Additionally, current serologic tests are measures of the adaptive immune response in celiac disease but do not directly measure intestinal inflammation. Promising work on intestinal Fatty Acid Binding Protein and other assays which directly measure intestinal damage may compliment traditional serologic tests and further improve our ability to non-invasively diagnose and monitor celiac disease.
Therapeutic double-balloon endoscopy

Dr. Maarten Jacobs
Medisch Centrum, Afd. MDL, Vrije Universiteit Amsterdam, The Netherlands

Since 2003 the strategy for diagnosis and treatment is changed due to two endoscopic techniques, capsule endoscopy (CE) and double-balloon endoscopy (DBE). Currently DBE is used for its therapeutic potentials in Crohn's disease and inherited polyposis syndromes (dilatation and polypectomy), as well as for diagnosing and treatment obscure gastrointestinal bleeding, and diagnosing small bowel tumors and malabsorption syndromes (biopsies, argon plasma coagulation (APC) and tattooing). Also, endoscopic retrograde cholangiopancreatography (ERCP) in Roux-en-Y patients is possible with DBE.

The DBE is a safe technique with an overall complication rate of 0.8% and includes mucosal injury, bleeding and perforation similar to normal endoscopy. A specific, sometimes severe complication of DBE is pancreatitis (0.3%). The complication rate in therapeutic DBE (APC, polypectomy and dilatation) is 4.3% which is higher as compared to therapeutic colonoscopy (Mensink 2007).

Celiac disease can be diagnosed with CE (Colin 2012), however, for refractory celiac disease (RCD) the DBE offers major advantages. In a study of Hadithi (2007) it was reported that 24 DBE procedures in 21 uncomplicated RCD patients showed two cases of ulcerative jejunitis and five lymphomas and also ruled out lymphomas in four patients where radiologic findings suggested a T-cell lymphoma. Taking biopsies of the lesion and marking with Indian ink might be important for treatment. Interventional DBE in RCD patients, e.g. dilatation of a stenosis can be potentially risky and should be avoided if possible.
Capsule endoscopy indications and timing

Emanuele Rondonotti, M.D., Ph.D.
Ospedale Valduce, Gastroenterology Unit, Como, Italy

Because of its technical characteristics and minimal invasiveness, Capsule Endoscopy (CE) has been tested as a possible substitute for EGD with biopsies in the diagnosis of patients with positive CD serology. Although CE has been found to be highly sensitive and specific, its performance is still considered insufficient to replace EGD with biopsies, whereas it can be proposed as a valid alternative in selected patients (i.e., in those unable or unwilling to undergo EGD). CE has so far failed to demonstrate any correlation between the length of small-bowel involvement and clinical presentation. Therefore, its use to evaluate the entire small bowel at the time of initial diagnosis does not seem to be justified.

The role of CE in monitoring patients with CD is less clear. Up to 30% of patients with celiac disease may fail to improve on a gluten-free diet. In these patients, a complete work-up is necessary to exclude other causes. Although some studies suggested that CE can be included in this work-up, the evidence supporting the systematic use of CE in these patients is limited.

In patients with refractory CD (RCD), the exploration of the entire small bowel is mandatory. In this setting, CE represents an attractive alternative, allowing to evaluate the entire small bowel in a non-invasive way. Nevertheless, in this setting, some CE technical features (i.e. inability to take tissue samples) can represent major limitations. In patients with RCD, CE has a complementary role (i.e. directing enteroscopy approach) to imaging and device assisted enteroscopy techniques.
MRI enteroscopy: First choice in diagnosis

S.J.B. Van Weyenberg
Leiden University Medical Center (LUMC), Leiden, The Netherlands

Modern small-bowel imaging techniques nowadays allow detailed depiction of small-intestinal abnormalities. The role of these techniques in the investigation of coeliac disease is increasing, especially in patients with suspected complicated coeliac disease.

In general, there is no need for radiological small-bowel imaging in uncomplicated coeliac disease. Both for diagnosis as for follow up, the diagnostic accuracy of small-bowel histology and specific serological tests exceeds that of small-bowel imaging by far. However, it is important that clinicians and radiologists are aware of certain specific radiological findings that may suggest coeliac disease, especially since coeliac disease is often not considered in adult patients with for instance malabsorption or diarrhoea, and small-bowel radiology may be performed before specific tests for coeliac disease. Radiological abnormalities can be observed with both conventional small-bowel radiology studies, like small-bowel follow through or double-contrast small-bowel enteroclysis, as with newer modalities, like computed tomography (CT) or magnetic resonance (MR) enterography or enteroclysis. These signs include small-bowel dilatation and small-bowel atonia, increased numbers of ileal folds and decreased numbers of jejunal folds, small intestinal wall thickening and intussusception.

There is increased recognition of the usefulness of small-bowel imaging in suspected refractory coeliac disease. Especially cross-sectional enteroclysis techniques, such as MR enteroclysis, seem useful to investigate the small-intestine in patients with persisting symptoms despite adherence to a gluten-free diet. Abnormalities congruent with refractory coeliac disease type II include a severe decrease in jejunal folds, infiltration of the mesenteric fat and thickening of the small-bowel wall. Additionally, decreased splenic volume may indicate complicated coeliac disease. Severe malignant complications of coeliac disease, such as enteropathy-associated T-cell lymphoma and small-intestinal adenocarcinoma, can be reliably investigated with cross-sectional enteroclysis techniques.

In conclusion, small-bowel imaging and especially cross-sectional enteroclysis techniques are important extensions to the diagnostic arsenal of clinicians involved in the care of patients with suspected complicated coeliac disease.
Session VII

Non-Celiac Gluten (Wheat) Sensitivity
Non-celiac gluten sensitivity: Evidence and clinical studies

A. Sapone
Second University of Naples, Department of Experimental Medicine, Naples, Italy

The recent rise of the gluten-free market in the USA, partially sustained by individuals who claim a medical necessity to undertake a gluten-free diet (GFD), raises questions about possible gluten reactions alternative to celiac disease (CD) and wheat allergy (WA). It is now becoming clear that, besides CD and WA, there are cases of gluten reactions in which neither allergic nor autoimmune mechanisms can be identified. These are generally defined as non-celiac gluten sensitivity (NCGS) or, more simply, gluten sensitivity (GS). Some individuals who experience distress when eating gluten-containing products and show improvement when following a GFD may have GS instead of CD. GS is a condition distinct from CD and is not accompanied by the concurrence of anti-tTG autoantibodies or other autoimmune comorbidities. The overall prevalence of GS in the general population is currently unknown. Anecdotal observations indicate that GS could be more common that CD, with an estimated frequency of 2–6%. Between 2004 and 2010, 5896 patients were seen at the Center for Celiac Research, University of Maryland. The criteria for GS were fulfilled by 347 (1:17; 6%) of the patients seen, however this is an estimate that does not apply to the general population due to selection bias. A recent survey found that 5% of New Zealand children reported non CD-related avoidance of gluten-containing food. In another study the identified predictors suggested that gluten avoidance was associated with nonspecific behavioural and gastrointestinal complaints. It remains to be elucidated how many children reporting gluten avoidance were indeed affected with GS. 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%. Although risk factors for GS have not been identified yet, the disorder seems to be more common in females, and in adult age.
Cereal ATIs as innate immune activators

Detlef Schuppan, M.D., Ph.D.
Institute of Translational Immunology and Celiac Center, University Medical Center of the Johannes-Gutenberg University Mainz, Germany

Ingestion of wheat, barley, or rye triggers small intestinal inflammation in patients with celiac disease, where the storage proteins of these cereals (gluten) elicit an adaptive Th1-mediated immune response in individuals carrying HLA-DQ2 or HLA-DQ8 as major genetic predisposition. We recently identified alpha-amylase/trypsin inhibitors (ATIs) of wheat, but not gluten proteins, as strong activators of innate immune responses in monocytes, macrophages, and dendritic cells, but not of intestinal epithelia. ATIs are a family of highly disulfide linked proteins of 120–150 amino acids that serve as pest resistance molecules for cereals (Altenbach SB, et al. BMC Res Notes. 2011). We established that ATIs engage the TLR4-MD2-CD14 complex, lead to up-regulation of maturation markers and elicit release of pro-inflammatory cytokines in cells from celiac and non-celiac patients and in celiac patients' biopsies. Mice deficient in TLR4 or TLR4 signaling are protected from intestinal and systemic immune responses upon oral challenge with ATIs (Junker Y, et al. J Exp Med. 2012). Apart from defining wheat ATIs as novel contributors to celiac disease, their mechanism of action makes it highly likely that they would fuel inflammation and immune reactions in other intestinal and extraintestinal immune disorders (Junker Y, et al. 2012; Tilg H, et al. Gastroenterology. 2013). The newly discovered activity of ATIs as nutritional activators of TLR4 is different from that of gluten in celiac disease and of wheat (rye, barley) proteins in allergy, where ATIs are inhalative allergens (Schuppan D, et al. Gastroenterology. 2009; Battais F, et al. Eur Ann Allergy Clinic. 2008; Uvackova L, et al. J Proteome Res. 2013).

Our preliminary data show that TLR4 activating activity is limited to ATIs present in gluten containing cereals, whereas non-gluten grains contain no or minimal activities (Zevallos VF, et al. submitted). Moreover, ingested ATIs are highly resistant to intestinal proteolytic degradation, and oral application to mice at concentrations equivalent to human ingestion with a normal gluten containing diet (1–2 g of ATIs per day) is sufficient to elicit significant innate immune activation in the intestine and colon, even of normal mice (Junker Y, et al. J. Exp Med. 2012).

Mice with a range of autoimmune disorders resembling human autoimmunity demonstrate an exacerbation of their autoaggressive diseases on feeding ATIs (ATI-containing gluten) vs. mice on a well defined gluten-free diet (Zevallos VF, et al. unpublished). We therefore conclude that innate immune activation by nutritional ATIs may also worsen chronic inflammation in patients, explaining the growing number of patients with well defined non celiac/non-allergy wheat sensitivity (Catassi C, et al. Nutrients. 2013).
Ataxia: When to prescribe the gluten-free diet

Professor Marios Hadjivassiliou
Neuroscience Department, Royal Hallamshire Hospital, Sheffield, UK

Gluten ataxia (GA) was originally defined as otherwise idiopathic sporadic ataxia in the presence of circulating antigliadin antibodies of IgG or IgA type. The development of newer serological markers, more specific to neurological manifestations (TG6 antibodies) may assist in improving such diagnosis.

In a series of over 1000 patients with progressive cerebellar ataxia evaluated over a period of 20 years in Sheffield, UK, GA had a prevalence of 15% amongst all ataxias and 41% amongst idiopathic sporadic ataxias.

GA usually presents with pure cerebellar ataxia primarily affecting gait and lower limbs. It is usually of insidious onset with a mean age at onset of 53 years. All patients have gait ataxia and the majority has lower limb ataxia. Less than 10% of patients with GA will have any gastrointestinal symptoms and only a 40% will have evidence of enteropathy on biopsy. Gastrointestinal symptoms are not a reliable indicator for the presence or absence of enteropathy. In this respect, gluten ataxia resembles dermatitis herpetiformis.

Recent evidence suggests that patients with newly diagnosed CD presenting to the gastroenterologists have abnormal cerebellar MR spectroscopy at presentation and that this is also associated with clinical evidence of cerebellar dysfunction (e.g. nystagmus, gait ataxia).

Response to treatment with a gluten-free diet depends on the duration of the ataxia prior to the diagnosis. Loss of Purkinje cells in the cerebellum, the end result of prolonged gluten exposure in patients with GA, is irreversible and early diagnosis and treatment is more likely to result in improvement or stabilisation of the ataxia. One systematic study of the effect of gluten-free diet on a cohort of patients presenting with ataxia has been published. Forty three patients with gluten ataxia were enrolled. Twenty six adhered strictly to the gluten-free diet, had serological evidence of elimination of antibodies and comprised the treatment group. Fourteen patients refused the diet and comprised the control group. There was significant improvement in ataxia scores and in the subjective global clinical impression scale in the treatment group when compared to the control group. The improvement was apparent even after excluding patients with an enteropathy.

Patients presenting with ataxia due to coeliac disease are significantly older from those being diagnosed with CD by the gastroenterologist (mean age 61 vs. 47, respectively). They are often more severely affected by their ataxia. It is possible that the presence of gastrointestinal symptoms in these patients offers a diagnostic advantage over patients presenting with ataxia by making them more likely to be tested for the disease and hence more likely to be diagnosed and treated early.
Other dietary confounders: FODMAPS et al.

Peter R. Gibson  
Department of Gastroenterology, Monash University and Alfred Hospital, Melbourne, VIC, Australia

While it is well documented and widely appreciated that ingestion of wheat (and less so rye and barley) is associated with gastrointestinal symptoms such as bloating or abdominal pain, the component of wheat to which such an effect is attributed is less well established. Wheat is a complex of proteins (predominantly but not exclusively gluten), carbohydrates (digestible and indigestible, long-chain and short-chain), lipids and lectins. The majority of attention has focused on gluten as the culprit in triggering symptoms, but rechallenge studies have nearly all used wheat flour-related products (such as bread) as the stimulus. When carbohydrate-deplete gluten was used as the challenge agent, gluten-specific gut symptoms were not but depressive symptoms were observed in those who fulfilled strict criteria of non-coeliac gluten sensitivity (NCGS), underlying the complexity of cereals. Candidate components other than gluten include: (a) **FODMAPs**, which are short-chain indigestible carbohydrates induce symptoms via luminal distension from their osmotic effects in the small bowel and rapid fermentation in the large bowel. FODMAPs co-exist with gluten in cereals – gluten-free cereals are low in FODMAPs and vice versa. There is randomised controlled trial evidence that reduction of FODMAP intake reduces gut symptoms in about 70% of patients with IBS. Furthermore, patients with NCGS adherent to a gluten-free diet have additional reduction of gut symptoms when other (non-cereal) sources of FODMAPs are reduced in the diet. (b) **Wheat proteins of uncertain relationship to gluten**: Wheat allergy is unlikely to be mistaken for NCGS. Yet-to-be characterised immune reactions to wheat-associated proteins may be implicated in some non-coeliac patients with wheat sensitivity, the majority of whom have intraepithelial lymphocytosis and eosinophilic infiltration in the mucosa and/or epithelium. (c) **Amylase-trypsin inhibitor** is a wheat-associated protein that is capable of activating innate immune mechanisms in experimental animals, but its role in humans has not been reported. (d) **Gluten ‘exorphins’**, released during the digestion of gluten, have been implicated in several putative effects of gluten, including psychological and cognitive effects form their ability to cross the blood-brain barrier, but data in humans are lacking. (e) **Lectins**, such as wheat-germ agglutinin, have biologically active effects, but there is a paucity of data regarding a role in NCGS. In conclusion, specific biological and/or clinical effects associated with gluten-free diets or wheat ingestion need to be carefully dissected before attribution to gluten can be claimed. Currently, coeliac disease is the only common condition that has been unequivocally linked to gluten. Inaccurate attribution will be associated with suboptimal therapeutic advice and at least partly underlies the current gluten-free epidemic gripping the Western world.
Session VIII

Novel Therapies
Glutenases and beyond

Katri Kaukinen
School of Medicine, University of Tampere and Department of Internal Medicine, Tampere University Hospital, Tampere, Finland

Currently, the only effective treatment for celiac disease is a strict life-long gluten-free diet. However, gluten-free dieting is restrictive, difficult to maintain and nutritionally less than optimal. The improved knowledge on celiac disease pathogenesis has enabled researchers to suggest alternative strategies to treat the disorder. The drug development poses a challenge, as any novel drug for celiac disease should be simultaneously effective and as safe as the gluten-free diet (1).

The rationale behind enzyme supplementation therapy as a future treatment option for celiac patients lies in the fact that wheat gliadin and other Triticeae prolams are only poorly digested by gastrointestinal proteases. Due to incomplete degradation in the gastrointestinal tract, fairly long peptides enter the small intestinal lumen and come into contact with the mucosal epithelium, and in celiac disease patients this encounter launches deleterious downstream effects. Enzyme supplementation therapy using either bacterial or fungal endopeptidases or proteases from germinating cereals has been proposed to promote complete digestion of prolams and destroy disease inducing gluten peptides. A major advantage of these glutenases is that they work in the lumen of the small intestine and do not themselves take part in the immunological cascade of events in the lamina propria, being thus unlikely to cause harmful side-effects to the host. Studies to test this rationale are already ongoing. Aspergillus niger prolyl endoprotease (AN-PEP) has been shown to digest gluten in a slice of bread and a whole meal in a dynamic gastrointestinal model mimicking conditions found in the stomach and small intestine in vivo (2). In a recent phase II study a combination enzyme product ALV003 was shown to attenuate gluten-induced (up to 2000 mg) mucosal injury in patients having celiac disease (3).

Other promising approaches include modulation of intestinal permeability, prevention of gluten presentation to T cells by blocking the binding of gluten epitopes to HLA-DQ2 molecules, use of TG2 inhibitors, down regulation of immune response by antibodies against proinflammatory cytokines, and promotion of tolerance by other immunomodulatory strategies. Some of the novel treatment/management options have already entered clinical trials but before any of the candidates can enter phase III trials, however, researchers must develop novel reliable non-invasive surrogate markers for intestinal injury and disease activity. The development of a novel medication for celiac disease is still in its early days and thus the conventional dietary treatment will hold its place for the time being.

References:

Vaccination and other antigen-specific immunomodulatory strategies in celiac disease

Mauro Rossi
Institute of Food Sciences, CNR, Avellino, Italy

Celiac Disease (CD) can be considered as the result of alteration of oral tolerance to dietary gluten. This process is normally tightly regulated, involving different subtypes of regulatory T cells secreting TGF-β and IL-10. Interestingly, concomitantly to pro-inflammatory cytokines, the inflamed CD mucosa also contains high levels of T cell-derived IL-10 when compared with treated CD or normal donors. Furthermore, most studies describe an increase of Foxp3⁺ Treg cells in CD patients compared to controls in the small intestinal mucosa. This paradoxical condition suggests that regulatory mechanisms might operate to counterbalance the gliadin-triggered, abnormal immune activation in untreated mucosa. Indeed, addition of exogenous IL-10 to mucosal cultures from treated CD patients can suppress gliadin-induced T cell activation. By considering the central role of adaptive immunity in CD, how to boost these mechanisms represents a key target in the perspective to restore gluten tolerance. Different immunomodulatory strategies have been explored to date. NexVax2, a desensitizing vaccine that uses three gluten dominant peptides administered subcutaneously with the goal of inducing a tolerogenic response in CD patients is under development. As a completely different approach, the potential of substituted, cyclic or dimeric peptide analogues as blockers to prevent HLA-binding of immunodominant gliadin epitopes has been shown in vitro. In line with these results, we recently found that modified (transamidated) gliadins influenced the immune response in intestinal biopsy samples from CD patients with overt disease by drastically reducing the IFN-γ production. Notably, in a mouse model, transamidated gliadins reverted the phenotype of the gliadin-inducible immune response from inflammatory to anti-inflammatory. Taken together, these findings suggest that masking of immunodominant gliadin epitopes could favor an alternative HLA binding of low-affinity gliadin-immune determinants with dramatic consequences on the outcome of the response. Specific studies are now required to test the efficacy of such strategies for preventing CD.
List of Chairpersons, Speakers and Scientific Organizers

Dr. Julio C. Bai  
Departamento de Medicina  
Hospital de Gastroenterologia  
Dr. Carlos Bonorino Udaondo  
Av. Caseros 2061  
1264 Buenos Aires  
Argentina

Dr. Frederico Biagi  
First Department of Internal Medicine  
Policlinico San Matteo  
Piazzale Golgi 19  
27100 Pavia  
Italy

Dr. Gerd Bouma  
Medisch Centrum  
Afd. MDL  
Vrije Universiteit  
de Boelelaan 1117  
1081 HV Amsterdam  
The Netherlands

Prof. Dr. Carlo Catassi  
Department of Pediatrics  
Università Politecnica delle Marche  
Via F Corridoni 11  
60123 Ancona  
Italy

Prof. Dr. Christophe Cellier  
Department of Gastroenterology and Digestive Endoscopy  
Hôpital Européen Georges Pompidou  
20, rue de Leblanc  
75908 Paris Cedex 15  
France

Dr. Nadine Cerf-Bensussan  
Université Paris Descartes  
Medical School  
INSERM U989  
156, rue de Vaugirard  
75730 Paris  
France

Melinda Dennis, M.S., R.D.  
Nutrition Coordinator, Celiac Center  
Beth Israel Deaconess Medical Center  
330 Brookline Avenue  
Boston, MA 02215  
USA

Charles O. Elson, M.D.  
Professor of Medicine  
Division of Gastroenterology and Hepatology  
University of Alabama at Birmingham  
SHEL 607  
1825 University Boulevard  
Birmingham, AL 35294-0005  
USA

Alessio Fasano, M.D.  
Division of Pediatric Gastroenterology  
MassGeneral Hospital for Children  
175 Cambridge Street, CPZS-574  
Boston, MA 02114  
USA

Prof. Dr. Peter R. Gibson  
Department of Gastroenterology  
Alfred Hospital and Monash University  
Melbourne, VIC 3004  
Australia

Peter H.R. Green, M.D.  
Celiac Disease Center  
Columbia University Medical Center  
180 Fort Washington Avenue  
New York, NY 10032-3784  
USA

Prof. Dr. Marios Hadjivassiliou  
Royal Hallamshire Hospital  
Glossop Road  
Sheffield S10 2JF  
Great Britain
Prof. Dr. Christinus J.J. Mulder
Medisch Centrum
Afd. MDL
Vrije Universiteit
de Boelelaan 1117
1081 HV Amsterdam
The Netherlands

Joseph Murray, M.D.
Professor of Medicine
Department of Gastroenterology, Hepatology and Immunology
Mayo Clinic
200 First Street SW
Rochester, MN 55905
USA

Dr. Guillaume Pineton de Chambrun
Gastroenterology Department
Lille University Hospital
North of France University
59000 Lille
France

Emanuele Rondonotti, M.D., Ph.D.
Gastroenterology Unit
Ospedale Valduce
Via Dante 10
22100 Como
Italy

Dr. Mauro Rossi
CNR - Institute of Food Sciences
Via Roma 64
83100 Avellino
Italy

Dr. Anna Sapone
Department of Experimental Medicine
Second University of Naples
Maggiore Lanzara
Via Pansini 5
80132 Naples
Italy

Prof. Dr. Dr. Detlef Schuppan
Institut für Translationale Immunologie
Innere Medizin I
Universitätsmedizin der
Johannes Gutenberg-Universität
Langenbeckstr. 1
55131 Mainz
Germany

Prof. Dr. Ludvig M. Sollid
Centre of Immune Regulation
Department of Immunology
University of Oslo and
Oslo University Hospital
Rikshospitalet
0372 Oslo
Norway

Dr. Rudolf Valenta
Division of Immunopathology
Medical University of Vienna
Währinger Gürtel 18–20
1090 Vienna
Austria

Dr. Stijn Van Weyenberg
Leiden University Medical Center
Albinusdief 2
2333 ZA Leiden
The Netherlands

Elena F. Verdu, M.D., Ph.D.
Farncombe Family Digestive Health Research Institute
McMaster University, HSc 3N8
1280 Main St. W.
Hamilton, Ontario L8S 4K1
Canada

Dr. Otto Visser
Medisch Centrum
Vrije Universiteit
de Boelelaan 1117
1081 HV Amsterdam
The Netherlands
POSTER ABSTRACTS

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Symptomatic giardiasis and intestinal bacterial overgrowth

H. Abaza*, M. Sharaf-Eldin* and A. Amin**
Departments of Tropical Medicine and Infectious Diseases* and Bacteriology**
Departments, Alexandria, and Tanta Universities, Tanta, Egypt

Introduction: The clinical spectrum of giardiasis varies from asymptomatic, mild symptomatic cases to patients with malabsorption. Whether or not bacterial colonization of the duodenum affects the outcome of giardial infection was investigated in this work.

Methods: Fifty Egyptian males with isolated Giardia were included in this study. The duration of illness varied from one week to two years. Accordingly, 3 groups of patients were included: Group I were 10 patients with an illness lasting for more than one year, group II included 10 other patients with an illness duration of 6 months to one year, group III comprised the remaining 30 cases whose duration of illness was less than 6 months. Stools were examined by the direct smear and modified formol ether concentration methods to detect Giardia cysts and trophozoites. Duodenal aspirate was studied microscopically for cysts and trophozoites and bacteriologically for aerobic and anaerobic organisms.

Results: Clinically, heartburn and epigastric pain were the commonest and most frequent symptoms. Recurrent loose motions, flatulence, vomiting and malaise were also prominent. Steatorrhea, weight loss and anaemia were present in groups of patients I and II, and being more severe than group III. Thirty-one out of the 50 cases (62%) had abnormal bacterial overgrowth in their duodenal fluid samples. Bacterial growth occurred only on the blood agar plates (aerobic and anaerobic). The Dominant types of bacteria were aerobic one. According to the frequency of growth, the most common organisms were staphylococci, streptococci (beta and alpha), and gram negative bacilli. The highest number of bacteria was detected in group I while the count was negligible in the third group of patients.

Discussion/Conclusion: A directly proportional relation could be detected between the presence and number of bacteria on one hand and the severity and duration of the disease on the other hand. It could be postulated that intestinal microbial overgrowth favours mucosal invasion by the parasite and aggravates its pathogenicity.
Do Turkish celiac disease patients stick to gluten-free diet?

Zehra Akpinar, Firdevs Topal, Elif Saritas Yuksel, Fatih Aslan, Sezgin Vatansever, Belkis Unsal
Katip Celebi University, Izmir Ataturk Training and Research Hospital, Izmir, Turkey

Introduction: Celiac disease (CD) is an enteropathy developing in genetically predisposed patients induced with gluten in the diet and the only known treatment is gluten-free diet (GFD). It can be hard to stick to a completely GFD lifelong. In this study we evaluated the adherence to diet in our adult CD patients.

Methods: Between January 2011–January 2013 CD patients who were seen at the out-patients clinic for follow up were questioned for adherence to GFD. First patients were asked “Do you adhere to your GFD?” second “Do you eat something containing gluten in difficult times when you feel you have to?” “How often?” was the next question when they replied “yes”. Adherence to diet was grouped in 6 groups as always, usually, often, sometimes, rarely, never on diet. Demographic values and duration disease was also recorded.

Results: 80 patients (59 F/21 M, age 41.8 ± 15.2 years) were included to the study. Duration of disease was mean 4.5 years [min1-max19 years]. 8,8% of the patients were never on a GFD. 73 (91.2%) of the patients answered “yes” to the first question and 39 (48.7%) were on a strict diet. The rest also answered “yes” to the second question. Adherence was as follows: 12.5% usually, 5.0% often, 15.0% sometimes, 10% rarely on GFD. There was relation between adherence to GFD and age and duration of disease.

Discussion/Conclusion: Gluten is widely used in food industry and hard to abstain. Less than half of the patients strictly adhere to a GFD. Although patients are aware of the complications they do not eliminate gluten from diet and may not tell the physician directly that they spoil their diet. Patients should be encouraged for diet, GFD products should be easily obtainable, and people should be informed about the disease to help patients for their GFD.
Presenting symptoms of adult celiac disease patients in Turkish population

Dr. Zehra Akpınar, Dr. Elif Saritas Yuksel, Dr. Firdevs Topal, Dr. Fatih Aslan, Dr. Sezgin Vatansever, Dr. Belkis Unsal
Katip Celebi University, Izmir Atatürk Training and Research Hospital, Izmir, Turkey

Introduction: Although Celiac disease (CD) is known as a childhood illness, it may also present at adult ages. Instead of classic CD with malabsorption symptoms like diarrhea, steatorrhea, and weight loss, other forms of CD is seen more commonly in the recent years. In this study we evaluated demographic features and presenting symptoms of our adult CD patients.

Methods: Data of 281 biopsy proven CD patients recorded between January 2006–April 2014 were evaluated. Demographic features, family history, age and presenting symptom at diagnosis were analyzed.

Results: There were 93 male, 188 female patients with mean ages 39.5 ± 14.4 and 37.4 ± 13.2 respectively. Age at diagnosis was 38.2 ± 15.9 for male, 32.2 ± 13.5 for female patients. Only 18 (6.4%) patients had known family history for CD. For the rest, family members were either negative or not tested for CD.

The presenting symptoms of CD were as follows: 58.2% diarrhea, 53.7% anemia, 33.7% weight loss, 21.7% abdominal pain/dyspepsia, 7.0% increase in transaminase levels, 6.8% fatigue and 6% nausea/vomiting. 5% of the patients had edema due to hypoalbuminemia, and 2.2% had dermatological problems like itching and hair loss. 2.8% of the patients were diagnosed while testing for early onset osteoporosis, 4% for short stature, 4% for neurological symptoms and 0.7% for small bowel lymphoma. 2.2% of the patients had no complaints but wanted to be tested because of family history.

Discussion/Conclusion: Despite the high prevalence of CD in our population (1/100–150) there are thousands of undiagnosed patients and the age at diagnoses has shifted to elder ages (mostly 10–40 years). Family scanning is important still many relatives are reluctant to be tested. Diagnosis is easier in patients with malabsorption, but physicians should keep CD in mind in patients with short stature, failure to gain weight, anemia, increase in transaminase levels, aphthous stomatitis, autoimmune diseases, chronic migraine attacks and history of multiple abortus.
Assessing health-related quality of life, presence of depression and anxiety celiac disease patients

Dr. Zehra Akpinar, Dr. Fatih Aslan, Dr. Firdevs Topal, Dr. Elif Saritas Yuksel, Dr. Sezgin Vatansever, Dr. H. Sinan Akay, Dr. Belkis Unsal
Katip Celebi University, Izmir Ataturk Training and Research Hospital, Izmir, Turkey

Introduction: Celiac disease (CD) is an autoimmune disease in the small bowel induced by gluten in diet. Because of the chronic and multi-dimensional state, health-related quality of life (HRQOL) decreases in CD. We investigated presence of depression, anxiety and HRQOL in CD patients in Turkish population.

Methods: Between April 2013–April 2014, 53 CD patients were asked to participate in this study by filling out self reporting questionnaires; namely Beck Depression Scale (BDS), Beck Anxiety Scale (BAS) and Short Form-36 (SF-36). Demographic features, presence of anemia, body mass index (BMI) physical (PCS) and mental component summary (MCS) scores of SF-36 and Beck scores were recorded separately. For Beck scales 17 points were used as cut-off value.

Results: Fifty-three patients agreed to participate in the study. There were 12 male and 41 female patients with age 37.6 years. 34% of the patients had anxiety, 24.5% had depression. Rate of anxiety and depression did not differ according to gender, age presence of anemia or duration of disease (p > 0.05). But depression was related with BMI. MCS decreased with age and increase in BMI.

Discussion/Conclusion: HRQOL of diseases are been evaluated frequently in chronic states. As CD is chronic with physical, emotional, social and cognitive aspects it can impair HRQOL. Among many scales, self reporting scales are easy to use and time saving in the outpatients clinics. Disease specific instruments are also available but to our knowledge there is no CD specific tools verified and validated in Turkish. Impairment of HRQOL is prominent before diagnosis in CD patients but unfortunately it has been also shown that the improvement after introducing GFD does not continue forever because of the difficulty in adhering to GFD.
Celiac disease and risk of *Clostridium difficile*

Masoumeh Azimirad¹, Mohammad Rostami Nejad¹, Soamyeh Jahani-Sherafat¹, Masoud Alebouyeh¹, Mohammad Mehdi Aslani², Mohammad Reza Zali¹, Kamran Rostami³

¹Celiac Disease Department, Gastroenterology and Liver Diseases Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
²Microbiology Department, Pasture Institute, Tehran, Iran
³Gastroenterology Department, Worcestershire Royal Hospital, Worcester, UK

**Introduction:** Intestinal bacterial overgrowth with *Clostridium difficile* related to antibiotic consumption is a possible etiology for persistent diarrhea in some patients with celiac patients. Therefore, the aim of present study is to investigation the prevalence of *Clostridium difficile* in celiac patients with persistent diarrhea.

**Methods:** Out of 120 patients with celiac disease, 10 patients (mean age 32 years) with persistent diarrhoea and suspected for refractory CD were referred and clinical data were collected including prescribed antibiotics and previous history of hospitalization. Their diet was checked out and fecal samples were collected from all of them simultaneously. All fecal samples were treated with methanol and yeast extract 5%, and then cultured on selective *Clostridium difficile* agar plates under anaerobic conditions. PCR reaction for TcdA, TcdB and cdd3 genes were conducted in all the bacteria isolates.

**Results:** Of 10 fecal samples, the result of culture media was positive for *C. difficile* in 4 cases (3.4%). PCR results showed a frequency of 3.4% (4 cases) toxigenic *C. difficile* isolates (3.4% tcdA and 3.4% tcdB). All these patients consumed metronidazole or vancomycin for 7–30 days. There was a statistically significant correlation between *C. difficile* and antibiotic usage (p < 0.05). Other 6 patients did not follow the strike gluten-free diet and after re-introduced the GFD, their symptoms were resolved.

**Discussion/Conclusion:** In this study we identified a strike association between presences and absence of toxigenic strains of *Clostridium difficile* in patients with celiac disease. The result of study indicated that *Clostridium difficile* is associated with CD and should be excluded in CD patients with persistent diarrhoea.
Mild histological abnormalities in non-coeliac gluten sensitivity do not represent early coeliac disease

Imran Aziz*, Tim Key, John G. Goodwin, David S. Sanders
Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals, Sheffield, United Kingdom

Introduction: Coeliac disease (CD) is defined by positive serology plus Marsh (M) grade 1–3 on duodenal biopsies; CD-M1 to CD-M3. In contrast, non-coeliac gluten sensitivity (NCGS) is defined by negative serology and M0–M1 on duodenal biopsies; NCGS-M0 to NCGS-M1. However, NCGS-M1 poses diagnostic uncertainty as celiac serology can be negative in those with mild histological abnormalities.

Aims: To determine whether NCGS-M1 actually represents early CD.

Methods: Baseline clinical characteristic, biochemical parameters and human leukocyte antigen (HLA) DQ2-DQ8 typing was compared between 100 NCGS-M0, 50 NCGS-M1 and 30 CD-M1 patients whilst on a gluten-containing diet. Finally, serological and histological response to a repeat gluten challenge was assessed between HLA-DQ positive NCGS-M1 and CD-M1.

Results: There was no statistical difference in age, sex, autoimmunity, family history of CD or baseline body mass index between the three groups. However, anaemia was significantly more prevalent in CD-M1 (20%) compared to NCGS-M1 (6.4%, p 0.05, OR = 4.7, CI: 1.0–21.6) and NCGS-M0 (3%, p 0.009, OR = 7.58, CI: 1.67–34.4).

Furthermore, HLA-DQ positivity was seen in 100% (n 30) of CD-M1 patients, in contrast to 70% NCGS-M1 (n = 35, p 0.001) and 55% NCGS-M0 (p < 0.001).

26/30 CD-M1 patients and 30/35 HLA-DQ positive NCGS-M1 individuals agreed to undergo repeat gluten challenge. In CD-M1 there was a significant rise in coeliac serology (mean TTG value 124 U/ml before: 164 U/ml after, p 0.04) and histological deterioration on duodenal biopsies (35% M1, 15% M2, 50% M3, p < 0.0001). In contrast, all individuals with HLA-DQ positive NCGS-M1 maintained negative coeliac serology (mean TTG value 7 U/ml before; 8 U/ml after, p 0.12) and the majority improved their duodenal biopsies from M1 to M0 (23/30, 77%, p < 0.0001), with 7 cases persisting as NCGS-M1.

Conclusion: NCGS-M1 individuals do not represent CD as demonstrated by i) negative HLA-DQ typing in 30% of cases or a ii) a lack of immune deterioration following repeat gluten challenge in those with HLA-DQ positivity. In cases with persisting NCGS-M1 duodenal immunohistochemical analysis may shed further light on the eventual diagnosis.
Change in awareness of gluten-related disorders amongst chefs and the general public in the United Kingdom: A 10 year follow-on study

Imran Aziz*, Mohammed A. Karajeh, Jossie Zilkha, Euan Tubman, Charlotte Fowles, David S. Sanders
Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals, Sheffield, United Kingdom

Introduction: There has been a recent rise in media coverage highlighting gluten-related disorders (GRD). We assessed whether knowledge of GRD has altered amongst the general public and chefs.

Methods: A face-to-face questionnaire about coeliac disease (CD) and gluten sensitivity (GS) was performed on the general public and chefs based in Sheffield, United Kingdom. The assessment was first conducted in 2003 and repeated in 2013.

Results: 513 public members in year 2003 (mean age 49.2 years, 62% female) were compared to 575 public members in year 2013 (mean age 37.8 years, 57% female). There was a significant rise in the awareness of GRD from the years 2003 to 2013; CD (44.2% to 74.4%, AOR = 3.9 [CI: 3–5.19]) and GS (58.3% to 89%, AOR = 7.1 [CI: 5–9.98]), p-value < 0.001.

322 chefs in year 2003 (mean age 37.6 years, 15% female) were compared to 265 chefs in year 2013 (mean age 27.1 years, 38% female). There was a significant rise in the awareness of GRD from the years 2003 to 2013; CD (17.1% to 78.1%, AOR = 12.5 [CI: 7.9–19.6]) and GS (9.3% to 87.5%, AOR = 65.7, [CI: 35.4–122]), p < 0.001.

Whereas in 2003 the public were significantly more aware of GRD than chefs, by 2013 this had reached similar prevalence in both groups. In addition, the correct recognition of the gluten-free symbol was 44% for the public and 40% for chefs (p 0.28). Gluten-free products were sold by 41% of restaurants and 27% of takeaways (p 0.07).

Conclusion: There has been a dramatic rise in both the public and chefs awareness of GRD. This may ease the social phobia that individuals with GRD have traditionally been accustomed to.
Predictors for coeliac disease in cases of lymphocytic duodenosis

Imran Aziz*, Tim Key, John G. Goodwin, David S. Sanders
Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals, Sheffield, United Kingdom

Introduction: Lymphocytic duodenosis (LD) is an early marker for coeliac disease (CD). However, the majority of cases are due to non-CD related conditions. We aimed to identify the predictors of CD when presented with LD.

Methods: 215 LD patients had undergone prospective and systematic evaluation for CD and other recognized associations.

The gold-standard diagnosis of CD was based upon the presence of HLA-DQ2 and/or DQ8, persistence or progression of LD following a gluten challenge, followed by symptomatic improvement on a gluten-free diet.

Binary logistic regression models, adjusting for age and gender, were subsequently performed to compare presenting variables between CD and non-CD cases, and to determine their sensitivity, specificity, positive and negative predictive values (PPV and NPV).

Results: CD was diagnosed in 48 cases (22%) and non-CD in 167 cases (78%). There was no statistical difference in demographics, clinical symptoms (i.e. diarrhoea, weight loss, abdominal pain), anaemia or haematinics between the CD and non-CD group.

Patients with CD, in comparison to non-CD, were significantly more likely to have a positive family history of CD (21% vs. 3.6%, OR 6.73; PPV 62.5%, NPV 81%, specificity 96.4%), positive HLA-DQ status (100% vs. 49.1%; PPV 36.4%, NPV 100%, specificity 50.9%), and presence of endomysial antibody [EMA] (48% vs. 0%; PPV 100%, NPV 87%, specificity 100%); all p \( \leq 0.001 \)

A normal tissue transglutaminase antibody (TTG) level was seen in 29.2% CD and 83.2% non-CD cases (OR 0.084, p < 0.001; PPV 9.2%). There was no difference in the prevalence of TTG levels 1-2 x upper limit of normal (ULN) between the groups (29.2% CD vs. 14.4% non-CD; PPV 33–38%). However, TTG levels between 3-20 x ULN were significantly more prevalent in the CD group (33.3% vs. 2.4%; PPV 66.6–89%), whilst a TTG > 20 x ULN was exclusive to CD (8.3%, p < 0.001, PPV 100%).

Conclusion: In the setting of LD, only the presence of a positive EMA or TTG > 20 x ULN at the outset can be used to make an immediate diagnosis of CD. Gastrointestinal symptoms, family history, anaemia, or other coeliac serology results do not reliably distinguish CD from non-CD without further investigations.
Non-coeliac gluten sensitivity can be present in inflammatory bowel disease, not just irritable bowel syndrome

Imran Aziz*, Stefanie Winfield, Alan Kelsall, Nathan Rugg, Kathryn Pearson, Josephine Priest, David S. Sanders
Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals, Sheffield, United Kingdom

Introduction: Self-reported gluten sensitivity (GS) commonly occurs in the absence of coeliac disease, and is termed non-coeliac gluten sensitivity (NCGS); a controversial, heterogeneous, clinical entity perceived by some to belong to the spectrum of irritable bowel syndrome (IBS) due its lack of putative biomarkers.

Aims: We evaluated whether NCGS may be reported in organic gastrointestinal pathologies.

Methods: A validated questionnaire screened for self-reported GS in four patient groups (cohort A); i) IBS, ii) crohns disease (CrD), iii) ulcerative colitis (UC) and iv) gastro-oesophageal reflux disease (GORD).
In addition, the prevalence of organic pathology in a separate group presenting and diagnosed with NCGS was also determined (cohort B).

Results: Cohort A: 59 cases of IBS (mean age 32.7 years, 80% female), 75 CrD (mean age 47.1 years, 59% female), 71 UC (mean age 43.2 years, 68% female) and 109 GORD (mean-age 51.7 years, 61% female); p value for age < 0.001 and gender 0.05.
The presence of GS was 42.4% for IBS, 29% CrD, 25.3% UC and 18.3% for GORD. Adjusting for age and sex, IBS individuals were significantly more likely to self-report GS compared to individuals with GORD (p 0.02, OR 2.56, CI: 1.15–5.73). However, there was no difference in self-reported GS between IBS, CrD or UC.

In CrD the presence of strictures (p 0.04, OR 3.12, CI: 1.03–9.45) and CrD-activity index > 220 (p 0.0001, OR 8, CI: 2.45–2.62) were predictors of self-reporting GS. In contrast, a CrDAI score < 150 was supportive of not being GS (p 0.002, OR 5.35, CI: 1.8–15.9). The simple colitis activity score did not influence the presence or absence of GS in UC.

Cohort B: Analysis of 200 NCGS patients (mean age 39.1 years, 83% female) shows that 3% were subsequently found to have organic pathology (two cases of UC, one case each of CrD and pyloric stricture).

Conclusion: NCGS is not exclusive to IBS and can also be seen in established organic gastrointestinal pathologies, such as inflammatory bowel disease. Its presence may be reflecting severe and stenotic disease. Occasionally, NCGS may be the first presentation of organic pathology.
Anaplastic large cell lymphoma (ALCL) in celiac disease. Case report

Alice Bartkova, Martin Liberda, Martin Hrbka, Dana Klezlova
Department of Gastroenterology, Valasske Mezirici Hospital, Valasske Mezirici, Czech Republic

Introduction: The incidence of lymphoma has more than doubled in the past four decades and continues to increase. Primary extranodal lymphomas constitute up to 1/3 of all lymphomas, and the gastrointestinal tract (GIT) is the most common extranodal site of involvement by non-Hodgkin lymphomas (NHL) in immunocompetent patients. GIT lymphomas are described in 10–15% of all NHL and in 30–40% of all extranodal lymphomas. Primary gastrointestinal lymphoma is very rare – it appears in only 1–4% of all GIT malignancies, 90% of which are of B cell lineage. Most frequently lymphomas occur in the stomach, followed by the small intestine, usually in terminal ileum.

Case description: The authors present a case of 70-year-old patient with recent weight loss, more than 15 kg during last 3 months, without any other gastrointestinal symptoms. Gastroscopic signs of coeliac disease were confirmed by serology and histology. Ultrasonography and subsequent CT scan revealed extensive retro- and intraperitoneal lymphadenopathy. The progression of the disease was very quick and the patient died within 5 weeks of his first presentation in the doctor's office. Rapid progression of the disease prevented the patient from the salvage therapy trial. Large tumour of proximal jejunum with the infiltration of pancreas was identified during the autopsy – histological results confirmed anaplastic large cell lymphoma (ALCL).

Discussion: ALCL constitutes approximately 3% of all NHL. It is a peripheral T-lymphoproliferative disease and its presence in GI tract is very rare. Coeliac disease is regarded as a precancerous condition.

Conclusion: Lymphomas are the most frequent coeliac-associated malignant diseases. However, the vast majority of lymphomas in coeliac disease are so-called EATL (Enteropathy-Associated T-cell Lymphomas). Since there are possibly no other reports on intestinal ALCL in untreated (undiagnosed) coeliac disease, this association could be only coincidental.
Clinical utility of serologic screening for celiac disease and HLA typing among children with autoimmune disorders

Oana Belei, Otilia Marginean
First Pediatric Clinic, University of Medicine and Pharmacy Victor Babes Timisoara, Romania

Introduction: Active-case finding in groups at risk for celiac disease (CD) is considered a cost/effective strategy. The association of CD with several autoimmune conditions is well-known.

Objectives: To determine the prevalence of CD in a pediatric population from the Western part of Romania diagnosed with autoimmune thyroid disorders (AITD) and insulin-depended mellitus diabetes (IDDM) compared to control lot and to assess the clinical forms of presentation and the HLA polymorphism in all cases.

Methods: 74 children with AITD (lot 1), 98 children with IDDM (lot 2) and 80 healthy children were screened for CD. In patients with at least one positive serologic test for CD, intestinal biopsy was performed. All children underwent HLA typing for DQ2/DQ8.

Results: CD prevalence in lot 1 was 7%, in lot 2 was 6% and in control lot was 0%. Most of the cases presented as silent CD (82%). All children diagnosed with CD presented DQ2/DQ8 haplotype. 20% of the control subjects associated heterozygous DQ2 alleles. From 69 children with AITD/without CD only 3 patients (4%) presented heterozygous DQ2 alleles. From 92 children with IDDM/without CD, 25 patients (27%) associated homo or heterozygous DQ2/DQ8 alleles. There were significantly more cases with IDDM without CD but with predisposing haplotype for CD (27%) compared to the number of patients with AITD seronegative for CD and with DQ2/DQ8 alleles (4%) p < 0.005.

Discussion/Conclusion: Recommending AITD and IDDM as selection parameters for CD screening in asymptomatic children is justified. HLA assessment cannot highlight a significant role of a certain allele in the pathogenesis of autoimmune comorbidity AITD/CD or IDDM/CD. DQ2 and DQ8 alleles are mandatory but insufficient for CD development. The intervention of environmental factors is very important. Performing as first line approaching HLA typing in asymptomatic at risk children is important. A negative result for DQ2/DQ8 alleles will render CD highly improbable and there will be no need for subsequent CD antibodies testing in such cases.
Clinical, histological and immune-genetic correlations among Romanian children with celiac disease

Oana Bele, Otilia Marginean
First Pediatric Clinic, University of Medicine and Pharmacy “Victor Babes”, Timisoara, Romania

Introduction: It has been postulated that IgA anti tissue-transglutaminase (tTG) or anti-endomisium antibodies (EMA) can be false negative in young children. IgA/IgG antibodies against deamidated gliadin peptides (DGP) were described as valuable diagnostic parameters in pediatric celiac disease (CD).

Objectives: To assess the correlation between different forms of CD, immunological, morphological parameters and haplotypes.

Methods: The study included 2 lots. The first lot was made of 30 children diagnosed with CD and the second contained 30 control subjects. The diagnosis was based on combined IgA/IgG DGP/tTG assay in addition to intestinal biopsy. We assessed DQ2 and DQ8 HLA using PCR to all patients and in control lot.

Results: From 30 celiac patients, 18 presented atypical forms, 4 presented silent forms and only 8 associated the classical forms of disease. Alleles distribution in group of celiac patients was: 28 were positive for DQ2HLA and from them 7 associated DQ2 homozygous and 21 associated DQ2 heterozygous haplotypes. 2 cases presented DQ8HLA. In the control lot, 2 subjects from 30 associated heterozygous DQ2HLA. The rest were negative for DQ2/DQ8 HLA. We correlated the clinical forms of disease with IgA/IgG DGP/tTG antibodies level, severity of villous injury and haplotypes. Bivariate and multivariate conditional logistic analyze were performed. We obtain a significant correlation between IgA/IgG DGP/tTG serum level and severity of villous injury (r = 0.621092). We established a positive correlation between subgroup Marsh IIIc and the severe classic form of CD. The forms of disease and the haplotypes didn’t correlate.

Conclusion: The polymorphism of CD presenting forms and the lack of concordance between clinical symptoms and the type of intestinal injury underline the importance of intestinal biopsy for cases with clinical suspicion of CD. HLA polymorphism has no impact on clinical forms of disease. The presence of DQ2/DQ8 is mandatory, but not sufficient for development of CD. Due to its high negative predictive value, the assessment of haplotype must be used in clinical practice only at uncertain cases.
Endoscopic features in celiac disease

N. Ben Mustapha, R. El Elj, M. Serghini, M. Fekih, J. Boubaker, S. Matri, A. Filali
Gastroenterology A Unit, La Rabta Hospital, Tunis, Tunisia

Introduction: Celiac disease is an immune mediated enteropathy caused by permanent sensitivity to gluten, affecting genetically susceptible individuals. The definitive diagnosis is based on duodenal biopsies and histopathological study. We aimed to correlate endoscopic features of the duodenum and histological aspects of celiac disease.

Methods: We conducted a retrospective study including 50 patients diagnosed for celiac disease in our unit between 2003 and 2013. Diagnosis was established, for all our patients, on the basis of histopathologic findings confirming villous atrophy.

Results: They were 12 males and 38 females of a median age of 29 years (10–64 years). Clinical symptoms were: Diarrhea (46%), weight-loss (16%), anemia (8%) and recurrent abdominal pain (6%). Endoscopic features suggesting villous atrophy were found in only 52% of cases: Mosaic mucosal pattern (34%), reduced duodenal folds (12%) and scalloping (6%). Duodeneal aspect was normal in 48% of patients. The majority of our patients had a total villous atrophy (74%). Partial villous atrophy was seen in 25.5% of cases. No correlation was found regarding endoscopic findings and Mash grade.

Discussion/Conclusion: Half of our patients with celiac disease had a normal macroscopic appearance of the duodenum. Histologic examination of duodenal biopsy is necessary when celiac disease is suspected even in patients with normal upper endoscopy.
Clinical polymorphism of celiac disease

N. Ben Mustapha, R. El Elj, M. Serghini, M. Fekih, J. Boubaker, S. Matri, A. Filali
Gastroenterology A Unit, La Rabta Hospital, Tunis, Tunisia

Introduction: Celiac disease is an autoimmune enteropathy that presents with a wide variety of symptoms. Atypical and asymptomatic presentations are being increasingly reported. This study aimed to describe the various clinical presentations, biochemical profile and endoscopic aspects in celiac disease patients.

Methods: This was a retrospective study including 50 patients diagnosed and managed for celiac disease who in our unit between 2003 and 2013. Epidemiological features were recorded. Biochemical, endoscopic and histological data were collected.

Results: They were 12 males and 38 females of a median age of 29 years (range 10–64 years). Six patients had a family history of celiac disease. Associated autoimmune disorders included type 1 diabetes mellitus (5 [10%]), autoimmune thyroiditis (5 [10%]), primary biliary cirrhosis (1 [2%]) and Sjögren's syndrome (1 [2%]). The most frequent symptom was diarrhea (46%), followed by weight-loss (16%), anemic syndrome (8%) and recurrent abdominal pain (6%). The quarter of patients were asymptomatic at diagnosis. A dermatitis herpetiformis was associated in one case. 88% of patients were anemic, the average of hemoglobin was 8.2 g/dl (range 4.3–11 g/dl). The antibodies (Anti-tissue transglutaminase and anti-endomysial antibodies) were strongly positive in half of cases. All patients underwent an upper gastrointestinal endoscopy and duodenal biopsy. Endoscopic features of villous atrophy were found in 52% of cases: Mosaic mucosal pattern (34%), reduced duodenal folds (12%) and scalloping (6%). Histologic examination of the duodenum has documented villous atrophy in 86% of cases.

Discussion/Conclusion: A significant proportion of patients with celiac disease are seen more commonly with non-diarrheal presentations and almost the quarter of patients were asymptomatic. Frequent diagnosis of atypical and silent forms of celiac disease is an indication to serological examination in patients with unclear clinical picture and genetic predisposition.
Whipple’s disease – A rare but not impossible cause of chronic diarrhea and malabsorption

Andreea Bengus¹, Radu Bogdan Mateescu¹, Cristiana Popp¹, Lucian Negreanu²
¹Colentina Clinical Hospital, Bucharest; Romania
²University Emergency Clinical Hospital, Bucharest, Romania

Introduction: A 52-year-old man presented with chronic diarrhea: 6–10 watery stools/day, without mucus, blood, low fever (37–38°C), asthenia, 15 kg weight loss starting 2 years before. He denied drinking alcohol and smoking. No personal or familial medical history.

Methods: Patient was repeatedly evaluated for infectious diseases, but stool cultures (Shigella, Salmonella, enteropathogenic or enterotoxigenic E. coli, Campylobacter jejuni) were negative. Because several times positive for Giardia lamblia, he received metronidazole, without improvement. Hyperthyroidism and celiac disease – excluded. Multiple gastrosopies – no lesions except some diffuse white small deposits in D2 (no histopathological anomalies). Clinically: palour, underweighted (BMI 20.1), 37.5°C, diffuse abdominal pain, increased bowel sounds; peripheral edema; without enlarged lymph nodes, skin lesions, or articular involvement.

Laboratory – hyposideremic anemia (Hb 9.12 g/dl, serum iron 10 µg/dl), hypoalbuminemia (2.9 g/dl), inflammation (CRP 84.7 mg/l) suggesting lesion of absorptive epithelium.

Results: Because he refused a new colonoscopy we used the new Pillcam 2 videocapsule – no anomalies in esophagus, stomach, first part of duodenum, but a “salt and pepper” aspect of entire small bowel, ending at the ileocecal valve was noticed, due to a myriad of 1–2 millimeters white deposits (suggesting small intraepithelial abscesses). Multiple biopsies were taken from small bowel mucosa (upper endoscopy + ileo-colonoscopy): HE stain - flattened villi, expanded by a dense infiltrate of foamy macrophages with finely granular eosinophilic cytoplasm; PAS – foamy macrophages with frequent PAS positive bacilli in cytoplasm, suggestive for Tropheryma whipplei.

Discussion/Conclusion: Given the lack of signs of neurologic involvement, we started oral cotrimoxazole (800/160 mg/day). Ten days later, general condition improved: increased appetite, slight reduction in bowel movements (4–5/day) and in CRP (51 mg/l) and, by the end of the second month of therapy, he had gained 7 kg. Stools decreased to 2–3/day, CRP fell to 19 mg/dl and temperature – normal.
Rhythm disturbances in young patients with celiac disease

Maria Cristina Bezna, Cristina Deliu, Adriana Coltescu
Emergency Hospital, University of Medicine and Pharmacy, Craiova, Romania

Diagnosis of celiac disease may be difficult in young patients with atypical or silent manifestations. We analyze this condition for prevention, for an out of the box view, to avoid erroneous diagnosis, because, in these cases, serologic and bioptic diagnosis is often delayed. The combination of non-gastrointestinal events, such as heart rhythm disturbances, with abdominal symptoms in young people orients towards the possibility of a celiac disease diagnosis.

Aim: Description of repetitive rhythm disorders in young people with digestive symptoms suggestive for a bowel disease, which proves to be celiac disease with delayed diagnosis.

Patients and methods: The study was conducted on 9 patients, aged 16–24, with minor, but persistent, digestive disorders, especially after eating products containing gluten. The major manifestations were extradigestive, characterized by palpitations, fatigue, anxiety. Arrhythmias were investigated, excluding etiology of heart pathology. Biological and imaging explorations resulted in the diagnosis of intestinal disease.

Results: Cardiac manifestations undue to cardiac pathology in young patients with digestive problems seemingly minor and underdiagnosed, may be secondary complications in silent or apparent asymptomatic celiac disease. Episodes of worsening, especially without a gluten-free diet led to complications such as anemia, abnormal ionic level due to diarrhea, hypotension. Complications (mostly anemia), without any other digestive pathology, conducted our study towards a differential diagnosis. Arrhythmias were: atrial extrasystoles (5 patients), sinus tachycardia (4 patients), ventricular extrasystoles (2 patients), bradycardia (2 patients). All patients had moderate anemia. The decrease of serum potassium was observed in 6 patients. Hypotension, with accelerated transit and abdominal pain were present in 5 patients.

Conclusions:
1. Functional arrhythmias in young patients with digestive disorders can be caused by complications of an underdiagnosed celiac disease.
2. Anemia, electrolyte disturbances, anxiety due to celiac disease can cause rhythm disorders in patients.
3. Association of cardiac events with intestinal disturbances, even minor, requires investigations for inclusion/exclusion of celiac disease.
Intestinal investigation by ultrasound and contrast with polyethylene glycol

Maria Cristina Bezna, Cristina Deliu, Adriana Coltescu, M. Bezna
Emergency Hospital, University of Medicine and Pharmacy, Craiova, Romania

The imagistic investigation of intestinal tract is difficult and by ultrasound is necessary a contrast agent which may improve the ultrasound image.

Aim: To mark the possibility of performing ultrasound images with significance in intestinal diseases by administration of polyethylene glycol electrolyte, (PEG) – 64 g\%.

Patients and methods: The study was made on 30 patients with intestinal perturbations to whom the ultrasound investigation was made before and after some hours (2–6 h) from oral PEG administration by drinking 3–4 l of this solution for intestinal lavage. This intake of PEG was made in patients without meals before some hours.

Results: Polyethylene glycol, initially proposed by Fordtran in 1980 is an osmotic substance with a low level of absorption and not submitted to the metabolism of disaccharides, associated with diverse salts (sodium sulfate, sodium chlorate and bicarbonate, sodium chloride). This solution exerts an osmotic outward pressure, creating neither absorption nor secretion of water and electrolytes. It is utilized for colonic lavage before endoscope, but PEG solution is a liquid and may offer in the same time a good contrast agent permitting the visualization of intestinal content and walls, the presence or absence of intestinal motility and pathological aspects.

Conclusions:
1. An intestinal ultrasound after oral administration of a polyethylene glycol electrolyte solution 64 g\% is useful in diagnosis.
2. PEG is a liquid sufficient to create a good intestinal contrast permitting normal or pathologic ultrasound images.
3. The method is with good tolerance, without toxicity and offers ultrasound intestinal informations.
Oxidative stress modifications in patients with celiac disease associated with autoimmune thyroiditis

Marinela Beza, Cristina Deliu, Adriana Coltescu, Maria Cristina Beza
Emergency Hospital, University of Medicine and Pharmacy, Craiova, Romania

Celiac disease, characterized by an exaggerated immune response of intestinal mucosa to gluten proteins, in genetical predisposed subjects may associate, in evolution, other autoimmune diseases (autoimmune thyroiditis, systemic lupus erythematosus, type 1 diabetes, rheumatoid arthritis, Sjögren's syndrome).

Aim: Observation of oxidative stress status in patients with associated autoimmune thyroiditis in the evolution of celiac disease.

Patients and methods: The study was performed in 3 patients aged 28–37 years, diagnosed with celiac disease, who presented manifestations of hyperthyroidism, associating an autoimmune thyroiditis. The diagnosis of both diseases was conducted by clinical and serological tests, biopsy and imaging of bowel and thyroid. In these patients, the level of oxidative stress markers (malondialdehyde as an indicator of lipid peroxidation, nitric oxide, antioxidant enzymes-glutathione peroxidase, superoxide dismutase) was determined in serum.

Results: Both celiac disease and autoimmune thyroiditis are diseases in which the immune disturbances can lead to disturbances in lipid peroxidation and changes of oxidant-antioxidant balance, with the occurrence of oxidative stress disorders. This fact is observed according to the increased level of oxidative enzymes and the decreased level of antioxidants. Management of celiac disease associated with autoimmune thyroid disorder involves, besides gluten restricted diet and antithyroid therapy, beta-blockers drugs and combinations of antioxidants in diet for patients to whom a high level of oxidative stress markers was currently determined biochemically.

Conclusions:
1. Determination of oxidative stress markers may be useful both in uncomplicated celiac disease but especially in the complicated with other autoimmune diseases ones.
2. The association with thyroid pathology has implications in metabolic disturbances and exacerbation of autoimmune celiac disease, which already disrupts the absorption of proteic nutrients from food.
3. Treatment involves, besides gluten restricted diet control and treatment of thyroid disease, in the case of increased level of oxidative stress markers, a proper antioxidant combination.
Predictive role of transabdominal ultrasonography in diagnosis and follow-up in patients with celiac disease

A. Chavoushian¹, A. Petrov¹, M. Antalavicheva¹, A. Michova²
¹Department of Gastroenterology, City Clinic, Sofia
²Department of Pathology, Military Medical Academy, Sofia, Bulgaria

Determination of the predictive role of transabdominal ultrasonography in diagnosis of celiac disease (CD) and guidance for further serological and histological tests.

Introduction: Transabdominal ultrasonography could be employed to facilitate the diagnosis of CD in cases of non-specific complaints and to focus further tests for definite identification of the disease.

Methods: After clinical examination conventional transabdominal ultrasonography of the small and large intestine was performed as routine initial examination in 2063 patients with non-specific chronic dyspeptic complaints in lower GI tract.

Results: The following ultrasonography changes were established in 11 patients between 18 and 62 years of age:
- slight small intestine loop dilatation – 11;
- increased peristalsis, "laundry phenomenon" – 8;
- increased intraluminal fluid in the fasting state – 11;
- abdominal lymph nodes up to 12 mm – 4;
- free abdominal fluid – 3.

The combinations of the above changes, suspicious of CD, suggested making of hematological, biochemical, serological tests and FGDS with duodenal biopsy. The following were established:
- Iron deficiency anemia – 7;
- Anti tTG antibodies – 11;

Histomorphological changes with different Marsh score – 4 patients. Seven patients denied FGDS.

Following a gluten-free diet (GFD) on the 12th month 9 patients showed clinical improvement and normalization of ultrasonography changes. The changes persisted in 2 patients. One patient had CD with complicated dilated cardiomyopathy and did not follow a strict GFD. The second patient showed slightly improved clinical symptoms, but persistent changes in the lab test parameters, positive anti tTG ab, ultrasonography changes. After removal of foods with concealed gluten the changes reversed to normal.

Discussion/Conclusion:
1. Transabdominal ultrasonography is a fast, cheap and non-invasive method, suggestive of CD.
2. Transabdominal ultrasonography provides guidance for further diagnostic steps in the event of non-specific dyspeptic complaints relevant to the lower GI tract.
3. In cases of diagnosed CD, ultrasonography monitoring allows to follow up the effect of gluten-free diet.
The effects of a prebiotic/probiotic combination in active celiac disease

I. Copaci, G. Chiriac, L. Micu
Center of Internal Medicine, Fundeni Clinical Institute, Bucharest, Romania

Introduction: The only effective treatment of celiac disease (CD) is gluten-free diet (GFD). GFD must be absolutely strict to avoid CD-related complications. The enteric microbiota modulates the functions of gut-associated lymphoid tissue. We designed a trial to determine the potential effect of probiotic/prebiotic bifidobacterium longum W11/fructo-oligosaharide (Zir-fos®) on perception of symptoms, histology and inflammatory markers in patients with active CD.

Methods: Twenty-five adult patients having 3 positive CD specific tests were randomized to receive 1 sachette Zir-fos before meals for 6 weeks (13 patients) or placebo (12 patients) while being on GFD. The gastrointestinal symptoms were assessed using the Gastrointestinal Symptom Rating Scale (GSRS). The CD serology and duodenal histology were performed at baseline, at the end of treatment and at 30 days after the treatment. Blood samples were collected for determination of IL-1beta, IL-6 and TNFα.

Results: In contrast to patients on placebo, the patients on treatment experienced a significant improvement in GSRS (p = 0.002 for indigestion; p = 0.003 for diarrhea; p = 0.041 for dyspepsia and abdominal pain). Final IgA tTG, IgA-EMA and IgG-antigliadin were lower in the B. longum arm (p = 0.048 for IgA tTG, p = 0.28 for IgA EMA and p = 0.21 for IgG-antigliadin). Final pro-inflammatory cytokines did not change significantly, but a lower number of intraepithelial lymphocytes was observed in the treatment group (p = 0.049).

Discussion/Conclusion: The study suggests that prebiotic/probiotic treatment may improve symptoms in celiac disease. This treatment alleviates serologic tests and the lymphocyte infiltrates in the mucosal biopsy specimens.
Giardiazis in a patient with celiac disease and common variable immunodeficiency syndrome

Hakan Demirci, Zulfikar Polat, Kadir Ozturk, Yusuf Serdar Sakin, Murat Kantarcioğlu, Ahmet Uygun, Sait Bagci
Gulhane Military Medical Academy, Department of Gastroenterology, Ankara, Turkey

Introduction: Common variable immunodeficiency syndrome a rare disease with characterized by hypoglobulinemia and dysfuction of B and T lymphocytes. B-lymphocytes have impaired differentiation to immunoglobulin secreting plasma cells. Upper-lower respiratory tract infections and parasitic infections are quite often in these patients. Lymphoma risk is 8 to 13 times higher. Involvement of the gastrointestinal tract occurs in approximately half of the patients with complaints of malabsorption and chronic diarrhea. Small bowel biopsy may show nodular lymphoid hyperplasia, diffuse lymphoid infiltration, and loss of villi.

Case report: A 24-year-old female patient was admitted to our clinic with complaints of abdominal pain, nausea, weight loss, and diarrhea. She had a 2-year history of diarrhea with 5–6 watery stools per day resulting in 8 kg weight loss during this period. Endoscopy and colonoscopy performed at another center revealed a diagnosis of Crohn's disease, mesalazine and budesonide treatment was started. When she referred to another hospital due to the persistence of her symptoms, she was diagnosed with seronegative Celiac disease and diet was suggested, but she still had symptoms despite diet. Stool analysis revealed the presence of giardiasis, and she was prescribed metronidazole treatment. Laboratory tests were normal. Stool analysis revealed the presence of Giardia cysts in stool. Endoscopy showed gastroduodenitis and duodenal nodularity and colonoscopy revealed widespread polipoid lesions. Protein electrophoresis albumin: 69.8, alpha-1: 3.9, alpha-2: 12.4, beta: 13.9, gamma: 0.0, IgA: 0.25 (0.7–4.0), IgG: 0.64 (7.0–16.0), IgM: 0.17 (0.4–2.3), IgE Total: 0.01 (0.0–85). Immun fixation electrophoresis revealed no monoclonal pathology, and evaluation of the patient for primary immune deficiency was detected.

Conclusion: Duodenal nodularity in endoscopic examination of patients suffering from treatment-refractory chronic diarrhea may be associated with giardiasis, and these patients should further be assessed for common variable immunodeficiency. Treatment includes the administration of IVIG 400 mg/kg once in 3 weeks.
Idiopathic pulmonary hemosiderosis with synchronous celiac disease

Hakan Demirci, Zulfikar Polat, Kadir Ozturk, Murat Kantarcıoglu, Ahmet Uygun, Sait Bagci
Gulhane Military Medical Academy, Department of Gastroenterology, Ankara, Turkey

Background: Idiopathic pulmonary hemosiderosis (IPH) is a rare disease of unknown etiology. Recurrent alveolar hemorrhages, hemoptysis and iron deficiency anemia may be seen during the course of IPH. Herein, we report a very rare occurrence of IPH and synchronous celiac disease.

Case report: A 24-year-old young male patient suffering from recurrent hemoptysis and dyspnea for 3–4 months was admitted to our clinic. Laboratory tests revealed Hemoglobin: 5 g/dl, and he received 2 units of erythrocyte suspension transfusion. High resolution computed tomography of the lungs revealed areas of micronodular infiltration and diffuse pattern of ground-glass opacity. Pulmonary function tests and diffusion capacity was normal. Bronchoscopy with transbronchial biopsy revealed the diagnosis of pulmonary hemosiderosis. The patient had no gastrointestinal complaints, nevertheless, anti-gliadin and anti-endomysial antibodies were found to be positive on laboratory tests. Endoscopic intestinal biopsy revealed histopathological findings consistent with Celiac disease (gluten enteropathy). Gluten-free diet was suggested without steroid medication since the patient had normal pulmonary function tests. Diffuse pattern of ground-glass opacity showed complete regression on follow-up at 2 months and complete resolution of hemoptysis and dyspnea was noted with normal hemoglobin levels.

Conclusion: Patients with IPH should be further assessed for the presence of synchronous celiac disease even without gastrointestinal symptoms. Gluten-free diet without steroid medication may be considered if the pulmonary function tests are normal.
Anti-tissue transglutaminase antibodies in patients with liver disease – Single center experience

P. Drastich, P. Wohl, M. Benes, J. Spicak
Institute for Clinical and Experimental Medicine, Prague, Czech Republic

Objective: Coeliac disease (CD) may cause liver injury ranging from mild hepatic abnormalities to a severe disease requiring liver transplantation. CD is also associated with autoimmune liver diseases such as primary biliary cirrhosis (PBC), primary sclerosing cholangitis and autoimmune hepatitis (AIH). CD affects around 1% of general population.

Aim: The aim of the current study was detection of auto antibodies directed against tissue transglutaminase (tTGAs) in patients with any kind of liver disease.

Material and methods: A total of 954 patients with liver disease treated in our department between 2009–2010 (152 patients with alcoholic liver disease, 264 patients with viral hepatitis, 32 patients with PBC, 75 patients with AIH, 30 patients with Wilson’s disease, etc.) were analyzed using recombinant BINDAZYMETM anti-tissue transglutaminase EIA kit. Positivity was defined as either tTGA IgA > 10 U/ml or tTGA IgG > 9 U/ml in IgA deficiency patients.

Results: In total, serological evidence of CD, positivity of tTGAs was found in 21 out of 954 evaluated patients (2.2%). Anti-tissue transglutaminase antibody positivity occurred in 4 patients with mild liver tests abnormalities and with liver steatosis, in 3 patients with AIH and Wilson’s disease, in 2 patients with polycystic liver and in 1 patients with PBC, Budd-Chiari syndrome, viral hepatitis B, toxic hepatitis and NASH. Sixteen of these patients were also positive for IgA and IgG anti-gliadin antibodies, whereas only 10 patients were also positive for IgA anti-endomysial antibodies. Thirteen of these tTGA positive patients showed some non-specific symptoms for CD.

Conclusion: Prevalence of tTGAs in patients with liver disease in our cohort was lower than expected from previously published studies (2.2%). tTGAs were associated with AIH in 4% and surprisingly high prevalence of CD was found in patients with Wilson’s disease (10%).
Can serologic markers of celiac disease be used to identify idiopathic portal hypertension? A prospective study

A.C. Dülger, Y. Dirik, H. Güdücüoglu, N. Ceylan, S. Ölmez
Yuzuncuyil University School of Medicine, Van City, Turkey, Turkey

Celiac disease is a small intestinal malabsorption syndrome due to hypersensitivity to gluten, which is derived from wheat, barley, and rye. Idiopathic portal hypertension (IPH) is a non-cirrhotic, intrahepatic presinusoidal hypertension due to mostly obscure environmental and genetic conditions. Hepatosplenomegaly and esophageal varices are the cardinal features of the disease. Environmental factors may have an important role in the development both of CD and IPH. There are few studies and case reports about coexistence IPH and CD.

Material and methods: 15 patients (3 male, mean age: 29.5 ± 8.9) with biopsy-proven IPH were screened for serum tissue transglutaminase antibodies and immunoglobuline A, and those antibody-positive were further investigated by intestinal biopsy. Histopathological examination was performed according to a Marsh classification. Ultrasonography of abdomen was performed on each case. Baseline characteristics of the patients are presented in the table.

Results: All the patients were resident in rural areas of the Iranian border of Turkey. Of the 15 patients, 8 were both serum tissue transglutaminase immunoglobulin A and G positive and 3 were serum tissue transglutaminase immunoglobulin A-negative but serum tissue transglutaminase immunoglobulin G-positive. Duodenal biopsy, performed in 11 cases, manifested celiac disease in 3 cases.

Conclusion: Persons with IPH have an increased risk of CD as compared with the general population. Increasing awareness for the presence of the CD should be needed in patients with IPH. On the other hand, serum tissue transglutaminase antibodies can be used to detect IPH patients. In sum, IPH and CD may share same etiologic properties as well as gut-oriented mechanisms.
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Diagnosis of gastrointestinal tuberculosis. A big series from a research hospital, Turkey

Meltem Ergun, M.D., Ph.D., Ali Rıza Köksal, M.D., Salih Boga, M.D., Mehmet Bayram, M.D., Hüseyin Alkim, M.D., Ph.D., Canan Alkim Alataş, M.D., Ph.D. Şişli Etfal Training and Research Hospital Department of Gastroenterology, Istanbul, Turkey

Gastrointestinal tuberculosis (GI tb) is the second most common type after pulmonary tuberculosis. Patients with abdominal tuberculosis may present with various symptoms and GI tb may mimic other diseases.

Introduction: While in developed countries, tuberculosis (tb) is commonly accompanied with immunodeficiency, in developing countries it is still a health problem in immune-competent adults. The accurate diagnosis of abdominal tuberculosis requires a high index of suspicion and combination of diagnostic modalities in clinical practice.

Methods: Between January 2009 and December 2013, the records of 54 patients (26 females, mean age: 34.8 years, range: 15–73 years) diagnosed with abdominal tuberculosis were analysed retrospectively. Patients’ characteristics, laboratory investigations, and radiological, endoscopic, surgical findings as well as survival of patients were evaluated. Follow-up information was obtained by telephone contact and scheduled visits.

Results: 54 patients were enrolled in the study. There are three different types of presentations:

1. Ileocolonic presentation: mainly diarrhea, and abdominal pain
3. Subacute/acute intestinal obstruction findings.

Typical tb signs like fever and night sweats may accompany all types. In all three groups, the most frequent symptoms were abdominal pain (n = 48, 89%), fever (n = 32, 60%), ascites (n = 21, 39%), diarrhea (n = 18, 33%), weight loss (n = 27, 50%), and night sweats (n = 17, 31%). Subacute/acute intestinal obstruction was found in 9 (17%) cases. History of pulmonary tuberculosis treatment and family history of tuberculosis were present in 10 (19%) and 12 (22%) patients, respectively. Two patients have both family history and pulmonary tuberculosis history; also two patients have more than one relatives diagnosed with tuberculosis. Distribution of methods to diagnose abdominal tuberculosis was as follows:

1. histopathology obtained by endoscopic/colonoscopic biopsies in 20 (37%),
2. ultrasound/computed tomography-guided biopsies in 6 (11%),
3. laparoscopic/surgical interventions in 18 (33%), and
4. ascites examinations in 5 (9%) patients.

Microbiological tests were positive in only 7 (13%) patients. The predominant site of involvement by abdominal tuberculosis was intestinal in 26 (48%), peritoneal in 23 (43%), and solid viscera/nodal in 5 (9%) cases.
**Discussion/Conclusion:** Pulmonary tuberculosis or family history of tuberculosis exists at least in one-third of patients with gastrointestinal tb. Nearly half of the patients present with ileocolonic type and the rest present with peritoneal type. Probability of tb should always be considered when patients present with vague abdominal symptomatology. A combination of multiple diagnostic tools is essential to make the correct diagnosis in such cases.
Bronchial and gastrointestinal asthma together?

Meltem Ergun, M.D., Ph.D., Ali Riza Köksal, M.D., Salih Boga, M.D., Mehmet Bayram, M.D., Kubra Habir, M.D., Deniz Tuncel, M.D., Hüseyin Alkim, M.D., Ph.D., Canan Alkim Alataş, M.D., Ph.D.

Şişli Etfal Training and Research Hospital Department of Gastroenterology

Eosinophilic digestive disorder is a rare and heterogeneous condition which is characterized by eosinophilic infiltration of gastrointestinal (GI) system. In patients with asthma and gastrointestinal symptoms like chronic diarrhea, abdominal pain and malabsorption; eosinophilic gastroenteritis should be included in differential diagnosis.

Introduction: In patients with asthma and malabsorption, eosinophilic gastroenteritis should be considered as a possible diagnosis. We describe a case of a 28-year-old man who had diagnosed with bronchial asthma complaining of diarrhea for five years. After the diagnosis of eosinophilic enterocolitis, budesonide was initiated which resulted in complete resolution of his symptoms.

Case summary: A 28-year-old man was admitted to our hospital with a 5 year history of diarrhea (3–4 movements daily), abdominal pain, and weight loss. He had also a history of bronchial asthma for five years. Laboratory tests showed anemia and hypoalbuminemia. He was suffering from diarrhea for five years and investigated for many times including upper GI endoscopy and colonoscopy, with no specific diagnosis. Eosinophilia was noticed at blood analysis (7.7%). Biochemical tests apart from albumin were normal. Tests for rheumatoid factor, antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-transglutaminase and anti-endomysium antibodies were all negative. Serum immunoglobulin (Ig) Ig E concentration was 869 IU/ml (100–240), other Igs were within normal limits. Hepatitis A, B, C, cytomegalovirus, Epstein-Barr virus and Human immunodeficiency virus serologies and stool examinations were negative. Upper GI examination showed pangastritis and reflux esophagitis and nodularity at the bulbus and postbulber duodenum (Figure 1). Colonoscopic examination showed mild edema at the colonic wall with faded vascularity and normal ileum (Figure 2). Pathologic assessment of biopsies showed eosinophilic infiltration of both stomach and duodenum and colon as well. There were 35 and 16 eosinophils per high power field in the duodenal and colonic mucosal biopsy specimens, respectively. The appearance was compatible with the clinical diagnosis of eosinophilic gastroenteritis (figure 3–5). Shortly after budesonide treatment, his symptoms resolved remarkably.

Discussion/Conclusion: Eosinophilic digestive disorder includes a broad spectrum of clinical presentations due to eosinophilic inflammation involving anywhere from the esophagus to the rectum. In patients with asthma and gastrointestinal symptoms like chronic diarrhea, abdominal pain and malabsorption; eosinophilic gastroenteritis should be included in differential diagnosis.
Fecal calprotectin as a marker in differentiating irritable bowel syndrome from organic intestinal disease in Egyptian patients

W. Farrag, S. El Saadany*, M. Sharaf-Eldin*, M. Abdullah** and S. Hammoudah**
Departments of Internal Medicine, *Tropical Medicine and **Clinical Pathology, Faculty Medicine, Tanta University, Tanta, Egypt

Introduction: The aim is to determine whether calprotectin alone or with other marker can differentiate irritable bowel syndrome (IBS) from other organic intestinal diseases

Methods: Thirty Egyptian patients were studied, in addition to 10 controls. The principal inclusion criteria were that patients who had symptoms of IBS for at least six months, and that it was deemed necessary to do an endoscopic and/or intestinal radiological procedure to confirm or exclude organic intestinal disease. Among the 30 patients 15 proved to have IBS (IBS group). The others were 8 with inflammatory bowel syndrome IBD (ulcerative colitis 7 and 1 Crohn's disease) (IBD group), while 7 demonstrated miscellaneous diagnosis (5 colorectal carcinoma and 2 patients had intestinal polyps). ESR and CRP, stool analysis to exclude pus (as sign of inflammation) and fecal calprotectin level assessment using ELISA technique were done for patients and controls, while all patients had colonoscopic examination with multiple biopsies for histopathological evaluation.

Results: ESR results showed significant difference between miscellaneous group and all other studied groups. While, non significant difference was detected in between control, IBS, and IBD groups. The results of CRP demonstrated significant difference between control and both IBS and IBD groups, and Miscellaneous. Fecal calprotectin demonstrated no significant difference between control and IBS group, while a significant difference was noticed between IBS and IBD group and IBS and miscellaneous group. The sensitivity, specificity, and positive and negative predictive values of the fecal calprotectin assay in distinguishing between organic causes of intestinal disease and IBS at cutoff (50 µg/g) showed a positive predictive value of 85% and negative predictive value 68% and sensitivity 100% and specificity of 92%.

Discussion/Conclusion: Fecal calprotectin has potential as screening procedure to differentiate between patients with IBS from other organic intestinal disease as calprotectin concentration is rarely within the normal range in patients with IBD or colorectal cancer/adenomatous polyps.
Prevalence of celiac disease in Egyptian children and adolescents with diabetes mellitus: A clinical, biochemical and histopathologic study

W. Farrag, M. Saleh¹, S. Esmail², S. El Saadany², M. Sharaf-Eldin², A. Menessy³, and H. Hamouda⁴
Internal Medicine, Pediatric¹, Tropical Medicine², Pathology³ and Medical Biochemistry⁴ Departments, Faculty of Medicine, Tanta University, Tanta, Egypt

Background/Aim: Diagnosis of atypical and silent celiac disease (CD) is important because of its serious complications. The association of type 1 diabetes and CD has been reported worldwide. The aim of the study was to determine the prevalence and clinical, biochemical and histopathological characteristics of CD among Egyptian children and adolescents with type 1 diabetes.

Subjects and methods: A total of 116 children and adolescents with type 1 diabetes (62 males and 54 females, age range 2–21 years) and 25 age and sex matched healthy persons were screened for CD using anti-gliadin (AGA), anti-tissue transglutaminase (t-TG), anti-reticulin (ARA) and anti-endomysial (EmA) antibodies. Clinical data, hemoglobin Alc, insulin requirements, hemoglobin concentration, mean red cell volume and serum ferritin levels were evaluated.

Results: Twenty-six (22.4%) patients were positive for AGA and t-TG antibodies, 14 of them were ARA positive. Ten of these patients were EmA positive and four were EmA negative. From the EmA negative patients three sera with IgA deficiency had high IgG class in AGA, anti-TG and ARA antibodies. All these 14 patients (EmA positive and negative) underwent intestinal biopsy. Thirteen had histological evidence of CD including the EmA negative patients with IgA deficiency, giving a prevalence of CD in diabetic children of 11.2% (13/116). Compared with the other diabetic patients, those with CD had a significantly higher scores.

Conclusion: The prevalence of CD in Egyptian type 1 diabetes children and adolescents was found to be high. Serologic markers for CD are useful for identifying asymptomatic type 1 diabetes children who should undergo a small intestinal biopsy.
Comparison of zinc concentrations in blood serum of patients with both celiac disease and Crohn’s disease

Fariba Fathi¹, Mohammad Rostami-Nejad², Moastafa Rezaei-Tavirani³, Kamran Rostami⁴, Mohammad-Reza Zali²
¹Dept of Chemistry, Sharif University of Technology, Tehran, Iran
²Gastroenterology and Liver Disease Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
³Proteomics Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
⁴Gastroenterology Department, Worcestershire Royal Hospital, Worcester, UK

Introduction: Crohn’s disease is a chronic and inflammatory abnormalities; it causes inflammation of the gastrointestinal tract. Also celiac disease is disease that damages the villi of the small intestine and caused by impaired absorption of nutrients. These patients cannot tolerate gluten. Zinc is an essential element that has important physiological role in the body. The levels of zinc in blood serum decrease in patients with celiac and Crohn’s disease, therefore the aim of this study was to compare levels of zinc in patients with celiac and Crohn’s disease.

Methods: Atomic absorption spectrophotometer was employed for estimating serum zinc level in 26 patients with celiac (12 males and 14 females with mean age of 34 ± standard deviation 11 years) and 26 with Crohn’s diseases (11 males and 15 females with mean age of 33 ± standard deviation 10 years). In this study, statistical analysis was done using MATLAB software version 6.5.

Results: No statistically significant difference observed between celiac and Crohn’s patients according to level of zinc. Our results show that serum samples in patients suffering from celiac had a mean Zn concentration of 71 ± 6 μg/l while Crohn’s had a mean concentration of 70 ± 6 μg/l.

Discussion/Conclusion: Zinc is played a significant role in removing free radicals and reactive oxygen and nitrogen species. Based on this feature, zinc can prevent the progression of gastrointestinal disease and prevent of infection in the body. So the lack of this element may be predicted in people with Crohn’s and celiac disease.
The demographic and clinical presentation of celiac disease in Iranian patients

Zeinab Fazeli1*, Mohamad Amin Pourhoseingholi1, Mohamad Rostami-Nejad1, Somayeh Jahani-Sherafat1, Kamran Rostami2, Mohammad Reza Zali1

1Gastroenterology and Liver Disease Research Center, Shahid Beheshti University of Medical Science, Tehran, Iran
2Gastroenterology Department, Worcestershire Royal Hospital, Worcester, UK
*Presenter: Dr Zeinab Fazeli

Background: This study aimed to explore demographic characteristics and clinical presentations of celiac disease (CD) in a group of CD patients in Iran.

Methods: This was a cross-sectional retrospective study of 100 patients referred to the Gastroenterology and Liver Diseases Research Center at Taleghani Hospital, Tehran, Iran, in the period of May 2009–May 2011. Intestinal biopsy and serum anti-tissue transglutaminase (anti-tTG) were used for diagnosis of CD and histopathological findings were evaluated according to the modified marsh classification. Also demographic information, GI and non-GI symptoms were recorded.

Results: Overall, 100 patients (64 females), with a mean age at diagnosis of 31 ± 13.6 years, were investigated. GI symptoms were reported in 62% of patients and the most frequent was abdominal pain (33%), followed by chronic diarrhea (32%), bloating (11%), and constipation (8%). Patients reported up to 79% of any type of non-GI symptoms, included anemia (55%), osteopenia (25%), neurological (21%), and menstrual abnormalities (14%). A positive family history of CD was found in just one person.

The common marsh classification was 3A (27%) followed by 1 (21%), 3C (20%), 2 (19%) and 3B (13%). Anti-EMA Ab resulted positive in 32.3% of cases and HLA-typing showed that HLA-DQ2 (52%) was the predominant genotype.

Conclusion: In Iran, CD was seen more commonly in females and abdominal pain, chronic diarrhea and bloating were considered as classic presentations, on the other hands, anemia was the most common non-GI symptom in the study population. Therefore, the screening for CD in unexplained abdominal discomfort and anemia would be beneficial.

Keywords: Celiac disease; clinical presentation; demographic characteristics; Iran
Bone metabolism, biochemical markers of bone resorption and formation processes and interleukin-6 cytokine level during coeliac disease

M. Fekih, M. Serghini, A. Laabidi, N. Ben Mustapha, S. Matri, L. Kallel, J. Boubaker, A. Filali
Department of Gastroenterology A, La Rabta Hospital, Tunis, Tunisia

Background: Celiac disease (CD) is characterized by a malabsorption syndrome. The bone anomalies are one of the principal complications of this disease. The osteoporosis frequency is high: 3.4% among patients having with CD versus 0.2% in the general population.

Aim: Study the bone mineral density during the CD and compare it to a control group; determine the anomalies of biochemical markers of bone turn over and level of interleukin-6 cytokine (IL6) in these patients.

Methods: All patients with CD have a measurement of bone mineral density by dual-energy x-ray absorptiometry (DXA), a biological exam with dosing calcemia, vitamin D, parathormone (PTH), the osteoblastic bone formation markers (serum osteocalcin, ALP phosphates alkaline), bone osteoclastic activity (C Telopeptide: CTX) and of the IL6.

Results: 42 patients were included, with a median age of 33.6 years. 52.8% of the patients had a low level of D vitamine associated to a high level of PTH. An osteoporosis was noted in 21.5% of patients. No case of osteoporosis was detected in the control group. The mean level of the CTX, osteocalcine and the IL6 was higher among patients having an osteoporosis or osteopenia compared to patients with normal bone (p = 0.017). The factors associated with a bone loss (osteopenia or osteoporosis) were: an age > 30 years, a weight < 50 kg, a level of ALP phosphates alkaline > 90 UI/ml, an hypoalbuminemia < 40 g/l and a level of CTX higher than 1.2.

Conclusion: Our study confirms the impact of the CD on the bone mineral statute. The relative risk to have an osteopenia or an osteoporosis was 5 in our series. The measurement of the osseous mineral density would be indicated among patients having a CD.
Mannose binding lectin deficiency is a protective factor in the development of celiac disease and associated with its clinical manifestations

Ildiko Foldi, M.D.¹, Zsuzsanna Vitalis, M.D., Ph.D.¹, Gyula Farkas, M.D.¹, Eva Nemes, M.D.², Jolan Harsfalvi, Ph.D.³, Tamas Dinya, M.D.⁴, Gabor Veres, M.D., Ph.D.⁵, Ilma R. Korponay-Szabo, M.D., Ph.D.²,⁶, Maria Papp, M.D., Ph.D.¹

¹2nd Department of Medicine, University of Debrecen, Debrecen, Hungary
²Department of Pediatrics, University of Debrecen, Debrecen, Hungary
³Clinical Research Center, University of Debrecen, Debrecen, Hungary
⁴Department of Surgery, University of Debrecen, Debrecen, Hungary
⁵1st Department of Pediatrics, Semmelweis University, Budapest
⁶Celiac Disease Center, Heim Pal Children's Hospital, Budapest, Hungary

Backgrounds: Mannose-binding lectin (MBL) is a soluble pattern-recognition molecule and important component of the innate host defense. The MBL pathway of complement system also contributes to the clearance of apoptotic cells and circulating immune complexes suggesting a possible implication in the aetiopathogenesis of systemic autoimmune diseases. The role of MBL in celiac disease is controversial in small studies. We investigated the prevalence of MBL deficiency in a Hungarian celiac patient cohort, and its possible association to the presenting symptoms.

Methods: 795 unrelated, biopsy-proven Hungarian celiac patients (357 children, 438 adults; severe malabsorption 35.7%, minor gastrointestinal symptoms 21.8%, iron deficiency anemia 8.8%, dermatitis herpetiformis 14.6%, silent disease 13.5%, other 5.7%) and 296 healthy subjects were studied. Serum concentrations of MBL were measured using a double-antibody sandwich enzyme-linked immunosorbent assay. MBL was classified as absolute deficient (< 100 ng/ml), relative deficient (100–500 ng/ml) and normal (> 500 ng/ml).

Results: Median MBL level was higher in celiac patients (1493 [IQR, 501–12,533 ng/ml]) than in controls (1027 [253–2120 ng/ml], p < 0.001). Celiac patients less frequently had absolute (6.0%) or relative (16.9%) deficient MBL compared with controls (15.6% [p < 0.001] and 25.7% [p = 0.0014], respectively). Patients having MBL deficiency were at decreased risk for severe malabsorption (OR = 0.5, 95% CI: 0.34–0.72) but increased risk for dermatitis herpetiformis (OR = 1.73, 95% CI: 1.12–2.66). MBL levels did not correlate with age at diagnosis.

Conclusions: MBL deficiency was a protective factor in the development of celiac disease and also in its more severe clinical course supporting the possible beneficial role of MBL deficiency in autoimmune process and the development of more aggressive autoimmune damage.
Clinical spectrum and diagnostic approach in Whipple’s disease – Report of eight cases

Diana Gancheva¹, Miglena Stamboliyska¹, Maria Atanassova¹, Iskren Kotzev¹, Maria Tzaneva²
¹Clinic of Gastroenterology, Hepatology and Nutrition, ²Department of General and Clinical Pathology, St. Marina University Hospital of Varna, Medical University of Varna, Bulgaria

Introduction: Whipple’s disease (WD) is a rare systemic infection caused by bacterium Tropheryma whipplei. Since the clinical features of the disease are non-specific, diagnosis still remains a challenge. The aim of the study is to analyse the clinical presentation and diagnostic approach in patients with WD.

Material and methods: Eight patients, six females and two males at an average age of 59 years (range, 46–79 years) were diagnosed with WD from January, 2012 to May, 2013 in the Clinic of Hepatogastroenterology, St. Marina University Hospital of Varna. Laboratory tests, endoscopic, radiologic, ultrasound and histomorphological examinations were performed.

Results: The main symptoms are abdominal pain, chronic diarrhea and meteorism. One female patient only presents with clinical signs of malabsorption such as weight loss, anasarca, ascites, pleural effusions and anemia. There are no extraintestinal manifestations. Tests for Chlamydia trachomatis, tuberculosis and Clostridium difficile are negative. Stool examination does not show any parasitic or bacterial infection. Coeliac disease (CD) serological tests are negative, except in one female with co-existing gluten enteropathy since childhood onwards, where Crohn colitis is diagnosed, too. Endoscopy demonstrates mild to moderate atrophy of the intestinal mucosa. Histological examination establishes mild villous atrophy, lymphoplasmatic infiltration and lymph vessel dilation. All the biopsies show PAS-positive inclusions in the macrophages. Doxycycline therapy exerts a favourable effect on the clinical symptoms in all the patients.

Conclusion: Whipple’s disease (WD) is a rare systemic disease that is commonly late or falsely diagnosed. The prognosis of non-treated patients is poor. The disease should be considered in any patients with prolonged gastrointestinal symptoms such as unexplained abdominal pain, diarrhea and features of malabsorption syndrome. The appropriate antibiotic treatment achieves remission and improves patients’ quality of life.
Gluten-free diet associated with budesonide-azathioprine combined therapy in patients with celiac disease in autoimmune hepatitis

Amelia Genunche-Dumitrescu, Daniela Badea, M. Badea, P. Mitrut, A. Badea
University of Medicine and Pharmacy, Clinical Hospital of Emergency, Craiova, Romania

Introduction: The aim of this study was the assessment the efficacy of association of gluten-free diet with budesonide-azathioprine combined therapy in patients with autoimmune hepatitis (AIH) and celiac disease (CD).

Methods: We studied 55 patients (37 females/18 males, mean ages 43.2 years) with AIH, treated with combined therapy with prednisone (40 mg/day and tapered to 10 mg/day) and azathioprine (1–2 mg/kg/day) or with Budenofalk® (3 mg, oral doses three times daily) in association with azathioprine (1–2 mg/kg/day). Six of these patients with AIH (6 cases, 10.9%) were tested positive in celiac blood tests (positive for anti-IgA tissue transglutaminase) and were subsequently confirmed to be affected with CD by small-bowel biopsy findings. After CD detection, patients diagnosed with both CD and AIH continued current therapy for AIH and were associated this treatment with a gluten-free diet (GFD). We monitoring, for a 12 months period, the activity disease and evaluated response of therapy.

Results: Structure of the lot of patients indicate predominant cases of AIH type I (40 cases, 72.73%) comparative with type II AIH (15 cases, 27.27%). The incidences of CD was significantly higher in type I AIH (5 cases, 12.5%) comparative with type II AIH (1 case, 6.66%). In one case (16.66%) celiac disease was asymptomatic. GFD was associated in all cases with AIH therapy: in 3 cases with budesonide-azathioprine combined therapy, in 2 cases with prednison-azathioprine and in one case with azathioprine monotherapy. After 6 months, intestinal biopsies were reported to be normal in two patients who associated GFD with budesonide-azathioprine combined therapy (66.67%). Also, disappearance of clinical symptoms of CD was observed in all patients with GFD and budesonide-azathioprine therapy. We have not found a correlation between GFD and rate of histological remission of AIH, but after 12 months on a GFD, normal liver biochemistry (liver enzyme tests) was observed in most patients with CD and AIH (3 cases, 50.0%).

Discussion/Conclusion: The gluten-free diet associated with budesonide-azathioprine combined therapy, is effective in induces and maintains remission in patients diagnosed with both CD and AIH. Long term gluten-free diet may have a beneficial effect in reversing autoimmune liver disease in patients with CD.
Prevalence and clinical presentation of adult celiac disease in the elderly: A single center experience

V. Gerova-Nankova, S. Stoynov, N. Tzolova, V. Nakov, B. Vladimirov, A. Chavuchian, R. Nakov
Clinical Center of Gastroenterology, University Hospital Queen Joanna, Sofia, Bulgaria

Introduction: Celiac disease (CD) appears at all ages and increasing prevalence in advanced age has been reported. The aim of the study is to analyse the prevalence, clinical features, associated conditions and the effect of a gluten-free diet in elderly patients aged 60 years or over.

Patients and methods: Retrospective analysis of 155 adult celiac patients aged between 18 and 77 years, diagnosed between 1987 and 2013 in our Clinical Center of Gastroenterology.

Results: A total of 155 patients with CD, 31 (20.0%; F: 23, M: 8) were diagnosed aged 60 years or over (mean age 65.7 ± 3.4 years, range: 60–77 years). The mean time of delayed diagnosis was 9.2 ± 5.6 years, range: 1–30 years. The presenting symptoms were diarrhea in 24 patients (77.4%), fatigue in 20 (64.5%), weight loss in 17 (54.8%), iron-deficiency anemia in 19 (61.3%), hypoalbuminemia in 17 (54.8%), hypocalcemia in 10 (32.3%) and steatorrhoea in 9 (29.0%). Associated conditions included thyroid disorders in 5 patients (16.1%), type I diabetes mellitus in 4 (12.9%), severe early osteoporosis in 3 (9.7%), secondary hyperparathyroidism in 3 (9.7%), peripheral neuropathy in 2 (6.5%). Two patients had elevated aminotransferases. Histological examination of duodenal biopsy specimens showed the characteristic inflammatory changes and villous atrophy in all patients. Clinical improvement after sticking to a gluten-free diet and nutritional substitution was seen in 29 of the patients. After steroids adding such improvement was achieved in the other two patients.

Discussion/Conclusion: In 20% of the adult celiac patients the disease is presented in elderly age. Surprisingly, the clinical manifestations are classical. In spite of that, the diagnosis was delayed in all patients. It is important to consider CD as a possible diagnosis in the elderly general population.
HLA class I and II genes in celiac disease in Belarus

J. Gorgun, G. Semenov, A. Portyanko
Belarusian Medical Academy of Postgraduate Education, The Republic Research and Production Center for Transfusiology and Medical Biotechnologies, Belarusian State Medical University, Minsk, Belarus

Introduction: Celiac disease (CD) is known to be a genetic determined condition, strongly associated with HLA-DQA1*05-DQB1*02 (DQ2) and DQA1*03-DQB1*0302 (DQ8). Nevertheless, rare DQ2/DQ8 negative cases have been described and some other HLA loci have been proposed to be responsible for additional CD risk and differences in regional CD risk variability. The aim of our study was to assess HLA status of CD patients from Belarus.

Methods: HLA-typing classes I and II was performed in 41 belarusian CD patients and 200 and 106 healthy controls respectively.

Results: 90.2% CD patients were DQ2/DQ8 positive. CD was significantly positively associated with DRB1*03, DQB1*02, A1, B8, Cw7, A1B8 and negatively – with B7, as was reported earlier by other investigators. An association with B13 (OR = 3.13, 95% CI: 1.37–7.14, p = 0.007) and A2B13 (OR = 4.29, 95% CI: 1.75–10.5, p = 0.0015) was also found, what has not been described earlier and could be characteristic of CD in Belarus. 48.8% CD patients had super-B8-haplotype (A1-Cw7-B8-DR3-DQ2). Distribution into genotype groups was the following: G1 – 43.2%, G2 – 5.4%, G3 – 32.4%, G4 – 10.8%, G5 – 5.4% and was significantly different from that one described for South Europe or Scandinavia. 9.8% patients were negative for the “classical” CD alleles, but had been found to have some other common alleles namely: DRB1*15, DRB1*08, DQB1*06, DQB1*04, A2, A24, B7, B13, B52, Cw6, Cw7. From these patients, three had haplotype DRB1*15-DQB1*06, two – DRB1*08-DQB1*04 and one – DRB1*04-DQB1*04. The same haplotypes were described somewhere in DQ2/DQ8 negative patients.

Discussion/Conclusion: Belarusian CD patients show an association with number of HLA genes known from previous studies. New association with HLA I class B13 and haplotype A2B13 has been also revealed. DQ2/DQ8 negative CD cases share some HLA genes and haplotypes and their role in CD pathogenesis should be investigated.
Celiac disease – Incidence of the “associated diseases“

J. Gregar¹, I. Gregar¹, M. Tichý², T. Tichý²
¹Department of Internal Medicine II – Gastroenterology and Hepatology, University Hospital Olomouc and Palacky University Olomouc, Czech Republic
²Department of Clinical and Molecular Pathology, University Hospital Olomouc and Palacky University Olomouc, Olomouc, Czech Republic

Introduction: Celiac disease (CD) – the gluten enteropathy is defined as a permanent gluten intolerance. The result of this intolerance is an immunity alteration, which can cause small intestinal mucose damage. The malassimilation resulting to the malnutrition is the main impact. Value of glutensensitivity is estimated 1:250 – 1:200 (Czech Republic and Central Europe). The „iceberg fenomen“ is known – only 20% of the total amount of all forms of CD is diagnosed/treated.

CD is associated with a lot of diseases and health risk. Therefore we decided to determine the incidence of the “associated disease“ in our file of the patients with the CD. We use the Corraza’s classification of associated disease (AD) in our study: proved AD: atopy, autoimmune thyreoditis, IDDM, revmatoide arhritis, epilepsy, Crohn’s disease and other colitis, deficity of IgA, IgA nephritis.

speculated AD: Sjögren’s syndrom, vasculitis, myasthenia gravis, Addison’s disease, polymyositis, sarcoidosis, iridocyclitis.

Our file: 67 patients with celiac disease (48 women and 19 men) observed in the our Department of Gastroenterology, University Hospital Olomouc. The average age was 36 years (19–89 years), the period of observation was from 5–26 years, most of the patients have been observed for more than 10 years. The aim of the study was to find the prevalence of the CD “associated diseases”.

Methods: CD has been diagnosed in accordance of the ESPGHAN criteria, modified by serological tests – EMA (endomysial) and tTGA (tissue transglutaminase antibodies). Retrospective analysis.

Results: We found out a huge appearance of arthropathy (28–54%), hepatopathy (25.3%), thyreopathy (20.8%). Quite low incidence of IDDM were discovered in our file. We notice several patients with other diseases: vasculitis, IgA nephritis, Sjögren’s syndrom, Turner syndrom, Crohn’s disease.

Discussion/Conclusion: CD associated diseases are quite common and their character and frequency differ according to the different authors. The aim of a long-term treatment of the celiac disease patients is to think about “associated diseases”.
Assessment of potential gluten-like properties of salivary proline-rich proteins

E.J. Helmerhorst¹, J. Hansen², D.A. Leffler², C.P. Kelly², D. Schuppan²,³, N. Tian¹
¹Department of Molecular and Cell Biology, Boston University Henry M. Goldman School of Dental Medicine, Boston, MA; ²Celiac Center, Beth Israel Deaconess Medical Center, Boston, MA; ³Institute of Translational Immunology and Research Center for Immunotherapy (FZI), University Medical Center, Mainz, Germany

Introduction: Gluten proteins are unusual due to their high content in proline (P) and glutamine (Q) residues. A high P and Q content of ~50% is also found in proline-rich proteins (PRPs) in human saliva. We hypothesized, based on their structural similarities and shared destination in the gastro-intestinal tract, that salivary PRPs may exhibit gluten-like properties.

Methods: Parotid secretions (PS), consisting for ~40% of PRPs, were collected from CD patients on a gluten-free diet, patients with refractory CD (RCD), patients with non-CD complaints (GI), and healthy controls (HC). PRP species were studied with SDS- and native PAGE, and PRP recognition by an anti-gliadin antibody was assessed by Western blotting. The induction of cytokines (TNF-α, IL-10, IFN-γ, and IL-21) was studied with PBMCs collected from CD patients, and gliadins or PRPs that were digested with pepsin (P) and trypsin (T) and deamidated with tissue transglutaminase 2 (TG2). Gliadin/PS protein combinations were evaluated to assess potential competition between the two protein species.

Results: PRP protein patterns revealed minor differences that were not specific in CD/RCD vs controls. Gliadin antibodies weakly reacted with a major PS band in all subjects, identified as amylase, but not with PRPs. PT-TG2 treated gliadins induced IL-10 and TNF-α responses in PBMCs, with low induction of INF-γ and IL-21. Salivary PS proteins did not induce any cytokine production above levels produced by PT-TG2 alone. Furthermore, they did not compete with gliadin-induced cytokine induction.

Discussion/Conclusion: Despite the high structural similarities, PRPs do not seem to harbor gliadin-like elements relevant in CD. Deciphering the structural basis for the lack of immunogenicity of salivary PRPs may be of interest to develop gluten that lack immunogenic epitopes. This study is supported by NIH/NIAID grants AI087803, AI101067, and a grant by the FZI.
Osteoporosis and bone alterations in adult celiac disease

Iva Hoffmanová
2nd Department of Internal Medicine, 3rd Faculty of Medicine, Charles University in Prague, 100 34 Prague, Czech Republic

Introduction: Both celiac disease (CD) and osteoporosis are common diseases with high prevalence in western population (1% and 7–8%, respectively). Low bone mineral density (BMD), osteopenia or osteoporosis are present not only in typical CD with overt malabsorption but in about 50% in suboptimally treated patients with CD, subclinical patients and asymptomatic adult CD patients, too. Etiology of pathologic bone alteration in celiac disease is multifactorial; with two main mechanisms: intestinal malabsorption and chronic inflammation. Bone alteration connected to the malabsorption are the consequence of impaired calcium and vitamin D absorption and secondary hyperparathyroidism resulting from the loss of villous cells in the proximal intestine. Chronic release of proinflammatory cytokines from intestinal mucosa to peripheral blood (TNF-α, IL-6, IL-1β) trigger osteoresorption. In addition, in CD is altered a dynamic balance in main pathway regulating osteoresorption, OPG/RANKL/RANK.

Methods: We started evaluate markers of calcium metabolism (total calcium/albumin, 25-OH vitamin D3 and parathormone in serum) and BMD by dual-energy X-ray absorptiometry (DEXA) in adult celiac patients in 2013. The study involves 20 patients yet. Longitudinal follow-up including treatment setting is planned.

Results: All of our patients have decreased level of 25-OH vitamin D3 (which could correlate partially to the latitude about 50° in Czech Republic) and are treated with vitamin D and calcium supplementation. Increased levels of PTH are found in about 35%, and correlate with decrease of BMD and with duodenal Marsh stage.

Discussion/Conclusion: The evaluation and treatment of bone alteration is necessity in celiac patients. As vitamin D is involved not only in calcium metabolisms but also in the immune regulation and in the maintaining of intestinal barrier integrity, we consider vitamin D and calcium supplementation an important part of the treatment of bone alteration in CD.
Balloon-assisted enteroscopy may be a diagnostic modality of choice for bleeding Meckel’s diverticulum in adults

Sung Noh Hong, MD, Hyun Joo Jang, MD, Byong Duk Ye, MD, Seong Ran Jeon, MD, Jong Pil Im, MD, Jae Myung Cha, MD, Seong-Eun Kim, MD, Soo Jung Park, MD, Eun Ran Kim, MD, Dong Kyung Chang, MD, Small Intestine Research Group of the Korean Association for the Study of Intestinal Diseases (KASID)

1Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, 2Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, 3Asan Medical Center, University of Ulsan College of Medicine, Seoul, 4Institute for Digestive Research, Soonchunhyang University College of Medicine, Seoul, 5Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, 6Gang Dong Kyung Hee University Hospital, Kyung Hee University College of Medicine, Seoul, 7Ewha Womans University College of Medicine, Seoul, 8Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea

Introduction: Although Meckel’s diverticulum (MD) forms part of the differential diagnosis of small-bowel bleeding, the difficulties encountered in diagnosing MD in symptomatic adults can result in diagnoses being delayed and missed before patients undergo exploratory surgery. Since the diagnostic accuracy of technetium-99m pertechnetate scintigraphy (Meckel’s scan) is low in adults compared with that in children, we aimed to determine the best diagnostic modalities for the preoperative diagnosis of bleeding MD in adults.

Methods: This multicenter study involved 20 consecutive bleeding MD patients who were aged 18 years and older, had been diagnosed with MD, and who underwent confirmatory surgery between 2005 and 2012. The accuracy of several diagnostic modalities was assessed and compared with Meckel’s scan.

Results: Of the 20 adult symptomatic MD patients, 15 (75.0%) were diagnosed preoperatively with certain or presumptive MD. The diagnostic accuracies for detecting adult bleeding MD were 25.0% (95% CI: 6.7–57.2%) for Meckel’s scan, 26.7% (95% CI: 8.9–55.2%) for CT, 58.3% (95% CI: 28.6–83.5%) for SBFT, 0.0% (95% CI: 0.0–69.0%) for angiography, 16.7% (95% CI: 0.9–63.5%) for CE, and 78.6% (95% CI: 48.8–94.3%) for BAE. BAE was the only diagnostic modality with a significantly greater accuracy than Meckel’s scan (p = 0.019).

Discussion/Conclusion: Diagnoses in approximately one-third of the adult bleeding MD patients were missed before exploratory surgery. The findings from this study suggest that BAE has the highest diagnostic accuracy among the available diagnostic modalities.
The role of Blastocystis hominis in bowel inflammatory chronic pathology

Gabriela Iliescu¹, Adriana Bold¹,², Alice Buteica², Viorel Biciusca²,³, Daniela Visan⁴
¹Clinical Emergency County Hospital, Craiova
²University of Medicine and Pharmacy, Craiova
³Filantropia Clinical Municipal Hospital, Craiova
⁴Medical Center SAMA, Craiova, Romania

Introduction: Even that most reports regarding the clinical significance and pathogenicity of Blastocystis hominis (B. hominis) have been contradictory, recent studies suggest an association of B. hominis with inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). It is widely accepted that B. hominis is causing intestinal inflammation with diarrhea and abdominal pain, nausea, anorexia, vomiting, weight loss, dizziness and flatulence. Also, affected histological, immunological and nutritional status of patients with celiac disease allow infection by parasites that cause no symptoms in immunocompetent patients, such as B. hominis

Methods: We evaluated the presence of B. hominis in celiac patients related to the diagnostic time. An observational descriptive study was performed, recording results of the stool tests from from twenty four symptomatic celiac patients, between 2012–2013 (16 women and 8 men, mean age 21 years old, range 16–48 years). For a positive diagnostic, we considered four B. Hominis on a optic microscopic field (Nikon Eclipse E 200, 40x10)

Results: The most commonly reported clinical manifestations were: diarrhea – 14 patients, anemia – 5 patients, weight loss – 3 patients. 18 patients had positive stool tests for B. hominis. Five patients had positive stools for B. hominis before cD diagnostic. Incidence of positive stools for B. hominis was 73.3%, more than 8 elements per field being statistically significant associated with patients with low weight and flares of diarrhea (p < 0.05) compared to cases with less than four elements per field. Treatment with Metronidazole ameliorated rapidly the clinical status

Discussion/Conclusion: Blastocystis hominis, a parasite of uncertain role in human pathology, may be implicated in pathogenic mechanism of celiac disease. Its treatment results in clinical improvement of the patients. In symptomatic celiac patients with weight loss, the finding of more than eight B.hominis per field should be considered as opportunistic.
Hypereosinophilia: An early alarm for milk allergy and gluten intolerance in the premature infants?

Gabriela Iliescu¹, Adriana Bold¹², Alice Buteica², Daniela Visan³
¹Clinical Emergency County Hospital, Craiova
²University of Medicine and Pharmacy, Craiova
³Medical Center SAMA, Craiova, Romania

Introduction: Eosinophilia (absolute eosinophil count (AEC) > 700/mmfc) is considered as a common finding in premature infants, associated with RBC transfusions, total parenteral nutrition, bronchopulmonary dysplasia, bacterial infection, necrotizing enterocolitis. Frequently, these babies present marked and persisting elevations of AEC- possible early signs of digestive or immune disorders as milk allergy and celiac disease.

Methods: Records of 150 premature infants were evaluated retrospectively during three months from birth, in 2013. Twenty of them were reviewed until 12 months old. Complete blood counts were performed twice a week in the first 3 months. These infants presented abdominal distension, apnea and/or bradycardia at feeding, vomiting, diarrhea, edema with hypoalbuminemia. We excluded from the final analysis prematures infants who received blood transfusions.

Results: All 150 infants had elevated AEC, with values from 600 to 2600/mmfc in the first week of life. 110 babies didn’t receive blood transfusions. In week 1: 32 were on casein hydrolysate formula as treatment for abdominal distension, apnea ± bradycardia at feeding or hemochezia; 20 were on cow milk protein-based formula, for abdominal distension, vomiting and diarrhea. As AEC values became marked elevated (1200–2600/mmfc), formula was switched to amino acid-based formula which resolved hypereosinophilia in the next 8 days. With normal feeding, in month 3, 80 infants had AEC 400–1800; 12 infants presented low weight, chronic intestinal disorders and anemia with recurrent high eosinophilia (1200–1800/mmfc) until month 12. Tested for high levels of anti-tissue transglutaminase antibodies or anti-endomysium antibodies, results were positive in 3 infants and diagnosed as celiac disease.

Discussion/Conclusion: In no premature infant, hypereosinophilia should not be ignored as a non-specific finding. In those with feeding or intestinal problems, milk protein or casein hydrolysate allergy can cause marked increase of AEC. In the most cases, using an amino acid-based formula, clinical improvement and reduction of AEC are rapidly obtain. But recurent and persisting high eosinophilia could be an early predictor for celiac disease in children, so checking of the hematologic status of premature infants should be extended over the first year of life.
Complex imaging in patients with suspected small bowel disorders

E. Ivanova, E. Fedorov, D. Sleznev, E. Tikhomirova, E. Polukhina
Moscow University Hospital №31, Medical Rehabilitation Center “Klinika+31”, Endoscopy Department, Moscow, Russia

Introduction: Capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE) are the modern tools for the small intestine imaging but each of them has specific limitations. The aim of this study is to estimate the benefits of complex use of CE and BAE in diagnosis of small bowel disease.

Methods: From 14.02.2007 to 10.01.2014 CE followed by BAE were performed in 93 patients (m: 43, f: 50, mean age 48.8 ± 17.3 years.) with suspected small bowel disorders. Oblique GI bleeding was an indication for VCE in 53 (57.0%) cases. The insertion route for DBE was determined according to the site of the suspected bowel lesions detected by CE.

Results: In 10 patients without a definite lesion detected by CE, the route of insertion was determined according to clinical picture, in all of them there were no any abnormalities found by the BAE as well. Small bowel lesions were suspected in 83 (89.2%) patients after the CE: tumors in 40 (48.2%) patients.; enteritis (incl. intestinal erosions and ulcers) in 24 (28.9%); vascular pathology in 19 (22.9%). The diagnosis was confirmed by BAE in 64 (77.1%) patients: tumors in 24 (60.0%); enteritis (incl. intestinal erosions and ulcers) in 22 (91.7%); vascular pathology in 18 (94.7%). In 2 patients, in view of clinical picture and CE suspicion with negative BAE we’ve performed laparoscopy and revealed tumors with extraorganic growth as well as in 1 case with bleeding after biopsy from the ulcer, Meckel’s diverticulum were revealed. The sensitivity, specificity, positive predictive value and negative predictive value, diagnostic accuracy of combined CE and BAE for small bowel lesions were 97.1%, 100.0%, 97.8%, 92.0% and 97.8%, respectively.

Discussion/Conclusion: CE can provide useful information on the indications and selection of the route for BAE. Complex use of CE and BAE has a high effectiveness (97.8%) in the diagnosis of small bowel disease.
The clinical value of mean platelet volume, plateletcrit and platelet/lymphocyte ratio in predicting Marsh classification in patients with newly diagnosed celiac disease

Cagdas Kalkan, Emra Asfuroglu, Sibel Akbaş, Ekin Kırcalı, Mustafa Yakut, Hülya Çetinkaya, Irfan Soykan
Ankara University, Faculty of Medicine, Gastroenterology, Ankara, Turkey

Introduction: Celiac disease (CD) is an autoimmune and inflammatory condition triggered by dietary gluten in genetically susceptible individuals. Small bowel biopsy is the gold standard for the diagnosis of CD. Morphologic spectrum of CD is classified according to Marsh grading system. Simple systemic inflammatory response markers such as mean platelet volume (MPV), plateletcrit (PCT) and platelet/lymphocyte ratio (PLR) may have diagnostic importance in some inflammatory diseases. Therefore, the aims of this study was to investigate whether systemic inflammatory response markers may have any role in predicting Marsh classification.

Methods: 170 patients with CD were evaluated by means of MPV, PCT and patients were further divided into three groups according to Marsh classification: Group I (Marsh type 1, n = 69), Group II (Marsh type 2, n = 13) and Group III (Marsh type 3, n = 88). Also included was a control group who had normal duodenum biopsies obtained for various reasons (Group IV, n = 43).

Results: MPV (8.7 ± 1.07 vs. 8.7 ± 1.2, p = 0.922), PCT (0.24 ± 0.06 vs. 0.22 ± 0.07, p = 0.145) and PLR (144.28 ± 61.54 vs. 148.59 ± 89.71, p = 0.711) values were not significant in patients with CD compared to control group. In subgroup analysis, any of the simple systemic inflammatory response markers showed significant changes between groups and control group.

Discussion/Conclusion: Our results showed that, MPV, PCT and PLR are not suitable biomarkers in predicting Marsh classification in patients with newly diagnosed CD.
Complicated Meckel’s diverticulum as a source of severe bacterial endocarditis in an adult patient (case report)

Marine Kanashvili¹, Rusudan Zabakhidze², Tamta Tkhiashvili¹, Manana Makhviladze¹, Lia Goladze¹, Alexsandra Maisuradze²
¹V. Bochorishvili Clinic “Sepsis”, ²Tbilisi State Medical University, Tbilisi, Georgia

Introduction: Meckel’s diverticulum is the most prevalent congenital anomaly of the gastrointestinal tract, affecting about 2% of the population. The complication of Meckel’s diverticulosis is common in younger patients, but it is rare in the adults. Herewith the major complications mostly include intra-abdominal localization. In our case, the complication of Meckel’s diverticulosis manifested in adult and became the source of severe, life-threatening extra-abdominal complication.

Methods/Results: A 41-year-old man presented with fever of unknown origin was admitted to our hospital after 2 months of onset of disease. 2 weeks before initial of disease, patient was done surgical treatment cause of perforation of Meckel’s diverticulum. After surgery antibiotic therapy was initiated with ampicillin/sulbactam during 5 days and patient was discharged in satisfactory condition. About 7 days after the operation, the patient started having moderate fever with chills that lasted for 2 days. Fever was resolved without treatment and was assessed as the flu. In the following weeks, 2–3 days of fever and 5–7 days of apyrexy episodes substituted on a regular basis. Operated wound as a source of fever was excluded. Routine and abdominal CT studies did not determine the cause of fever. In dynamics patient manifested shortness of breath and because of this he was admitted to hospital. Clinical, instrumental and laboratory investigations confirmed the diagnosis of primary bacterial endocarditis and destruction of aortic valve. With the failure of 10 days antibacterial treatment and normal temperature background patient underwent emergency aortic valve replacement surgery because of the high threat of disease progression and rupture of aortic valve. Both from blood culture and operative specimen intestinal commensal bacteria – Enterococcus Faecalis was identified.

Discussion/Conclusion: Complication caused by Meckel’s diverticulosis may rarely occur in adults and become the source of severe, life-threatening extra-abdominal complication of bacterial endocarditis.
Changes in nutritional status and laboratory parameters characteristic for celiac disease among patients with suspected malabsorption syndrome

Alina Kanikowska, M.D., Ph.D., Prof. Marian Grzymislawski, M.D., Ph.D.
Department of Internal Medicine, Metabolic Diseases and Dietetics, Pozna, Poland

Introduction: Celiac disease rate is growing particularly in the elderly. Low BMI, diarrhea and bloating are common symptoms of malabsorption syndrome, but maybe also associated with irritable bowel syndrome and small intestine bacterial overgrowth (SIBO). The rate at which celiac disease is diagnosed depends on the level of suspicion for the disease, particularly in patients with many complaints from gastrointestinal problems.

The aim of the study was to detect changes in nutritional status and laboratory parameters characteristic for the patients with celiac disease among patients with suspected malabsorption syndrome.

Methods: Nutritional status and laboratory parameters of 65 patients admitted to the hospital with suspicion of malabsorption syndrome were analyzed. In 32 patients, mean age 56 ± 20, BMI 19.2 ± 3.1, diagnosis of celiac disease was confirmed by duodenum biopsy while in 33 patients, mean age 50 ± 15, BMI 18.5 ± 2.9, microscopic examination was negative for the disease. All the patients had undergone gastroscopy, hydrogen breath test for SIBO, body composition measurement by Tanita analyzer and blood tests.

Results: In group with celiac disease statistically significant difference was observed for higher concentrations of amylase, erythrocyte sedimentation rate, C-reactive protein, aspartate and alanine transaminases, triglycerides, international normalized ratio and glucose, lower concentrations of hemoglobin, albumin and total protein. There was no significant difference for BMI, body composition parameters, alkaline phosphatase, γ-glutamyl-transpeptidase, total, HDL and LDL cholesterol, leukocytes count and vitamin B₁₂ concentration. Higher number of positive SIBO tests (n = 21) among patients without celiac disease confirmation was observed comparing to the group with celiac disease (n = 15).

Discussion/Conclusion: Gastrointestinal symptoms and body composition maybe similar in patients with malabsorption syndrome, but there are characteristic laboratory parameters that may help to raise suspicion for celiac disease among this group of patients.
HLA typing increases the diagnostic yield in patients investigated for possible celiac disease

J.A. Karagiannis, A. Giannakopoulos, K.D. Paraskeva, N.G. Mathou
“Konstantopoulio” Hospital, Athens, Greece

Introduction: Celiac disease consists a common condition with high incidence and prevalence in most of the Western populations. Because of mild symptoms and minimal impairment of laboratory tests it remains undiagnosed in a high proportion of patients up to the end of their life. Aim of the study was to investigate if HLA typing can be of diagnostic value in subjects with non-diagnostic distal duodenal biopsies (Marsh score < 2) and negative antibodies in whom celiac disease could not be excluded.

Methods: In the last three years 115 subjects were investigated for possible celiac disease. In 23 of these (9 male, 14 female, median age 29 years, range 19–54) distal duodenal biopsies were non-diagnostic and serum serology (antigliadin antibodies IgA/IgG, endomysial antibodies and anti-tTG IgA/IgG) was negative (with none being IgA deficient).

All subjects had mild symptoms indicative of either irritable bowel syndrome and/or dyspepsia (for 6 months up to 11 years). 5/23 (~23%) had mild iron deficient anemia, 8/23 (~32) mild iron deficiency and 2/23 (~9) marginally elevated AST. 8/23 (~32%) had normal hematology and biochemistry. All patients had normal upper and lower GI endoscopy. All subjects were HLA typed with both molecular and serological techniques.

Results: In 12/23 (~52%) heterodimers compatible with celiac disease were determined.

In 8/12 (~66.6%) DQ2, in 2/12 (~16.6%) DQ2/DQ8 and in 2/12 (~16.6%) DQ8. From these: 6/8 (75%) positive for DQ2 had both specific alleles DQA1*05 and DQB1*02 and 2/8 (25%) one of the two (“half DQ2 positive”). 2/2 (100%) positive for DQ8 had both specific alleles DQA1*03 and DQβ1*0302. 2/12 with heterodimers DQ2/DQ8 had at least one of the above specific alleles (DQA1*05 or DQB1*02 for DQ2 and DQA1*03 or DQβ1*0302 for DQ8).

Discussion/Conclusion: HLA typing in subjects investigated for celiac disease with non-diagnostic biopsies and negative serology turns out to be positive in about ~50% of these.
Primary intestinal lymphangiectasia in 42-year-old adult with a moderate response to parenteral nutrition after a two year follow-up period

Michał Kłoska¹, Dorota Mańkowska Wierzbicka¹, Magdalena Andrzejewska¹, Marcin Kucharski², Katarzyna Karwowska³, Alina Baturo¹, Krzysztof Linke¹, Agnieszka Dobrowolska Zachwieja¹

¹University of Medical Science Department of Gastroenterology Human Nutrition and Internal Medicine
²University of Medical Science, Department of Internal Medicine, Metabolism and Dietetics
³University of Medical Science, I Department of Anesthesiology and Intensive Care Therapy, Poznan, Poland

Primary intestinal lymphangiectasia is a rare protein-losing gastroenteropathy characterized by the impaired drainage of lymphatic vessels. This pathology results in dilatation of intestinal lacteals and leads to leakage of protein, lymphocytes, and immunoglobulin rich lymphatic fluid into the intestinal lumen. Most commonly described in the young, but the prevalence of late-onset primary intestinal lymphangiectasia cases has increased. Clinical diagnosis is based on exclusion of secondary intestinal lymphangiectasia and is based primarily on histopathological examination of the small intestine via biopsy or surgically acquired specimen. Other examinations like CT scan, capsule endoscopy, double balloon enteroscopy proved to be useful but are of less diagnostic value. Clinical manifestations include generalized edema, associated with lymphedema, weight loss with inability to gain weight, diarrhea or malaise. However, it appears that most adults develop very few symptoms, if any at all. Here we report the case of a 41-year-old male patient who was admitted for evaluation of generalized edema, fatigue, hypoalbuminemia, hypoproteinemia and severe hypertriglyceridemia. The patients past medical history was unremarkable until he reached 39 years of age. The patient was initially diagnosed with exudative enteropathy of unknown origin. Furthermore until admission the patient experienced right subclavian and jugular vein thrombosis, and was diagnosed with factor V Leiden thrombophilia. Myeloproliferative disorders, lymphomas and other neoplasm were excluded prior to admission. The final diagnosis was made by histopathological examination of small bowel biopsy. Home parenteral nutrition support based on medium-chain triglycerides was introduced. After a good response to the nutrition support at the beginning the patient condition worsened several times and gradually improved due to the ongoing nutrition support.

Discussion/Conclusion: In a treatment of primary intestinal lymphangiectasia low fat and high in medium-chain triglycerides diet should be administered. If necessary parenteral nutrition support based on medium-chain triglycerides should be considered.
Utility of narrow band imaging in diagnosing celiac disease

Rakesh Kochhar, Saroj K. Sinha, Pradeep K. Siddappa, Jahangeer Basha, Kim Vaiphei¹, Kaushal K. Prasad, Sreekanth Appasani, Neha Berry, Munish Ashat, Kartar Singh
Departments of Gastroenterology and Histopathology¹, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

Introduction: Image enhancement with narrow band imaging (NBI) delineates intestinal villous pattern better than routine endoscopy. We compared the diagnostic accuracy of NBI with histopathology in predicting duodenal villous morphology in celiac disease (CD).

Methods: Amongst the 116 subjects (mean age 27.21 ± 13.22 years, 67 females) studied, 86 were fresh CD, another 14 CD patients were on gluten-free diet and 16 had dyspepsia and served as controls. Subjects underwent esophagogastro-duodenoscopy (EGD) along with NBI (Olympus GIF-180) to evaluate the villous pattern of duodenal mucosawhen 4 biopsies were taken from descending duodenum. Digitally recorded images were analyzed by two experienced endoscopists and histopathology by an experienced pathologist, all of whom were blinded to patient data. Villous patterns on NBI were classified as normal-villous pattern (NVP), distorted/blunted villous pattern (DVP) and absent villous pattern (AVP). Histopathology was graded according to modified Marsh criteria. For statistical analysis, grade 0 was taken as no villous atrophy (stages 1 and 2), grade 1 as partial villous atrophy (stage 3a), and grade 2 as total villous atrophy (stages 3b and 3c). NBI findings were correlated with histopathology using Chi-square test.

Results: On EGD scalloping was present in 56.8% (66 subjects), and grooving in 59.4% (69 subjects). In the whole study group NBI (n = 116) revealed AVP in 46, DVP in 38 and NVP in 32 patients. In those with CD (n = 100) 46 had AVP, 37 had DVP and 17 had NVP, while on histopathology 50 had total villous atrophy, 35 partial villous atrophy and 15 no villous atrophy. 4/14 CD patients on gluten-free diet and the 12/16 dyspepsia patients had normal villous pattern on both NBI and histopathology. A significant correlation was observed between NBI and histology (p < 0.001). The overall sensitivity and specificity of NBI for delineating villous pattern were 88.76% and 81.48% and the positive and negative predictive values were 94% and 68.75%.

Conclusion: NBI can predict villous atrophy with high sensitivity and has high positive predictive value in patients with CD.
Prevalence of inflammatory bowel disease among coeliac disease patients in a Hungarian coeliac centre

D. Kocsis¹, G. Veres², Z. Toth³, E. Jocsak¹, L. Lamboy¹, A. Csontos¹, P. Miheller¹, L. Herszényi¹, M. Tóth¹, Z. Tulassay¹, M. Juhasz¹
¹Semmelweis University, 2nd Dept. Med., Budapest, Hungary
²Semmelweis University, 1st. Department of Pediatrics, Budapest, Hungary
³Peterfy S. u. Kh., Gastroenterology Unit, Budapest, Hungary

Introduction: Celiac disease (CeD) and IBD are inflammatory disorders of the gastrointestinal tract. The aim of this study is to determine the prevalence of IBD in our celiac patient cohort over a 15-year-long study period.

Methods: To diagnose CeD, serological tests (tissue transglutaminase antibody: tTG, endomysium antibody: EMA) were used, and duodenal biopsy samples were taken to determine the degree of mucosal injury. To set up the diagnosis of IBD, clinical parameters, imaging techniques, colonoscopy and histology were applied. DEXA for measuring bone mineral density (BMD) was performed on every patient.

Results: In our material, 8/245 (3.2%) CeD patients presented IBD (4 males, mean age 37, range 22–67), 6/8 Crohn (CD), and 2/8 ulcerative colitis (UC). In 5/8 patients the diagnosis of CeD was made first and IBD was identified during follow-up. The average time period during the set up of the two diagnosis was 10.7 years. CeD serology was positive in all cases (2/8 tTG 6/8 EMA). The distribution of histology results according to Marsh classification: 1/8 M1, 2/8 M2, 3/8 M3a, 2/8 M3b. The distribution according to the Montreal classification: 4/6 CD patients are B1, 2/6 CD patients are B2, 1/2 UC patient is S2, one UC patient is S0. Biological therapy was administered to 2/8 patients. Normal BMD was detected in 2/8 case, osteopenia in 4/8 and osteoporosis in 2/8 patients. The mean BMI for males was 22.25 kg/m² (females 20.74 kg/m²).

Discussion/Conclusion: Within our cohort of patients with CeD, IBD was significantly more common (3.2%) than in the general population. Diagnosis of CeD mostly preceded the diagnosis of IBD. The dominant behaviour of IBD was of the inflammatory type. Interestingly, the loss on BMD for these patients with two different disease leading to malabsorption syndrome were not worse than for those suffering in only one of these disorders.
Tissue acido-alcohol resistant bacteria and tuberculosis culture results of ileo-colonic biopsies

Ali Riza Koksal, Huseyin Alkim¹, Meltem Ergun¹, Salih Boga¹, Mehmet Bayram¹, Banu Bayraktar², Canan Alkim¹
Sisli Etfal Education and Research Hospital, Gastroenterology¹ and Microbiology² Clinics, Istanbul, Turkey

Introduction: Intestinal tuberculosis, which can be confused with inflammatory bowel disease, is relatively common in Turkey. We retrospectively examined results of our patients whom colonic or terminal ileal biopsies were sent for acido-alcohol resistant bacteria (AARB) examination and tuberculosis culture.

Methods: We found 84 patients with tissue AARB and tuberculosis culture results between January 2009 and December 2013 who underwent colonoscopy for different indications, mostly with suspicion of inflammatory bowel disease. All of the tissues were sent to the laboratory in isotonic saline solution. Also demographic, clinical and pathological findings of the patients were retrospectively collected from hospital database.

Results: The mean age of the patients was 43.6 ± 11.2 years. Forty-five (53.5%) of the patients were male. Between the colonoscopy indications the most common one was suspected inflammatory bowel disease with 27 (32.2%) patients. The other indications were anemia and suspected malignancy in 19 (22.6%) patients, abdominal pain in 16 (18.9%) patients, chronic diarrhea in 11 (13.1%) patients, positive radiologic findings in 8 (9.6%) patients and lower gastrointestinal bleeding in 3 (3.6%) patients. In 21 of the patients terminal ileum could not be intubated because of the active disease and stenosis at the ileocaecal valve. In 4 of the patients caecum could not be reached because of the stenosis at the distal colonic segments. In all of the patients multiple ulcers and mucosal inflammation were seen at the ileal and/or colonic segments with some atypical findings in clinical, laboratory, radiologic or colonoscopic examinations. Tissue tuberculosis cultures were positive in 6 (7.1%) patients (Table 1). In all of the patients AARB results were found negative. According to the antibiogram results all of the cases were sensitive to all anti-tuberculosis medications.

Discussion/Conclusion: In the evaluation of patients with ileo-colonoscopic findings suspecting inflammatory bowel disease, taking tissue cultures in the isotonic saline solution for tuberculosis culture provides important contribution to the diagnosis. The result of tuberculosis cultures should be waited even though AARB results are negative.
Table 1: Table showing distribution of the patients according to indications and tuberculosis culture results

<table>
<thead>
<tr>
<th>Indications</th>
<th>All of the patients</th>
<th>Tissue tuberculosis culture positive patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Suspected IBD</td>
<td>27</td>
<td>32.2</td>
</tr>
<tr>
<td>Anemia and suspected malignancy</td>
<td>19</td>
<td>22.6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>16</td>
<td>18.9</td>
</tr>
<tr>
<td>Chronic diarrhea</td>
<td>11</td>
<td>13.1</td>
</tr>
<tr>
<td>Significant radiologic findings</td>
<td>8</td>
<td>9.6</td>
</tr>
<tr>
<td>Lower GI bleeding</td>
<td>3</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>84</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

GI: gastrointestinal system; IBD: Inflammatory bowel disease
In vivo coeliac antibody binding to pancreas – A preventable cause of type 1 diabetes mellitus?

Ilma R. Korponay-Szabo¹,², Maarit Oikarinen³, Jutta E. Laiho³, Kaija Laurila², Katalin Szabados⁴, Markku Mäki², Heikki Hyöty³ and the nPOD Study Group
¹University of Debrecen, Debrecen, Hungary; ²Tampere Center for Child Health Research; ³Virology, University of Tampere Medical School, Tampere, Finland; ⁴Hetényi Geza County Hospital, Szolnok, Hungary

Introduction: Coeliac disease and type 1 diabetes (T1D) are often co-existing. It is still a question whether coeliac disease can directly induce damage of the pancreas. We investigated if anti-transglutaminase (TG2) antibodies target the pancreas in vivo and whether the development of T1D can be prevented by coeliac disease mass screening and early treatment.

Methods: Frozen pancreas and full thickness duodenum specimens from cadaveric organ donors with T1D (n = 22), diabetes antibody positive subjects (n = 11) and non-diabetic controls (n = 21) were obtained through the Network of Pancreatic Organ Donors with Diabetes (nPOD). and investigated for TG2 expression, glucagon, insulin, in vivo bound anti-TG2 IgA antibodies, CD3 and gamma-delta T cells. A one-year birth cohort in Szolnok county, Hungary had been screened for coeliac disease at the age of 6 years in 2005 (BMJ. 2007;335:1244–7) where 77% of the population participated and coeliac cases were treated. Prevalence data of T1D were collected in primary care services for the screened cohort and for the previous two (-2y and -1y) and following two years (+1y and +2 y) birth cohorts in 2014.

Results: IgA class antibodies bound to TG2 were detected around the islets and acinar structures in 5 diabetic and in one autoantibody positive pancreas specimens, and in the mucosa and endomysium of corresponding duodenum samples; villous atrophy was also confirmed in 5 of these. All control pancreas samples were negative. Prevalence of T1D was 2.69/1000 children in the control cohorts and 0.93/1000 children in the coeliac-screened and treated population cohort.

Discussion/Conclusion: Pancreas tissues express the TG2 autoantigen important for coeliac disease pathology. Celiac antibodies bound to pancreas may initiate inflammation and tissue damage leading to diabetes. Population screening for coeliac disease and treatment from age 6 decreases the childhood prevalence of T1D.

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Food-grade glutenases to treat dietary transgressions in coeliac adolescents

I.R. Korponay-Szabo1,2, J. Tumpek2, J. Gyimesi2, K. Laurila3, M. Papp1, M. Maki3, C. Khosla4
1Paediatrics, Univ. of Debrecen, Debrecen; 2Coeliac Centre, Heim Pal Children's Hospital, Budapest, Hungary; 3Tampere Center for Child Health Research, University of Tampere, Tampere, Finland; 4Stanford University, Palo Alto, USA

Introduction: Some microbial enzymes commonly used as food supplements demonstrated gluten degrading activity in laboratory when used in combination. We investigated whether disease activity could be diminished in persistently anti-transglutaminase antibody (anti-TG2) positive CD patients by taking a cocktail of such food grade enzymes at the time when meals with possible gluten are consumed.

Methods: In a placebo-controlled, randomised, double-blind trial biopsy-proven CD patients with stably persisting anti-TG2 for > 1 year on a self-reportedly fairly followed gluten exclusion diet received placebo for the initial 4 weeks. Then subjects were randomised into enzyme (A) or placebo (B) groups for 12 weeks. After 12 weeks, group B received enzymes and group A continued with enzymes plus 2 x 500 mg per day gluten powder for another 12 weeks. Disease activity was monitored by serum anti-TG2, small bowel biopsy and diet questionnaire. Primary endpoints were seronegativity or > 50% decrease in serum TG-Ab levels.

Results: 35 CD patients (median age 17 years) were randomized, of them 26 completed all periods and 17 volunteered for biopsy before and after the treatment. Large changes (-60%+420%) in serum anti-TG2 occurred in the first 4 weeks. In the subsequent periods, no significant differences were observed between placebo (10.6% increase in median anti-TG2, range: -31+148%) and enzyme-treated groups (27.6% increase, range -38.7+198%) and villous atrophy persisted in all but 2 cases. Only 3 treated patients achieved primary endpoints. Addition of 1 g/day gluten to the diet did not result in changes in antibodies.

Discussion/Conclusion: Although such CD patients represent an important target for future non-dietary therapies, drug candidates should be able to protect against a daily consumption of more than 1 g gluten. Second, a subset of patients in such a study will likely feel adequately protected and will consequently increase gluten consumption.
Quality of life of patients with inflammatory bowel diseases in Poland

M. Korzonek*, B. Borkowska**
Long-Term Care Unit, Pomeranian Medical University, Szczecin, Poland*
Department of Digestive Endoscopy, Regional Hospital, Szczecin, Poland**

Introductions: Inflammatory bowel diseases affect several aspects of life of patients. The quality of life depends not only on the physical condition but also on the subjective psychological assessment. Currently, it is worthy noticing that apart from the efficient therapy, improvement of psychological, physical and social functioning of patients seems to be a crucial factor.

Methods: The research involved a group of 101 patients with IBD, including 37 patients with Crohn’s disease and 64 patients with ulcerative colitis. The RFIPC – Rating Form of IBD Patient Concerns survey was conducted. Kruskal-Wallis test and Mann-Whitney U test were carried out to analyze the assessment of quality of life. A significance α level was set at 0.05. Calculations were done using MS EXCEL 2007 spreadsheet application and certain modules of STATISTICA 7.7PL software.

Results and conclusions: Patients with IBD value low their quality of life. Patients with Crohn’s disease (CD) assessed the quality of life lower than patients with ulcerative colitis (UC), (p < 0.022313 in Mann-Whitney U test). Generally, 74% of patients estimated their quality of life low and 25% of patients high. Patients, who did not develop illness-related complications (54% of patients) assess quality of life higher than patients with complications (p < 0.009365 in Mann-Whitney U test). There were significant statistical differences in perceiving own body among various age groups (p = 0.039836 in Kruskal–Wallis test for patients over 50). Age, relationship, job, education, stage of illness do not influence the assessment of the quality of life in the researched spheres: everyday life, sexual life and complications of illness.
Gliadin-induced neutrophil responsiveness is impaired in celiac disease

Karen M. Lammers¹, Sunaina Khandelwal², Debby Santora², Alessio Fasano¹
¹Mucosal Immunology and Biology Research Center, Massachusetts General Hospital, Boston, MA, USA; ²University of Maryland School of Medicine, Baltimore, MD, USA

Introduction: We have observed that gliadin is a chemoattractant factor for neutrophils from healthy individuals (HC) with similar potency as N-formyl-Methionine-Leucine-Phenylalanine (fMet-Leu-Phe). In this study we assessed the gliadin-induced neutrophil responsiveness in HC and CD patients.

Methods: Isolated neutrophils from 10 HC and 8 CD patients were applied in an under-agarose assay to monitor neutrophil migration to gliadin or fMet-Leu-Phe. Neutrophil phagocytosis and respiratory burst were measured with commercial Phagotest and Phagoburst kits. Resting neutrophils and gliadin- or fMet-Leu-Phe-stimulated neutrophils from 3 HC and 3 CD patients were analyzed by flow cytometry for surface markers involved in neutrophil extravasation and migration.

Results: Compared to HC neutrophil migration to gliadin (5.7 ± 1.3 net neutrophil migration [nnm]), CD neutrophil migration was markedly reduced (0.4 ± 0.3 nnm, p < 0.001). Similarly, compared to HC neutrophil migration to fMet-Leu-Phe (vs. 11.9 ± 2.9 nnm), CD neutrophil migration was reduced (4.8 ± 1.1 nnm) albeit without reaching statistical significance. Phagocytic and oxidative burst activity were similar between HC and CD neutrophils, with this exception that the fMet-Leu-Phe-induced oxidative burst activity was significantly higher in HC neutrophils after 7 minutes than in CD neutrophils (13.6 ± 1.1 vs. 8.5 ± 1.3 MFI, p = 0.018), but after 10 minutes fMet-Leu-Phe-induced oxidative burst activity was similar in both groups (11.4 ± 1.0 vs. 12.3 ± 1.6 MFI, p = n.s.). The percentage of L-selectin-expressing neutrophils (resting 67 ± 15) diminished after fMet-Leu-Phe- (52 ± 22) and gliadin-stimulation (44 ± 19) in HC, but remained unchanged in CD (resting 86 ± 5, fMLP 61 ± 24, PTG 90 ± 6).

Discussion/Conclusion: CD neutrophils showed an impaired chemotactic responsiveness to gliadin and fMet-Leu-Phe that may involve L-selectin and a subtle delay in respiratory burst activity upon incubation with fMet-Leu-Phe. This impaired neutrophil function may become important in the context of increased permeability, as seen in active CD, where a failure to initiate a strong innate immune response may lead to the autoimmune enteropathy typical of CD.
Expression profiles of CXCR3 splice variants in celiac disease and non-celeic gluten sensitivity

Karen M. Lammers¹, Gloria Serena¹,², Anna Sapone¹,³, Laura de Magistris³, Gabriele Riegler³, Alessio Fasano¹
¹Mucosal Immunology and Biology Research Center, Massachusetts General Hospital, Boston, MA, USA; ²University of Maryland School of Medicine, Baltimore, MD, USA; ³Department of Internal and Experimental Medicine Magrassi-Lanzara, Seconda Universita' degli Studi di Napoli, Naples, Italy

Introduction: Mucosal expression of CXCR3, the receptor to which gliadin can bind, is increased in active celiac disease (CD). Recently, we found that gliadin can induce interleukin (IL)-8 production by phagocytic cells from both healthy controls (HC) and CD patients, and interestingly, that this IL-8 production is CXCR3-mediated only in CD. This finding points to a structural difference of CXCR3 in CD. Structural diversities of CXCR3 by alternative splicing have been reported. Two splice variants, the conventional CXCR3-A and a second CXCR3-B isoform, have been identified and shown to have opposite biological functions. The study aim was to assess the potential involvement of both isoforms by measuring their gene and protein expression profiles in biopsies and peripheral blood from HC, CD patients and patients with another gluten-related disorder, the recently recognized non-celeic gluten sensitivity (GS).

Methods: Duodenal biopsy specimens were collected during endoscopy from 10 dyspeptic controls, 26 CD and 20 GS patients. Immune cells were isolated by ficoll density-gradient centrifugation from venous blood of 18 HC, 14 active CD, 12 CD-in-remission and 4 GS patients. Gene expression was studied with real time RT-PCR, protein expression was visualized by immunofluorescence microscopy.

Results: Both isoforms are expressed. Relative to CXCR3-B, mucosal CXCR3-A expression was 9.5 fold more expressed in CD patients (p < 0.0001), while much lower and similar in HC and GS patients (3.5 and 4.5 fold, respectively). Immunofluorescence microscopy revealed strong CXCR3-A staining in epithelium and lamina propria in CD patients, and predominant epithelial CXCR3-B expression in HC. Peripheral blood CXCR3 isoform distribution from HC followed the mucosa, but was opposite (higher CXCR3-B expression) in active CD and GS patients.

Discussion/Conclusion: CXCR3 isoforms are expressed differentially in HC, GS and CD. Studies to understand the distribution and function of both isoforms at intestinal epithelial level, are currently underway.
Gliadin peptide motifs induce human neutrophil chemotaxis via the engagement of formyl peptide receptor 1

Karen M. Lammers¹, Marcello Chieppa², Lunhua Liu³, Carole A. Parent³, Alessio Fasano¹
¹Mucosal Immunology and Biology Research Center, Massachusetts General Hospital, Boston, MA, USA; ²Laboratory of Experimental Immunopathology, National Institute of Gastroenterology “de Bellis” 70013 Castellana Grotte (BA), Italy; ³Laboratory of Cellular and Molecular Biology, Center for Cancer Research, NCI, NIH, Bethesda, MD, USA

Introduction: We have previously shown that gliadin induces neutrophil chemotaxis with similar potency as the primary bacterial-derived product, N-formyl-Methionine-Leucine-Phenylalanine (fMet-Leu-Phe). Given that of the three existing formyl peptide receptors (FPR)-1, -2 and -3, only FPR1 recognizes fMet-Leu-Phe, we sought to understand the involvement of FPR1 in gliadin-induced neutrophil chemotaxis.

Methods: Human neutrophils (n = 5) were isolated, tested for purity and applied to the EZ-TAXIScan chemotaxis assay to measure migration to gliadin, fMet-Leu-Phe and leukotriene B4 with or without pretreatment with cyclosporine H, a specific inhibitor of FPR1.

Results: Neutrophil chemotaxis to fMet-Leu-Phe (Speed: 11.39 ± 0.28 µm/min) was completely inhibited after pretreatment with cyclosporine H (Speed: 0.33 ± 0.02 µm/min), while leukotriene B4-mediated chemotaxis, that does not involve FPR1, remained unaffected under similar conditions (Speeds: 9.68 ± 0.30 µm/min (LTB4) and 9.23 ± 0.07 µm/min (after cyclosporine H pretreatment)). Remarkably, we found that the PT-gliadin-induced chemotaxis (speed: 10.26 ± 0.38 µm/min) was completely abrogated in the presence of cyclosporine H (speed: 0.31 ± 0.00 µm/min). In order to find an alpha-gliadin peptide motif responsible for the observed migration, our alpha gliadin synthetic peptide library consisting of 25 peptides was tested in the same conditions. We identified thirteen out of the 25 peptides that induced neutrophil migration with speeds ranging from 6.68 to 10.17 µm/min and found that FPR1 antagonism completely abrogated neutrophil migration to these peptide motifs, confirming both the specificity of the gliadin-induced neutrophil migratory response and its binding to FPR1.

Discussion/Conclusion: These findings show that gliadin motifs induce neutrophil migration in an FPR1-dependent manner. The present study emphasizes an emerging concept that PT-gliadin is interpreted and handled by the host mucosa as a danger signal similar to that provided by fMet-Leu-Phe, likewise exerting direct and robust chemoattractant effects on neutrophils. These observations provide new insight into our understanding of how gliadin triggers inflammatory and autoimmune responses.
Nutritional wheat alpha-amylase/trypsin inhibitors (ATIs) increase the endocannabinoid receptor expression in the liver

J.M. Laparra, D. Schuppan
Institute of Translational Immunology, Univ. Medical Center of the Johannes-Gutenberg University Mainz, Mainz, Germany. E-Mail: jlaparra@uni-mainz.de

Introduction: Celiac disease (CD) is triggered by gluten proteins involving innate and adaptive immunity and has been found in up to 3.5% of patients with non-alcoholic fatty liver disease (NAFLD). Additionally, overactivity of the endocannabinoid (eCBr-1) system has been associated with a pro-inflammatory state that could contribute to CD and the development of insulin resistance and NAFLD. ATIs (i.e., CM3 and 0.19) present in gluten containing cereals are strong activators of the innate immune response(s) via toll like receptor (TLR)-4; however, their influence on neurohormonal systems has not been described.

Objective: To evaluate the effect of orally administered ATIs on the duodenal and hepatic expression of TLR4 and the eCB receptor 1 (eCBr-1).

Method/Design: Commercially available gliadins (Sigma) were extracted with phosphate buffered saline and the supernatants analysed for ATIs by TripleTOF. Newborn rats were sensitized with interferon-γ (1000 U) at birth and fed the enriched ATIs or the remaining ATI-de-enriched gliadin fraction (GF), at a dose of 100 µg/daily by oral gavage for 30 days. Then, animals were sacrificed and the intestinal and hepatic expression of TLR4 and eCBr-1 mRNA was measured by rt-qPCR.

Results: TripleTOF demonstrated the major presence of CM3 and 0.19 in the ATI fraction. Animals that were administered ATIs revealed a significantly increased in both duodenal and hepatic TLR4 mRNA expression. ATIs only increased the hepatic eCBr-1 mRNA expression comparison to animals receiving GF, and was associated with an increased macrophage population (by 38%) in the liver of animals fed ATIs.

Conclusions: Oral challenge with ATIs significantly increases innate immune activation in the intestine and liver, but only the hepatic eCBr-1 mRNA in line with their potential to CD and NAFLD. These results point to a cross-talk within the gut-liver axis via inflammatory signals that stem from ingested ATIs and the intestinal mucosa.

Keywords: α-amylase/trypsin inhibitors, macrophage, liver, intestine, inflammation.

References:
The neo-epitope only positive test in celiac disease biopsy-proven children with high Marsh grades

Aaron Lerner1,2, Orit Rozenberg3, Mira Barak3
1Pediatric Gastroenterology and Nutrition Unit, Carmel Medical Center
2Rappaport School of Medicine, Technion – Israel Institute of Technology,
3Central Laboratory of Haifa and Western Galilee, Clalit Health Services, Haifa, Israel

Introduction: Deamidated Gliadin peptides (DGP)/tTG complexes are found in small intestine biopsies of patients with celiac disease (CD). The Neo-epitope ELISA assay detects these complexes formed by cross linking of DGP to tTg. We have previously shown that this assay provides earlier detection of CD than other tTG ELISA assays, especially in patients with low Marsh grading.

The present study was aimed to verify whether the Neo-epitope assay was superior also in detecting CD patients with progressive intestinal damage (high Marsh grading = III–IV).

Methods: We prospectively reviewed serological results of 86 symptomatic biopsy-proven celiac children (age 1–18 years, median, 7 years; F/M: 1.8/1).

Results: We found 8 biopsy-proven celiac patients with positive Neo-epitope IgA/IgG but negative tTg results (9.3%) that otherwise could be missed by a tTG ELISA assay (6 females and 2 males, aged 1.5–12 with a median of 6.5). The Marsh grades of their biopsies were: Marsh I – 2 patients, Marsh II – 1 patient, Marsh III – 2 patients and Marsh IV – 3 patients. The Neo-epitope IgA/IgG antibody levels ranged from 26.9 U/ml to > 300.0 U/ml (Median, 81.3, Cut-off = 23 U/ml). All patients except one (Marsh III) had normal total IgA levels. In one of those patients the tTg levels increased in a following sample, concomitantly with a more than 4 times increase in the neo-epitope level.

Discussion/Conclusion: We concluded that the sensitive Neo-epitope IgA/IgG assay can detect not only questionable low Marsh CD but also high grade disease otherwise not detected with the tTg assays.
Selective including HLA testing neo-epitope based celiac disease (CD) detection algorithm

Aaron Lerner¹,², Mira Barak³, Orit Rozenberg³
¹Pediatric Gastroenterology and Nutrition Unit, Carmel Medical Center
²Rappaport School of Medicine, Technion – Israel Institute of Technology,
³Central Laboratory of Haifa and Western Galilee, Clalit Health Services, Haifa, Israel

Based on the current ESPGHAN guidelines for the diagnosis of CD, we adopted and validated an algorithm that included celiac screening with a sensitive test, the neo-epitope, sequentially confirmed by a more specific IgA anti-tTG and EmA tests. We found that the combination of the neo-epitope > 10 UNL (upper normal limit = 23) with positive anti tTG will result in no misclassifications of patients and will reduce the biopsy rate to 27.5%. However our algorithm did not include HLA tests due to their high cost and lack of authorization to perform the test. Based on those data and on more than 100,000 serology results performed in the local Clalit HMO in 2012, we hypothesized that the HLA test should be performed only in 1.2% of our patients:

<table>
<thead>
<tr>
<th>group</th>
<th>neo-epitope titer</th>
<th>Confirmatory serological test</th>
<th>follow up</th>
<th>%</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>0–23</td>
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<td>none</td>
<td>93.6</td>
</tr>
<tr>
<td>2</td>
<td>23–230</td>
<td>V</td>
<td>HLA</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>23–230</td>
<td>V</td>
<td>serology</td>
<td>3.8</td>
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<tr>
<td>4</td>
<td>&gt; 230</td>
<td>V</td>
<td>CELIAC</td>
<td>1.4</td>
</tr>
<tr>
<td>5</td>
<td>≥ 230</td>
<td>V</td>
<td>HLA</td>
<td>0.2</td>
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As a preliminary study we checked the prevalence of HLA DQ2 and/or DQ8 in 36 patients who had randomly performed the test according to the groups assigned above: group 4 – no need of HLA-in no patient CD was excluded; group 1 – no need of HLA-but only in 33% CD was excluded; group 3 – proposed follow up only by serology, HLA- excluded only 33%; group 2 – in no patient CD was excluded (even low Marsh grades); group 5 – only one patient was excluded by the HLA.

According to those limited data, it is suggested that HLA determination should be performed only in group 2 and 3. A more extensive study including HLA typing, serology and intestinal biopsies is warranted.
IL-8 secretion and iron-related proteins abnormalities are attenuated by β-carotene in inflammed Caco-2 cell line

A. Lerner¹, O. Katz², R. Reifen²
¹Pediatric Gastroenterology and Nutrition Unit, Carmel Medical Center, B. Rappaport School of Medicine, Technion – Israel Institute of Technology, Haifa, ²Faculty of Agriculture, Food and Environment, Institute of Biochemistry, Food Science and Nutrition, School of Nutritional Science, The Hebrew University of Jerusalem, Rehovot, Israel

Introduction: Iron restricted anemia is frequent in chronic inflammatory conditions. Several pathophysiological explanations have been suggested, one of them being the development of anemia due to iron sequestration in enterocytes. The dynamics of the intestinal, iron-related protein levels in Caco-2 cells was evaluated during IL-1β/iron induced inflammation and after alleviation of the inflammation by carotenoids.

Methods: Caco-2 cells were treated by IL-1β to induce inflammation confirmed by IL-8 release. Iron application on the cells was studied in a time and dose dependent manner. The effects on H-, L-ferritin, ferroportin, transferrin receptor and intracellular iron levels were compared in inflamed Caco-2 cells with or without application of the anti-inflammatory agents: β-carotene and vitamin A.

Results: IL-1β treatment led to IL-8 release, surge of L-, H-ferritin and suppression of ferroportin and transferring receptor expressions. β-carotene significantly reduced IL-8 (1306.2 pg/ml to 253.75 pg/ml), decreased L-, H-ferritin by 77.8% and 45.8% respectively and increased ferroportin by 59.9% (p < 0.05). Increasing iron concentrations and incubation periods resulted in an increase in IL-8 release. A strong correlation between IL-8 and L-, H-ferritin was found. Intracellular iron sequestration was induced by IL-1β and iron and alleviated by β-carotene.

Discussion/Conclusion: β-carotene normalized the main iron-related proteins’ levels, diminished IL-8 production and released intracellular trapped iron, in an inflammation induced Caco-2 cell model. These results suggest that by applying anti-inflammatory compounds, less iron is locked in inflamed intestinal epithelial cells, leading to increased iron bioavailability. This may indicate a possible approach to combat iron deficiency anemia associated with intestinal inflammation.
**CTLA4 and TNF-α gene polymorphisms in celiac disease**

Vanja Licul¹, Brankica Mijandrusic Sincic¹, Nada Starcevic Cizmarevic², Smiljana Ristic², Miljenko Kapovic², Davor Stimac¹

¹Department of Gastroenterology, University Hospital Centre, Rijeka, Croatia
²Department of Biology and Medical Genetics, School of Medicine, University of Rijeka, Croatia

**Introduction:** Only 40% of the genetic susceptibility to celiac disease can be attributed to the HLA class II genes. The aim of our study was to determine the possible impact of specific polymorphisms of the cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and tumor necrosis factor-α (TNF-α) genes on the predisposition of celiac disease.

**Methods:** The study included 202 patients with celiac disease and 400 healthy controls. Polymerase chain reaction – restriction fragment length polymorphism (PCR-RFLP) method was used for the identification of TNF-α -238, TNF-α -308, and CTLA4 +49 and CTLA4 CT60 gene polymorphisms.

**Results:** The presence of the CTLA4 +49 and CT60 polymorphisms had no individual impact on the genetic susceptibility to celiac disease. However, the interaction of risk alleles for both CTLA4 polymorphisms showed significant impact on the occurrence of the disease, which was confirmed by the analysis of the haplotype (OR = 4.66, p = 0.0003). The presence of the TNF-α -308 gene polymorphism strongly correlated with the presence of the disease at the significance level of p < 0.001, while TNF-α -238 polymorphism showed no correlation (p > 0.05). Examining the interaction of the TNF-α gene -308 and -238 polymorphisms has shown that TNF-α -308/-238 AG haplotype represents a risk factor for the development of the disease (OR = 2.53, p < 0.0001). The investigation of TNF-α and CTLA4 genes showed the importance of the interaction between TNF-α -308, CTLA4 +49 and CTLA4 CT60 polymorphisms. Patients who are carriers of all three risk alleles also had an associated autoimmune disease in 25.6% of cases.

**Discussion/Conclusion:** The presence of the TNF-α -308 gene polymorphism and the interaction between CTLA4 +49G, CT60G and TNF-α -308A polymorphism affect the predisposition to celiac disease in our patients, but further investigations with larger number of patients are necessary.
An increasing tendency in the incidence of celiac disease coexisting with eosinophilic esophagitis in biopsy material in pediatric patients

Joanna M. Lotowska¹, Maria E. Sobaniec-Lotowska², Urszula Sulikowska³, Marek Baltaziak¹, Elzbieta Jarocka-Cyrta⁴, Sylwia B. Lotowska⁵

¹Department of General Pathomorphology, ²Department of Medical Pathomorphology, Medical University of Bialystok, ³Department of Diagnostic Histopathology and Cytology, Jedrzej Sniadecki Memorial Hospital, Bialystok, ⁴Department of Pediatrics, Gastroenterology and Allergology, Medical University of Bialystok, ⁵Department of Laboratory Diagnostics, Maria Sklodowska-Curie Memorial Bialystok Oncology Center, Bialystok, Poland

Introduction: Celiac disease (CD) and eosinophilic esophagitis (EoE) – distinct disorders with specific clinicopathological characteristics – are usually considered to be separate gastrointestinal entities. However, these two conditions may coexist more frequently than expected. The main aim of the report was to assess the incidence of celiac disease in coexistence with eosinophilic esophagitis, diagnosed in the Department of Medical Pathomorphology, Medical University of Bialystok, in our own biopsy material obtained from children in 2013 as compared to the years 2012 and 2011.

Methods: Histopathological reports of duodenal biopsies performed between January 2013 and December 2013 were surveyed to identify all cases of CD. Of this group, patients with histopathological diagnosis of concomitant EoE were selected. Then, the percentage of the concomitant CD and EoE cases in 2013 was compared to those in the years 2012 and 2011. The EoE cases were diagnosed when there were ≥ 15 eosinophils per high power field (hpf) in the affected esophageal mucosa. Clinical symptoms found in children with CD coexisting with EoE were taken into consideration.

Results: In 2013, we found 71 children with CD, 21 patients with EoE and 6 (8.45%) with both disorders. Two of the six latter cases were in the age range of 1–6 years, one in the age range of 7–12 and three at the age of 13–18. The vast majority of CD+EoE cases concerned boys (5/6). The incidence of CD coexisting with EoE in pediatric patients in 2013 showed a growing tendency, as compared to the years 2011 and 2012, when CD was noted in 33 and 41 patients, EoE in 12 and 11 children and the two pathologies were diagnosed in 2 and 3 cases (i.e. 6.06% and 7.3%, respectively).

Discussion/Conclusion: The current study showed an increase in the concomitant incidence of CD and EoE in children in the year 2013 as compared to the years 2011 and 2012. The increase in the incidence of the two coexisting pathologies seems to suggest that EoE should be considered in all pediatric patients with CD who have persistent upper gastrointestinal symptoms. In such cases, esophageal biopsies should be obtained, irrespective of whether esophageal mucosa appears normal or abnormal at endoscopy.
The pattern of \textit{STK11} gene mutations and its phenotypical manifestation in patients from Ukraine with hamartomatous polyposis of intestine

Institute of Hereditary Pathology, Lviv, Ukraine
*Institute of Human Genetics, Poznan, Poland
**Lviv National Medical University, Lviv, Ukraine

\textbf{Introduction}: Peutz-Jeghers syndrome (PJS) is an autosomal dominant rare disease caused by mutations in the suppressor \textit{STK11} gene. Hereditary predisposition of PJS characterized by the presence of hamartomatous polyps in the gastrointestinal tract and a significantly increased risk of malignant tumors of various internal organs. The aim was to study the \textit{STK11} gene mutations spectrum and its phenotypical manifestation in probands and their relatives from Ukraine.

\textbf{Methods}: The clinical examination, genealogical and molecular genetic analysis of the probands and the risk group of three families with PJS were carried out. The material for investigations was the DNA obtained from 3 probands with PJS and 2 individuals-relatives of the risk group. We have used high resolution melting analysis (HRM) for the detection of small mutations. To detect deletions of one or more exons multiplex ligation dependent probe amplification technique (MLPA) was also used. One proband was born in an oil industry polluted region.

\textbf{Results}: Here we report the results of the first Ukrainian collaborative study on PJS. The mutations of \textit{STK11} gene in exons 1, 2, 3 and 4, that lead to the formation of truncated protein and loss of its kinase activity, were confirmed in probands and in two persons of the risk group. The medium age of the disease manifestation of the colon symptoms was 25 (16–34) years. The typical features of the disease were the conglomerate of hamartomas and intestinal invaginations. Polyps were found in different part of the digestive tract: in stomach, small intestine, gall bladder and large bowel. The disturbances of reproduction functions, congenital abnormalities and neurologic pathology were observed in probands with PJS. Two relatives of the probands had cancer of small and large intestine in young age.

\textbf{Discussion/Conclusion}: All observed probands with PJS carried mutations of \textit{STK11} gene (two sporadic and one familial cases). The patients with PJS need regular endoscopic investigation with obligatory observation of small intestine, the ultrasonic examination of internal organs, mammography, the detections of \textit{STK11} gene mutations for early identification of the malignancy and genetic consultation for detection of the risk group.
Acute liver failure unmasks celiac disease

M. Mahmoudi, L. Hamzaoui, S. El Bouchtili, H. Ezzine, A.A. Azouz
Division of Gastroenterology, Mohamed Taher Maamouri Hospital, Nabeul, Tunisia

Introduction: Liver involvement in celiac disease (CD) varies from asymptomatic mild non specific hepatitis to liver failure.

Methods: Here we report the case of a celiac disease revealed by an acute liver failure.

Case report: A 21-year-old man presented with fatigability and diarrhea for 6 months and jaundice for 8 weeks. On examination, he has somnolence and splenomegaly. Liver function tests revealed elevated liver enzymes, an INR 1.5, anemia and low albumin level. Extensive investigations excluded infectious, metabolic, toxic and endocrine causes of acute liver failure. Because of the diarrhea and the anemia CD was suspected. Histopathological examination of small intestine biopsies showed total villous atrophy consistent with CD. Liver biopsy showed no specific lesions (periductular fibrosis, ductopenia). He started a gluten-free diet, but he died within a few days in a hepatic encephalopathy context.

Discussion/Conclusion: Celiac disease is a potentially treatable cause of liver failure. All patients with severe unexplained liver disease should undergo serological screening for CD.
Evaluation of dynamic changes in expression of Toll-like receptors 2,4,6 in Crohn’s disease

L. Mamedova, G. Tarasova, A. Galushkin
Rostov Medical State University, Rostov-on-Don, Russia

**Introduction**: According to one of the priority of development theories, inflammatory bowel disease (IBD) may result from defects in innate immunity, significant components of which are Toll-like receptors (TLR).

**Methods**: We investigated 19 patients with a diagnosis of CD aged 39.3 ± 2.7 years. The control group included 20 healthy volunteers aged 26.2 ± 8.3 years. TLR expression on peripheral blood monocytes was determined by immunofluorescence assay with monoclonal antibodies TLR2 (CD282), TLR4 (CD284) and TLR6 (CD286), conjugated with FITC (Hycultbiotechnology, The Netherlands) and the corresponding isotype controls during the medication-induced relapse and remission.

**Results**: Expression of TLR 2,4,6 during relapse CD was 81.1 ± 2.4%, 12.8 ± 1.3% and 7.2 ± 0.9%, respectively, in clinical remission: 56.0 ± 2.9%, 6.8 ± 1.4% and 4.1 ± 0.8% respectively (p < 0.05). In the control group these indexes were 66.2 ± 0.9%, 3.7 ± 0.3% and 3.4 ± 0.2%, respectively, which was significantly different from the expression of TLR 2,4,6 during relapse (p < 0.05), and had no significant differences compared with the data rates during clinical remission (p < 0.05). The expression of TLR 2,4,6 depending on the severity of the inflammatory process and long term morbidity revealed significant differences. Sensitivity of the expression of TLR 4 to determine the activity of the disease was highest and was 89.5%. The highest specificity was determined for the expression TLR 2 and TLR 6 – 88%. The high positive predictive value result is typical for TLR 2 – 84.2%, the highest negative predictive value result is typical for TLR 4 – 90.9%.

**Discussion/Conclusion**: Increased expression of TLR 2,4,6 is directly dependent on the activity of the inflammatory process, the severity and duration of illness. Reduced expression of TLR 2,4,6 with basic therapy CD may be an diagnostic marker that characterizes development of clinical remission.
Gluten-dependent atrophy recognition and it’s degree with high definition (HD) and/or magnification (M) endoscopy with NBI

K. Marakhouski
RSCP “Mother and Child”, Minsk, Belarus

Introduction: Duodenal mucosa atrophy diagnostic used to standard definition endoscopy with white light have some limitation. Attempt's to classify pattern which visualized on HD and/or M endoscopy were undertaken since 2006 year, but the main problem is a low number of cases.

Methods: Endoscopy was performed by GIF – Q160Z, GIF – H180, GIF – HQ190 with video processor and light source 180 and 190 series Olympus, Japan. Adobe Power Pro professional edition was used. The histology assessment was carried out according Marsh and Oberhuber.

Results: 27 cases of gluten dependent atrophy were selected. Atrophy assessment was from II to IIIC. 5 pattern type were detected.

Type 1: Villy aren't visualized. Any structures on the mucosa aren't visualized. There can be visible irregular vessels located of a submucosal layer.

Type 2A: Villy aren't visualized. On the mucosa are visualized “honeycombs like” pattern drawing where "honeycombs" reflect light to a lesser extent than surrounding mucosa.

Type 2B: “Moulds” of villy are visualized. The villy basis is accurately visualized. The internal part of a "mould" is connected to others with formation of a "labyrinth" pattern. Intravilly capillaries aren't visualized.

Type 2C: “Brain like” pattern. This pattern looks like as a negative of 2B pattern. It concern with changing of reflection of light wave.

Pattern type 3: Villy are visualized, their number are normal. The inravilly vessel is visible. Ratio villy lengths/widths less than 2.5.

Simple correlation analysis Endoscopy/Histology(E/H) scores found: Pearson = 0.68 (Standardized Cronbachs Alpha = 0.81) and Spearman = 0.68. Results functions regression analysis shown endoscopic degree can be estimated by linearly model with Asymptotic Correlation = 0.97. Canonical Correlations = 0.68 at probability level = 0.00006.

Multinomial Logistic Regression Report. ROC Section for pattern 1 – Area Under ROC Curve (AURC) = 0.93; ROC Section for pattern 2C – AURC = 0.67; pattern 2B – labyrinth like – AURC = 0.69; pattern 2A – honeycomb like – AURC = 0.68; pattern 3 – AURC = 0.50.

Discussion/Conclusion: Endoscopic picture of duodenal mucosa atrophy highly precisely detected with HD and/or M endoscopy with NBI. Endoscopic picture of Marsch 3c level atrophy характеризуется большой вариантыностью.
The motoric and dysbiotic disorders relationship in the pathogenesis of diabetic enteropathy

G.S. Maslova, I.N. Skrypnyk, Y.A. Mandryka
Ukrainian Medical Stomatological Academy, Poltava, Ukraine

The diabetes mellitus (DM) long duration and the lack of adequate carbohydrate metabolism correction lead to the early macro- and microangiopathy and autonomic polyneuropathy development with secondary lesions of target organs. The gastrointestinal (GI) tract motor-evacuation function and intestinal microbiota violation is a pathogenetic substrate for the enteropathy formation on a diabetes background, clinical manifestations of which significantly reduce the patients quality of life.

**The aim** – to improve the diagnostic quality of bacterial overgrowth syndrome (BOS) and motor dysfunction on the intestinal enteropathy background in patients with diabetes type 2.

**Materials and methods:** The study involved 104 patient with the enteropathy on the background of diabetes type 2, including 57 (54.8%) women, 47 (45.2%) men, mean age 58.7 ± 16.2 years, the diabetes duration 6–10 years. The type 2 diabetes was in subcompensation phase: the level of HbA1c ≤ 7.5%, without ketoacidosis. To correct carbohydrate metabolism patients received combined glucose-lowering therapy. The enteropathy with the obstipation syndrome was diagnosed in 71 (68.2%) patients and with the diarrhea syndrome – in 33 (31.8%). The glucose hydrogen breath test was conducted with 50 g glucose dissolved in 250 ml of water. The concentration of hydrogen was measured in expired air before taking and after 15, 30, 60, 90 and 120 minutes.

The gradual increase in the hydrogen concentration was noted in patients suffered from the enteropathy with the prevalence of constipation with maximum values on 60 and 90 minutes, 28.09 ± 3.5 ppm and 30.71 ± 4.09 ppm, respectively. There were two peaks of the hydrogen concentration at 15 and 30 minutes under the enteropathy with diarrhea syndrome background: 34.26 ± 4.08 ppm and 38.92 ± 3.94 ppm, respectively. After 60 minutes, was noted the decrease in hydrogen level 16.47 ± 2.9 ppm with its increase at 90 and 120 minutes to 42.05 ± 4.12 ppm 40.26 ± 3.1 ppm.

Thus, the increase in intestinal transit time in the presence of enteropathy with constipation was marked, and while the prevalence of diarrhea syndrome the BOS with a high proportion of anaerobic organisms was present, accompanied by enhanced intestinal propulsive activity.
Microbial transglutaminase – A possible trigger for celiac disease

T. Matthias¹, S. Neidhöfer², P. Jeremias¹
¹AESKU.Kipp Institute, Wendelsheim, Germany
²AESKU.Diagnostics, Wendelsheim, Germany

Transglutaminases are common enzymes in different organisms and responsible for a broad range of processes. Due to their ability to cross-link proteins they are of broad interest in science and have found various applications. In the food industry, microbial transglutaminase (mTG) is used to modulate texture and improve the properties of food products. In contrast to tissue transglutaminase (tTg), mTg is a calcium independent transglutaminase and is less substrate specific.

Due to their common enzymatic function, the question arose whether complexes of mTg formed by transamidation reactions could be a relevant health risk for celiac patients. This is all the more important as the use of mTg in food needs not be indicated on the label. Therefore, the antigenicity of mTg-Gliadin complexes (mTg neo-epitopes) was tested in an ELISA format and compared to results obtained by detection of autoantibodies against the tTg complexes (tTg neo-epitopes) and tTg. Evidence for a common epitope is provided by a competition assay wherein the detection of autoantibodies against tTg neo-epitopes can be impaired by the presence of mTg neo-epitopes. Moreover, the structure of both complexes was compared. Despite the absence of sequence homology and 3D congruence between mTg and tTg, the mTg-neo-epitopes and tTg-neo-epitopes were found to be similar in structure.

The existing data – performed on an in-house sample cohort of CD patient sera, indicate that a risk for those affected by celiac disease cannot be excluded and therefore adequate labeling of mTg containing food is required.
Ten-year experience of celiac disease in a Romanian tertiary center

Roxana Maxim¹, Anca Trifan¹, Irina Gîrleanu¹, Oana Stoica¹, Irina Ciortescu¹, Alina Plesa¹, Carol Stanciu²
¹University of Medicine and Pharmacy “Gr. T. Popa”, Iasi, Romania
²Institute of Gastroenterology and Hepatology, Iasi, Romania

Introduction: Celiac disease (CD) is a common autoimmune multisystemic disorder. In the present study we aimed to evaluate the experience of a single celiac centre over a 10-year-long study period.

Methods: All the patients admitted with CD between January of 2003 and December of 2013 were tested by multiple duodenal biopsies, anti-tissue transglutaminase and anti-gliadin antibodies, and baseline demographic, clinical, biological and immunological parameters.

Results: Histological samples were available in 133 cases, distribution according to Marsh-Oberhuber classification: M0 in 7%, M1–M2 in 4%, M3a in 26%, M3b in 13%, and M3c in 50% of cases, respectively. Anti-tissue transglutaminase and anti-gliadine antibody tests were available in 145 cases, 109/158 showed seropositivity. The mean body mass index result was 20.6 kg/m², range: 15.1 kg/m²–35.8 kg/m². Correlations between anti-tissue transglutaminase antibody titers and Marsh-Oberhuber classification were found to be statistically significant.

Discussion/Conclusion: Celiac disease can be diagnosed at any age and even overweight patients can have celiac disease. Female predominance is significant. Histology usually showed advanced villous atrophy.
Hematological tools for accurately predicting celiac disease

Roxana Maxim¹, Anca Trifan¹, Irina Gîrleanu¹, Oana Stoica¹, Irina Ciortescu¹, Alina Plesa¹, Carol Stanciu²
¹University of Medicine and Pharmacy “Gr. T. Popa”, Iasi, Romania
²Institute of Gastroenterology and Hepatology, Iasi, Romania

Introduction: Celiac disease (CD) is a common chronic enteropathy associated with diverse serological abnormalities. The aim of this study was to determine the frequency of blood count abnormalities in patients with CD upon presentation.

Methods: We performed a retrospective descriptive study which included consecutive adult patients who had serologic testing and underwent an intestinal biopsy in the period between January 2011 to December 2013 at a tertiary referral center in Iasi Romania. Erythrocyte and platelet indices such as hemoglobin level, mean corpuscular volume (MCV), red blood cell distribution width standard deviation (rdw-sd) platelet count, mean platelet volume (MPV) and iron levels were analyzed. All patients signed a consent form.

Results: A total of 70 cases of CD, 57 female (81.4%), mean age 40.2 ± 12.03 were identified. Twenty two (31.4%) patients had an elevated red cell distribution width; 33 (47.1%) had anemia and 24 (43.2%) had a low mean corpuscular volume. Low iron levels were found in 48 (68.5%) cases and mpv was elevated in one case only. Low iron levels and elevated rdw correlated well with villous atrophy. High anti-transglutaminase titers correlated with elevated rdw (r = 0.411, p < 0.0001). The red cell distribution width was 79% sensitive and 89% specific for CD.

Discussion/Conclusion: An elevated red cell distribution width and low iron levels may help better identify those patients who should be referred for further testing for celiac disease. The increase of red cell distribution width was less common than iron-deficiency anemia. Elevated red cell distribution width with low iron levels can thus be considered new predictors of coeliac disease.
Associations between the use of anti-secretory drugs and subsequent development of celiac disease: Just a coincidence?

Roxana Maxim¹, Anca Trifan¹, Irina Gîrleanu¹, Oana Stoica¹, Irina Ciortescu¹, Alina Plesa¹, Carol Stanciu²  
¹University of Medicine and Pharmacy “Gr. T. Popa”, Iasi, Romania  
²Institute of Gastroenterology and Hepatology, Iasi, Romania

Introduction: It is now thought that the use of proton pump inhibitors (PPI) and histamine-2 receptor antagonists (anti-H2) drugs can influence the development of celiac disease (CD). The aim of this study was to see whether any type of correlation can be made between the use of anti-secretory drugs and the onset of CD.

Methods: We performed a case-control study which included adult patients diagnosed with CD matched by age and gender and admitted at a tertiary referral centre in Iasi Romania between January 2011–December 2013. We identified prior prescriptions for PPI and anti-H2 antagonists in all subjects. All patients underwent clinical, biological, serological and histological evaluations and medical charts were analyzed. Associations were calculated as odds ratios (OR) and corresponding 95% confidence intervals (CI).

Results: A total of 70 cases of CD, 57 female (81.4%), mean age 40.2 ± 12.03 and 469 controls (73.6% female) were identified. Overall, all subjects diagnosed with celiac disease had at least one prior PPI or anti-histamine prescription. CD patients were more likely to have a prior PPI prescription compared to controls (26% vs. 7%, OR = 4.35; 95% CI: 3.17–4.51). The use of anti-H2 mainly famotidine (25%) alone or in association with PPI was found to be less frequent compared to PPI-pantoprazole products. There were no statistical differences between the use of PPI alone or in association with anti-H2 drugs and the subsequent diagnosis of CD. Use of pantoprazole correlated strongly with an increased risk for CD.

Discussion/Conclusion: Use of PPI is associated with an increased risk for developing CD unmodified by age and gender. It may be considered a risk factor for CD in adults.
Accuracy of clinical suspicion in celiac disease

Roxana Maxim¹, Anca Trifan¹, Irina Gîrleanu¹, Oana Stoica¹, Irina Ciortescu¹, Alina Plesa¹, Carol Stanciu²
¹University of Medicine and Pharmacy “Gr. T. Popa”, Iasi, Romania
²Institute of Gastroenterology and Hepatology, Iasi, Romania

Introduction: Celiac disease (CD) is defined as a chronic small intestinal immune-mediated enteropathy. The aim of the study is to find specific correlations between clinical presentation, clinical utility of serology testing and degree of mucosal injury.

Methods: This prospective study was performed with 236 patients evaluated at a tertiary center in North-Eastern Romania between January 2012 to January 2013 for clinical suspicion of CD. All patients underwent serological (antibody antiendomisium-EmA) and histological testing. Based on clinical presentation, patients were divided in three groups 1. high-risk, with anemia, weight loss, chronic diarrhea and dermatitis herpetiformis; 2. intermediate risk, with abnormal liver function, low iron levels, chronic fatigue; 3. low risk, with dyspeptic symptoms, joint pain and chronic headache. Degree of duodenal mucosal damage was classified using the Marsh-Oberhuber score. The diagnosis of CD was established on the presence of positive antibodies and typical histology.

Results: Celiac disease was diagnosed in 78/236 patients (33%). From 34 patients enrolled in group 1, 14 (37.5%) tested positive for EmA serology and 12 out of 14 had also severe mucosal damage (Marsh III villous atrophy), thus being diagnosed with CD in a proportion of 35.2%. In the second group, a cohort of 72 patients, 53 (73.6%) had high EmA levels and 39 out of 53 had positive histology for Marsh III, with an accurate diagnosis of CD in 54.1% of the cases. CD was found in 8/130 patients (6.1%) in the low-risk cohort. Fifty one out of 130 patients (39.2%) had minimal to moderate mucosal damage with negative serology.

Discussion/Conclusion: This study shows that clinical features alone cannot distinguish patients with or without celiac disease, but in regards to EmA positivity, this is a strong predictor of subsequent CD diagnosis in subtle or atypical presentation.
Prevalence of celiac disease among first-degree relatives of patients with celiac disease

Asha Mishra, V. Sreenivas, Siddhartha Datta Gupta, Vineet Ahuja, Govind K. Makharia
Department of Gastroenterology and Human Nutrition, Biostatistics and Pathology, All India Institute of Medical Sciences, New Delhi, India

Introduction: Celiac disease, once thought to be uncommon, is now known to affect almost 1% of population in Northern part of India. We estimated the prevalence of CeD in first degree relatives (FDRs) of patients with CeD.

Methods: The FDRs of our cohort of patients with CeD were invited to participate in this study and those who agreed, underwent a questionnaire based interview and were screened for CeD using IgA anti-tissue transglutaminase antibody (anti-tTG Ab). Those with anti-tTG Ab positive were requested to undergo duodenal biopsies. Duodenal biopsies were assessed using modified Marsh Oberhuber classification. HLA haplotype was also assessed in 127 FDRs. A diagnosis of CeD was based on presence of a positive serology and presence of villous abnormality.

Results: Four hundred and thirty four FDRs of 176 CeD index patients were recruited. Four FDRs had already been diagnosed to have CeD even before this study was initiated. Two eighty two (64.9%) were symptomatic and majority had non-classical manifestations. Fifty eight FDRs were detected to have anti-tTG Ab positive indicating a seroprevalence of CeD to be 13.3%. Sero-prevalence of CeD was higher in female (17.5%) than males (8.5%) and in siblings (16.9%) and parents (13.6%) than that in children (5.9%). Genotyping for HLA DQ2 and DQ 8 could be done in only 127 FDRs of which 87.4% were either of HLA-DQ2 and HLA-DQ8 or both positive. Overall the prevalence of CeD was 11.9% amongst FDRs.

Conclusions: The seroprevalence of CeD in FDRs was 13.3% and was higher in females and siblings. Eighty seven percent of FDRs had HLA-DQ2 or -DQ8 haplotype. The prevalence of CeD in FDRs was 11.9%. Therefore, all FDRs of patients with CeD should be screened for CeD even if they are asymptomatic or have non-classical manifestations.
Adherence to duodenal biopsy guidelines increases the detection of coeliac disease: A multicentre UK study

Peter D. Mooney¹, Michael Finegan², Faisal Khan³, Richard Keld², Greg Naylor³, David S. Sanders¹
¹Royal Hallamshire Hospital Sheffield ²Royal Albert Edward Infirmary, Wigan ³Chesterfield Royal Hospital, Chesterfield, UK

Introduction: Coeliac disease (CD) is a common autoimmune condition affecting 1% of the adult population. However, large numbers of patients remain undiagnosed which may have significant health consequences and so methods to increase detection should be sought. Guidelines suggest that at least 4 duodenal biopsies should be taken to rule out CD. A previous US study showed that biopsy guidelines were only followed in 35% of cases. The aim of the present study was to see whether guidelines were being followed in the UK and if adherence to the guidelines improved detection of CD.

Methods: Endoscopy and histology reports were retrospectively reviewed for all patients who had a duodenal biopsy in a 3 month period between November 2012 and January 2013 from 4 UK hospitals. Indications for biopsy, role of the endoscopist (physician, surgeon, nurse endoscopist), number of duodenal biopsies received by histopathology and the final diagnosis were recorded. The presence of villous atrophy was required for CD diagnosis. Patients were excluded if they had known CD. The difference between a double and single bite biopsy technique was also assessed.

Results: 1423 patients underwent duodenal biopsy for possible CD across the 4 sites in the study period. 97 (6.8%) of these were diagnosed with CD. Guidelines to take at least 4 biopsies were met in 40% of patients and the median number of duodenal biopsies taken for all patients was 3. CD was more likely to be diagnosed if guidelines were followed (10.1% vs. 4.6%, \(p < 0.0001\)). The median number of biopsies was greater in patients diagnosed with CD (4 vs. 3) \(p < 0.0001\). Gastroenterologists and nurse endoscopists were more likely than surgeons to follow guidelines (41.8% vs. 51.2% vs. 18.2%, \(p < 0.0001\)) and took a higher median number of biopsies (3 vs. 4 vs. 2, \(p < 0.0001\)). As a result gastroenterologists and nurse endoscopists made a diagnosis of CD in more cases than surgeons (7.1% vs. 6.7% vs. 3.0%, \(p 0.1\)). All presenting characteristics (other than positive serology in which guidelines were followed in 65%) were associated with poor adherence to guidelines. 12.4% of newly diagnosed CD patients had at least 1 non-diagnostic gastroscopy in the 5 years prior to diagnosis. Changing biopsy technique to single bites resulted in improvement of median D2 biopsies from 3 to 4. \(p 0.02\).

Discussion/Conclusion: We have shown that 12.4% of patients with CD had a previous gastroscopy 5 years prior to their diagnosis. Taking 4 duodenal biopsies results in increased detection of CD. We are the first investigators to demonstrate that there is variation in biopsy rates based on the speciality of the endoscopist and
biopsy technique (single or double bite). Furthermore this variability has a direct relationship with the detection rate of CD. Education of all groups of clinicians in duodenal biopsy techniques may result in more patients receiving a prompt diagnosis of CD.
Predicting histological remission in patients with coeliac disease on a gluten-free diet

Peter D. Mooney, Matthew Kurien, Simon Wong, David S. Sanders
Royal Hallamshire Hospital, Sheffield, UK

Introduction: Up to 30% of patients with coeliac disease will have persistent symptoms despite the introduction of a gluten-free diet. Assessment of adherence in coeliac disease can involve any combination of patient self-reporting adherence, dietetic assessment, serology and biopsy with histology. Histology is considered to be the 'gold standard' but this requires a repeat endoscopic examination with its associated risks and problems with tolerance. As a result surrogate markers of persistent gluten exposure and histological changes such as serology are frequently used but the relationship between serology and persistent histological changes is not linear. A structured interview with a dietician has been shown to be the most accurate method of assessing gluten exposure however this is time consuming and requires extra clinic visits. The aim of this study was to assess the usefulness of two novel options. Firstly a previously internally validated scoring system for assessing dietary adherence (which has never been externally validated) and secondly a rapid de-amidated gliadin peptide based point of care test (POCT, Simtomax) for the prediction of persistent VA.

Methods: All patients with known coeliac disease and persistent symptoms coming to a specialist coeliac endoscopy list for the re-assessment of histology were invited to take part. All patients were tested for Endomysial Antibody (EMA), tissue transglutaminase (tTG), immunoglobulins and the POCT. They were also asked to complete a questionnaire to calculate a 5 point score (0–4) with a high score representative of improved adherence to a gluten-free diet. All patients underwent gastroscopy with at least 4 biopsies from the second part of the duodenum and 1 to 2 biopsies from the bulb.

Results: 60 patients (78% female, mean age 51.4 range 16–79) were recruited between April 2013 and April 2014. 22 (36.7%) of these patients had persistent VA on duodenal biopsy. The POCT was the most sensitive marker with 73% of patients with VA having a positive test. EMA was the most specific surrogate marker at 84% although it was highly insensitive with only 36% of patients with VA having a positive EMA. No patients with completely normalised histology had a positive EMA. The adherence score could not be reliably used to predict villous atrophy with a sensitivity of only 32%.

<table>
<thead>
<tr>
<th>Marsh Score</th>
<th>Adherence Score</th>
<th>tTG +ve</th>
<th>tTG -ve</th>
<th>EMA +ve</th>
<th>EMA -ve</th>
<th>POCT +ve</th>
<th>POCT -ve</th>
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<tr>
<td>3a–3c</td>
<td>0–2</td>
<td>7</td>
<td>12</td>
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<tr>
<td>Adherence Score</td>
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<td>82%</td>
<td>50%</td>
<td>67%</td>
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<td>tTG</td>
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<td>57%</td>
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<tr>
<td>POCT</td>
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<td>66%</td>
<td>55%</td>
<td>81%</td>
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**Discussion/Conclusion:** Currently a duodenal biopsy is the best method for assessing adherence to a gluten-free diet and may help to risk stratify patient’s long term risk of complications. An accurate surrogate marker could reduce the number of endoscopies required however none of the methods assessed for the prediction of persistent VA could be reliably used to replace duodenal biopsy in assessing remission in coeliac disease.
Is a gluten challenge required to diagnose adult coeliac disease in equivocal cases: A single centre experience of “real” clinical practice

Peter D. Mooney, Suneil Raju, David S. Sanders
Royal Hallamshire Hospital, Sheffield, UK

Introduction: Coeliac disease (CD) is under diagnosed which may result in significant morbidity. The gold standard for diagnosing CD is the demonstration of villous atrophy. However in some cases there is a strong suspicion of CD but histology is normal or equivocal. In these cases the gold standard is a 6 week gluten challenge and repeat duodenal biopsy. To date there is little clinical data reported in the adult literature for outcomes or effectiveness of a gluten challenge outside of research studies. This study aims to determine the clinical utility of gluten challenge and predictive factors that could be used to aid diagnosis.

Methods: We undertook a prospective analysis of all patients who were asked to undertake a gluten challenge over a 5 year period. Data were recorded from referral to outcome. Presenting characteristics, baseline haematinics, tissue trans-glutaminase (tTG) and endomysial antibody (EMA) and HLA type were recorded prior to gluten challenge. Repeat coeliac serology and biopsy results were then recorded post gluten challenge. CD diagnosis required an appropriate HLA phenotype, positive coeliac serology and deterioration in duodenal histology

Results: 64 patients (46 female, mean age 48.8, SD 16.5) were reviewed. 4 (6.3%) declined gluten challenge. 42/60 (70.0%) of patients challenged were HLA DQ2 or DQ8 positive (6 homozygous). 21/60 (35.0%) patients were diagnosed with CD and 32/60 (53.3%) had CD excluded. 7/60 (11.7%) patients were diagnosed with potential CD based on an HLA type compatible with CD and positive serology but a normal duodenal biopsy on gluten challenge.

6/60 (10%) were unable to complete the full 6 week challenge (median 14.5 days) due to gluten induced symptoms. A conclusive diagnosis was made in all 6 of these patients.

Gluten challenge caused an increase in tissue tTG of 50.6% (p = 0.034) in patients with CD. No cut off for tTG prior to gluten challenge could be used to diagnose CD. Of 30 EMA negative patients prior to endoscopy 6 (20%) became positive on gluten challenge all of whom were diagnosed with CD. A combination of tTG > 20 times the upper limit of normal and a positive EMA prior to challenge (n = 7) had a positive predictive value of 85.7%.

There was no difference in presenting characteristics, baseline bloods or demographics between those diagnosed with CD, potential CD or those who had CD ruled out.

Discussion/Conclusion: No presenting characteristics, blood results or genotype could reliably predict a diagnosis of CD. Increased tTG or new EMA positivity on gluten challenge were associated with CD diagnosis. A gluten challenge will ensure
the best chance of recognition or exclusion of patients with CD. A 2 week gluten challenge may be sufficient to make conclusive diagnosis. A shortened gluten challenge could reduce the length of distress to patients with significant gluten induced symptoms and ensure prompt diagnosis.
Do patients with lactose maldigestion tolerate small amounts of lactose?

Radislav Nakov, Ventsislav Nakov, Borislav Vladimirov, Vanya Gerova
Clinical Center of Gastroenterology, University Hospital Queen Joanna, Medical University of Sofia, Bulgaria

Introduction: Lactose maldigestion (lactase deficiency) can be primary, secondary and congenital. Genetically determined reduction of lactase activity occurs after weaning in most of the mammals. Congenital lactose maldigestion is a very rare, autosomal recessive genetic disorder that prevents lactase expression from birth. Secondary lactose maldigestion is caused by an injury to the small intestine (celiac disease, intestinal inflammation, resection, etc.). The frequency of lactase deficiency in Europe is between 11 and 60%. Our aim is to investigate patients with diagnosed lactose deficiency, using small amounts of lactose when performing hydrogen breath test (HBT) and to assess the persistence or absence of clinical symptoms.

Methods: This study enrolled 17 patients with clinically manifestated lactose maldigestion (10 females and 7 males; age range 20–66; median 41.2). Diagnosis was made with 25 g lactose HBT, preceded by 15 ml lactulose HBT that excluded small intestinal bacterial overgrowth and determined the orocaecal transit time. HBT with small amount of lactose (0.5 g) was performed a few days later.

Results: The patients with lactase deficiency had level of hydrogen above 20 ppm (or methane above 12 ppm) over the lowest preceding value within the test period (90–150 min) when 25 g lactose HBT was used. Moreover, they had symptoms as bloating, colicky abdominal pain, diarrhea. When HBT with 0.5 g lactose was performed, the initial values did not change with more than ± 2 ppm for the test period. In addition, the patients did not experience any symptoms.

Discussion/Conclusion: In conclusion the results of our study demonstrate that the intake of small amounts of lactose do not lead to clinical manifestation and to positive HBT in patients with diagnosed lactose maldigestion.
Identifying fructose malabsorption in patients with irritable bowel syndrome by hydrogen breath test

Ventsislav Nakov, Radislav Nakov, Vanya Gerova, Borislav Vladimirov
Clinical Center of Gastroenterology, University Hospital Queen Joanna, Medical University of Sofia, Bulgaria

Introduction: The aim of this study was to investigate the diagnostic value of the hydrogen breath test as a non-invasive method proving the presence of fructose malabsorption (FM) in patients with irritable bowel syndrome (IBS).

Methods: Thirty-eight patients with IBS and 10 healthy controls were enrolled. The diagnosis was made on the basis of Rome III criteria. HBT was conducted with a breath gas analyzer. The fructose HBT (FHB T) was considered as positive for FM when there was an increase in hydrogen concentrations of more than 20 ppm above the basal value and an appearance of symptoms after the intake of 15 g fructose, both occurring at about 60 min after starting the test.

Results: All the controls had negative FHB T. Moreover, they had not any complaints during the test. In 7 of the IBS patients (18.4%) FHB T was positive. The rest 31 patients had negative test. The patients with positive FHB T had an appearance of gastrointestinal symptoms shortly before or during the values of exhaled hydrogen rose.

Discussion/Conclusion: In conclusion, we believe that the hydrogen breath test is easy to perform and not cumbersome method for identifying FM. Because of the accurate selection of patients and the maximum exclusion of false positive results, the obtained data are lower than currently reported in the world’s literature. Future studies and mostly testing of large groups of healthy, asymptomatic individuals, especially monitoring the effects of dietary restriction on identified FM will answer the following questions: is FM more common in IBS, do some individuals actually have just FM, without IBS and will their symptoms disappear completely when limiting the intake of free fructose.
Anemia in celiac disease children: Iron deficiency and high serum hepcidin

N. Narinskaya, S. Belmer, E. Mitina, N. Smetanina, L. Karpina
Pirogov Russian National Research Medical University, Russia, Moscow

Introduction: Anemia is the frequent symptom of celiac disease (CD) due to iron malabsorption and/or proinflammatory cytokines synthesis. Aim of our study was to evaluate mechanisms of development of anemia in children with CD.

Methods: We collected hematologic parameters from a group of 29 children (1.2–8 years old) with typical CD, including serum iron and ferritin levels, total serum iron-binding capacity (TSIBC). Serum hepcidin, interleukin-6 (IL6), interleukin-2 (IL2) and tumor necrosis factor alpha (TNFα) levels were also measured.

Results: Anemia was diagnosed in 11 of 29 untreated CD children. Serum iron was low (7.5 ± 1.6 μmol/l vs. reference value (RF) of 12.33 ± 1.68 μmol/l, p < 0.05), TSIBC was high (69.6 ± 2.5 μmol/l vs. RF of 58.62 ± 2.28 μmol/l, p < 0.01), serum ferritin was low (9.6 ± 2.0 ng/ml vs. RF of 20.09 ± 3.18 ng/ml, p < 0.05) in untreated CD children. We found also high serum hepcidin (80.1 ± 7.32 ng/ml vs. RF of 21.66 ± 4.51 ng/ml, p < 0.01). The serum IL2, IL6 and TNFα were increased respectively in 48% (14/29), 41% (12/29) and 55% (16/29) of untreated celiac patients. The IL6 level correlated negatively (Pearson’s correlation coefficient) with serum iron (R = -0.334; p < 0.001) and serum ferritin (R = -0.612, p < 0.05), but no correlations with hepcidin were observed. In 11 of 13 children hematologic parameters improved following 6 month of a gluten-free diet (in 9 cases with iron donation). We also noted a trend to decrease in cytokines levels, but reduction in serum hepcidin were observed in 5 from 7 children only.

Discussion/Conclusion: Proinflammatory cytokines and iron deficiency plays an important role in the development of anemia in children with CD. We propose the direct role of IL6 on iron homeostasis control in addition to hepcidin-depended pathway.
Success and time course of reaching the therapeutic goals with a gluten-free diet in coeliac disease: A prospective five-year study from diagnosis

E.D. Newnham¹, S.J. Shepherd¹, P. Hosking², B. Strauss and P.R. Gibson³
¹Monash University, Eastern Health Clinical School, Melbourne, Australia; ²Department of Pathology, Eastern Health; ³Monash University, Central Clinical School, Alfred Health, Melbourne, VIC, Australia

Introduction: It is intuitive that the primary aim of treatment should be resolution of the intestinal pathology and that healing should result in improvements in bone mineralisation, body composition, and nutrition. This prospective 5-year study aimed to determine the degree of success and time course of achieving those goals with a gluten-free diet (GFD).

Methods: 99 patients were enrolled at diagnosis and taught the gluten-free diet (GFD) by a specialist dietitian. The first 57 were reassessed at one year and 46 at 5 years, 25 being assessed at the three time points. Assessment included dietary compliance (dietitian-assessed), coeliac serology (tissue transglutaminase IgA, tTG), bone mineral density (BMD) and body composition analysis by DEXA, and histology of small bowel biopsies.

Results: The population studied had a mean age of 39.7 (range 18–71) years, 48 (76%) being female. Compliance was judged as very good to excellent in all but one. Persistently elevated tTG were noted in 23 (44%) at one and 14 (30%) at five years. Rates of mucosal remission (Marsh 0) and response (Marsh 1 or better) were 37% (19/57) and 54% (28/57) at one year and 50% (23/46) and 85% (39/46) at 5 years, respectively. Coeliac antibodies were poorly predictive of mucosal disease activity (PPV 63 [95% CI: 41–81], NPV 35 [18–54] at one year; PPV 26 [10–48], NPV 78 [56–93] at 5 years). Compared with indices at diagnosis, weight and body mass index (BMI) increased between baseline and 12 months (by mean 3.0 kg and 0.9 kg/m² respectively) and between 12 months and 5 years (by 0.5 kg and 0.4 kg/m²). Increases in per cent body fat (by 2.6%) and fat mass (by 4.8 kg) occurred only in the first year, while increased fat-free mass (FFM) (by 2.9 kg) and skeletal muscle mass (SMM) (0.9 kg) were only observed at 5 y (all changes p < 0.001; paired t test). Increases in fat mass were found only in those with BMI < 25, but increases in skeletal mass were unrelated to prediagnosis body habitus. BMD increased only in the first year of treatment and only in those with osteopenia or osteoporosis (by 65 [30–101] vs. -11 [-36–13] g; p < 0.0001).

Discussion/Conclusion: Strict compliance with a GFD is associated with a very high chance of healing the intestinal lesion and correction of specific abnormalities in body composition. The time course of changes differed with BMD, fat mass and per cent body fat improving rapidly (within one year) and correction of the mucosal lesion, FFM and SMM taking longer. Coeliac serology is a poor predictor of the state of the duodenal mucosa. Thus, strict adherence to the GFD will not only heal the intestinal mucosa, but will have healing effects on body composition.
Dental status in celiac disease

Liudmila Oreshko, Larisa Deryabina, Stanislav Sitkin
I.I. Mechnikov North-Western State Medical University, St. Petersburg, Russia

Introduction: Celiac disease is characterized by the malabsorption syndrome, which is accompanied with the violation of parietal digestion and absorption of nutrients in the small intestine. Although in recent years celiac disease may progress without striking clinical manifestations, and the number of patients are without diarrhea and steatorrhea, symptoms of the mineral and vitamin deficiency are often observed in patients with celiac disease. It is known that the level of mineral components in the body determines the mineralization of the teeth and their lack adversely affects the condition of the teeth and surrounding bone tissue. In the case of structural inadequacy of enamel and dentin and high resistance of periodontal tissue the pathological abrasion of teeth takes place, in the case of the normal morphological structure of the enamel and the dentin reduced tolerance periodontal tissues lesions begins. The foregoing indicates the necessity to perform the research of this category of patients. The aim of this study was to evaluate the condition of the teeth and tooth enamel in patients with celiac disease.

Methods: 16 patients with celiac disease, proved by positive results of clinical and anamnestic methods, upper-endoscopy, histology of duodenum biopsy specimens and HLA-typing, were observed. The age of the patients ranged from 24 to 54 years. Patients had gastric and intestinal dyspepsia complaints: nausea, belching, heartburn, bloating, flatulence and abdominal pain.

Results: Pathological abrasion of the tooth enamel took place in 100% of observed persons. According to A.L. Krasovskii classification the horizontal form of increased tooth abrasion was identified in 14 patients, the front form – in 2 patients, herewith the first degree of enamel abrasion was determined in 11 patients, the second degree of enamel abrasion – in 5 patients. The tooth crowding was revealed in 5 patients, which was attributed to the dental signs of connective tissue dysplasia and was combined with other signs of connective tissue dysplasia in these patients. The partial edentulous was diagnosed in 2 patients. The secondary edentulous was identified in one patient with the malabsorption syndrome. The signs of periodontal disease were observed in 2 patients. The hygienic status of the patient’s dentition was assessed as satisfactory.

Discussion/Conclusion: Thus, the revealed dentition anomalies in patients with celiac disease dictate the necessity of the selection of this category of patients in outpatient group to observe and provide highly specialized dental care.
The value of endoscopic features in celiac disease

Department of Gastroenterology, Habib Thameur Hospital, Tunis, Tunisia

Introduction: Celiac disease, also known as gluten-sensitive enteropathy, is increasingly recognized worldwide. Although earlier studies have focused on endoscopic markers as predictors of celiac disease, there are still no certainties about the value of these markers.

In a retrospective cohort study, we assessed the relationship between endoscopic features and the age of patients at the time of diagnosis, the clinical form of the disease and the histological damage in patients with celiac disease.

Methods: All the patients underwent upper gastrointestinal endoscopy. Endoscopic markers for celiac disease were documented and duodenal biopsies were obtained from the second part of the duodenum and from the duodenal bulb when it had a micronodular appearance. We devised our own grading system for the endoscopic appearance of the duodenum, which ranged from “normal” appearance to “mild”, “moderate”, or “severe” alterations. The histopathological findings were expressed according to modified Marsh classification. The diagnosis of celiac disease was based on abnormal duodenal histology and positive serology.

Results: We studied the endoscopic features of newly diagnosed celiac disease in 86 consecutive adult patients (mean age 26 years, range 18–63 years). Seventy-one had the classical form of the disease, 4 the subclinical and 11 the silent form.

A normal endoscopic appearance in the duodenum was found in 11/86 patients (12.8%). Endoscopic features suggestive of CD were observed in 75 (87.2%) patients. The most commonly seen markers were a mosaic pattern mucosa and scalloping of duodenal folds. Moderate and severe alterations were seen respectively in 57 and 18 patients. Normal appearance of the duodenum as well as mild damage seen at endoscopy were associated with a low histological grading (Marsh I, II, IIIa), p = 9.10^{-3}, while severe endoscopic damage was related to a Marsh IIIb-IIIc-IV grading. However, there wasn’t a relationship between the endoscopic appearance and neither the age (p = 0.48) of the patients nor the clinical form (p = 0.84).

Discussion/Conclusion: This study showed that the endoscopic appearance of the duodenum may be predictive of histological damage grading.
Biochemical, structural, immunological characterization and IgE epitope mapping of an important wheat food allergen, Tri a 37

Sandra Pahr1,2, Regina Selb3, Claudia Constantin1, Milena Weber1, Margit Focke-Tejkl1, Gerhard Hofer4, Andela Dordić4, Walter Keller4, Nikolaos G. Papadopoulos5, Stavroula Giavi5, Mika Mäkelä6, Anna Pelkonen6, Irene Mittermann1,2, Verena Niederberger3, Susanne Vrtala1,2, Rudolf Valenta1

1Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center of Pathophysiology, Infectiology and Immunology, Medical University of Vienna
2Christian Doppler Laboratory for the Development of Allergen Chips, Medical University of Vienna, Austria
3Department of ENT, Medical University of Vienna, Vienna
4Institute of Molecular Biosciences, Karl-Franzens University Graz, Graz, Austria
5Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece
6Skin and Allergy Hospital, Helsinki University Central Hospital, Helsinki, Finland

Introduction: Wheat is an important staple food that can cause IgE-mediated food allergy. Recently, we identified Tri a 37 as a new wheat food allergen. IgE recognition of Tri a 37 was found to be responsible for severe allergic reactions to wheat-containing products. The purpose of our study was the recombinant expression of Tri a 37 in two different expression systems and their characterization regarding molecular, structural and immunological properties. Furthermore, we aimed to characterize relevant epitopes of Tri a 37 and to evaluate antibody responses.

Methods: Recombinant Tri a 37 was expressed in a prokaryotic expression system using E.coli cells and in a eukaryotic expression system using baculovirus-infected insect cells, purified to homogeneity and characterized by means of SDS-PAGE, mass spectrometry, circular dichroism, chemical crosslinking, non-denaturing RAST-based binding assays and competition ELISA. Five overlapping peptides were synthesized and used for epitope mapping. Tri a 37-specific rabbit antibodies were raised to perform inhibition experiments and to study its resistance to digestion.

Results: Tri a 37 expressed in the prokaryotic system (EcTri a 37) was unfolded whereas when using the eukaryotic expression system, we obtained an α-helically folded protein (BvTri a 37). In non-denaturing RAST-based experiments, both allergens showed comparable IgE-reactivity. IgE and IgG epitope mapping using synthetic peptides revealed that Tri a 37 contains sequential epitopes.

Discussion/Conclusion: Since major IgE epitopes of Tri a 37 are sequential epitopes both recombinant allergen versions can be used for the in-vitro diagnosis of severe wheat food allergy.
Yield of double balloon enteroscopy in the investigation of possible or recurrent Crohn’s disease

Clare Parker¹, Rachael Perowne¹, David Nylander², Simon Panter¹
¹South Tyneside District General Hospital, South Shields, UK
²Royal Victoria Infirmary, Newcastle upon Tyne, UK

Introduction: An audit of the use of Double Balloon Enteroscopy (DBE) to investigate Crohn’s disease at our hospital was performed.

Methods: Records of patients attending for DBE were reviewed and those referred with suspected or known CD were identified and further information was gathered.

Results: 46 DBE’s have been performed on 42 patients, 20/42 were referred for investigation of possible or known CD. 5 had known CD, 15 were suspected CD.

5 with known CD had abnormal imaging:
- 3/5 imaging suggested a stricture and all had abnormal DBE.
- 2/5 cases had a normal DBE, (imaging suggested inflammation)

15 patients were referred with suspected CD:
- 2/15 both imaging and capsule endoscopy (CE) were normal and DBE was performed due to symptoms- DBE normal.
- 4/15 had abnormal CE– DBE was abnormal and confirmed CD in 2/4, and in other 2/4 bidirectional DBE was normal (suspicion that the abnormal area not reached).
- 9/15 had abnormal capsule and/or abnormal radiology: 2/9 had abnormal CE with normal radiology and normal DBE; 6/9 had abnormal radiology, 4 of these had abnormal DBE; 1/9 had abnormal capsule and abnormal imaging with abnormal DBE.
- 6/15 possible CD patients were definitively diagnosed with CD on the basis of DBE findings and histology and in 50% of patients DBE informed a change in management.

Discussion/Conclusion: Our findings suggest that DBE is a useful tool in the evaluation of patients with suspected or known Crohn’s disease. It appears to add little to the management of those who have symptoms/biochemical abnormalities alone. Our findings would suggest that DBE is a valuable tool in assisting in management in those with known Crohn’s disease with possible recurrence or strictureing and also appears to be of benefit in the confirming the diagnosis of Crohn’s disease especially in those with abnormal radiological imaging.
Improvement of gastrointestinal symptoms and motility in non-celiac gluten-sensitive patients after the gluten-free diet

Maria Ines Pinto-Sanchez¹, Daniel Basra¹, Justin McCarville¹, Yikang Deng¹, Suzanne Hansen¹, Andrea Nardelli¹, Sonia Niveloni², Edgardo Smecuol², David Armstrong¹, Paul Moayyedi¹, Julio C. Bai², Elena F. Verdu¹, Premysl Bercik¹
¹McMaster University, Hamilton, ON, Canada
²Hospital de Gastroenterología B. Udaondo, Buenos Aires, Argentina

Introduction: Gastrointestinal (GI) dysmotility is common in celiac patients and improves after gluten-free diet (GFD). Non-celiac gluten sensitivity (NCGS) is a reaction to gluten in which allergic and autoimmune mechanisms have been excluded. Its pathophysiology is poorly understood but previous studies showed that gliadin triggers intestinal hypercontractility and cholinergic nerve dysfunction in gluten-sensitive mice. Here, we evaluate GI symptoms and motility before and after GFD in patients with NCGS.

Methods: NCGS was defined by GI symptoms (Rome-III criteria), normal duodenal biopsy (Marsh 0–I), negative IgA anti-tissue transglutaminase (TTG) and positive anti-gliadin antibodies (IgA/IgG-AGA). HLA-DQ2/DQ8 status was determined but did not constitute inclusion criteria. Symptomatic and functional assessments were performed before and after 1-month of GFD. The following questionnaires were used: Birmingham-Bristol scale and GSRS (GI symptoms), HAD scores (anxiety/depression), PHQ-15 (somatic symptoms) and DQESV2 (dietary habits). Gastric emptying and intestinal transit were studied by videofluoroscopy and SHAPE-study, respectively. Fecal microbiota was analysed by 16S rRNA-based Illumina. A dietician assessed GFD compliance.

Results: Eleven NCGS patients were enrolled (Median age 36.5; 8 female). Five patients initially presented with slow, 4 with accelerated, and 2 with normal intestinal transit. Six patients (4 slow and 2 accelerated transit) normalized transit scores after GFD. Overall GI symptoms improved after GFD, particularly indigestion. Anxiety, depression and somatization scores decreased while overall wellbeing improved, especially for positivity and vitality after GFD. This was accompanied by individual shifts in microbiota abundance, with overall mild decrease in Firmicutes/Bacteroidetes ratio.

Discussion/Conclusion: In patients with NCGS with positive AGA antibodies, GI motility was affected by GFD. One month after starting GFD, overall GI transit normalized in most patients along with improvement in GI symptoms, mood and wellbeing. In patients with NCGS, changes in GI motility may underlie symptomatic improvement after GFD and explain, in part, the microbiota shifts described.
Changes in claudins expression in celiac disease

A. Portyanko, J. Gorgun
Belarusian State Medical University, Belarusian Medical Academy of Postgraduate Education, Minsk, Belarus

Introduction: Claudins are the components of intercellular tight junctions regulating intestinal permeability. Gut permeability is increased in celiac disease (CD). The aim of the study was to clarify whether CD is associated with changes in claudins expression in duodenal mucosa.

Methods: Claudins -2, -3, -4, -7 and -15 were assessed immunohistochemically and by immunofluorescence in duodenal biopsy specimens from two groups of patients: 1) 14 normal controls with unremarkable duodenal mucosa, negative for AGA-IgA, AGA-IgG and anti-tTG-IgA; 2) 30 untreated CD-patients, positive for at least two of the above CD markers and HLA DQ2/DQ8 and having duodenal histology corresponding to Marsh IIIA-C; 15 from them were also assessed after gluten-free diet (GFD) period, median 13 months (95% CI: 9.0–16.0).

Results: In duodenal epithelium of CD patients, there was a significant reduction of apical membrane staining for claudin-2 (3.7% vs. 100%, p < 0.0001), decrease in membrane basolateral and perinuclear staining for claudin-4 (23.1% vs. 91.7%, p < 0.0001), decrease in membrane basolateral staining for claudin-3 (28.6% vs. 100%, p = 0.007), decrease in membrane basolateral staining for claudin-7 (38.5% vs. 78.6%, p = 0.022), increase in membrane apical and basolateral staining for claudin-15 (semiquantitative assessment, 2.0 (95% CI: 2.0–3.0) vs. 0.5 (95% CI: 0.0–1.0), p < 0.0001). We also revealed increase in claudin-2 expression in lamina propria in CD in relation to normal controls. After GFD, all changes in epithelial claudins expression restored, along with mucosa recovering, but increase in claudin-2 expression in lamina propria persisted. Double immunofluorescence staining with antibodies to claudin-2 and HLA-DR revealed colocalization of both molecules and confirmed expression of claudin-2 in antigen-presenting cells.

Discussion/Conclusion: Untreated CD is associated with decrease in epithelial expression of claudins-2, -3, -4 and -7 and increase in claudin-15, which are reversible on GFD and seem to be secondary to the mucosal atrophy. Lamina propria macrophages, expressing claudin-2, can be involved in CD pathogenesis.
Newly diagnosed pediatric celiac patients in the last five years. A single center experience

Maria Rogalidou¹, Theodoros Palianopoulos¹, Anna Challa², Konstantinos Katsanos³, Dimitrios Christodoulou³, Nikolaos Tzbouras³, Gerasimos Baltayannis³, Eleni Loutsi¹, Meropi Tzoufi¹, Epameinondas Tsianos³, Antigoni Siamopoulou-Mavridou¹

¹Pediatric-Gastroenterology Unit, Pediatrics Department, University Hospital of Ioannina, Greece
²Child Health Department, University of Ioannina, Medical School
³Division of Gastroenterology, University of Ioannina, Greece

Introduction: The prevalence of celiac disease in Greece was estimated (1:500) of population. According new studies the prevalence of celiac disease is higher than previously thought (1:154) reaching the prevalence observed in many other European countries. Aim of our study was to analyze the epidemiological data of pediatric patients diagnosed with celiac disease (CD) in our department during the last five years.

Methods: Medical charts of children diagnosed with celiac disease between January 2009 and January 2014 were collected. Diagnosis, age sex, symptoms and data from investigations made were recorded.

Results: 17 new patients aged 1.75–13.9 (mean age 6.6) years, were diagnosed during this period. The majority of patients were between at 10–50th centile for weight and 50–75th for height. Main presenting symptoms were failure to thrive, diarrhoea, constipation and intermittent abdominal pain. One patient presented intermittent intussusception. Interestingly 9 patients were asymptomatic. Main laboratory finding was low ferritin levels without anaemia. The age at diagnosis, sex, presenting symptoms, celiac antibodies and histological findings appear in table I.

<table>
<thead>
<tr>
<th>Table I</th>
<th>N</th>
<th>Age</th>
<th>Presentation</th>
<th>Antibodies</th>
<th>Histological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>boys</td>
<td>6</td>
<td>1.75–12.3 y mean 4.9 y</td>
<td>GI symptoms &amp; FFT 3/6 2/6 Diabetes (IMDD) 1 screening</td>
<td>EMA (+) 4/6 DGP (+) 5/6 tTG (+) 6/6</td>
<td>Marsh 3a 2/6 Marsh 3b 2/6 Marsh 3c 2/6</td>
</tr>
<tr>
<td>girls</td>
<td>11</td>
<td>2–13.9 y mean 7.6 y</td>
<td>GI symptoms &amp; FFT 5/11 1/11 Diabetes (IMDD) 1/11 Autoimm. Thyroiditis 1/11 screening 1/11 (+ Family history) 2/11 Hypertransaminasaimia</td>
<td>EMA (+) 10/11 DGP (+) 6/11 tTG (+) 11/11</td>
<td>Marsh 3a 1/11 Marsh 3b 1/11 Marsh 3c 9/11</td>
</tr>
</tbody>
</table>

Discussion/Conclusion: In our population 52% of patients with celiac disease were asymptomatic. 47% presented with mild gastrointestinal symptoms. High suspicion and early investigation can increase the diagnosis of Celiac disease. More studies needed to estimate the increased incidence of CD in our region.
**Toxoplasma gondii** infection may have a role in the histopathology of celiac disease

Mohammad Rostami Nejad\(^1\), Kamran Rostami\(^2\), Seyed Hossein Hejazi\(^3\), Koroush Cheraghipour\(^3\), Mohammad Amin Pourhoseingholi\(^1\), Somayeh Jahani-Sherafat\(^1\), Mohammad Reza Zali\(^1\)

\(^1\)Celiac disease Department, Gastroenterology and Liver Diseases Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
\(^2\)Gastroenterology Department, Worcestershire Royal Hospital, Worcester, UK
\(^3\)Parasitology and Mycology department, Isfahan University of Medical Sciences, Isfahan, Iran

**Introduction:** *Toxoplasma gondii* infection has been implicated in the pathogenesis of many autoimmune diseases such as celiac disease (CD) and detected using the immunoglobulin IgG and IgM antibodies. In the present article we examined the association between infection with *Toxoplasma gondii* and severity in mucosal damage of celiac disease patients.

**Methods:** During 2013, sera of 150 patients diagnosed with CD were analyzed by ELISA for the presence of antibodies specific for *Toxoplasma gondii* (IgG and IgM) and titers above 10 were considered positive. Then the severity in mucosal damage of celiac disease patients was compared in those who were positive or negative for *Toxoplasma gondii*.

**Results:** High levels of IgG antibodies against *T. gondii* were found in the sera of CD patients (52.6%). Among the CD sero-positive subjects, predominant gastrointestinal symptoms were bloating (70%) and weight loss (64.7%). By comparing the level of anti-*T. gondii* IgG and mucosal damage in celiac disease, we found significant relationship between the severity of mucosal damages and anti-*T. gondii* IgG \((p = 0.02)\). Patients with severe mucosal damage such as Marsh IIIc had higher antibody levels than patients with less severe mucosal damage such as Marsh I and II.

**Discussion/Conclusion:** Our results imply that Toxoplasmosis may generate an immunological environment that disfavors future appearance of certain autoimmune conditions such as celiac disease. In conclusion this association with *T. gondii* will result in a more severe mucosal abnormality in coeliac disease.
The influence of the prebiotic “Zacol NMX®” on molecular pathways in celiac disease

Dr. I. Sarvilina
Medical Centre “Novomedititsina”, Rostov-on-Don, Russia

Introduction: this study is aimed at researching the influence of the “Zacol NMX®” (calcium salt of butyric acid – 250 mg, inulin – 250 mg) on molecular pathways in CD.

Methods: 23 adult patients with CD (HLA-DQ2, n = 23; HLA-DQ8, n = 18) were included in the study (37–48 years old, female – 15, male – 8). Serum samples were analyzed for IgA – tTG. Small bowel biopsy was performed by endoscopically, mucosal specimens were light-microscopically graded according to Marsh: II (n = 10), III A (n = 7), IIIB (n = 6). Patients were on GFD, treated with pancreatin, folic acid, ferrous sulfate during 3 years (T-CD). “Zacol NMX®” 3 times a day was taken for 6 months in the 3rd year (Z-T-CD). Additional methods: culture-dependent methods, capillary gas-liquid chromatography, DNA-PCR analysis, 2DE/MALDI-TOF-TOF-MS. Control group – 10 healthy people. "Statistica 12.0" was applied.

Results: all patients had high level of serum IgA- tTG. The reduction of symptoms was noticed in 19 Z-T-CD. Escherichia coli, E. faecium, Bacteroides spp. was lower and Bifidobacterium spp., L. plantarum, L. casei, L. rhamnosus was higher on faecal samples of Z-T-CD compared to T-CD patients and control. The reduction of the acetic, i-caproic acids concentratons and increase of n-butyrate concentration in faecal samples of Z-T-CD were noticed. The increase of the expression of RBP4, PPAR γ, β2-glycoprotein 1, vitronectin and the decrease of kininogen-1, serum amyloid P in serum were revealed in Z-T-CD.

Discussion/Conclusion: “Zacol NMX®” effects on molecular pathways of CD: PPAR signalling, transport vitamin A, complement pathway, c-Jun and STATs pathway. Molecular effects of the prebiotic were associated with the recovery of the protective and aggressive bacteria ratio and the increase of butyric acid in fecal samples.
Reduced T cell receptor variability in refractory celiac disease type II as revealed by next generation sequencing

M. Schumann¹, J. Ritter¹, K. Zimmermann¹, B. Siegmund¹, A. Rosenwald², M. Hummel¹, S. Daum¹
¹Departments of Gastroenterology and Pathology, Charité, Berlin, Germany; ²Institute of Pathology, University of Würzburg, Würzburg, Germany

Introduction: Refractory celiac disease (RCD) is a Marsh III enteropathy with accompanying malabsorption in spite of stringent gluten-free diet (GFD) for > 1 year. Contrary to type-I RCD, a clonal T cell population builds up in type-II RCD and develops further to overt T cell lymphoma in a high percentage of cases. In most institutions, diagnostics to differentiate the two subtypes is based on Genescan technology determining fragment sizes of PCR-amplified T cell receptor (TCR) DNA sequences and immunohistology. However, “oligoclonality” and “pseudoclonality” are frequently found in Genescans and add to a specificity problem. Moreover, the sequences of the variable regions of the involved TCRs are unknown.

Methods: Determination of the T cell repertoire of duodenal mucosa by multiplex PCR of TCRβ-CDR3 regions. Next generation sequencing (NGS, Illumina HiSeq 2000) of amplicons in controls, active celiacs (ACD), celiacs with GFD, unclassified Marsh I cases, RCD type-I and RCD type-II.

Results: On average, $10^6$ sequences per sample were analyzed, yielding ~1000 TCR rearrangements. Clonotypes were defined as identical sequences of CDR3 amplicons. Averaging all RCD type-II, the most frequent clonotype was 52.5% of all clonotypes per sample, which was significantly higher than in controls (16.7%; p < 0.01) or RCD type-I (17.3%; p < 0.001; cut-off > 0.5%). ACD revealed a non-significant tendency towards a higher frequency. The technique was validated by identifying the same top clonotypes in various individuals receiving two examinations months apart. Alignments of high frequency clonotype sequences (HFCS) with CDR3 motifs found in the literature (mainly DQ2-restricted) did not show significant homology. Interestingly, HFCS of individual RCD II patients did not reveal cross-homology, arguing against specific TCR motifs in RCD II pathophysiology.

Discussion/Conclusion: TCRβ-NGS-analysis reproducibly detects monoclonal T cell populations in RCD-II. The TCR-CDR3-HFCS in RCD-II are not previously described, gliadin-associated TCR sequences, which might explain their potential to expand gliadin-independently.
Refractory celiac disease: A case of the untimely and late recognized disease

D. Seleznev, E. Ivanova, E. Tikhomirova, E. Fedorov
Moscow University Hospital №31, Medical Rehabilitation Center "Klinika+31", Endoscopy Department, Moscow, Russia

Introduction: Refractory celiac disease is an inflammatory disease of small bowel which is rare and associated with a higher risk of serious complications and mortality.

Methods: From 14.02.2007 until 01.05.2014 we performed 366 single- and double-balloon enteroscopies. In surgical department celiac disease is a rare medical condition and we’ve got just 3 (0.8%) histologically confirmed cases. One of the cases we was faced with a refractory celiac disease. A 41-year-old woman with suspected diagnosis of lymphoproliferative disease of small intestine admitted to our Hospital for the small bowel examination. The patient complained of severe diarrhea, abdominal pain, weakness, unexplained weight loss, anemia, nausea. She had got such complains 6 months and was twice hospitalized for the general assessment because of deterioration in condition. Recommended gluten-free diet and conservative therapy (infusion therapy, spasmolytics, albumin, prednisolone) was with no evidence of a positive effect. Status of the patient progressively worsened, joined with a massive edema of the lower limbs and back, hypoalbuminemia (21 g/l). The diagnosis was unclear.

Results: In our Hospital capsule endoscopy was performed. According to the results we suspected celiac disease and besides there were multiple ulcerative lesions over a length of small bowel. A peroral single-balloon enteroscopy was performed next and total ulcerative enteritis was detected on the background of villous atrophy. Multiple biopsies confirmed celiac disease (Marsh stage 3) and ulcerative enteritis. Immunohistochemical study, which we performed for the avoidance of T-cell lymphoma, showed no data for lymphoproliferative disease. After the diagnosis of refractory celiac disease the patient was remitted to a specialised hospital where in spite of the massive drug treatments, nutrition, prednisolone, etc. the disease was complicated with progressive multi-organ failure, severe malnutrition and deep venous thrombosis that led the patient to death.

Discussion/Conclusion: This case demonstrates the difficulties of diagnosis of refractory celiac disease. Novel endoscopic techniques are available to visualize the entire small bowel mucosa and allow to make precise diagnosis but to avoid complications enteroscopy should be made timely.
Gut microbiome differences in celiac disease patients, first-degree relatives and effect of gluten-free diet

Sudarshan A. Shetty¹, Dhiraj P. Dhotre¹, Khushboo Bhatia², Anil K. Verma², Asha Mishra², Gurvinder Kaur², Vineet Ahuja², Govind K. Makharia², Yogesh S. Shouche¹

¹Microbial Culture Collection, National Centre for Cell Science, Pune, India
²Department of Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, New Delhi, India

Introduction: While recent studies have suggested imbalance in gut microbiome in patients with celiac disease (CeD), the comprehensive understanding of the community level dysbiosis and dysfunction in the gut microbiome is lacking. We investigated the gut microbiome (both the small intestinal and fecal microbiome) in patients with CeD (both before and after six months of gluten-free diet), first-degree relatives (FDRs) and non-CeD controls.

Methods: The 16S rRNA gene (V3 region) amplicon sequencing of the gDNA extracted from duodenal biopsies and fecal samples (Whole gut) of treatment naïve celiac disease (TnCeD) and 6-month after gluten-free diet (CeD on GFD), FDRs, and non-CeD controls (DC) was done using Illumina HiSeq2000. Metagenomes for identified microbial operational taxonomic units were imputed using PICRUSt, and were analyzed using STAMP.

Results: The gut microbiome composition and structure was different in CeD patients (both before and after GFD), FDRs, and DC. The microbiome of TnCeD had a higher abundance of pathogenic pro-inflammatory bacteria from the family Enterobacteriaceae. However, after six months of gluten-free diet, increase in species richness was observed with concomitant reduction in abundance of pathogenic bacteria. The FDRs microbiome was characterized by significant abundance of Bifidobacteriaceae. The imputed metagenome revealed higher virulence genes and anti-oxidative stress response pathways in TnCeD compared to FDRs and controls. Additionally, the FDRs had a higher abundance of metabolic pathway for vitamins and co-factors, especially riboflavin metabolism.

Conclusion: Patients with CeD are characterized by a dysbiotic gut microbiome compared to FDRs that is enriched constitutionally in pathogenic bacteria and functionally in virulence genes and oxidative response pathways. The significant abundance of beneficial bacteria i.e. Bifidobacteriaceae suggest a potential protective role in genetically susceptible individuals. The observation of differences in the gut microbiome composition and function is intriguing and warrants further functional investigations.
Celiac disease in women with infertility: A meta-analysis

Prashant Singh¹, Shubangi Arora², Tor A. Strand³, Govind K. Makharia²
¹Department of Medicine, Massachusetts General Hospital, Boston, MA, USA; ²Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi India; ³Centre for International Health, University of Bergen, Bergen, Norway

Introduction: Celiac disease (CeD) is now known to be a systemic disease with manifestations not limited to small intestine. The data on association between CeD and infertility is contradictory. Neither gynecological societies nor gastroenterological societies have provided any recommendation for the screening of female patients with infertility for CeD. We, therefore conducted a meta-analysis of available studies to find out if women with infertility are at higher risk of CeD.

Methodology: We searched Medline, Pubmed and directory of open access journals using the MeSH keyowrds “celiac disease” “gluten” and “infertility”. Diagnosis of CeD was based on positive serology and duodenal biopsy showing villous atrophy. Data was extracted about CeD patients in each of three groups – women with infertility (including unexplained infertility), unexplained infertile and controls. Pooled odds ratio (OR) and prevalence, with 95% confidence intervals (CI), were calculated.

Results: Of available 105 relevant studies, six studies which met required inclusion and exclusion criteria were included for calculation of pooled OR. Four additional studies, where data on controls was not available, were also considered for calculation of pooled prevalence of CeD in women with infertility. Women with infertility had 4.6 times higher odds of having CeD in comparison to that in control population (OR = 4.6, 95% CI: 2.2–9.7; p < 0.001). Similarly, women with unexplained infertility also had six times higher odds of having CeD in comparison to control population (OR = 6, 95% CI: 2.4–14.6). Of total 1084 women with infertility, 26 had CeD indicating a pooled prevalence of CeD to be 2.4% (95% CI: 1.6–3.5). Of 623 women with unexplained infertility, 20 had CeD. The pooled prevalence of CeD in women with unexplained infertility was 3.2 (95% CI: 2–4.9). There was no evidence of publication bias.

Conclusion: Women with infertility are at higher risk of CeD and they should be screened for CeD.
Serum metabolome in celiac disease is influenced by gut microbiota

Stanislav Sitkin, Evgenii Tkachenko, Liudmila Oreshko
I.I. Mechnikov North-Western State Medical University, St. Petersburg, Russia

Introduction: Celiac disease is caused by an abnormal immune reaction to the dietary gluten and primarily affects the small intestine. Gut microbiota is involved in the development and maintenance of autoimmune inflammation in celiac disease. Gas chromatography-mass spectrometry (GC-MS) of serum generates comprehensive metabolic profiles, reflecting integrated human (systemic) and gut microbial metabolism which may be altered in disease. The aim of this study was to evaluate the effect of an oral butyrate plus inulin on GC-MS-based serum metabolome and gut microbiota features using quantitative real-time polymerase chain reaction (qRT-PCR) in celiac disease patients and healthy controls.

Methods: Serum metabolomic profiles and faecal samples were collected from 35 celiac disease patients and matched healthy controls. ROC curve analysis, principal components analysis (PCA) and other methods were used to identify of biomarkers and to assess differences between groups. The quantitative real-time polymerase chain reaction (qRT-PCR) was used for quantitative faecal microbiota assessment.

Results: We characterized 84 serum metabolites by use GC-MS and multivariate analysis to differentiate between diseased and non-diseased individuals. 18 metabolites at least have a combined (human + microbial) origin. Serum of celiac disease patients showed significant increases in 3-indolyacetic acid (IAA), 3-indolepropionic acid (IPA), benzoic acid, succinic acid (SA) and fumaric acid (FA). Differences in some serum metabolites levels in celiac disease patients and controls may indicate the difference in the metabolic activity of gut microbiota (some Clostridia and Bacteroides spp., Eggerthella lenta, etc.) involved in metabolism of bioactive compounds (e.g. in phenylalanine and tyrosine metabolism). Oral butyrate plus inulin (Zacofalk® NMX, Dr. Falk Pharma GmbH, 3 tablets per day for 4 weeks) as supplement to gluten-free diet (GFD) was effective in an improvement of symptoms, serum metabolomic profiles and gut microbiota (including reduction of Bacteroides fragilis/Faecalibacterium prausnitzii ratio and rising of butyrate-producing bacteria pool) in celiac disease. There were no any adverse events.

Discussion/Conclusion: Oral butyrate plus inulin can be effective therapeutic option in celiac disease, improving symptoms, serum metabolomic profile and gut microbiota composition. Quantitative metabolomic profiling of serum using GC-MS discriminates between celiac disease patients and healthy controls.
The role of endothelial dysfunction and lipid peroxidation in pathogenesis of the enteropathy in diabetes mellitus type 2 patients

I.N. Skrypnyk, G.S. Maslova, Y.A. Mandryka
Ukrainian Medical Stomatological Academy, Poltava, Ukraine

The formation and progression of enteropathy on the background of the insulin-independent diabetes mellitus (DM) type 2 are associated with the combination of injuring factors, first of all, intestinal dysbiosis and diabetic autonomic neuropathy with the development of gastrointestinal motor-evacuation function dyscoordination. However, some pathogenetic mechanisms of DM type 2 and enteropathy combinations are studied insufficiently.

The aim was to determine the endothelial dysfunction and lipid peroxidation role in the enteropathy development in DM type 2 patients.

Materials and methods: The study involved 74 enteropathy patients with DM type 2, including 41 (55.4%) women, 33 (44.6%) men, the mean age 56.4 ± 9.8 years and the duration of DM type 2 was 7–10 years. The DM type 2 was in subcompensation phase: the level of HbA1c ≤ 7.5% without ketoacidosis. To correct carbohydrate metabolism patients received combined glucose-lowering therapy. The level of nitrite, the total nitric oxide synthase (NO-synthase) activity, the malonaldehyde (MDA) and the catalase were determined in the blood serum.

The enteropathy with the obstipation syndrome was diagnosed in 49 (66.2%) patients with DM (group I); with the diarrhea syndrome – in 25 (33.8%) (group II).

Results: The imbalance of the free radicals generation and their inactivation was noticed in patients with DM type 2 in combination with enteropathy: increased concentration of the MDA in groups I and II in 1.2 and 1.4 times respectively, while reducing the catalase activity in 1.3 times (p < 0.05). The reduction of the nitrite concentration in 1.48 times in blood serum of group II patients was detected on the background of increased in 1.6 times (p < 0.05) total NO-synthase activity, with a tendency to change these parameters in patients of group I. The increase in the total production of NO-synthase, primarily inducible, promotes the high-power NO release, with its metabolism in an aggressive free radical – peroxynitrite, which has a direct damaging effect on the organism.

Conclusion: DM type 2 associated with the reduction of endothelial NO-synthase, leading to a decrease production of NO in the vascular endothelium, including the intestinal mucosa, which can be considered as a risk factor for enteropathy. The maximum lipid peroxidation processes activity and endothelial dysfunction in DM type 2 is noticed on the background of enteropathy proceeding with the diarrhea syndrome.
Duodenal nodularity in pediatric patients: Histopathological study of 15 cases

Maria E. Sobaniec-Lotowska¹, Joanna M. Lotowska², Sylwia B. Lotowska³, Elżbieta Jarocka-Cyrta⁴
¹Department of Medical Pathomorphology, ²Department of General Pathomorphology, Medical University of Bialystok, ³Department of Laboratory Diagnostics, Maria Sklodowska-Curie Memorial Bialystok Oncology Center, Bialystok, ⁴Department of Pediatrics, Gastroenterology and Allergology, Medical University of Bialystok, Poland

Introduction: Duodenal nodularity is defined as an uncommon endoscopic appearance of numerous discrete, 0.2–0.5 cm in diameter, visible mucosal nodules in the proximal part of the duodenum. The exact etiology of this pathology has not been explained yet. The main aim of our retrospective study was to determine histopathological features of duodenal nodularity in pediatric patients.

Methods: Histopathological reports of biopsies assessed in the Department of Medical Pathomorphology, Medical University of Bialystok, collected from 15 patients with duodenal nodularity diagnosed by upper endoscopy, aged 6–18 years, were reviewed. The biopsies were taken from the nodular areas of the duodenum and from antral mucosa by biopsy forceps. Clinical symptoms were also considered.

Results: In the group of 15 patients with endoscopically defined duodenal nodularity (including 8 cases within the age range of 6–12 years and 7 cases at the age of 13–18 years), there were 8 males and 7 females. Abdominal pain (47.3%) was the most common clinical symptom and antral nodularity (42.6%) was the most common endoscopic finding in patients with duodenal nodularity. Histopathological assessment of duodenal nodules revealed variously pronounced chronic inflammation, ranging from mild to severe in all the study children, an increased number of eosinophils in the intercryptal and intraepithelial area in 73.3%, varying degrees of villous atrophy in 47.3%, and coexistence with Helicobacter pylori positive gastritis in 37.2% of cases. In seven biopsies, in cases with severe chronic inflammatory infiltration, hyperplastic lymphoid follicles were found that were suggestive of nodular lymphoid hyperplasia.

Discussion/Conclusion: Our study revealed that although the endoscopic patterns of duodenal nodularity are alike, pathologic features are not so similar. Thus, there are no specific histopathological findings for this nodular pattern. The major morphological indices of this pathology included a prominent inflammatory reaction in duodenal mucosa manifesting itself as increased lymphocyte and/or eosinophil infiltration, which suggests that duodenal inflammation is the cause.
Celiac disease overlap with Whipple’s disease and Crohn’s disease

Miglena Stamboliyska, Diana Gancheva, Lily Grudeva, Maria Atanassova, Avgustina Georgieva, Iskren Kotzev
Clinic of Gastroenterology, Hepatology and Nutrition, St. Marina University Hospital of Varna, Varna, Bulgaria

Introduction: The combination of various rare diseases in one the same patient is a rare occurrence. A clinical case with a combination of three relatively rare diseases of the gastrointestinal tract such as celiac, Whipple’s and Crohn’s disease was presented.

Methods: Upper endoscopy with morphology and assessment for antitransglutaminase and antigliadine antibodies, a Helicobacter pylori was performed.

Results: A 56-year-old female patient complained of diarrhoea (up to 15 defecations daily), without any pathological secretions. There was weight reduction by about 25 kg. A gluten enteropathy was diagnosed in childhood. She was on gluten-free diet for a certain time that was ceased after the achieved improvement of her status. In 2012, because of the diarrhea, antitransglutaminase and antigliadine antibodies were examined that proved positive. That was why the aforementioned diet therapy was repeated. Additional examinations demonstrated Helicobacter pylori-positive chronic pangastritis, chronic duodenitis and PAS-positive inclusions. There was evidence of Whipple’s disease. There were lesions along the ileum and colon suggesting terminal ileitis and Crohn’s disease based on the pathohistological findings. The antibiotic therapy included doxycycline (two tablets daily), Salofalk® in a routine dosage, and Budenfalk® in a dosage of 3 capsels daily. After six months, the patients did not complain anymore. She presented with normal stool and normalized weight. The control examination established negative values of antitransglutaminase and antigliadine antibodies, a Helicobacter pylori-negative slight gastritis, slight chronic duodenitis and no PAS-positive inclusions. There were no lesions along the gastrointestinal tract. The treatment with doxycycline and Salofalk® continued for additional six months. Patient’s quality of life improved.

Conclusion: Probably, the long-lasting chronic autoimmune inflammation of the small intestine like celiac disease represented a predisposition for the overlap of the other autoimmune and infectious-autoimmune diseases such as Whipple’s and Crohn’s disease. The correct diagnostic and therapeutic approach warranted the successful solution of this difficult clinical problem.
Beneficial opportunities of the "deep" enteroscopy in diagnosis of inflammatory bowel disease

E. Tikhomirova, E. Ivanova, D. Seleznev, E. Fedorov
Moscow University Hospital №31, Medical Rehabilitation Center "Klinika+31", Endoscopy Department, Moscow, Russia

Introduction: Capsule endoscopy and balloon-assisted enteroscopy (BAE) have made a great contribution in precise diagnostics of small bowel diseases and created the conditions for differential diagnostics with other diseases. The aim of the study is to estimate the benefits of BAE in precise diagnostics of inflammatory bowel diseases (IBD).

Methods: From II.2007 till V.2014 we’ve performed 366 BAE in 319 patients. Indication for small bowel examination in 76 (23.8%) patients was suspected IBD, in 129 (40.4%) patients small bowel bleeding, in 66 (20.7%) patients tumors, in 48 (15.0%) patients others. The signs of enteritis were revealed in 77 (24.1%) patients during BAE, including 46 (59.7%) patients from those with suspected IBD and 31 (40.3%) patients with suspected tumor or small bowel bleeding. For precise diagnosis biopsy was performed in 61 (79.2%) of 77 patients. We also launched EUS in 6 patients, using long mini-probes for the small bowel wall assessment.

Results: According to histology results the diagnosis of IBD was confirmed in 46 (59.7%) patients: chronic enteritis in 11 (23.9%) patients, erosive enteritis in 6 (13.0%) patients, eosinofic enteritis in 4 (8.7%) patients, exudative enteropathy in 3 (6.5%) patients, celiac disease in 3 (6.5%) patients, radiation enteritis in 2 (4.3%) patients, primary intestinal lymphangiectasia in 1 (2.2%) patient. Crohn’s disease was diagnosed according endoscopic criteria in 16 (34.8%) patients, according to morphology Langhans giant cells were detected in 5 (31.2%) patients. During EUS there was thickening of the wall up to 6 mm in 2 patients with Crohn’s disease while in the other 4 patients with erosions and ulcers the wall was normal – less than 4 mm. Endoscopic treatment – balloon-dilatation (1) and dilation by the scope (5) was performed in 6 patients with the radiation enteritis and Crohn’s disease.

Discussion/Conclusion: Balloon-assisted enteroscopy gives all the opportunities for precise diagnostics of IBD and in some cases it helps to provide treatment. Small bowel EUS in IBD patients might be useful and needs more clinical experience.
Evaluation of osteoporosis with bone densitometry findings in celiac patients

Firdevs Topal, Zehra Akpinar, Elif Saritas Yuksel, Fatih Aslan, Sezgin Vatansever, Belkis Unsal
Katip Celebi University, Izmir Ataturk Training and Research Hospital, Izmir, Turkey

Introduction: Celiac disease (CD) is a chronic inflammatory disease of the small intestine derived in genetically disposed patients after exposure to gluten in diet. Decrease in bone mineral density (BMD) due to vitamin D and calcium malabsorption can be seen. In this study we evaluated the rate of osteoporosis in our adult CD patients.

Methods: Between January 2009–April 2014, data of biopsy proven 94 patients with CD were included to the study. Demographic features, body mass index (BMI), duration of disease, serum calcium levels and T scores of bone densitometry for lumbar spine and femur neck were recorded.

Results: There were 94 patients (64 F/30 M, age 40.4 ± 12.8 years). Average value for serum calcium was 9.0 g/dl, 15 patients had hypocalcaemia. Bone densitometry revealed mean T scores -1.06 and -1.51 for lumbar and femur neck, respectively. Average BMI was 22.5. BMI was > 25 in 22 patients and < 18.5 in 19 patients. 27 patients had osteoporosis. The presence of osteoporosis was not related to BMI, duration of disease or serum calcium levels, but osteoporosis increased with age and was more often seen in females (p < 0.05).

Discussion/Conclusion: CD osteopenia and osteoporosis can be seen. It has been even been suggested that the decrease in BMD can be seen before villous atrophy. The decrease in BMD can be secondary to hyperparathyroidism, malabsorption, cytokine activity and can improve with gluten-free diet (GFD) but the risk of fracture can last for years after introducing GFD. In addition it is known that obesity can occur despite GFD. In our patient population strict adherence to diet is low. Presence of anemia, hypocalcaemia, osteoporosis and positive serology can be signs for low adherence to diet when there is no marked clinical signs. Follow-up for nutritional status after diagnosis should be provided.
Celiac disease metabonomics using NMR spectroscopy

Deepti Upadhyay\(^1\), Uma Sharma\(^1\), Sujeet Mewar\(^1\), Asha Mishra, Prasenjit Das\(^2\), Siddhartha Datta Gupta, Govind K. Makharia\(^3\), Naranamangalam R. Jagannathan\(^1\)
Departments of NMR & MRI Facility\(^1\), Pathology\(^2\) and Department of Gastroenterology & Human Nutrition\(^3\), All India Institute of Medical Sciences, New Delhi, India

**Introduction**: Recently a characteristic spectrum of metabolic profile in urine and plasma has been identified in patients with CeD using proton (\(^1\)H) magnetic resonance spectroscopy. Although the main site of the disease in CeD is small intestinal mucosa, the metabolic profile in the small intestinal mucosa is not well known. Therefore, we assessed complete metabolic profile of duodenal mucosal biopsies in patients with CeD and controls using in-vitro \(^1\)H NMR spectroscopy and multivariate analysis to find out the metabolic signature/s and a biomarker for villous atrophy in these patients.

**Methods**: The small intestinal mucosal biopsies were collected from CeD patients (\(n = 35\); mean age 25.9 ± 10.6 years) and controls (\(n = 31\); mean 34.4 ± 10.1 years) and subjected to high resolution \(^1\)H NMR spectroscopy at 700 MHz following perchloric acid extraction. All NMR spectra were phased, baseline corrected and segmented into regions of 0.02 width in the region of 0.5 ppm–9.5 ppm. Assignment of resonances was carried out and their concentrations were determined. Multivariate analysis was applied to determine the metabolic signature of disease.

**Results**: Partial least square discriminant analysis (PLS-DA) exhibited clear distinction between CeD patients and diseased controls. The separation between two groups was due to differences in the variables such as lactate, valine, alanine, acetate, arginine, glucose, succinate and tryptophan. These alterations in metabolites in intestinal mucosa suggest abnormalities in energy metabolic pathways (glycolysis and Kreb’s cycle) and amino acid metabolism, which may affect the biosynthetic pathways and consequently may contribute to villous abnormalities that seen in patients with CeD.

**Discussion/Conclusion**: NMR spectroscopy with multivariate analysis revealed a characteristic metabolic signature for the diagnosis of CeD. This study provides an insight into biochemical changes that occur in intestinal mucosa and has a potential in identifying a biomarker for villous atrophy in patients with CeD.
Prevalence of celiac disease in adult type 1 diabetics

O. Uygur-Bayramici1, B. Dogan2, C. Öner3, E. Yorulmaz4, G. Feyizoglu5, A. Oguz6
1Istanbul Maltepe University Goztepe, Department of Gastroenterology
2Istanbul Medeniyet University Goztepe Training and Research Hospital, Family Medicine Clinic
3Istanbul Bilim University, Department of Family Medicine
4Istanbul Bağcılar Education and Research Hospital, Department of Gastroenterology
5Istanbul Medeniyet University Goztepe Training and Research Hospital, Diabetes Nursing Department of Internal Medicine
6Istanbul Medeniyet University Goztepe Training and Research Hospital, Department of Internal Medicine, Istanbul, Turkey

Introduction: Celiac disease (CD), an autoimmune disease, was related with immune mediated intolerance to gluten. In Turkey it was estimated that the prevalence of CD was 1:87 (1.2%). Recent studies reveal that 1–8% of the type 1 diabetics have CD (7–9). A study conducted in Turkey found CD prevalence in adult type 1 diabetes as 6%. The objective of our study was to evaluate the prevalence of celiac disease in hospital based type 1 diabetic adults.

Material and method: Our study was carried out retrospectively in Medeniyet University Göztepe Training and Educational Hospital in Istanbul between 2012–2013. The cohort composed of 482 type 1 diabetic patients (264 males and 218 females) attending the diabetes outpatient clinic. The records of patients were evaluated. The data were analyzed by SPSS 10.5 package programme. The t test used for comparative analyses. A p value less than 0.05 was considered statistically significant.

Results: The cohort includes 482 type 1 diabetic patients. 57 of them were not evaluated for anti EMA positivity. 15 of the remaining 425 patients were positive for anti endomysial antibody (3.5%). 1 of the patients do not anti EMA positivity but she is symptomatic for celiac disease. 14 patients underwent upper gastrointestinal endoscopy and distal duodenal biopsies are taken. Morphologic changes were consistent with celiac disease in 10 of them. Duodenal biopsy samples of these patients revealed grade 3a in 6 patients and 3b in 4 patients according to modified Marsh classification. The prevalence of biopsy proven celiac disease was 2.3% (10/425).

Conclusion: This study confirms that the celiac disease is common in type 1 diabetics. The prevalence of celiac disease among low risk populations was 1–1.3% (13,14). Since a small proportion of celiac patients are symptomatic this disorder should be screened in all adult type 1 diabetics by antiendomysium antibody.
Isolation of fecal bacteria degrading gluten at acidic pH

A. Valery1, G. Wei1, D. Schuppan2,3, E.J. Helmerhorst1
1Department of Molecular and Cell Biology, Boston University Henry M. Goldman School of Dental Medicine, Boston, MA, USA; 2Celiac Center, Beth Israel Deaconess Medical Center, Boston, MA, USA; 3Institute of Translational Immunology and Research Center for Immunotherapy (FZI), University Medical Center, Mainz, Germany

Introduction: Celiac disease is a chronic inflammatory disorder of the small intestine characterized by an aberrant immune response to gluten proteins (primarily gliadins) in genetically predisposed individuals. Gluten proteins are rich in proline and glutamine residues, and certain immunogenic domains are highly resistant to degradation by human digestive enzymes. We have previously shown that gluten-degrading microbes naturally colonize the oral cavity. Since the distal region of the human gastrointestinal tract harbors more microbes than any other body compartment, the aim of the present study was to isolate gluten-degrading bacteria from human feces, whereby we focused on bacteria with activities at acidic pH that would be able to digest gluten in the upper GI tract.

Methods: Aliquots of human fecal samples were collected under aseptic conditions from 3 healthy human subjects, diluted in sterile PBS and plated on gluten-limited agars adjusted to pH 4.0 and 7.0. Colonies were subcultured to purity on blood agar. Enzyme activities towards gliadins were determined in gel (zymography) and in solution at pH 2.0, 4.0, and 7.0.

Results: A total of 278 fecal strains were isolated of which 43 showed evidence for gliadin-degrading enzymes with prominent activities in the ~150–250 kDa region. Select strains exhibited activities in gel from pH 2.0–7.0, and in solution from pH 4.0–7.0. Speciation by 16S rDNA analysis revealed that all those strains belonged to the same species.

Discussion/Conclusion: Using gluten agars with pH values adjusted to near gastric values, low pH active gluten-degrading microorganisms were successfully isolated. Gluten-degrading enzymes with a low pH activity profile are of interest to be further exploited in the treatment of celiac disease. These studies were supported by NIH/NIAID grants AI087803, AI101067, and by a grant from the FZI.
Serological update on celiac disease diagnostics

Tsvetelina Velikova¹, Zoya Spassova², Kalina Toumangelova-Yuzeir¹, Ekaterina Ivanova-Todorova¹, Dobroslav Kyurkchiev¹, Iskra Altankova³
¹University Hospital St. Ivan Rilski, Department of Clinical Laboratory and Clinical Immunology - Medical University, Sofia, Bulgaria
²Clinic of Gastroenterology, University Hospital St. Ivan Rilski, Medical University, Sofia, Bulgaria
³University Hospital Lozenets, Sofia University, Sofia, Bulgaria

Introduction: Celiac disease (CeD) is an inflammatory disorder of the small intestines which serological diagnosis has come to the forefront with the development of the immunological testing. Our aim was to explore the performance characteristics of a panel of serological tests in patients with CeD.

Methods: We collected serum samples of 35 newly diagnosed adult patients with biopsy proven CeD at mean age 41 ± 3 years and 25 age- and sex-matched healthy persons. We assessed the serum levels of anti-tissue transglutaminase (anti-tTG), anti-deamidated gliadin peptides (anti-DGP), anti-actin (AAA), anti-gliadin antibodies (AGA) and cytokine IL-17A by performing ELISA (IgA+IgG); and anti-tTG, AGA and anti-Sacharomyces cerevisiae antibodies (ASCA) by immunoblot (IgG). We also followed-up 12 of the CeD patients for changes in anti-tTG and anti-DGP levels after gluten-free diet (GFD).

Results: Anti-DGP antibodies showed highest diagnostic sensitivity (100%), followed by AGA and anti-tTG antibodies within the CeD group. The average serum levels of anti-tTG, anti-DGP, AGA, AAA and ASCA were at significantly higher levels in patients with CeD compared to average levels in healthy persons, which stayed below the cut-off value (p < 0.001). ROC curve analysis revealed the excellent performance of anti-DGP, anti-tTG and AGA in diagnosis of CeD patients (AUC 1.000, 0.994, 0.992 respectively, p < 0.001). We found also that the cytokine IL-17A is higher in patients with no decrease of antibodies after at least 3 months of GFD compared to patients with decreased antibodies after GFD.

Discussion/Conclusion: Despite the diagnosis of CeD relays on biopsy, immunological parameters could be employed with advantages in diagnosis and monitoring of CeD patients. The role of IL-17A in CeD pathogenesis is still debated and open to investigation, but we could speculate that IL-17A may be involved in refractory celiac disease and could be used as prognostic factor for GFD response in these patients.
Introduction: Celiac disease (CD) is a common autoimmune disorder with a prevalence of 1% in western population. CD is frequently associated with other conditions and nongastrointestinal manifestations.

Methods: To determine demographic and clinical features of patients with CD in Carinthian region (Northeast Slovenia). Medical documentation of 38 consecutive patients (all Slovene, Caucasians) with confirmed CD was analyzed. Following data were determined: gender, age, mean time from confirmation of diagnosis, monitoring the response to a gluten-free diet (GFD) with serologic testing, consultation with a skilled dietitian including education about the disease, nutritional deficiencies, concomitant diseases, access to an advocacy group and screening of family members.

Results: There were 38 patients: 28 (73.7%) female and 10 (26.3%) male, mean age 41.8 ± 12.0 years (range 18–70).
Mean time from diagnosis of CD was 5.9 ± 3.5 years (range 1–23).
All patients were monitoring the response to a gluten-free diet with serologic testing: 4 patients (10.5%) had positive IgA tissue transglutaminase (TTG) due to the non-compliance.
All patients on GFD (24 out of 28 = 85.7%) were in clinical remission (without gastrointestinal symptoms).
Thirty-three patients (86.8%) had consultation with a skilled dietitian including education about the disease.
Nutritional deficiencies were found in following percentages: vitamin D 76.3%, iron 18.2%, ionized calcium 2.8% and folate 5.7%.
Concomitant diseases were found in following percentages: lactose intolerance 60.7%, osteopenia/osteoporosis 45.5%, skin disorders 13.2%, pancreatic exocrine insufficiency 8.8%, microscopic colitis 5.3% and Hashimoto thyroiditis 5.3%.
All patients were advised to join the support group (Slovene Celiac Society).
Screening of family members were advised in all patients and CD was found in close relatives in 6 families (15.8%).

Discussion/Conclusion: Vitamin D deficiency is most common nutritional deficiency in patients with CD.
Lactose intolerance is most common concomitant disease in patients with CD.
All patients with good compliance (on GFD) are currently without gastrointestinal complaints.
Prevalence of celiac disease among patients with type 1 diabetes mellitus

Miroslav Vujasinovic¹, Bojan Tepes², Jelka Zalete³, Betka Popic¹, Jana Makuc¹, Lenart Metka Epsek¹, Marjana Predikaka¹
¹Department of Internal Medicine; Slovenj Gradec General Hospital, Gosposvetska 1, 2380 Slovenj Gradec, Slovenia
²Abakus Medico Diagnostic Centre, Prvomajska 29, 3250 Rogaska Slatina, Slovenia
³Department of Endocrinology, Diabetes and Metabolic Diseases, University Medical Centre Ljubljana, Zaloska 7, 1000 Ljubljana, Slovenia

Introduction: Celiac disease (CD) is a systemic immune-mediated disorder triggered by dietary gluten in genetically susceptible persons. It affects 0.6 to 1.0% of the population worldwide. CD is one of the most frequent autoimmune disorders occurring in Type 1 diabetes mellitus (T1DM). HLA class II molecules DQ8 and DQ2 have been identified as key genetic risk factors in both diseases. The prevalence of CD in T1DM varies in different studies – from 2.6% to 13.8%.

Methods: To determine prevalence of CD among patients with T1DM in carinthian region (Northeastern Slovenia). Forty-four eligible consecutive patients with T1DM were included in the study. Diagnosis of T1DM was established from health records. Diagnosis of CD was established by IgA tissue transglutaminase antibodies (IgAtTg). Data are shown as numerous (%) and mean ± standard deviation.

Results: Forty-four consecutive patients with T1DM have been screened for CD. There were 20 (45.5%) female and 24 (54.5%) male, mean age 47.3 ± 12.5 years. Three patients (6.8%) had positive IgAtTg (6.8%).

Discussion/Conclusion: Study confirmed a high prevalence of CD in adult patients with T1DM. Our data is comparable with results of similar studies around the world. Because of the high association between these two diseases, screening for CD in T1DM patients is recommended.
The concentration of calprotectin in the stools of children with diagnosed cystic fibrosis

Sabina Więcek, Halina Woś, Bożena Kordys-Darmolińska, Magda Sankiewicz-Szkolka, Urszula Grzybowska-Chlebowczyk
Department of Paediatrics, Medical University of Silesia, Katowice, Poland

Calprotectin is a protein which plays a regulatory role in inflammatory reactions as an antibacterial and antiproliferative factor. As it has chemokine-like properties it stimulates neutrophils and the production of IL-8 and is an acknowledged marker that an inflammatory process in course.

The aim of the study is to assess the concentration of calprotectin in the stools of patients with diagnosed cystic fibrosis.

Patients and method: 41 patients were included in the study, 24 boys (58.8%) and 17 girls (41.5%) aged from 7 weeks to 18 years (the average was 4 years old). Two subgroups were created from the group of patients. Subgroup 1 (23/41–56.1%) was composed of patients with cystic fibrosis diagnosed following screening. Subgroup 2 included 18 children (18/41–43.9%) who were not subject to screening and their CF was concluded based on clinical symptoms and genetically confirmed. The concentration of calprotectin in stools was assessed with the ELISA method and using the Phical test (Calpro). The analysis included clinical symptoms and the results of laboratory tests involving the level of protein, aminotransferase, C-reactive protein, the stool’s acid steatocrit and the type of mutation. The obtained results were later statistically processed.

Results: An elevated level of calprotectin in the stool was observed in 4/41 (9.7%) patients with cystic fibrosis and delta F508/delta F508 mutation, mainly older children, aged over 10. The correlation between the concentration of calprotectin and clinical symptoms, age, increased indicators of an inflammatory process in the blood serum, the levels of protein and aminotransferases in blood serum and the values of acid steatocrit of the stool, was not proved.

Conclusions:
1. High concentrations of calprotectin in the stools of children with diagnosed cystic fibrosis do not correlate with the level of advancement of lesions within the gastrointestinal tract (the pancreas and the liver).
2. Elevated concentrations of calprotectin in the stools of patients with cystic fibrosis may indicate inflammation of intestine and should be further scrutinised.
Celiac disease accompanied by selective Ig A deficiency

Kemal Yıldız, Mukaddes Tozlu, Ali Tüzün İnce, Kürşad Türkdoğan, Hakan Şentürk
Bezmialem Foundation University Medical Faculty, Gastroenterology Department
İstanbul, Turkey

Introduction: Celiac disease is an enteropathy in which the immunologic response against gluten increases; which is particularly involved in proximal small intestine; and which causes malabsorption. Although the patients frequently apply for failure to thrive and growth retardation, puberty and neuropathy may also be observed. Besides, the reasons for application include iron deficiency anemia and elevated liver enzymes. Diagnosis is made by serologic tests (anti endomysium Ig A-G, anti tissue transglutaminase Ig A–G) and histopathology findings. Despite the fact that histopathology supports celiac disease in patients with Ig A deficiency, however, the antibody can be negative. Here, the phenomenon in which Anti gliadin, anti endomysium and anti tissue transglutaminase are negative due to selective Ig A deficiency, but that we have diagnosed with celiac disease, will be presented.

Case: A 20-year-old woman patient. She has been suffering from diarrhea attacks and failure to thrive since her childhood, and has received iron replacement treatment frequently within this period due to anemia. It was detected in the physical examination of the patient, whose sister was also learned to have anemia and growth retardation, that her weight was 38 kg, her height was 150 cm, her BMI was 16.8 as well as she had finger clubbing and 2 cm of hepatomegaly. The laboratory analysis demonstrated the following: leukocytes: 6950/mm^3, hematocrits: 27.9%, blood platelets: 332,000/mm^3; and that hypochromic microcytic erythrocyte was detected in peripheral smear. Creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), total bilirubin, total protein, albumin, prothrombin time, INR, iron, total iron binding capacity (TIBC) and ferritin was detected to be 0.5 mg/dl, 124 U/l, 103 U/l, 0.33 mg/dl, 6.1 g/dl, 2.5 g/d, 16.1 sec, 1.29, 38 ug/dl, 196 ug/dl and 17.5 ng/ml, respectively. Hepatomegaly and grade 1 hepatosteatosis were noted in abdominal ultrasonography. At serologic tests; Ig A < 20 mg/dl was detected to be low, which was checked after detection of Anti gliadin IgG as (+), Anti gliadin IgA as (-), Anti endomysium IgG as (+), Anti endomysium IgA as (-), Tissue transglutaminase IgG as (+), Tissue transglutaminase IgA as (-). At her gastroscopy, gastric mucosa was observed to be pale, to have a nodular appearance in antrum, to have a edema at 2nd part of duodenum and to be faint. As the result of the biopsy from duodenum, villous atrophy and intraepithelial lymphocytosis were detected. The patient was diagnosed with celiac disease accompanied by selective Ig A deficiency, and a diet without gluten started. The patient started to gain weight at her visits, while iron deficiency anemia was also observed to improve.

Conclusion: At our case; it was detected by the serologic tests (i.e. Anti gliadin, Anti endomysium and tissue transglutaminase) in a patient with the symptoms and signs of celiac disease that Ig G was (+) and Ig A was (-). Selective Ig A deficiency may accompany in about 3% of patients with celiac disease, though rare, and is required to be confirmed with biopsy if clinical and laboratory suspect continues in patients with antibody negative.
Is anemia and hypocalcaemia related to duration of disease and body mass index in celiac disease patients?

Elif Sarıtaş Yüksel, Zehra Akpinar, Firdevs Topal, Sezgin Vatansever, Fatih Aslan, Belkis Ünsal
Katip Celebi University, Izmir Ataturk Training and Research Hospital, Izmir, Turkey

Introduction: Celiac disease (CD) is an enteropathy causing malabsorption. Weight loss, anemia and osteoporosis due to hypocalcaemia can be seen in these patients and can be the presenting sign. The aim of this study is to evaluate whether levels of hemoglobin, iron and calcium correlate with duration of disease and body mass index (BMI) in adult CD patients.

Methods: Demographic features, levels of hemoglobin, iron and calcium, BMI values and duration of disease were recorded in 117 biopsy proven adult CD patients. Hemoglobin values < 12 g/dl, serum calcium < 8.5 mg/dl, serum iron < 50 mg/dl, BMI < 20 and > 30 were accepted pathologic. Correlation analysis was done and p < 0.05 was accepted as statistically significant.

Results: A total of 117 patients (38 M/79 F) with mean age 39.1 ± 14.0 years were included into the study. In 38 patients (32.5%) hemoglobin, in 40 patients (34.2%) calcium, in 71 patients (60.7%) serum iron levels were found pathologic. BMI was < 20 in 27 (23.1%), > 30 in 10 (8.5%) patients. No correlation could be found with calcium levels and other parameters. Although there was no correlation between hemoglobin and iron levels with age, gender and BMI a negative correlation was found with duration of disease.

Discussion/Conclusion: Villous atrophy and signs of malnutrition improves with gluten-free diet (GFD). It is hard to stick to a completely GFD, intake of some gluten may continue; the tolerable amount differs in each patient. A partial villous atrophy which does not cause diarrhea or decrease in calorie intake but interferes with absorption of trace elements due to this small intake may be a reason. Patients should be encouraged to stick to GFD also in absence of prominent symptoms and supportive treatment can be given when needed.
Dyspepsia in patients with retroperitoneal non-organic tumors

A. Yusupbekov, J. Hadjimatova
Tashkent City Cancer Centre, Tashkent Paediatric Medical Institute, Republican Research Institute of Medical Rehabilitation and Physiotherapies, Tashkent, Uzbekistan

The purpose: Study of denominated dyspepsia in patients with retroperitoneal non-organic tumors (RNT).

Stuff and methods: The study was in 187 patients with RNT, which was complex examined. So in 174 (94.0%) patients was established dyspepsia which was given by secondary functional violations under RNT. Herewith more denominated violations was in gastrointestinal tract organs (GIO) (67.8%) by comparison hepatopancreatobiliar system (HPBS) (31.2%). In 23.2% patients dyspepsia was arisen after invasion of RNT into this organ, and in other cases – was given by compression. In 43 (23.2%) with tumor invasion was performed combined surgery: extirpation of RNT + hemicolecotmy in 16, + small bowel resection – in 9, + sigmoid resection – in 5 and pancreatic resection – in 5.

Then dyspepsia was under mechanical compression of GIO or HPBS surgery was limited with tumour extirpation only and with conservative treatment. So in this full effect was determinate in 67.3%.

Conclusion: Our research was shown, that in patients with RNT dyspepsia was determinate in 94% cases. In RNT with invasion to GIO or HPBS good results was established by combined radical surgery. But in secondary functional violation of intestinal organs under RNT without germination reasonable tumor extirpation with drug correction of dyspepsia.
Alpha-amylase/trypsin inhibitors (ATIs), novel nutritionals triggers of innate immunity: Stimulatory effect in-vitro and in-vivo

Victor Zevallos¹, Muhammad Khan¹, Stefan Tenzer², Hansjörg Schild², Detlef Schuppan¹,³
¹Institute for Translational Immunology, Univ. Medical Center, Johannes Gutenberg University, Mainz, Germany
²Institute for Immunology, University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany
³Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Introduction: We have identified cereal alpha-amylase/trypsin inhibitors (ATIs), such as wheat CM3 and 0.19, as potent activators of innate immunity in celiac disease and likely other immune disease (Junker Y et al. 2012). Here, we determined the spectrum of ATI variants in various plants and foods and the innate stimulatory effects in-vitro and in-vivo.

Methods: ATIs were extracted using salt solutions and comparatively dialyzed against acidic and neutral buffers, sterile filtrated and lyophilized. Extracts were cultured with stable human cells lines, bone marrow derived dendritic and TLR4 transfected cells. ATIs were analyzed by Western-blotting, quantified by reverse phase (RP) HPLC and mass spectrometry. C57BL/6 mice received a single oral gavage of ATIs and expression of pro-inflammatory genes and immunohistochemical markers of myeloid inflammation were evaluated in the intestine (duodenum, jejunum and colon).

Results: We classified staple foods/plant seeds based on their relative potency to induce innate immune reactions. Modern gluten containing cereals (wheat, rye, barley) contained the highest amount of stimulatory ATIs and TLR4 activating bioactivity, being up to 100-fold higher than gluten-free staples/seeds (amaranth, corn, rice, oats). Transcript levels of inflammatory markers (MCP-1, IL-8, IFNγ and IL-6) in the intestine were significantly up-regulated after feeding ATIs to C57BL/6 mice kept on a gluten-free diet compared to mice fed with control protein (zein). F4/80 and CD68 positive macrophages were increased in the group gavaged with ATIs.

Discussion/Conclusion: ATIs from plants and food products can be extracted, quantified and their innate stimulatory activity measured using our bioassay. We can classify plants according to stimulatory activity. ATI activity was also confirmed in-vivo. The in-vitro and in-vivo stimulatory capacity of ATIs is by far highest in gluten containing cereals; ATIs appear to be a major nutritional trigger of innate immunity, with strong implications for celiac disease and related autoimmune disorders.
Isolation and partial purification of a low pH-active gluten-degrading enzyme from human fecal bacteria

Y. Zhong¹, G. Wei¹, A. Valery¹, D. Schuppan²,³, E.J. Helmerhorst¹
¹Department of Molecular and Cell Biology, Boston University Henry M. Goldman School of Dental Medicine, Boston, MA; ²Celiac Center, Beth Israel Deaconess Medical Center, Boston, MA, USA; ³Institute of Translational Immunology and Research Center for Immunotherapy (FZI), University Medical Center, Mainz, Germany

Introduction: Celiac disease is a T-cell mediated-inflammatory disorder of the small intestine caused by the ingestion of gluten-containing foods in genetically predisposed individuals. Gluten proteins are difficult to digest by mammalian digestive enzymes, resulting in immunogenic gluten domains causing intestinal inflammation. We have previously shown that gluten proteins are degraded by fecal microbial strain FA-10 at low pH, which would cause degradation before ingested gluten reaches the duodenum. We therefore aimed to isolate and purify the enzyme from strain FA-10.

Methods: Proteins in the culture supernatant of FA-10 were separated by DEAE and MonoQ chromatography. Enzymatic activities were monitored towards mixed gliadins in gel and in solution, and towards the immunogenic gliadin-derived 33-mer peptide.

Results: DEAE chromatography yielded 11 fractions, of which anionic fractions 2–6 contained the gliadin degrading enzyme activity. Active fractions were further separated by MonoQ chromatography yielding 8 fractions, with one showing a clear band in the gliadin zymogram and a single band of Mr ~250 kDa in SDS chromatography. The purified enzyme preparation degraded 250 µg/ml of 33-mer peptide by 17%, 20%, 32% and 58%, respectively, after 0.5 h, 2 h, 5 h and 24 h incubation at 37°C.

Discussion/Conclusion: The low pH-active gliadin-degrading enzyme, derived from a natural colonizer of gastrointestinal tract could provide novel therapeutic perspectives in the treatment of celiac disease. These studies were supported by NIH/NIAID grants AI087803, AI101067, and a grant from the FZI.
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