Charles University, Faculty of Science

Special Chemical and Biological Programmes:

Molecular Biology and Biochemistry of Organisms

Department of Genetics and Microbiology

Kateřina Chudá

Viruses in the pathogenesis of celiac disease

Viry v patogenezi celiakie

Bachelor thesis

Supervisor: doc. MUDr. Ondřej Cinek, Ph.D.

Laboratory of Molecular Genetics

Department of Pediatrics and Institute of Medical Microbiology, Charles University

2nd Faculty of Medecine and Motol University Hospital

Prague 2017

Prohlášení

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze, 14. 5. 2017

Kateřina Chudá

Acknowledgement

I would like to take this opportunity and thank my supervisor doc. MUDr. Ondřej Cinek, Ph.D. for his guidance, a rich and helpful input into the thesis and for his support. I would also like to show my gratitude to my consultants Ketil Størdal, MD, Ph.D. and German Tapia, Ph.D., University of Oslo and National Institute of Public Health, Oslo, for their advice and help.

Abstract

Celiac disease is a chronic inflammatory disorder affecting the small bowel. It develops in genetically susceptible individuals upon yet unknown environmental stimuli. Environmental triggers such as infections, dietary change or other “hits” are clearly required for disease development, as only a tiny fraction of genetically susceptible subjects develops celiac disease upon gluten exposure. This thesis aims to summarize the current evidence on viruses in the pathogenesis of celiac disease regarding their relevance in population or their involvement in immune processes leading to celiac disease. Rotavirus, orthoreovirus, adenovirus, astrovirus, respiratory syncytial virus, hepatitis viruses and herpesviruses are discussed. In addition, prospective cohort studies are presented that investigate environmental triggers of type 1 diabetes and celiac disease, two diseases sharing genetic predispositions.

Keywords:

celiac disease, orthoreovirus, rotavirus, adenovirus, astrovirus, respiratory syncytial virus, hepatitis C virus, hepatitis B virus, prospective cohort study

Abstrakt

Celiakie je chronické zánětlivé onemocnění tenkého střeva. Pro manifestaci nemoci je nezbytná konzumace lepku, která vede k poškozování střevní sliznice v důsledku imunitní reakce namířené vůči složkám lepku. Propuknutí nemoci ovlivňuje řada faktorů majících příčiny v genetických predispozicích daných osob, ale také v prostředí, jakému jsou tito jedinci vystaveni. Z environmentálních faktorů může k rozvoji nemoci přispět například změna jídelníčku nebo prodělaná infekce. Tato práce se zabývá především virovými infekcemi ve vztahu k celiakii – jejich možnou rolí v rozvoji tohoto onemocnění, způsobem interakce s hostitelem nebo jejich významem v populaci. Jako možné kandidátní viry jsou představeny některé herpesviry, reoviry, adenovirus, astrovirus, respirační syncytiální virus a viry hepatitidy B a C. Práce také shrnuje nejvýznamnější současné kohortové studie, jejichž smyslem je, mimo jiné, přispět k objasnění rolí různých vlivů prostředí podílejících se na rozvoji diabetu 1. typu a celiakie, dvou nemocí se společnými genetickými prediktory.

Klíčová slova:

celiakie, orthoreovirus, rotavirus, adenovirus, astrovirus, respiratory syncytial virus, virus hepatitidy B, virus hepatitidy C, prospektivní kohortová studie

Abbreviations

HAdV-12	human adenovirus type 12
HAdV-40	human adenovirus type 40
APC	antigen presenting cell
CMV	cytomegalovirus
CI	confidence interval
CD	celiac disease
DCs	dendritic cells
EBV	Epstein-Barr virus
EmA	endomysium antibodies
ESPGHAN	The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition
GFD	gluten-free diet
HBV	hepatitis B virus
HCV	hepatitis C virus
HLA	human leukocyte antigen
HSV-1	herpes simplex virus type 1
IEL	intraepithelial lymphocyte
OR	odds ratio
pDC	plasmacytoid dendritic cell
RCD	refractory celiac disease
RSV	respiratory syncytial virus
T_H1	type 1 T helper cells
tTG	tissue transglutaminase
tTGA	tissue transglutaminase antibodies

Table of contents

1 Introduction

Celiac disease is a chronic inflammatory disorder affecting the small bowel that develops in genetically susceptible individuals of all ages. The ingestion of gluten (the major storage protein of wheat and similar grains) in these subjects causes damage in the small intestine (Abadie et al. 2011). Celiac disease is the most common food intolerance, it is estimated to affect approximately 1 % of the people in the USA and Europe (Rubio-Tapia et al. 2012, Gandolfi et al. 2000). Nevertheless, the prevalence varies among countries. For instance, the prevalence in Finland is over 2 % according to the screening study (Mustalahti et al. 2010). Currently, the basis of the therapy is avoidance of the dietary antigen – a gluten-free diet leads to the recovery of the intestinal mucosa and reduces the risk of complications (Abadie et al. 2011).

Celiac disease is a multifactorial disorder whose etiology comprises both genetic and environmental components. The overwhelming majority of people with the disease carry the HLA-DQ2 molecule, the HLA-DQ8 molecule or both (Green et al. 2015). Affected individuals meet conditions of gluten intake, but additional environmental triggers such as infections, dietary change or other "hits" appear to be required for disease development (Cenit et al. 2015).

During the last decades, the incidence of celiac disease (CD) is increasing (Rubio-Tapia et al. 2009, Lohi et al. 2007). It cannot be explained solely by improvements in diagnosis, as the diagnosis criteria have not substantially changed over the last decade or two (Ludvigsson et al. 2014). We cannot expect any significant changes in proportion of susceptible alleles over such a short period of time (Stene et al. 2014). It implies that there must exist environmental changes that play a role in immune processes and also in the pathogenesis of the disease (Abadie et al. 2011). Advances in prevention or even in treatment could be achieved upon identification of such factors. Currently, the only cure is based on strict, lifelong gluten-free diet.

1.1 Aims

Aims of the thesis is to:

- review the current evidence on viruses and bacteria in celiac disease pathogenesis,
- create a priority list of candidate viruses – including their frequency and the ability to inflict a gut mucosal injury,
- compare the state-of-the-art methods testing similar associations in type 1 diabetes and other polygenic diseases.

2 Celiac disease

For proper understanding of the main topic, it is essential to summarize our current knowledge on celiac disease, with a focus on diagnosis and mechanisms of pathogenesis.

2.1 Clinical summary of celiac disease

Clinical manifestations of CD vary and can include intestinal symptoms (diarrhea, abdominal pain, etc.) or extra-intestinal symptoms often being a consequence of malabsorption (anemia, osteoporosis, growth deficits etc.). Some CD patients manifest also with dermatitis herpetiformis, a skin rash. However, symptoms may not develop (silent form). CD can occur at all ages. Symptoms in childhood often differ from those of adults. In childhood, digestive symptoms (abdominal pain, vomiting, diarrhea), failure to thrive and weight loss are more common, whereas symptoms in adults can be often less specific such as anemia, fatigue, osteoporosis (Green et al. 2015).

If gluten-free diet (GFD) is followed, symptoms disappear in most cases. A special case is refractory celiac disease without improvement in patients on GFD. Those patients are highly endangered by enteropathy-associated T-cell lymphoma if they have refractory celiac disease type II. Similarly, untreated patients have an increased risk of certain types of intestinal cancer and other complications, however, the absolute risk is not dramatically high (Green et al. 2015).

2.2 Pathogenesis

CD is a multifactorial disorder that involves HLA and several non-HLA genes, adaptive and innate immunity and environmental factors (Abadie et al. 2011) as depicted in Figure 1.

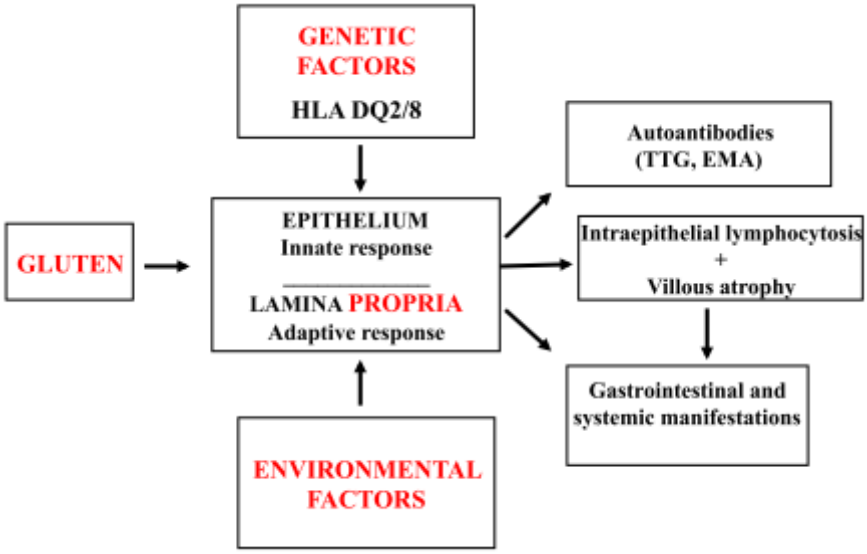

Figure 1 Celiac disease is a result of three main causative factors – genetic predisposition, gluten ingestion and environmental triggers. From Green et al. 2015.

In CD, gluten causes immune attack to small intestine. Gluten, found in wheat and related grains, comprises (in the case of wheat) proteins called gliadin and glutenin. In celiac disease, specific amino acid sequences in gliadin are responsible for the patient's abnormal immune response (Abadie et al. 2011). Visser et al. suggested that genes, environment and loss of intestinal barrier function are all necessary to develop CD autoimmunity (Visser et al. 2009).

Briefly, gluten is broken down in the stomach into gliadin and other components. As shown in Figure 2, gliadin peptides get to the small intestine and come across the intestinal epithelium through the enterocyte into the lamina propria, or crosses the epithelium paracellularly due to increased permeability. Afterwards, the enzyme tissue transglutaminase (tTG) deamidates gliadins, by which the affinity of gliadin to HLA-DQ2 or HLA-DQ8 is increased. The modified gliadin is endocytosed by an antigen presenting cell, which later presents fragments of gliadins bound to HLA-DQ2 or HLA-DQ8 on its surface (Abadie et al. 2011).

Celiac disease is associated with specific alleles of class II HLA. The two chains of the HLA-DQ heterodimer are encoded by the *HLA-DQA1* and *HLA-DQB1* genes. Over 95 % of people with celiac disease carry HLA-DQ2, HLA-DQ8, or both molecules. Only low proportion of patients carry neither of the HLA-DQ2 or HLA-DQ8 molecules. The effect of non-HLA genes is very low in comparison with the HLA (Liu et al. 2014, Abadie et al. 2011).

These specific HLA molecules present gliadin more readily due to tighter binding into their antigen groove. The deamidated gliadin presented on the background of the susceptibility HLA-DQ molecules is presented to a T helper CD4+ cell that recognizes the complex by its TCR receptor. This leads to the immune reaction and destruction of enterocytes. The T helper CD4+ cells also interact with B cells producing antibodies against gliadin and tTG (making CD partly an autoimmune disease) (Abadie et al. 2011).

Interestingly, T helper CD4+ cell mediated antigliadin response is not sufficient to induce intestinal damage on its own, which implies that additional factors such as episodes of hyperpermeability, effects of intestinal infection, increased dietary gluten etc. are involved (Abadie et al. 2011).

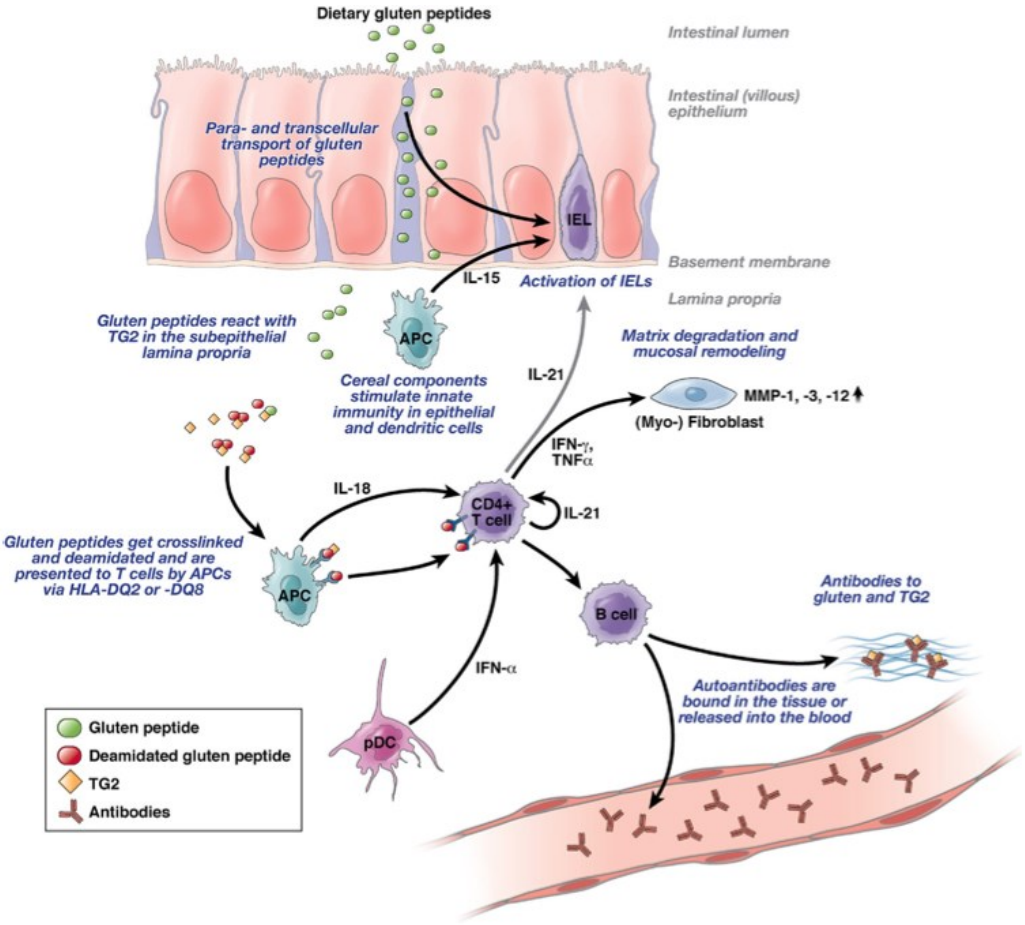

Figure 2 Illustration of immune processes occurring in CD pathogenesis. From Vassali et al. 2016.

2.3 Gluten

Gluten plays a central role in CD pathogenesis. The development of intestinal damage is tightly linked with gliadin, a part of gluten. The gliadin belongs among prolamins, proteins with a high glutamine and proline content and low content of acidic residues. Gliadin's typical residues (especially proline ones) make gluten difficult for intestinal enzymes to digest, but also account for its antigenic role. For instance, prolamins with lower content of glutamines and prolines are not antigens in CD (prolamins are found in rice, corn etc.) (Abadie et al. 2011).

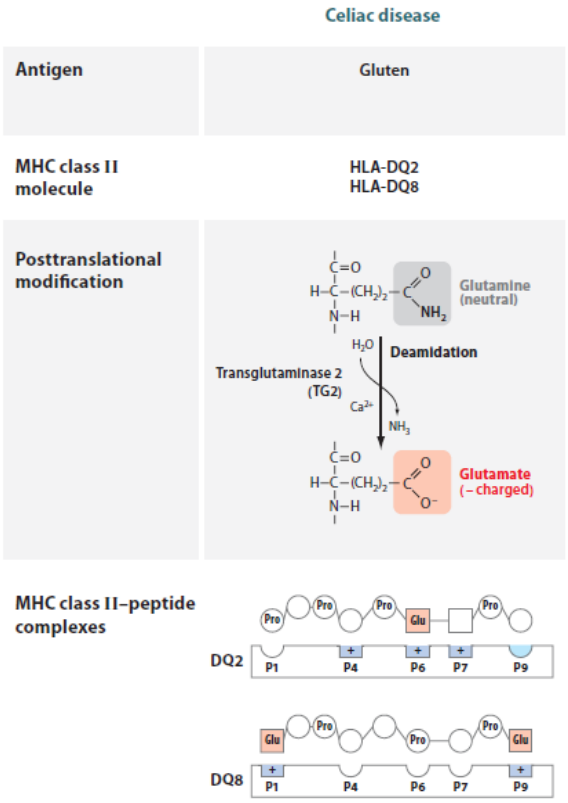

Figure 3 Gluten as a substrate for tTG converting its glutamines to glutamates. From Abadie et al. 2011.

As described in Figure 3, gluten is a good substrate for tTG, which converts glutamines to glutamates. Negatively charged glutamates have better affinity to HLA-DQ2 or HLA-DQ8 molecules having positive charged pockets (Abadie et al. 2011).

The distribution of HLA-DQ2 and HLA-DQ8 molecules, in association with gluten consumption along with its comparison with the prevalence of CD over the globe can serve as good evidence for the influence of environmental factors on CD prevalence. As can be seen in Figure 4, there

are outlier countries in which CD prevalence clearly does not depend only on gluten consumption and genetic predisposition. The differences in CD prevalence among countries suggests the influence of other important factors in the environment (Abadie et al. 2011). Aware of the existence of environmental triggers, scientists have studied a several factors such as dietary habits (for instance introduction of gluten into a diet) (Kemppainen et al. 2016), dietary supplements (Størdal et al. 2014), use of antibiotics (Canova et al. 2014), birth weight, duration of breastfeeding and cumulative effect of infections (Mårild et al. 2015b).

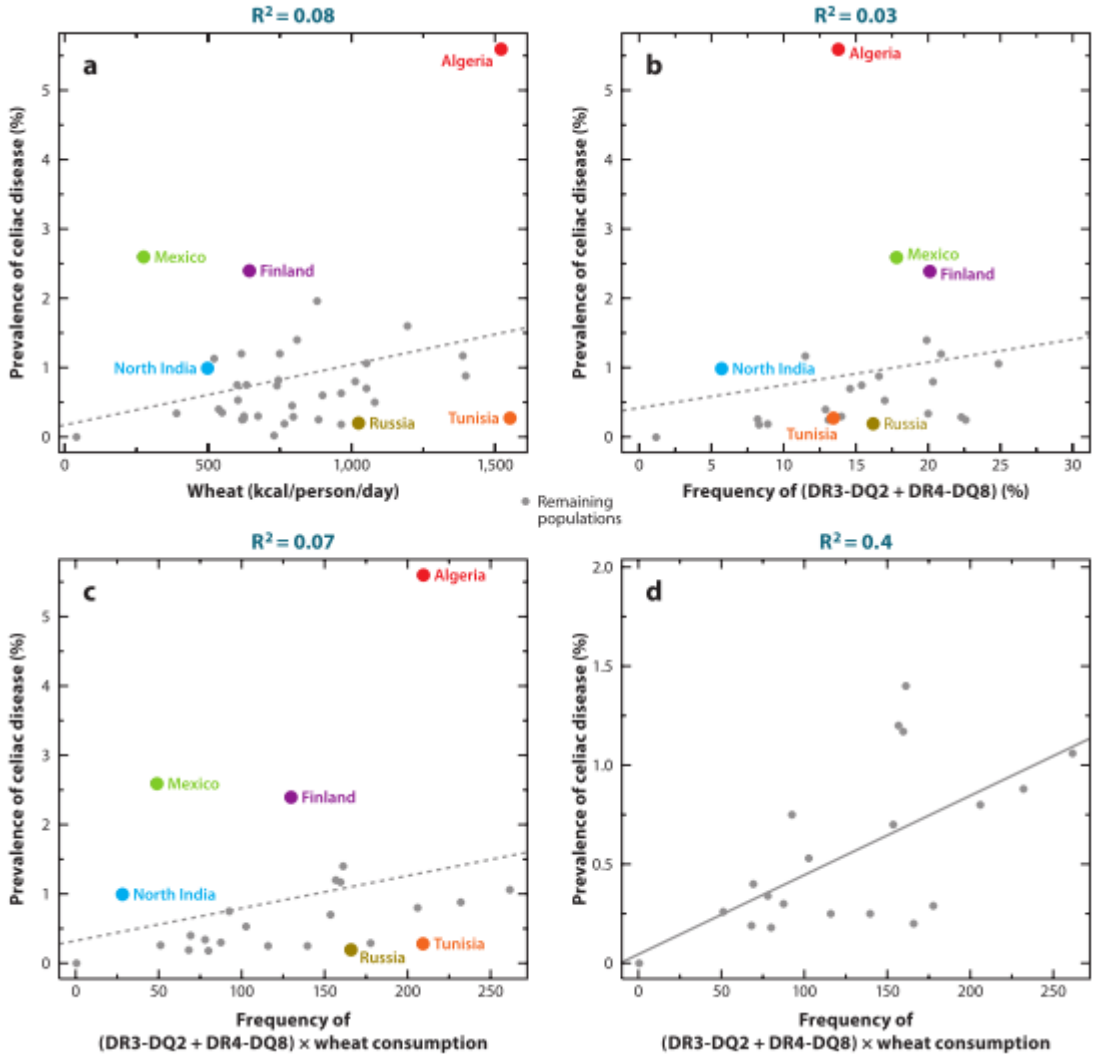

Figure 4 Relations between the prevalence of CD and the quantity of wheat consumption (a), prevalence of CD and the frequency of susceptible genotypes (b), prevalence of CD and the product of the susceptible genotype frequencies along with the quantity of wheat consumption (c) and the same relation, but without outlier countries (d). The distribution of countries in graphs suggest the presence of additional environmental factors. From Abadie et al. 2011.

2.4 Diagnosis

Methods of diagnosis are important for comparison of epidemiological studies. Celiac disease can manifest as various perceived symptoms (overt CD), or it can have no symptoms at all (silent form of CD), but both forms have potential serious consequences if CD is untreated. CD is also detectable by screening in the general population. Nevertheless, CD is mostly tested in patients with CD-associated symptoms or in subjects belonging to risk groups (patients and relatives with type 1 diabetes or autoimmune thyroid disease) (Frühauf et al. 2012).

The gold standard and the most reliable method is the intestinal biopsy. Marsh-Oberhuber classification is used with grade 0 being a normal finding, while grade I reflects the presence of microscopic enteritis with intraepithelial lymphocytes, grade II has also hyperplastic crypts, and grades III have various degrees (a, b, c) of villous atrophy. As confident microscopic diagnosis is based on grades IIIa onwards (Marsh II is usually also classified as celiac disease), and mucosal pattern can be patchy, it is important to obtain more specimens from different parts of duodenum. It may be also prudent to take into account that interpretation in different laboratories can vary (Frühauf et al. 2012, Husby et al. 2013).

As almost all patients carry typical HLA molecules DQ2 or DQ8 (Abadie et al. 2011), genotyping can be a test for excluding CD (Frühauf et al. 2012); it has very low positive predictive value, because these alleles are common and just a fraction of carriers suffer from the CD (Frühauf et al. 2012, Abadie et al. 2011). The 2012 ESPGHAN guidelines (The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition) consider HLA-genotyping useful in the first phase of testing in risk groups (patients with T1D and/or patients with autoimmune thyroid disease, and their relatives) (Frühauf et al. 2012). Authors think that upcoming studies can confirm whether combination of HLA-genotyping and positive endomysium antibodies (EmA) and tTG antibodies can be sufficient for the diagnosis (Husby et al. 2013).

Autoantibodies alone are not reliable as the means of diagnosing CD. Anti-tTG and EmA can be found in patients with CD, but their occurrence varies. They are not absolutely sensitive – their presence depends on the consumption of gluten, the phase of the disease and on a concrete patient – IgA deficiency can occur in some individuals. Also, they can appear during infections, other autoimmune diseases etc. However, the tTG antibodies have high specificity and sensitivity

(both ~ 90 %) in general (Husby, Murray 2013). Nevertheless, despite high accuracy of main CD autoantibodies anti-tTG, it seems that high titers are not sufficient to diagnose CD and biopsy should be required in adults (Elitsur et al. 2016).

Other autoantibodies that can be detected in CD are IgA and IgG of deamidated gliadin peptide, but apparently these are of low specificity (Frühauf et al. 2012).

Besides established rules from 2012, there are specific cases when biopsies are not required. In these cases, patients have celiac symptoms, level of anti-tTG antibodies ≥10× upper limit of normal titers (common threshold for positivity is >3× higher upper limit of normal), EmA positivity and typical HLA alleles (Frühauf et al. 2012).

As can be seen, the diagnosis is still relatively challenging. Approaches and methods have been changing and these aspects can complicate the comparison of studies. The combination of diagnostic tools such as detection of autoantibodies, presence of symptoms and the evaluation of duodenal biopsy is being used. In most cases, antibodies in blood are detected and on the basis of their presence the biopsy is considered (Frühauf et al. 2012).

3 Intestinal microbiota

Dysbiosis, defined as microbial imbalance in affected individuals in comparison with healthy subjects, has been detected in CD patients at diagnosis. The factors influencing microbiota are both environmental (nutrition, breastfeeding, use of antibiotics, infections) and genetic (host alleles possibly determined specific immunological background establishing which types of bacteria can live in the intestinal milieu). In addition, there can be unknown epigenetic modifications present, which must also be taken into consideration (Cenit et al. 2015).

Regarding bacteria, the picture is complex, and most studies come from already established CD patients, compared to control subjects not having the disease. None of the studies have studied the role of microbiota during the development of CD by a longitudinal approach, with samples preceding manifest disease. There are several studies, mostly rather limited in size and differing in their design. The possible reverse causality is the primary limitation of all so far published works: it is simply unclear whether the microbiota composition is just a consequence of the inflammatory changes in the intestine or the consequence of GFD (Cenit et al. 2015).

Wacklin et al. found that patients with dermatitis herpetiformis had a different duodenal microbiota (more abundant in *Firmicutes* phylum) in comparison with patients with gastrointestinal symptoms (more abundant in *Proteobacteria* phylum). Higher microbial diversity was noticed in CD patients with dermatitis herpetiformis manifestation than in CD patients with gastrointestinal symptoms. The study investigating this relations included biopsy samples from 33 CD patients at the time of the diagnosis (Wacklin et al. 2013).

Collado et al. investigated the composition of duodenal microbiota in 25 CD patients at the time of diagnosis and in 8 control subjects. *Bacteroides* and *Clostridium* were more abundant in duodenum of CD patients, to the detriment of *Biffidobacterium* (Collado et al. 2009). Other study, however, also tested duodenal microbiota in 21 CD untreated children and 21 control children but found no significant difference in diversity and composition of bacteria between groups (De Meij et al. 2013).

Figure 5 describes potential mechanisms of bacterial interaction with processes involved in CD pathogenesis. The first way of contribution to the pathogenesis is (1) the generation of immunogenic peptides from gluten by proteolysis. Secondly (2), specific strains of bacteria can increase or decrease intestinal permeability. Thirdly (3), some microbiota components can cause modulation of releasing different cytokines (Olivares and Sanz 2015).

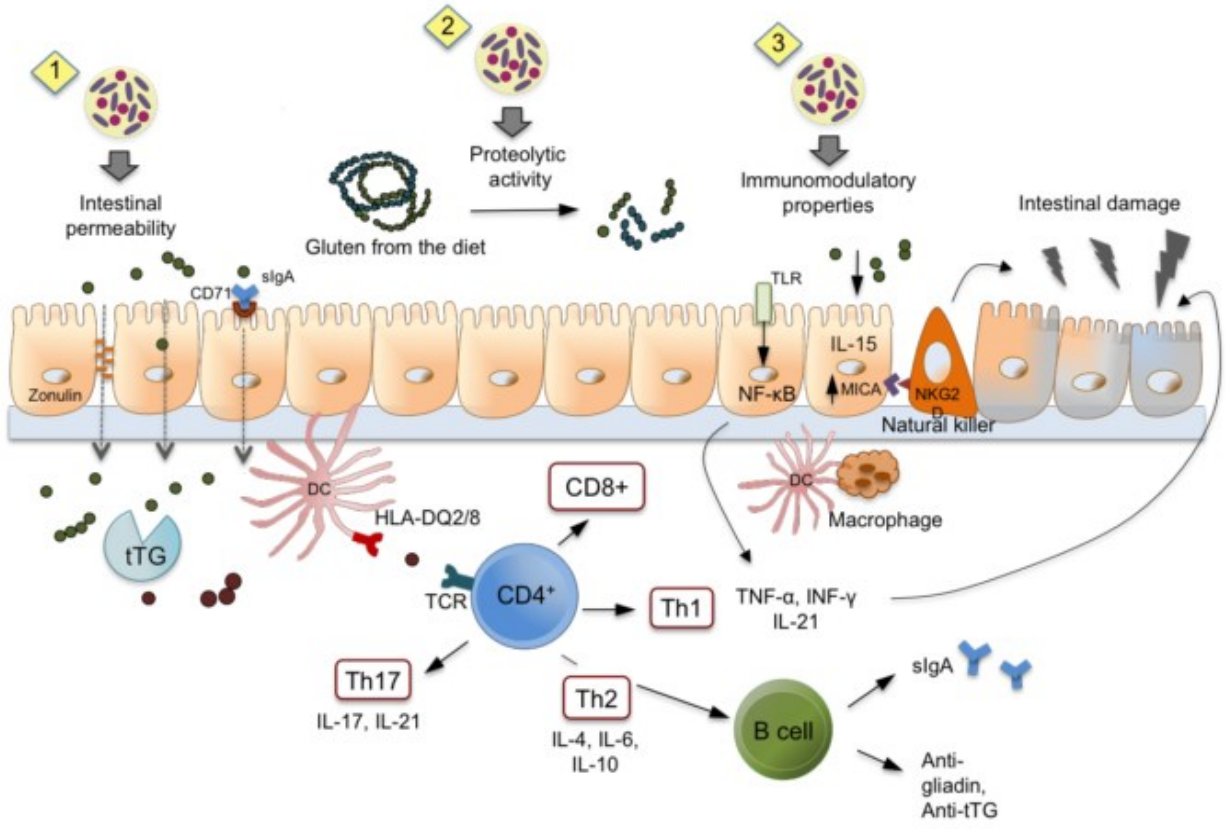

Figure 5 Description of interactions between intestinal microbiota and the host. From Olivares et al. 2015.

In addition, the situation becomes even more complicated when the virome is taken into account. The virome interacts both with bacteria and host cells. The virome has an impact on the bacterial composition and could shape the function of the immune system. It was observed that intestinal mucosal surface has a high concentration of viruses and even higher virus-to-bacteria ratio than there is in the intestinal lumen (Barr et al. 2013). Understanding the networks of associations in the intestinal ecosystem can help clarify and improve the efficacy of fecal transfer used as intervention in some patients. In this respect, the published case history of RCD patient who was cured by fecal microbiota transfer is remarkable (Beurden et al. 2016).

Regarding microbial dysbiosis, there is the proper evidence of different gut microbial composition between CD patients and controls. However, the evidence suffers from the lack of information about causality and from the lack of duodenal samples.

4 Viral infection and their role in celiac disease

Observations suggest that infections play a role in the pathogenesis of CD (Mårild et al. 2015). Among the first suspected infections studied in the relation to CD are obviously gastrointestinal. Specifically, viruses are responsible for approximately 70 % of infectious diarrhea in children (Webb and Starr 2005). Many virus infections are asymptomatic, but there is a possibility for their involvement in modifying the susceptibility for CD (Bouziat et al. 2017, Focà et al. 2015). In addition, there is an evidence of extra-intestinal diseases associated with the occurrence of CD (Tjernberg and Ludvigsson 2014, Abid et al. 2015). For instance, hepatitis C virus (HCV) and hepatitis B virus (HBV) infections may likely trigger immunologic gluten intolerance in susceptible people (Ruggeri et al. 2008, Abid et al. 2015). Other studies describe possible associations of respiratory or herpesvirus infections with the CD onset (Perfetti et al. 2016). Viral infections have also been reported to protect from CD (Jansen et al. 2016). Researchers have suggested possible mechanisms describing various pathways in which viruses can be involved in immune processes (Focà et al. 2015).

4.1 Orthoreovirus

Orthoreoviruses, belonging to the *Reoviridae* family, are non-enveloped viruses with a double-stranded RNA genome placed in an icosahedral capsid. Orthoreovirus infections, transmitting through respiratory droplets or through fecal-oral route, can be asymptomatic, or cause mild respiratory disease and gastroenteritis in children (Day 2009).

In 2017, researchers (Bouziat et al. 2017) found a role of orthoreovirus infection in triggering CD using mouse models. In their study, two orthoreovirus strains were used (T1L – type 1 Lang capable to infect the intestine and T3D-RV – type 3 Dearing reassortant virus, virus with added segments allowing T3D virus to infect the intestine). The authors compared the effect of different immunopathological ways of these viruses varying in their biology.

Authors showed that T1L infection can break oral tolerance to dietary antigens and promote tTG activation in a CD mouse model (with HLA-DQ8). It suggested that orthoreovirus infection can contribute to CD development.

In addition, a survey including 160 CD patients and 73 controls was conducted. Patients with CD were significantly overrepresented among subjects with very high titters of anti-orthoreovirus

antibodies as shown in Figure 7. Authors concluded that orthoreovirus infection can trigger the onset of CD in a subset of CD patients. Furthermore, the research examined if the occurrence of anti-orthoreovirus antibodies correlates with the occurrence of anti-rotavirus antibodies and anti-HSV-1 antibodies. Such a correlation was not confirmed which suggested that orthoreovirus infections are not a feature for general increased amount of virus infections and does not have the influence on CD beyond orthoreovirus infections.

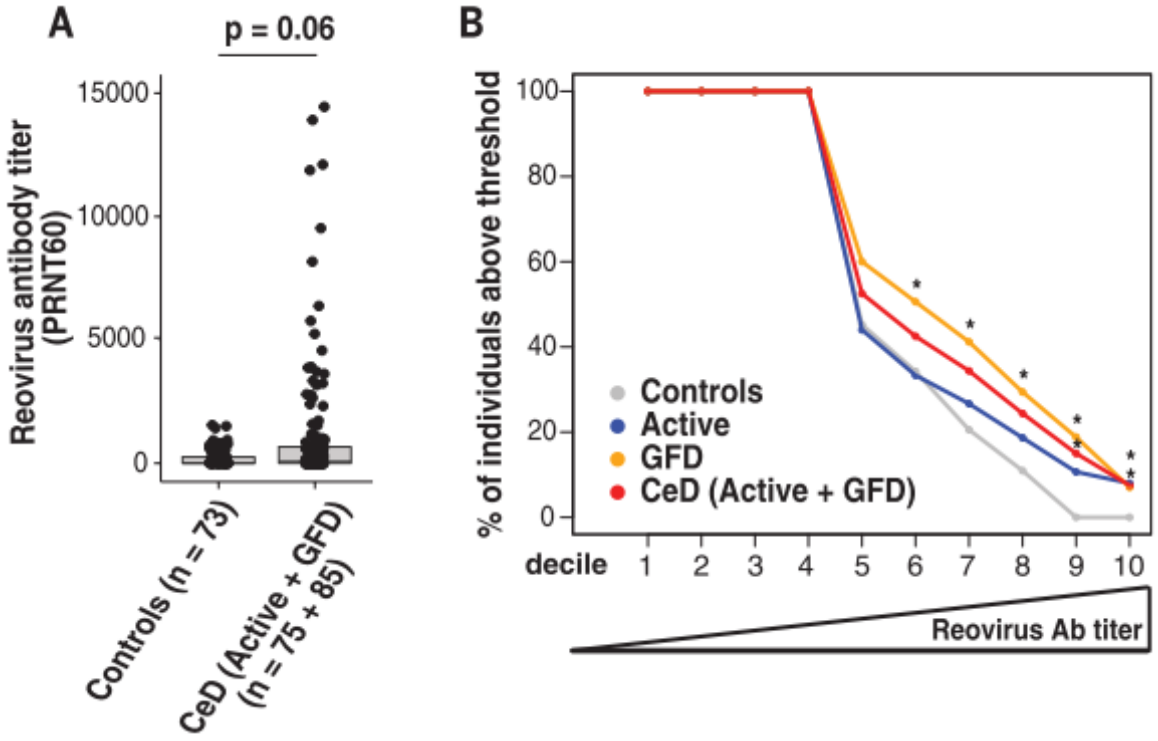

Figure 7 Boxplot showing levels of orthoreovirus antibodies in 160 CD patients and 73 controls (A). Percentage of controls and CD patients with orthoreovirus antibodies. Patients with CD are significantly overrepresented among subjects with high orthoreovirus titers (B). From Bouziat et al. 2017.

The study supports the possibility that even an avirulent T1L orthoreovirus can cause intestinal damage and induce T_H1 immunity to a dietary antigen. It was noticed that the ability of virus to trigger the loss of oral tolerance to antigen corresponds with the ability of a virus to disrupt immune homeostasis in the gut. Findings suggest that orthoreovirus infections may cause development of T_H1 immunity to gluten and activate tTG. However, additional events are required for causing villous atrophy and producing of tissue transglutaminase antibodies (tTGA) (Bouziat et al. 2017).

4.2 Rotavirus

Rotavirus, being the most frequent cause of gastrointestinal infections in childhood (Kozderka et al. 2014), has been the focus of several studies on CD (Stene et al. 2006, Dolcino et al. 2013).

Rotaviruses are non-enveloped double-stranded RNA viruses belonging to the *Reoviridae* family. The RNA is surrounded by an icosahedral capsid. Rotavirus invades epithelial cells of the duodenum and jejunum. The transmission is fecal-oral, with a very low infective dose and the virus is resistant in the external environment, which makes it ideal for spreading among young children. In addition, rotavirus infection can occur without symptoms (especially for breastfed infants and children which have already encountered the infection). In adults, symptoms are less common due to acquired immunity. Rotaviruses are ubiquitous – almost every child is infected by rotavirus by the age of five (Parashar et al. 2006, Kozderka et al. 2014).

Rotavirus infection was associated with risk of celiac disease in a study by Stene et al. who found a positive correlation between rotavirus infections in childhood and CD autoimmunity development in genetically susceptible individuals. The authors noticed that higher risk of CD autoimmunity development in children may be increased almost four times when the child has experienced two or more rotavirus infections, and two times if a child has experienced only one infection (both values relative to no infection) (Stene et al. 2006).

Thanks to the methodology chosen in this study, authors were able to capture even asymptomatic cases – rotavirus antibodies were measured in children and the frequency of rotavirus infections was estimated as an elevated level of produced antibodies between particular blood collections (in 9, 15 and 24 months of age and then annually). Children that were tTGA positive twice in sequence or have undergone duodenal biopsy, were marked as patients with CD autoimmunity development (Stene et al. 2006).

Dolcino et al. investigated whether mechanism of molecular mimicry can play a role in the case of rotavirus. This was demonstrated by antibody cross-reaction: the authors found out that rotavirus VP7 protein, “celiac peptide” (a peptide that authors found in protein database as one that is recognized by immunoglobulins of patients with active CD) and tTG share a sequence homology, as is exemplified in Figure 6 (Dolcino et al. 2013).

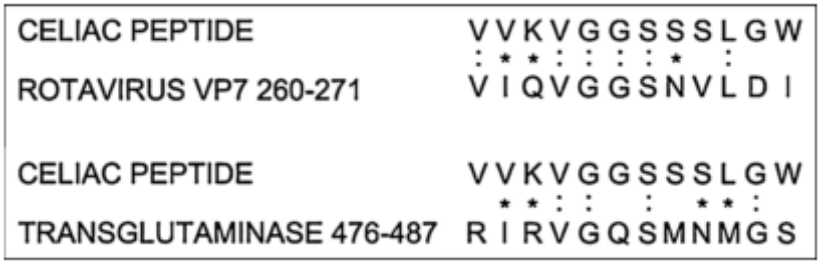

Figure 6 Sequence homology between the celiac peptide, the rotavirus VP7 protein and the tissue transglutaminase. Dots represent identity while asterisks depict conservative substitutions. From Dolcino et al. 2013.

The research group demonstrated that rotavirus VP7 antibodies were present in 81 % (21/26 studied individuals) of patients with T1D and CD, in contrast to only 27 % (10/37 studied patients) T1D patients not suffering from CD. In addition, anti-VP7 peptide antibodies were detected before the onset of CD in 6 out of 8 studied patients (Dolcino et al. 2013). On the other hand, a study published in 2016 (Ziberna et al. 2016) does not support previous findings. In this study, researchers measured anti-VP7 antibodies in sera of more than 118 CD patients and of about 200 healthy individuals in order to assess the role of rotavirus in the onset of CD. Authors did not confirm the existence of molecular mimicry. In addition, a study (Bouziat et al. 2017) testing 118 CD patients and 60 controls failed to demonstrate an association between rotavirus infection and CD. Further studies are needed before it is possible to conclude whether rotavirus infections play a role in the pathogenesis of CD.

For children that have the highest risk for CD development, it is possible to consider vaccination against rotavirus and by this way at least try to reduce the risk of celiac disease. According to one study, risk of celiac disease autoimmunity was diminished in children vaccinated against rotavirus and introduced to gluten before the age of 6 months (HR = 0.57; 95% CI, 0.36-0.88) (Kemppainen et al. 2016). More studies regarding the effect of rotavirus vaccination on CD onset are required. Ideally, the association can be examined in countries, where the rotavirus vaccination was set recently as mandatory.

In the Czech Republic, vaccination against rotavirus is optional (oral live vaccine in three doses) (Kozderka et al. 2014). Nevertheless, it is recommended to take into consideration this vaccine regardless of CD susceptibility. Hovewer, the risk of CD onset appears to be influenced by complex interactions among infections, genetic factors, and a diet, so this recommendation is

merely a little tool to help us fight against the likelihood of disease development. (Kozderka et al. 2014, Kemppainen et al. 2016).

4.3 Adenovirus

Adenovirus is a non-enveloped virus with an isosahedral capsid containing a double stranded DNA genome. Adenovirus infections are common and ubiquitous. More than 50 adenoviral serotypes have been found in humans. Adenoviruses can be spread by respiratory droplets or fecal-oral (Echavarria et al. 2007). Infections caused by adenoviruses can be symptomatic or asymptomatic (e.g. adenovirus type 40 can cause gastroenteritis) (Uhnoo et al. 1984).

In 1984, Kagnoff et al. demonstrated the presence of amino acid sequence homology between α-gliadin and E1b protein of human adenovirus type 12 (HAdV-12). The homologous region spans 12 amino acids (approximately the length of the oligopeptide sequence recognized by T-cells), containing identical pentapeptide and 3 identical amino acid residues. Moreover, this segment is found within a wider hydrophilic region, indicating its likely presence on the surface of proteins in both α-gliadin and E1b protein, and hence the availability of this sequence being a possible epitope for antibody production. The authors also succeeded in verifying that antibodies produced against this adenovirus protein (54-kD HAdV-12 E1b protein) also react with α-gliadin. Thus, they came up with a hypothesis for the possible development of celiac disease in the course of the intestinal viral infection caused by HAdV-12, where antibodies are produced against the released E1b human adenovirus serotype 12 protein (Kagnoff et al. 1984).

Based on this finding, the same research group (Kagnoff et al. 1987) conducted a study in 80 CD patients and 135 controls. The study confirmed the association between CD and the previous HAdV-12 infection. Nearly 90 % of untreated CD patients had anti-HAdV-12 antibodies, in contrast to only 12.8 % of controls. In treated patients, the anti-HAdV12 antibodies prevalence was only 30 %. This observation was further supported by a Finnish study evaluating serum antibodies in 41 non-treated CD children and 57 controls where the presence of antibodies against HAdV-12 (against non-homologous part to α-gliadin) in the CD patients group was significantly higher than in the control group (Lahdeaho et al. 1993).

In addition, the monitoring of the previous human adenovirus type 40 (HAdV-40) infection (the detection of antibodies to non-homologous E1b HAdV-40 peptide in relation to α-gliadin) showed a significantly higher prevalence of HAdV-40 antibodies in CD patients (Lahdeaho et al. 1993).

Other studies did not confirm the association. For example, one study examined the presence of HAdV-12 by PCR in biopsy samples of 18 CD patients and 24 controls. In total, 4 CD patients and 2 controls were HAdV-12 positive, thus non-significant difference is found between groups (Mahon et al. 1991). The disadvantage is the small sample size, thus the association between CD and HAdV-12 cannot be statistically ruled out.

Similar results to those coming from Mahon et al. were obtained in 1994 (Lawler et al. 1994). PCR biopsies were performed in 17 adult CD patients, 16 adult controls, 10 CD children and 7 healthy children. Adenovirus positivity was confirmed in 3/17 CD adults, 5/16 control adults, 3/10 CD children and in 1/7 control children. Thus, the HAdV-12 prevalence in biopsies was similar in both adults and children, indicating that HAdV-12 infections already occurs in early childhood. There was not a significant difference in HAdV-12 positivity among patient groups and controls, but the effect of HAdV-12 infection in early childhood cannot be ruled out and could trigger a series of processes leading to later CD development (Lawler et al. 1994).

We still do not know much about the role of adenovirus infections in relation to CD in early childhood. Previous studies are cross-sectional or limited in design to a small number of patients. It would be suitable to perform a prospective study following children from birth and to monitor the adenovirus infections that children encountered, in order to verify their impact on the possible development of CD in real time.

In 2016, Tarish et al. aimed to evaluate the role of adenovirus infections in CD pathogenesis. Authors had a large set of patients – they investigated anti-adenovirus antibodies in blood of 80 CD patients and 80 healthy controls. The age of patients ranged from 1 to 45 years. There was no significant difference in anti-adenovirus antibodies between CD group and healthy group. Authors mean that findings implies that there is no evidence of previous adenovirus infection associated with celiac disease development (Tarish et al. 2016). However, the causality is still unclear, prospective studies should be conducted.

In total, there is no direct evidence supporting the role of adenovirus infections in celiac disease development. However, none of the studies, mentioned above, was prospective and their results cannot exclude the influence of adenovirus infection operating early in life.

4.4 Astrovirus

Astrovirus is a virus with single-stranded RNA genome within a non-enveloped icosahedral capsid. Astrovirus is associated with gastroenteritis in young children. Adults are less prone to the infection. The virus is transmitted through the fecal-oral route. Recently, non-typical astroviruses emerged as causes of serious systemic infections (Vu et al. 2017).

In 2010, a case report suggested a link between infection caused by a rare human astrovirus (which is very similar to the VA1 astrovirus and can cause intestinal infection) and the development of celiac disease. A four-year old patient was diagnosed with celiac disease and the presence of this variant of VA1 was confirmed. Consequently, 328 Dutch patients with diarrhea were tested, but none of them had VA1, so the etiological fraction could be negligible, if any (Smits et al. 2010).

Because of the current detection ability of new viruses described by Smits et al. (Smits et al. 2010), it might be interesting to extend the study and include more patients, and find out the distribution of VA1 in people among various areas. Because of the extreme rarity of this virus, it is possible to estimate that this infection does not involve many CD onsets. Should there be any significant connection with CD, the number of patients whose disease would be explained is likely low. However, it could be beneficial to verify the distribution of this astrovirus in areas, where CD is most prevalent. Thanks to the new detection methods, it is possible to expect the discovery of further viruses involving CD.

4.5 Respiratory syncytial virus

Respiratory syncytial virus (RSV) belongs to the *Paramyxoviridae* family. RSV is an enveloped single-stranded RNA virus placed in a helical capsid. It causes respiratory tract infections, and is a common cause of respiratory infections (including acute fatal ones) in young children (Čihař et al. 2002). In adults, RSV usually has a mild course, similar to that of

a common cold or influenza-like illness (Gamino-Arroyo et al. 2016). Respiratory syncytial virus is transmitted by direct contact or by droplets, and is generally highly prevalent (Berger 2017).

There was a weak, nearly significant indication of a link between RSV infection and CD in the Swedish study published in 2014. The study, including nearly 4 000 children with celiac disease diagnosed before the age of two (matched by gender and age with more than 19 thousand control subjects), came up with an observation that children that have experienced RSV infection or other viral bronchitis before the age of one, were nearly twice as likely to develop CD in the future (OR = 1.82, 95 % CI 0.91-3.62). As for monitoring RSV infection/bronchitis during the first 2 years of age, the risk of later development of CD increases 1.5×. Epidemiologic data on RSV infections and CD were obtained from the Swedish Patient Register (Tjernberg and Ludvigsson 2014).

Indisputably, the advantage of this study is the number of patients included in the study. However, it is necessary to consider whether the seemingly elevated likelihood of CD diagnosis among hospitalized children with bronchitis, in comparison with the children without this infection, had not been caused by their thorough monitoring, even though those cases would probably be very rare. Another aspect worthy of consideration is the possibility to regard RSV infection as an indicator of a higher risk for encountering with other infections affecting the pathogenesis of CD.

The authors also consider whether vitamin D plays a role such as factor involved in both CD, and susceptibility to RSV infection. Decreased level of vitamin D may be associated with more frequent occurrence of CD and with a higher susceptibility to RSV infection and the severity of its progress (Tjernberg and Ludvigsson 2014, Margoni et al. 2012, Roth et al. 2010). Also, the causative association with CD is not obvious. It is possible to regard RSV infection as an indicator of a higher risk for encountering with other infections affecting the pathogenesis of CD.

Nowadays, there is not proven vaccination (Čihař et al. 2002). However, if the current development of RSV vaccines succeeds and RSV infection has a role in pathogenesis, vaccination could be a potential candidate for prevention of CD.

4.6 Hepatitis viruses

Further candidate viruses that are suspected to be associated with CD are hepatitis B virus (HBV) and hepatitis C virus (HCV). It has been suggested that proteins of these viruses can share a sequence homology with gliadin and therefore act through mechanism of molecular mimicry (Plot and Amital 2009). In another way, they could interfere due to the ability to activate immune processes of elimination of the virus. Afterwards, immune processes would get out of control and start to produce autoantibodies (Iglesias et al. 2010, Marconcini et al. 2013).

4.6.1 Hepatitis C virus

HCV is an enveloped single strand RNA virus of the *Flaviviridae* family, that is transmitted through blood and about 3 % of the world population is infected. Acute infections may be asymptomatic. In some patients, the disease ceases without treatment, but most patients pass through the chronic phase which can lead to the development of cirrhosis or liver cancer (Wieland and Chisari 2005). Hepatitis C virus (HCV) can also initiate autoimmune disease process and products various autoantibodies (Marconcini and Fayad 2013).

According to some evidence, HCV has a link to CD (Ruggeri et al. 2008, Fine et al. 2001). For instance, results supporting this hypothesis were provided by a study that investigated CD-related antibodies in 244 HCV patients and 1 230 healthy blood donors, representing control subjects. The prevalence of tTG autoantibodies in 244 HCV patients was nearly 13× higher than in the control group (OR = 12.3, 95% CI = 2.4-66), which can signify CD autoimmunity. EmA were found in 2 % of HCV-patients (5/244) and 0.16 % of control subjects (2/1230) (Ruggeri et al. 2008). However, because HCV generally causes production of various autoantibodies (Marconcini, Fayad 2013), confirmation by biopsies in suspected CD subjects was warranted - but could not be done.

Similarly, Fine et al. noticed a significantly higher prevalence of AGA in HCV patients than in controls. The study included 259 patients with chronic HCV infection, 59 patients with autoimmune liver disease and 137 patients with other liver disease, that were compared with 356 patients with various GI syndromes and 221 healthy controls. A total of 5 patients had CD confirmed by biopsy. Four of the six cases of CD patients were infected by HCV (Fine et al. 2001).

Other did not observe associations: in a study with 624 HCV patients, out of which 25 patients underwent biopsy on the basis of previous detection CD-related antibodies, none had CD (Thevenot et al. 2007).

4.6.2 Hepatitis B virus

HBV is an enveloped double-stranded DNA virus belonging to the *Hepadnaviridae* family. HBV is transmitted by blood or by bodily fluids. About 3 % of the world population is infected, although in industrialized countries it is less than 1 % of the population. An acute phase of infection need not occur. If a patient passes to a chronic phase, there is a high chance of developing cirrhosis or liver cancer (Shepard et al. 2006).

In 2010, Iglesias et al. reported two patients in whom an acute HBV infection was followed by the onset of CD. Authors immediately suggested hypotheses of possible mechanisms of HBV influence on CD initiation. During HBV infection, interferons and interleukins are released in order to clear the virus, but they also cause damage to intestinal mucosa structure. Then, immunogenic peptides can go through and activate immune cells followed by higher expression of HLA-DQ2/HLA-DQ8 molecules. A different model represents the mechanism of molecular mimicry (Iglesias et al. 2010).

In addition, a study conducted in Brazil in 2013, including 50 HBV patients, found that 6 out of these 50 infected were histologically abnormal (on the basis of previous detection of tTG and EmA). Four patients (8 % of HBV patients) were clearly diagnosed with CD (Nau et al. 2013). This 8 % prevalence is above average in general population (Mustalahti et al. 2010, Rubio-Tapia et al. 2012). Unfortunately, it is not clear whether subjects had CD already before HBV diagnosis or not.

A recent survey, including 75 HBV patients and 50 control individuals, demonstrated significantly higher AGA prevalence among HBV patients (Abid et al. 2016). However, it does not show any relevant information on CD without biopsy evaluation.

The results suggest that there could be an epidemiological link between these two diseases, although several issues are disputable and we still need further research on this topic. Especially, studies are needed where CD is confirmed by biopsies.

Considering the prevalence of the viruses mentioned in this overview and our ability to decrease their world prevalence, the best candidate virus is HBV, because the vaccine against HBV does already exist and the world prevalence is estimated to be 3 % of the world population. If there is a real association between HBV infection and CD, vaccination could also diminish the CD onsets.

4.7 Herpesviruses (HSV-1, CMV, EBV) and rubella virus

Herpes simplex virus type 1 (HSV-1), cytomegalovirus (CMV) and Epstein-Barr virus (EBV) all belong to the *Herpesviridae* family. They are enveloped double-stranded DNA viruses with icosahedral capsid (Rao 2014).

HSV-1 is transmitted via saliva or skin-to-skin contact and can manifest as a skin, eye or mouth infection. HSV-1 is usually acquired during childhood and persists in ganglia (Rao 2014). It is found in 52 %-84 % of people in Europe (Pebody et al. 2004).

CMV infects about 60 % of individuals older than 6 years in the USA (Staras et al. 2006). CMV is transmitted by body fluids such as saliva. In some people, a syndrome with symptoms similar to infectious mononucleosis or glandular fever appear. Most infections are asymptomatic. After infection, the virus remains latent in myeloid cells (Rao 2014).

EBV is known as the cause of infectious mononucleosis. However, many children become infected with EBV and have no symptoms at all. EBV is transmitted by saliva and infects B cells and epithelial cells (Rao 2014). Among children (6-19 years old) the EBV prevalence varies between 54 % and 83 % in the USA (Dowd et al. 2013).

Noteworthy, there are studies showing that herpesvirus infections may have a protective character. Negative association between the occurrence of CD and herpesvirus infections was noticed. Such a notion came up from a cross-sectional study published in 2009 investigating antibodies against CMV, rubella virus and EBV in 90 CD patients in comparison with 297 controls. A significantly higher prevalence of CMV-IgG and rubella-IgG antibodies was found in the control group. An interesting situation appears in the case of antibodies to EBV. Among CD patients, IgM antibodies were more prevalent than in the control group, and this observation almost reached statistical significance ($P < 0.06$). In the control group, EBV-IgG was

significantly more frequent. The observed phenomenon can be understood as the result of different immunological background in CD patients in comparison with healthy controls. In conclusion, CMV, EBV and rubella virus infections could be responsible for decreasing a risk of CD (Plot et al. 2009). Generally, the presence of IgM antibodies is considered to be a mark of active infection and they disappear subsequently, while IgG antibodies persist in individuals (Štork et al. 2008). Therefore, an alternative explanation could be that CD patients were infected by EBV recently and having already undergone a CD onset, whereas individuals in control groups were infected long before it could possibly protect them from CD development.

A recent study from 2016 investigated antibodies against tTG and CMV, EBV and HSV-1 in more than 4 000 children, at the age of 6 (Jansen et al. 2016). Among children, 1.3 % subjects were tTGA positive. The occurrence of high titers of tTGA correlated with lower titters of antibodies against these three viruses (aOR = 0.38, 95% CI 0.18-0.78, $P < 0.01$) even after adjusting for ethnicity, socioeconomic status, breast-feeding, and day-care attendance. Therefore, authors suggested that there is a possible protective role of herpesvirus infections in the development of CD autoimmunity. The inverse distribution of CMV antibodies regardless EBV and HSV-1 antibodies and tTG antibodies was also significant. The authors suggested an interesting hypothesis – the increase of CD cases the last decades can be caused by children's first encounter with these infections later in life than children in the past. According to this hypothesis, nowadays children lose a protective effect of such infections, while there would still be a time to prevent CD. The results can also indicate this possibility: children that encountered herpesvirus infections are also more likely to be encountered by lots of other infections and just these infections or their coordination can have an influence in CD pathogenesis. Another explanation as to why these viruses could have a protective effect, is that herpesvirus infection can protect the host from further infections caused by other viruses or bacteria through a cross-protective mechanism. Finally, there is a possibility that the children with CD-oriented immune profile are less prone to herpesvirus infections and produce less anti-herpesvirus antibodies. Unfortunately, tTGA positivity remains to be just an indicator leading to possible CD diagnosis. It is not mentioned how many children were diagnosed with CD. Also, authors considered only CD autoimmunity (Jansen et al. 2016).

In contrast, there is an indication that CD markers may develop during acute infections caused by CMV or EBV. Sarmiento et al. tested patients infected by CMV or EBV infections, and nobody had CD before onset of infection. Among 20 EBV-IgG positive patients, 5 patients were tTGA positive, whereas all matched controls were negative. Regarding CMV infections, results were 2/21, which means 9.5 % CMV patients were tTGA positive, while nobody in the control group was tTGA positive, but the observation is not statistically significant. Finally, authors suggested that tTGA antibodies can develop during these infections (Sarmiento et al. 2012), which is not supported by the studies mentioned before. We can hypothesize that tTG antibodies can develop during CMV or EBV infection, but from a long-term point of view, experience with CMV or EBV infections can protect patients from the onset of CD autoimmunity. More studies are needed in the future to verify the association.

In 2016, it was shown that active EBV infection is predominantly present in patients with refractory celiac disease (RCD) in comparison to controls (patients with uncomplicated CD). RCD patients are those patients without any improvement of intestinal tissue inflammation despite strict GFD. This situation increases the possibility of complications such as enteropathy-associated T-cell lymphoma. In this study, 70.5 % (12/17) RCD patients were EBV positive in comparison to 16.6 % (4/24) EBV positive CD patients ($P < 0,01$). In addition, EBV infection was more frequent in RCD II (clonal aberrant intraepithelial lymphocytes - IEL, high risk for developing an enteropathy associated T-cell lymphoma) in comparison with RCD I (normal IEL). Data shows that EBV infects lymphoid and epithelial cells and infections are mainly active. Biopsies were taken when patients did not take any steroids. However, previous usage of steroids could contribute to manifestation of EBV infections (Perfetti et al. 2016).

The influence of herpesvirus infections in the pathogenesis of CD remains controversial. In addition, it is needed to evaluate, if EBV infections is just a consequence of immunosuppressive treatment in RCD patients, or if the infection can be a causative factor of RCD.

5 Cohort studies investigating type 1 diabetes and celiac disease

Similar investigation methods of virus infections in disease pathogenesis have been used in type 1 diabetes (T1D), a chronic immune-mediated disease caused by the destruction of pancreatic insulin-producing β-cells. This kind of research has a long tradition in T1D, dating back to the late 1960s, when a notion of similar seasonality of T1D and Coxsackie B infections stimulated the first studies and led to a seminal discovery (Gamble et al. 1971). CD and T1D share many features, such as similar genetic predispositions, a common outbreak during infancy, both show similar chronic and incurable attributes, and the incidence of both is presently observed to be increasing. These two diseases are hypothesized to be trigger by environmental factors, including infections (Frisk et al. 2008).

Several cohort studies are aiming to investigate the natural course of type 1 diabetes, and might also be instrumental in the research of celiac disease. Epidemiologic methods that have performed well in T1D are now being implemented in CD in order to find environmental factors responsible for its pathogenesis.

5.1 Type 1 diabetes and enterovirus

In T1D, enterovirus as an environmental trigger has been studied for over four decades which makes it the longest studied viral candidate for a non-infectious disease. Enterovirus is a single stranded RNA virus belonging to the *Picornaviridae* family. Enterovirus infections are very common and mostly asymptomatic. The virus first replicates in mucosa of pharynx or in the gut and mesenteric lymph nodes, occasionally causing viremia, and very rarely invading secondary sites like nervous system, liver, or pancreas occurs. It is assumed to cause T1D by infecting the β-cells of islets of Langerhans, but the mechanisms are still unknown. It is thought to be caused by either a direct infection of β-cells, mechanism of molecular mimicry, a bystander damage or viral persistence (Craig et al. 2013).

In comparison with studying the duodenum in CD, it is challenging to study viruses in pancreas, since the specimens are extremely difficult to obtain (Krogvold et al. 2014). Therefore, the research performed so far has mostly resorted to detection of the virus from the site of its primary replication (stool, gut biopsies), or from blood and its components. It appears that the virus in

stool is not associated with an increased risk of T1D (with a potential exception of a recent study from Finland (Honkanen et al. 2017)). On the other hand, there are convincing studies linking the presence of enteroviruses in blood to an increased risk of islet autoimmunity leading to T1D, or T1D itself (Craig et al. 2013, Hyoty 2016).

5.2 Prospective cohort studies

Environmental factors have long been studied in several longitudinally monitored neonatal cohorts of individuals, preselected based on their increased genetic risk of T1D (Rønningen 2013). This approach has not been previously used in CD, despite the well-known shared genetic determinants of the disease. This has recently changed. Currently, several cohorts (TEDDY, MIDIA, DAISY and PAGE) are being actively studied for CD apart of T1D, by utilizing similar design and biological samples.

The first of the cohorts primarily following T1D pathogenesis were **BABYDIAB**, which recruited German newborns from 1989 to 2000. In total, more than 123 000 children with T1D afflicted first-degree relative underwent screening. Islet autoantibodies were detected in 165 children, that were selected. Regular blood sampling and questionnaires were required. However, this study does not focus on the presence of CD (BABYDIAB 2017).

The DAISY study (The Diabetes and Autoimmunity Study in the Young), beginning in 1993 in Denver, is the first study investigating circumstances of both T1D and CD onset. It is a population based study, where newborns were recruited between 1993 and 2004. Altogether, 30 000 children were tested for T1D-associated HLA alleles. The study included over 2 000 children with high-risk HLA genotypes for CD and T1D or children with T1D in their family. Repeatedly, children have been screened for CD- and T1D-related autoantibodies and rectal swabs, blood samples and questionnaires were collected (Stene et al. 2010).

DIPP (Diabetes Prediction and Prevention study) is a population-based study conducted in Finland, established in 1994. Altogether 150 000 newborns have been tested for T1D-typical HLA alleles. Autoantibodies are measured every 3 months until 2 years of age, then annually until the age of 15 years. Approximately 12 000 children have been followed (DIPP 2017).

Studies, presented above, share several disadvantages, such as differences in exposure measurement and recall bias. A newer study from 2003 managed to avoid most of these. **TEDDY** (The Environmental Determinants of Diabetes in the Young) have started in 2003 in four countries, Germany, the USA, Finland and Sweden. Currently, it is the largest study on T1D pathogenesis. With 421 000 children screened for T1D risk genotypes and 26 000 subjects in the follow-up. The protocol includes prospectively collected specimens of blood (every 3 months until the age of 4, then every 6 months until the age of 15), stool samples (monthly until 4 years of age, then biannually until the age of 15) and regularly collected questionnaires. Thanks to the design of the study, valuable insights into environmental influences are expected. TEDDY provides a unique opportunity to study the relations between the environment and the disease onset (TEDDY 2017).

Further projects studying children at risk of T1D or CD are MIDIA and PAGE studies. The PAGE study is a sub-study in the prospective population-wide Norwegian mother and child cohort (MoBa). MoBa, beginning in 1999, has studied mothers and their children since pregnancies, collecting biological materials and data on infections, diet and medications by questionnaires. More than 100 000 children were included (MoBa 2017).

The PAGE study (Prediction of Autoimmune diabetes and celiac disease in childhood by Genes and perinatal Environment) is a nested-case control study recruiting individuals from the Norwegian Patient Register and the Norwegian Childhood Diabetes Registry, while the prospective information about them are gained from MoBa project. PAGE study examines factors occurring early in life using questionnaires, genotyping and biomarkers from maternal and cord blood. The focus is on the influence of diet, dietary supplements, antibiotics, infections and possible risk of maternal microchimerism on the later development of CD or T1D (Stene et al. 2014).

The MIDIA study (a Norwegian acronym for The Environmental Triggers of Type 1 Diabetes Study) is a population-based longitudinal prospective cohort study of Norwegian newborns with genetic predispositions for T1D and CD. Over 50 000 newborns were screened and approximately 950 of them, carrying the highest-risk genotype for T1D, were included and followed. Individuals were recruited from the general population between 2001 and 2006. Subjects are monitored until the age of 15. The protocol includes collection of monthly fecal

samples (month 3-36), quarterly questionnaires and annually blood samples. To date, 27 patients with CD and approximately 40 diabetic patients have been identified in the cohort (About MIDIA, 2017).

The aforementioned studies offer special opportunity for the study of environmental triggers of T1D and CD. For instance, such collections of samples could verify the role of enterovirus in T1D pathogenesis, since the timing and serotypes of enteroviruses can be readily investigated in connection with the beginning of T1D-related autoantibodies production. Considering the previous overview of viruses involved in CD, studies could offer data evaluating whether infections with e.g. adenovirus, a long-known candidate, or recently implicated orthoreoviruses (Bouziat et al. 2017), may influence the risk of CD later in life.

As compared to T1D, only a few studies have also been focused on CD. The general design of longitudinal studies investigating early stages of CD and T1D must respect several typical pathogenic features of these diseases: (1) Their onset is the most common in childhood, thus studies are focused on children. (2) Because of the rate of incidence of these two diseases, studied cohorts must be relatively large and contain genetically susceptible subjects. (3) Such studies are best performed in countries with high disease prevalence, and adequate resources, such as Nordic countries (4) Due to the multifactorial character of these diseases, it is required to filter out other influences apart from the studied ones – matched controls are used primarily for elimination of local and temporal peaks in infection rates. (5) Large datasets from questionnaires and other metadata are instrumental in the control of confounding factors.

6 Conclusion

Celiac disease and type 1 diabetes, being among the most common chronic diseases in children, are increasing in the population and much effort is devoted to the research of their environmental triggers.

Large-scale prospective studies are performed to evaluate the influence of the environment. Since the processes leading to the onset of these diseases are probably triggered early in life, children are followed since birth or even during their mother´s pregnancy. In Nordic countries, where the prevalence of these two diseases is one of the highest, such studies are conducted. It is expected that these projects will provide valuable insights into disease etiology and suggest ways to identify – and eventually eliminate – environmental triggers.

Among environmental factors involved in celiac disease development, there is a clear evidence suggesting the association between various infections and CD onset. Attention is paid to microbiota composition. It is suggested that gut dysbiosis precedes CD, and can alter the susceptibility to CD onset.

Considering viral infections in CD pathogenesis, there are several good candidates identified by previous research. Among them, the focus is logically on gastrointestinal viruses that are being intensively studied. Also, there is evidence of a possible link between hepatotropic viruses and celiac disease. Thanks to novel detection methods, it is expected that also new viruses will become candidates for association with celiac disease, as has been exemplified by astrovirus. Noteworthy, there is evidence supporting that "protective" infections may exist and possibly reduce the likelihood of CD onset. To date, it has not been possible to judge the importance of individual viruses, and more studies must be conducted.

Apparently, there are many unclear issues in the etiology of CD. The development of CD requires several "hits" and it is difficult to identify all of them and their interaction. Future studies are needed to identify further risk factors and to possibly suggest approaches diminishing the likelihood of CD onset.

7 References

ABADIE, V., SOLLID, L. M., BARREIRO, L. B. and JABRI, B., 2011. Integration of Genetic and Immunological Insights into a Model of Celiac Disease Pathogenesis. *Annual Review of Immunology* [online]. **29**(1), 493–525. ISSN 0732-0582. Available at: doi:10.1146/annurev-immunol-040210-092915

ABID, S. G., ABOUD, R. S., FADIL, H. Y. and ABOUD, A. S., 2015. Relationship between Chronic Hepatitis B Virus and Pathogenicity of Celiac Disease in the Iraqi Patients. *Journal of Pharmaceutical, Chemical and Biological Sciences* [online]. **3**(4), 578–583 [accessed. 2017-03-07]. ISSN 2348-7658Available at: http://www.jpcbs.info/2015_3_4_17_Shiamaa G Abid.pdf

About MIDIA - NIPH [online] [accessed. 2017-05-06]. Available at: https://www.fhi.no/en/studies/midia/about-midia/

BABYDIAB-Studie | www.diabetes.med.tum.de [online] [accessed. 2017-05-06]. Available at: http://www.diabetes.med.tum.de/de/node/233

DIPP | Research | DIPP Project [online] [accessed. 2017-05-06]. Available at: http://dipp.utu.fi/index.php?mid=8&language=en

The Environmental Determinants of Diabetes in the Young (TEDDY) Web Site [online] [accessed. 2017-05-06]. Available at: https://teddy.epi.usf.edu/

BOUZIAT, R., STENCEL-BAERENWALD, J. E., IKIZLER, M., MAYASSI, T., MEISEL, M., KIM, S. M., DISCEPOLO, V., PRUIJSSERS, A. J., ERNEST, J. D., ISKARPATYOTI, J. A., COSTES, L. M. M., LAWRENCE, I., PALANSKI, B. A., VARMA, M., ZURENSKI, M. A., KHOMANDIAK, S., SAMSOM, J. N., REINECKER, H. and KUPFER, S. S., 2017. Reovirus infection triggers inflammatory responses to dietary antigens and development of celiac disease. *Science* [online]. **50**(April), 44–50. ISSN 0036-8075. Available at: doi:10.1126/science.aah5298

CANOVA, C., ZABEO, V., PITTER, G., ROMOR, P., BALDOVIN, T., ZANOTTI, R. and SIMONATO, L., 2014. Association of Maternal Education, Early Infections, and Antibiotic Use With Celiac Disease: A Population-Based Birth Cohort Study in Northeastern Italy. *American Journal of Epidemiology* [online]. **180**(1), 76–85 [accessed. 2017-03-27]. Available at: doi:10.1093/aje/kwu101

CENIT, M., OLIVARES, M., CODOÑER-FRANCH, P. and SANZ, Y., 2015. Intestinal Microbiota and Celiac Disease: Cause, Consequence or Co-Evolution? *Nutrients* [online]. 17. 8., **7**(8), 6900–6923 [accessed. 2017-04-18]. ISSN 2072-6643. Available at: doi:10.3390/nu7085314

COLLADO, M. C., DONAT, E., RIBES-KONINCKX, C., CALABUIG, M. and SANZ, Y., 2009. Specific duodenal and faecal bacterial groups associated with paediatric coeliac disease. *Journal of Clinical Pathology* [online]. **62**(3), 264–269. ISSN 0021-9746. Available at: doi:10.1136/jcp.2008.061366

CRAIG, M. E., NAIR, S., STEIN, H. and RAWLINSON, W. D., 2013. Viruses and type 1 diabetes: A new look at an old story. *Pediatric Diabetes* [online]. **14**(3), 149–158. ISSN 1399543X. Available at: doi:10.1111/pedi.12033

ČIHAŘ, M., LIŠKA, K. and KLENKOVÁ, K., 2002. RSV infekce - současné možnosti léčby a imunoprofylaxe [online]. 58–61. Available at: https://www.pediatriepropraxi.cz/pdfs/ped/2002/02/03.pdf

DAY, J. M., 2009. The diversity of the orthoreoviruses: Molecular taxonomy and phylogentic divides. *Infection, Genetics and Evolution* [online]. **9**(4), 390–400. ISSN 15671348. Available at: doi:10.1016/j.meegid.2009.01.011

DE MEIJ, T. G. J., BUDDING, a E., GRASMAN, M. E., KNEEPKENS, C. M. F., SAVELKOUL, P. H. M. and MEARIN, M. L., 2013. Composition and diversity of the duodenal mucosa-associated microbiome in children with untreated coeliac disease. *Scandinavian Journal of Gastroenterology* [online]. **48**(5), 530–536. ISSN 00365521 (ISSN). Available at: doi:10.3109/00365521.2013.775666

DOLCINO, M., ZANONI, G., BASON, C., TINAZZI, E., BOCCOLA, E., VALLETTA, E., CONTREAS, G., LUNARDI, C. and PUCCETTI, A., 2013. A subset of anti-rotavirus antibodies directed against the viral protein VP7 predicts the onset of celiac disease and induces typical features of the disease in the intestinal epithelial cell line T84. *Immunologic Research* [online]. **56**(2–3), 465–476. ISSN 0257277X. Available at: doi:10.1007/s12026-013-8420-0

DOWD, J. B., PALERMO, T., BRITE, J., MCDADE, T. W. and AIELLO, A., 2013. Seroprevalence of Epstein-Barr Virus Infection in U.S. Children Ages 6-19, 2003-2010. *PLoS ONE* [online]. **8**(5), 2003–2010. ISSN 19326203. Available at: doi:10.1371/journal.pone.0064921

ELITSUR, Y., SIGMAN, T., WATKINS, R., PORTO, A. F., LEONARD PUPPA, E. L., FOGLIO, E. J. and PRESTON, D. L., 2016. Tissue Transglutaminase Levels Are Not Sufficient to Diagnose Celiac Disease in North American Practices Without Intestinal Biopsies. *Digestive Diseases and Sciences* [online]. B.m.: Springer US, **62**(1), 1–5. ISSN 15732568. Available at: doi:10.1007/s10620-016-4354-4

FINE, K. D., OGUNJI, F., SALOUM, Y., BEHARRY, S., CRIPPIN, J. and WEINSTEIN, J., 2001. Celiac sprue: Another autoimmune syndrome associated with hepatitis C. *American Journal of Gastroenterology* [online]. **96**(1), 138–145. ISSN 00029270. Available at: doi:10.1016/S0002-9270(00)02257-7

FOCÀ, A., LIBERTO, M. C., QUIRINO, A., MARASCIO, N., ZICCA, E. and PAVIA, G., 2015. Gut inflammation and immunity: what is the role of the human gut virome? | Read by QxMD. *Gut inflammation and immunity: what is the role of the human gut virome?* [online]. B.m.: Hindawi Publishing Corporation, **2015**. Available at: http://dx.doi.org/10.1155/2015/326032 Review

FRISK, G., HANSSON, T., DAHLBOM, I. and TUVEMO, T., 2008. A unifying hypothesis on the development of type 1 diabetes and celiac disease: Gluten consumption may be a shared causative factor. *Medical Hypotheses* [online]. **70**(6), 1207–1209. ISSN 03069877. Available at: doi:10.1016/j.mehy.2007.05.058

FRÜHAUF, P., SZITÁNYI, P. and VYHNÁNEK, R., 2012. Nové doporučení ESPGHAN pro diagnostiku celiakie. *Pediatrie pro Praxi*. **13**(3), 211–213. ISSN 12130494.

GAMBLE, D. R., TAYLOR, K. W. and CUMMING H., 1971. Coxsackie Viruses and Diabetes. *The Lancet* [online]. **298**(7739), 1423. ISSN 01406736. Available at: doi:10.1016/S0140-6736(71)90697-0

GAMINO-ARROYO, A. E., MORENO-ESPINOSA, S., LLAMOSAS-GALLARDO, B., ORTIZ-HERNANDEZ, A. A., GUERRERO, M. L., GALINDO-FRAGA, A., GALAN-HERRERA, J. F., PRADO-GALBARRO, F. J., BEIGEL, J. H., RUIZ-PALACIOS, G. M. and NOYOLA, D. E., 2016. Epidemiology and clinical characteristics of respiratory syncytial virus infections among children and adults in Mexico. *Influenza and other Respiratory Viruses* [online]. (July 2016), 48–56. ISSN 17502659. Available at: doi:10.1111/irv.12414

GANDOLFI, L., PRATESI, R., CORDOBA, J. C. M., TAUIL, P. L., GASPARIN, M. and CATASSI, C., 2000. Prevalence of celiac disease among blood donors in Brazil. *The American Journal of Gastroenterology* [online]. B.m.: Nature Publishing Group, 3., **95**(3), 689–692 [accessed. 2017-04-28]. ISSN 0002-9270. Available at: doi:10.1111/j.1572-0241.2000.01847.x

GREEN, P. H. R., LEBWOHL, B. and GREYWOODE, R., 2015. Celiac disease. *Journal of Allergy and Clinical Immunology* [online]. B.m.: Elsevier Ltd, **135**(5), 1099–1106. ISSN 10976825. Available at: doi:10.1016/j.jaci.2015.01.044

HONKANEN, H., OIKARINEN, S., NURMINEN, N., LAITINEN, O. H., HUHTALA, H., LEHTONEN, J., RUOKORANTA, T., HANKANIEMI, M. M., LECOUTURIER, V., ALMOND, J. W., TAURIAINEN, S., SIMELL, O., ILONEN, J., VEIJOLA, R., VISKARI, H., KNIP, M. and HYÖTY, H., 2017. Detection of enteroviruses in stools precedes islet autoimmunity by several months: possible evidence for slowly operating mechanisms in virus-induced autoimmunity. *Diabetologia* [online]. B.m.: Diabetologia, 1–8. ISSN 0012-186X. Available at: doi:10.1007/s00125-016-4177-z

HUSBY, S. and MURRAY, J. A., 2013. New aspects of the diagnosis of celiac disease in children, adolescents, and adults. *Mayo Clinic Proceedings* [online]. **88**(6). ISSN 00256196. Available at: doi:10.1016/j.mayocp.2013.03.018

HYOTY, H., 2016. Viruses in type 1 diabetes. *Pediatric Diabetes* [online]. **17**(5), 56–64. ISSN 13995448. Available at: doi:10.1111/pedi.12370

JANSEN, M. A., VAN DEN HEUVEL, D., VAN DER ZWET, K. V, JADDOE, V. W., HOFMAN, A., ESCHER, J. C., FRAAIJ, P. L., HOOIJKAAS, H., VAN ZELM, M. C. and MOLL, H. A., 2016. Herpesvirus Infections and Transglutaminase type 2 Antibody Positivity in Childhood: The Generation R Study. *Journal of Pediatric Gastroenterogy and Nutrition* [online]. **63**(4), 423–430. ISSN 1536-4801. Available at: doi:10.1097/MPG.0000000000001163

KAGNOFF, B. Y. M. F., AUSTIN, R. K., HUBERT, J. J., BERNARDIN, J. E. and KASARDA, D. D., 1984. Possible role for a human adenovirus in the pathogenesis of celiac disease. *Gut*. **160**, 1544–1557.

KAGNOFF, M. F., PATERSON, Y. J., KUMAR, P. J., KASARDA, D. D., CARBONE, F. R., UNSWORTH, D. J. and AUSTIN, R. K., 1987. Evidence for the role of a human intestinal adenovirus in the pathogenesis of coeliac disease. *Gut*. **28**, 995–1001.

KEMPPAINEN, K. M., LYNCH, K. F., LIU, E., LÖNNROT, M., SIMELL, V., BRIESE, T., KOLETZKO, S., HAGOPIAN, W., REWERS, M., SHE, J.-X., SIMELL, O., TOPPARI, J., ZIEGLER, A.-G., AKOLKAR, B., KRISCHER, J. P., LERNMARK, Å., HYÖTY, H., TRIPLETT, E. W. and AGARDH, D., 2016. Factors That Increase Risk of Celiac Disease Autoimmunity After a Gastrointestinal Infection in Early Life. *Clinical Gastroenterology and Hepatology* [online]. 11. [accessed. 2017-04-03]. ISSN 15423565. Available at: doi:10.1016/j.cgh.2016.10.033

KOZDERKA, C., PAZDIORA, P., PRYMULA, R., ŠEBKOVÁ, A. and VANČÍKOVÁ, Z., 2014. Doporučení pro očkování proti rotavirovým infekcím. *Česká vakcinologická společnost* [online]. 3–4. Available at: http://www.mzcr.cz/dokumenty/doporuceni-pro-ockovani-proti-rotavirovym-infekcim-v-ceske-republice_8892_1985_5.html

KROGVOLD, L., EDWIN, B., BUANES, T., LUDVIGSSON, J., KORSGREN, O., HYÖTY, H., FRISK, G., HANSSEN, K. F. and DAHL-JØRGENSEN, K., 2014. Pancreatic biopsy by minimal tail resection in live adult patients at the onset of type 1 diabetes: Experiences from the DiViD study. *Diabetologia* [online]. **57**(4), 841–843. ISSN 14320428. Available at: doi:10.1007/s00125-013-3155-y

LAHDEAHO, M. L., PARKKONEN, P., REUNALA, T., MAKI, M. and LEHTINEN, M., 1993. Antibodies to E1b Protein-Derived Peptides of Enteric Adenovirus Type 40 Are Associated with Celiac Disease and Dermatitis Herpetiformis. *Clinical Immunology and Immunopathology* [online]. 12., **69**(3), 300–305 [accessed. 2017-03-31]. ISSN 00901229. Available at: doi:10.1006/clin.1993.1184

LAWLER, M., HUMPHRIES, P., O'FARRELLY, C., HOEY, H., SHEILS, O., JEFFERS, M., O'BRIAIN, D. S. and KELLEHER, D., 1994. Adenovirus 12 E1A gene detection by polymerase chain reaction in both the normal and coeliac duodenum. *Gut*. **35**(9), 1226–1232. ISSN 0017-5749.

LIU, E., LEE, H.-S., ARONSSON, C. A., HAGOPIAN, W. A., KOLETZKO, S., REWERS, M. J., EISENBARTH, G. S., BINGLEY, P. J., BONIFACIO, E., SIMELL, V. and AGARDH, D., 2014. Risk of Pediatric Celiac Disease According to HLA Haplotype and Country. *New England Journal of Medicine* [online]. **371**(1), 42–49. ISSN 0028-4793. Available at: doi:10.1056/NEJMoa1313977

LOHI, S., MUSTALAHTI, K., KAUKINEN, K., LAURILA, K., COLLIN, P., RISSANEN, H., LOHI, O., BRAVI, E., GASPARIN, M., REUNANEN, A. and MÄKI, M., 2007. Increasing prevalence of coeliac disease over time. *Alimentary Pharmacology and Therapeutics* [online]. **26**(9), 1217–1225. ISSN 02692813. Available at: doi:10.1111/j.1365-2036.2007.03502.x

LUDVIGSSON, J. F., BAI, J. C., BIAGI, F., CARD, T. R., CIACCI, C., CICLITIRA, P. J., GREEN, P. H. R., HADJIVASSILIOU, M., HOLDOWAY, A., VAN HEEL, D. A. and SANDERS, D. S., 2014. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. *Gut* [online]. **63**, 1210–1228. Available at: doi:10.1136/gutjnl-2013-306578

MAHON, J., BLAIR, G. E., WOOD, G. M., SCOTT, B. B., LOSOWSKY, M. S. and HOWDLE, P. D., 1991. Is persistent adenovirus 12 infection involved in coeliac disease? A search for viral DNA using the polymerase chain reaction. *Gut* [online]. 10., **32**(10), 1114–6 [accessed. 2017-04-01]. ISSN 0017-5749. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1955164

MARCONCINI, M. and FAYAD, L., 2013. Autoantibody profile in individuals with chronic hepatitis C. *Revista da Sociedade Brasileira de Medicina Tropical* [online]. **46**(2), 147–153. Available at: http://dx.doi.org/10.1590/0037-8682-0039-2013

MARGONI, D., CHOULIARAS, G., DUSCAS, G., VOSKAKI, I., VOUTSAS, N., PAPADOPOULOU, A., PANAYIOTOU, J. and ROMA, E., 2012. Bone health in children with celiac disease assessed by dual x-ray absorptiometry: effect of gluten-free diet and predictive value of serum biochemical indices. *Journal of pediatric gastroenterology and nutrition* [online]. 5., **54**(5), 680–4 [accessed. 2017-04-01]. ISSN 1536-4801. Available at: doi:10.1097/MPG.0b013e31823f5fc5

MÅRILD, K., KAHRS, C., TAPIA, G. and STENE, L., 2015a. Infections and risk of celiac disease in childhood: a prospective nationwide cohort study. *The American journal of* [online]. [accessed. 2017-03-07]. Available at: http://www.nature.com/ajg/journal/vaop/ncurrent/full/ajg2015287a.html

MÅRILD, K., KAHRS, C., TAPIA, G. and STENE, L., 2015b. Infections and risk of celiac disease in childhood: a prospective nationwide cohort study. *The American Journal of Gastroenterology* [online]. [accessed. 2017-03-07]. Available at: http://www.nature.com/ajg/journal/vaop/ncurrent/full/ajg2015287a.html

MUSTALAHTI, K., CATASSI, C., REUNANEN, A., FABIANI, E., HEIER, M., MCMILLAN, S., MURRAY, L., METZGER, M.-H., GASPARIN, M., BRAVI, E. and MÄKI, M., 2010. The prevalence of celiac disease in Europe: Results of a centralized, international mass screening project. *Annals of Medicine* [online]. 11. 12., **42**(8), 587–595 [accessed. 2017-04-28]. ISSN 0785-3890. Available at: doi:10.3109/07853890.2010.505931

NAU, A. L., FAYAD, L., LAZZAROTTO, C., BEATRIZ, M., SHIOZAWA, C., DANTAS-CORRÊA, E. B., SCHIAVON, L. D. L. and NARCISO-SCHIAVON, J. L., 2013. Case Report Article Prevalence and clinical features of celiac disease in patients with hepatitis B virus infection in Southern Brazil. *Revista da Sociedade Brasileira de Medicina Tropical* [online]. **46**(May), 397–402. Available at: http://dx.doi.org/10.1590/0037-8682-0093-2013%0AMajor

OLIVARES, M. and SANZ, Y., 2015. Intestinal Microbiota and Celiac Disease [online]. 193–221 [accessed. 2017-04-18]. Available at: doi:10.3926/oms.253

PARASHAR, U. D., GIBSON, C. J., BRESEE, J. S. and GLASS, R. I., 2006. Severe Childhood Diarrhea. *Emerging Infectious Diseases* [online]. **12**(2), 304–306. ISSN 1080-6040. Available at: doi:10.3201/eid1202.050006

PEBODY, R. G., ANDREWS, N., BROWN, D., GOPAL, R., DE MELKER, H., FRANÇOIS, G., GATCHEVA, N., HELLENBRAND, W., JOKINEN, S., KLAVS, I., KOJOUHAROVA, M., KORTBEEK, T., KRIZ, B., PROSENC, K., ROUBALOVA, K., TEOCHAROV, P., THIERFELDER, W., VALLE, M., VAN DAMME, P. and VRANCKX, R., 2004. The seroepidemiology of herpes simplex virus type 1 and 2 in Europe. *Sexually Transmitted Infections* [online]. **80**(3), 185–191. ISSN 1368-4973. Available at: doi:10.1136/sti.2003.005850

PERFETTI, V., BALDANTI, F., LENTI, M. V., VANOLI, A., BIAGI, F., GATTI, M., RIBONI, R., DALLERA, E., PAULLI, M., PEDRAZZOLI, P. and CORAZZA, G. R., 2016. Detection of Active Epstein-Barr Virus Infection in Duodenal Mucosa of Patients With Refractory Celiac Disease. *Clinical gastroenterology and hepatology* [online]. B.m.: Elsevier, Inc, **14**(8), 1216–1220. ISSN 1542-7714. Available at: doi:10.1016/j.cgh.2016.03.022

PLOT, L. and AMITAL, H., 2009. Infectious associations of Celiac disease. *Autoimmunity Reviews* [online]. 2., **8**(4), 316–319 [accessed. 2017-03-07]. ISSN 15689972. Available at: doi:10.1016/j.autrev.2008.10.001

PLOT, L., AMITAL, H., BARZILAI, O., RAM, M., NICOLA, B. and SHOENFELD, Y., 2009. Infections may have a protective role in the etiopathogenesis of celiac disease. *Annals of the New York Academy of Sciences* [online]. **1173**, 670–674. ISSN 00778923. Available at: doi:10.1111/j.1749-6632.2009.04814.x

RAO, K. B., 2014. Herpes Viruses – An Overview. *Journal of Pharmacy* [online]. **4**(10), 39–41. Available at: http://www.iosrphr.org/papers/v4i10/G041039041.pdf

RØNNINGEN, K. S., 2013. Type 1 diabetes: Prospective cohort studies for identification of the environmental trigger. *Archivum Immunologiae et Therapiae Experimentalis* [online]. **61**(6), 459–468. ISSN 0004069X. Available at: doi:10.1007/s00005-013-0247-9

ROTH, D. E., SHAH, R., BLACK, R. E. and BAQUI, A. H., 2010. Vitamin D status and acute lower respiratory infection in early childhood in Sylhet, Bangladesh. *Acta paediatrica* [online]. 3., **99**(3), 389–93 [accessed. 2017-04-01]. ISSN 1651-2227. Available at: doi:10.1111/j.1651-2227.2009.01594.x

RUBIO-TAPIA, A., KYLE, R. A., KAPLAN, E. L., JOHNSON, D. R., PAGE, W., ERDTMANN, F., BRANTNER, T. L., KIM, W. R., PHELPS, T. K., LAHR, B. D., ZINSMEISTER, A. R., MELTON, L. J. and MURRAY, J. A., 2009. Increased Prevalence and Mortality in Undiagnosed Celiac Disease. *Gastroenterology* [online]. B.m.: Institute American Gastroenterological Association, **137**(1), 88–93. ISSN 00165085. Available at: doi:10.1053/j.gastro.2009.03.059

RUBIO-TAPIA, A., LUDVIGSSON, J. F., BRANTNER, T. L., MURRAY, J. A. and EVERHART, J. E., 2012. The Prevalence of Celiac Disease in the United States. *The American Journal of Gastroenterology* [online]. B.m.: Nature Publishing Group, 31. 10., **107**(10), 1538–1544 [accessed. 2017-04-28]. ISSN 0002-9270. Available at: doi:10.1038/ajg.2012.219

RUGGERI, C., LA MASA, A. T., RUDI, S., SQUADRITO, G., DI PASQUALE, G., MAIMONE, S., CACCAMO, G., PELLEGRINO, S., RAIMONDO, G. and MAGAZZA, G., 2008. Celiac disease and non-organ-specific autoantibodies in patients with chronic hepatitis C virus infection. *Digestive Diseases and Sciences* [online]. **53**(8), 2151–2155. ISSN 01632116. Available at: doi:10.1007/s10620-007-0146-1

SARMIENTO LUIS, 2012. Type 1 diabetes associated and Tissue Transglutaminase Autoantibodies in Patients Without Type 1 Diabetes and Coeliac Disease With Confirmed Viral Infections. *Journal of Medical Virology* [online]. **30**(12), 4799–4804. ISSN 02507005. Available at: doi:10.1002/jmv

SHEPARD, C. W., SIMARD, E. P., FINELLI, L., FIORE, A. E. and BELL, B. P., 2006. Hepatitis B virus infection: Epidemiology and vaccination. *Epidemiologic Reviews* [online]. **28**(1), 112–125. ISSN 0193936X. Available at: doi:10.1093/epirev/mxj009

SMITS, S. L., VAN LEEUWEN, M., VAN DER EIJK, A. A., FRAAIJ, P. L. A., ESCHER, J. C., SIMON, J. H. and OSTERHAUS, A. D. M. E., 2010. Human astrovirus infection in a patient with new-onset celiac disease. *Journal of Clinical Microbiology* [online]. **48**(9), 3416–3418. ISSN 00951137. Available at: doi:10.1128/JCM.01164-10

IGLESIAS, S., VÁZQUEZ RODRÍGUEZ, S., ULLA ROCHA, J. L., BALTAR ARIAS, R., DÍAZ SAÁ, W., BARRIO ANTORANZ, J., GONZÁLEZ CARRERA, V. and VÁZQUEZ ASTRAY, E., 2010. [Onset of celiac disease after acute hepatitis B infection]. *Gastroenterologia y hepatologia* [online]. 1., **33**(1), 17–20 [accessed. 2017-03-27]. ISSN 0210-5705. Available at: doi:10.1016/j.gastrohep.2009.06.005

STARAS, S. A. S., DOLLARD, S. C., RADFORD, K. W., FLANDERS, W. D., PASS, R. F. and CANNON, M. J., 2006. Seroprevalence of cytomegalovirus infection in the United States, 1988-1994. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* [online]. **43**(9), 1143–51. ISSN 1537-6591. Available at: doi:10.1086/508173

STENE, L. C., HONEYMAN, M. C., HOFFENBERG, E. J., HAAS, J. E., SOKOL, R. J., EMERY, L., TAKI, I., NORRIS, J. M., ERLICH, H. A., EISENBARTH, G. S. and REWERS, M., 2006. Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: A longitudinal study. *American Journal of Gastroenterology* [online]. **101**(10), 2333–2340. ISSN 00029270. Available at: doi:10.1111/j.1572-0241.2006.00741.x

STENE, L. C., OIKARINEN, S., HYÖTY, H., BARRIGA, K. J., NORRIS, J. M., KLINGENSMITH, G., HUTTON, J. C., ERLICH, H. A., EISENBARTH, G. S. and REWERS, M., 2010. Enterovirus infection and progression from islet autoimmunity to type 1 diabetes: The Diabetes and Autoimmunity Study in the Young (DAISY). *Diabetes* [online]. **59**(12), 3174–3180. ISSN 00121797. Available at: doi:10.2337/db10-0866

STENE, L., JONER, G. and STØRDAL, K., 2014. Prediction of autoimmune diabetes and celiac disease in childhood by genes and perinatal environment: Design and initial aims of the PAGE study. *Norsk epidemiologi* [online]. [accessed. 2017-03-07]. Available at: http://www.ntnu.no/ojs/index.php/norepid/article/view/1811

STØRDAL, K., HAUGEN, M., BRANTSÆTER, A. L., LUNDIN, K. E. A. and STENE, L. C., 2014. Association Between Maternal Iron Supplementation During Pregnancy and Risk of Celiac Disease in Children. *Clinical Gastroenterology and Hepatology* [online]. 4., **12**(4), 624–631.e2 [accessed. 2017-04-05]. ISSN 15423565. Available at: doi:10.1016/j.cgh.2013.09.061

ŠTORK, J., 2008. *Dermatovenerologie* [online]. B.m.: Galén [accessed. 2017-04-01]. ISBN 9788024613604. Available at: http://eds.b.ebscohost.com/eds/detail/detail?vid=2&sid=e1048cca-ec83-4341-bf82-fe8e4deba645%40sessionmgr103&hid=122&bdata=Jmxhbmc9Y3Mmc2l0ZT1lZHMtbGl2ZSZzY29wZT1zaXRl#AN=kup.000966009&db=cat04374a

TARISH, H. R., HAMEED, W. S., ABDUL-MEHDI, R. J., ALI, H. and ALSHEREES, A., 2016. Role of Previous Adenovirus Infection and Its Association with IFN- α in Occurrence of Celiac Disease in Iraqi Patients Authors. *Journal of Medical Science And Clinical research*. **4**(4), 10326–10330.

THEVENOT, T., DENIS, J., JOUANNAUD, V., MONNET, E., RENOU, C., LABADIE, H., ABDELLI, N., NGUYEN-KHAC, E., DUMOUCHEL, P., BRESSON-HADNI, S., CHOUSTERMAN, M., DI MARTINO, V. and CADRANEL, J.-F., 2007. Coeliac disease in chronic hepatitis C: a French multicentre prospective study. *Alimentary pharmacology & therapeutics* [online]. **26**(9), 1209–16. ISSN 0269-2813. Available at: doi:10.1111/j.1365-2036.2007.03499.x

TJERNBERG, A. R. and LUDVIGSSON, J. F., 2014. Children with celiac disease are more likely to have attended hospital for prior respiratory syncytial virus infection. *Digestive Diseases and Sciences* [online]. ISSN 15732568. Available at: doi:10.1007/s10620-014-3046-1

UHNOO, I., WADELL, G., SVENSSON, L. and JOHANSSON, M. E., 1984. Importance of enteric adenoviruses 40 and 41 in acute gastroenteritis in infants and young children. *Journal of Clinical Microbiology* [online]. **20**(3), 365–372. ISSN 00951137. Available at: doi:0095-1137/84/090365-08$02.00/0

VAN BEURDEN, Y. H., VAN GILS, T., VAN GILS, N. A., KASSAM, Z., MULDER, C. J. J. and APARICIO-PAGAS, N., 2016. Serendipity in refractory celiac disease: Full recovery of duodenal villi and clinical symptoms after fecal microbiota transfer. *Journal of Gastrointestinal and Liver Diseases* [online]. **25**(3), 385–388. ISSN 18418724. Available at: doi:10.15403/jgld.2014.1121.253.cel

VASSSALI, C., 2016. *La celiachia Indice* [online]. Available at: http://www.scuolatao.com/corsi_agopuntura_tuina_mtc/images/tesi/TesiVassalli_ago_Celiachia.pdf

VISSER, J., ROZING, J., SAPONE, A., LAMMERS, K. and FASANO, A., 2009. Tight Junctions, Intestinal Permeability, and Autoimmunity Celiac Disease and Type 1 Diabetes Paradigms. *New York Academy of Sciences* [online]. [accessed. 2017-04-02]. Available at: doi:10.1111/j.1749-6632.2009.04037.x

VU, D.-L., BOSCH, A., PINTÓ, R. and GUIX, S., 2017. Epidemiology of Classic and Novel Human Astrovirus: Gastroenteritis and Beyond. *Viruses* [online]. **9**(2), 33. ISSN 1999-4915. Available at: doi:10.3390/v9020033

WACKLIN, P., KAUKINEN, K., TUOVINEN, E., COLLIN, P., LINDFORS, K., PARTANEN, J., MÄKI, M. and MÄTTÖ, J., 2013. The duodenal microbiota composition of adult celiac disease patients is associated with the clinical manifestation of the disease. *Inflammatory bowel diseases* [online]. **19**(5), 934–41. ISSN 1536-4844. Available at: doi:10.1097/MIB.0b013e31828029a9

WEBB, A. and STARR, M., 2005. Acute gastroenteritis in children. *Australian family physician* [online]. 4., **34**(4), 227–31 [accessed. 2017-04-29]. ISSN 0300-8495. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15861741

WIELAND, S. F. and CHISARI, F. V., 2005. Stealth and Cunning: Hepatitis B and Hepatitis C Viruses. *Journal of Virology* [online]. 1. 8., **79**(15), 9369–9380 [accessed. 2017-04-02]. ISSN 0022-538X. Available at: doi:10.1128/JVI.79.15.9369-9380.2005

ZIBERNA, F., DE LORENZO, G., SCHIAVON, V., ARNOLDI, F., QUAGLIA, S., DE LEO, L., VATTA, S., MARTELOSSI, S., BURRONE, O. R., VENTURA, A. and NOT, T., 2016. Lack of Evidence of Rotavirus-Dependent Molecular Mimicry as a Trigger of Celiac Disease. *Clinical and experimental immunology* [online]. 356–363. ISSN 1365-2249. Available at: doi:10.1111/cei.12855