Enhanced monitoring and screening in pediatric coeliac disease

Wessels, M.M.S.

CHAPTER 1

General introduction and outline of the thesis

Coeliac disease (CD) is an immune-mediated systemic disorder elicited by gluten in genetically susceptible individuals. It is characterized by anti-tissue transglutaminase type 2 antibodies (TG2A) and enteropathy[1]. In individuals carrying the human leucocyte antigen (HLA)-DQ2 and/or DQ8 haplotype, the ingestion of gluten (a group of proteins present in cereals such as wheat, barley and rye) can cause a T cell-initiated inflammatory response, damaging the small bowel mucosa[2]. In the general population, the prevalence of CD amongst adults as well as children is nearly 1-3%[3,4]. The disease is even more frequent in individuals with other autoimmune diseases such as type 1 diabetes mellitus (T1DM), auto-immune thyroiditis or in specific syndromes such as Down and Turner syndrome (10-15%)[5]. In first degree relatives of coeliac patients, the prevalence is 5-15%[6,7].

Clinical presentation

The disease has a variable clinical presentation, ranging from malabsorption with diarrhoea, abdominal distension and weight loss, to nonspecific signs and symptoms such as fatigue, osteoporosis or iron deficiency anaemia. This diversity of signs and symptoms, in combination with the fact that some individuals do not even have complaints, leads to the so-called ice-berg phenomenon, with most cases of CD being unrecognised and thus untreated[8,9]. These different types of presentation have led to a classification into different subcategories: classical, silent and potential CD (**Table 1**)[10,11]. A high index of suspicion is warranted by doctors but also by the general population, in order to diminish the diagnostic delay most patients encounter[12].

Table 1 *Subcategories of coeliac disease*

Coeliac disease	Symptoms	CD-specific antibodies	Small bowel histological abnormalities
Classical	+	+	+
Silent	-	+	+
Potential	+/-	+	-
Excluded	+/-	-	-

Diagnostic tools

CD-specific antibodies

When CD is suspected, non-invasive tests can be used, measuring CD-specific antibodies (IgA class tissue transglutaminase antibodies, TG2A, anti-endomysium antibodies (EMA) or antibodies against deaminated gliadin peptides (DGPA))[13,14]. Interpretation of these autoantibodies starts with total IgA assessment, since coeliac disease is associated with selective IgA deficiency[15,16]. In IgA deficiency, IgG dependent antibodies can be tested, with IgG EMA, TG2A and DGPA being available. Sensitivity and specificity of both IgA EMA and TG2A and DGPA are high and in concordance with small bowel histological abnormalities: 98% and 90% in severe duodenal lesions, and 97% and 98% in less severe intestinal damage respectively[17].

HLA-genotyping

Furthermore, genotyping for HLA-DQ2 and HLA-DQ8 adds value to the diagnostic scheme, since CD has a strong genetic component. Approximately 90% of coeliac patients carry the HLA-DQ2 haplotype, about 5% the HLA-DQ8 molecule[18–21] and the rest usually one half of the HLA-DQ2 heterodimer (DQA1-0505). The different heterodimers formed by HLA-DQA1* and HLA-DQB1* genes on the surface of antigen presenting cells contribute to the development of CD by the capacity to present gluten to T-cells which initiates the immune response. The HLA-DQ2 and DQ8 haplotypes are present in more than 25% of the general population[20], but only 1% actually develops CD[4]. This indicates that HLA-DQ2 and/or HLA-DQ8 haplotypes are necessary but not sufficient for disease development. In recent years, non-HLA genes have been reported to be associated with CD but with only a modest effect[22,23].

Intestinal histology

Finally, CD is characterized by small bowel mucosa alterations, referred to as gluten-sensitive enteropathy, which is categorized according to the Marsh classification[14]. Marsh classification type 3 or type 2 together with specific coeliac serology support the diagnosis of CD. These small bowel biopsies are obtained by means of esophago-gastro-duodenal endoscopy, an invasive method, especially in children needing general anaesthesia or deep sedation for the procedure. Until recent years, the histological assessment of duodenal biopsies has been the gold standard for the diagnosis of CD. However, patchiness of villous atrophy[24,25] but also difficulties with regard to proper interpretation, cutting and orientation of duodenal biopsies in order to come to a precise Marsh-classification can lead to false negative but also false positive biopsy results. Therefore, the histological interpretation needs to be done by an experienced pathologist with the patient's clinical complaints, serology and HLA-type in mind. In 2012, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) proposed an exception with regard to performing duodenal biopsies for a well-defined

group of children, having high titers of TG2A (>10 times upper limit of normal), positive EMA and positive HLA-DQ2/DQ8[1]. This strategy has been shown to be valid in 2017 by a multicentre European prospective study[26]. However, it still raises a lot of debate in adults suspected of CD and it is challenged for example by pediatric gastroenterologists from the United States of America[27].

Treatment

CD can be successfully treated with a gluten free diet (GFD) which restores small bowel histology and improves symptoms. However, this diet may be difficult to follow and may lead to social constraints. It is known that dietary adherence differs among individuals, with noncompliance varying from 25-50% among children and adolescents[28-30]. Noncompliance can be intentional, but accidental gluten ingestion also happens because of contamination of non-toxic cereals such as oats or corn due to co-culture or spilling during transport. Contamination can also take place during food-processing either in factories or at home. The capacity of gluten to improve the properties of food and non-food such as pencils and glue, increases the risk of contamination even more. Besides the impact of a GDF on a patient's daily and social life, the GFD can also lead to nutritional deficiencies since gluten-containing cereals like wheat, barley and rye are important sources of dietary iron, calcium, folate and vitamin B12[28,31,32,33]. Gluten-free grains such as buckwheat or quinoa are naturally rich in group B vitamins[34] but commercially available gluten-free products do not contain the same amount of iron, vitamin B12 and folate as the wheat flour products that they aim to replace[35,36]. Therefore, testing for anaemia, iron status and calcium, folic acid, vitamin B12 and vitamin D is common practice in patients with CD treated with a GFD. At the time of initiating this thesis, studies investigating the actual presence of nutritional deficiencies in children on a GFD, however, were lacking.

Follow-up

Despite the knowledge that non-compliance often occurs, a gold standard to assess compliance is lacking[37]. An extensive dietary evaluation by a trained dietitian is considered the best method[38], but not very practical due to its time-consuming nature. Repeat duodenal biopsies to monitor mucosal recovery is usually not a practical option, especially in children wherein endoscopy to obtain biopsies is done under anaesthesia or deep sedation. Serologic testing is not sensitive enough to detect infrequent gluten exposure[39-41], although it is usually performed in CD patients who are on a GFD. When this thesis commenced, several short dietary questionnaires had been developed in order to save time and to address compliance in a standard manner. However, they were tested only in adult CD patients and not in the pediatric CD population.

Risk groups

The Dutch and European CD guidelines recommend testing for CD in asymptomatic individuals with increased risk for CD: other autoimmune diseases such as T1DM, autoimmune thyroid and liver disease, Down, Turner and Williams syndrome, selective IgA deficiency and first degree relatives (FDRs) of coeliac patients[1,42]. Because of the high negative predictive value of HLA-typing for CD, unnecessary investigations in HLA-DQ2 and DQ8 negative individuals can be avoided. Therefore, HLA-typing can be offered to these individuals, albeit that due to its high costs in combination with a shared genetic background already predisposing to the same HLA-type, it is debated in certain risk groups, such as T1DM[43,44]. At the time of initiating this thesis, the impact of screening for CD on parents and perceived health of FDRs had not been studied, neither was the best suited screening frequency.

With regard to children with diabetes, several consensus based guidelines have different screening and treatment recommendations. Some suggest to screen all T1DM patients for CD[1,45,46], but state that while it seems sensible to put also an asymptomatic child on a GFD to avoid the development of complications, limited data are available to support this. Conversely, other guidelines advise screening only in symptomatic T1DM patients and emphasize informing parents that the treatment of asymptomatic CD in T1D is controversial[47,48]. Despite high sensitivity and specificity, the interpretation of TG2A and EMA in children with T1DM has proven difficult. The 2012 ESPGHAN guideline recommends duodenal biopsies if TG2A titers are >3xULN in asymptomatic individuals[1]. However, elevated TG2A titers often show spontaneous normalization in children with T1DM[49] and people at genetic risk for CD (like children with T1DM) have more often false-positive TG2A results[50]. Altogether, it leaves clinicians without a concrete method of patient management and speak to the absence of available literature for development of an evidence-based approach.

Outline of this thesis

With much attention in CD related research on diagnostics, prevention and new therapeutic modalities, the focus of this thesis has been on two clinical aspects of pediatric CD: the monitoring methods used during follow-up (Part I) and the screening process of individuals at risk (Part II). The specific questions addressed in my thesis are presented in **Table 2**.

Table 2 *Questions addressed in this thesis*

1	Do nutritional deficiencies persist in coeliac children after start of a GFD?
2	Do short GFD questionnaires detect infrequent dietary transgressions in coeliac children?
3	What is the impact of HLA-screening in children at risk for coeliac development?
4	What is the best screening method in FDRs of newly diagnosed coeliac patients?
5	When should duodenal biopsies be performed in T1DM children with elevated TG2A serology, since serology is often found to be false positive and/or declining spontaneously in these children?

Part I Follow-up

In **Chapter 2**, the results of a retrospective analysis of all complementary serologic investigations done at time of diagnose and during annual follow-up of children with CD are presented in order to describe the course of nutritional deficiencies after treatment. **Chapter 3** investigates whether a short standardized dietary questionnaire correlates with the dietary interview performed by a dietician in children with CD and how both match with CD specific serology.

Part II Risk Groups

The impact of HLA-typing in healthy children from coeliac families on parents is discussed in **Chapter 4**, together with the parental knowledge on the genetic background of CD and whether they would repeat HLA-typing in future children. **Chapter 5** also addresses coeliac families and describes the effect of sex, HLA-type and age of FDRs at time of CD diagnosis in the index coeliac patient in order to establish a better screening protocol for these high risk individuals. **Chapter 6** challenges the current recommendation for asymptomatic diabetic children with TG2A titers >3x the upper limit of normal (ULN) to be biopsied by means of Receiver Operating Characteristic (ROC) analyses of TG2A levels and corresponding duodenal histology.

Reference list

1 Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr.* 2012;54(1):136–60.

2 Vriezinga SL, Schweizer JJ, Koning F, Mearin ML. Coeliac disease and gluten-related disorders in childhood. *Nat Rev Gastroenterol Hepato*l. 2015;12(9):527–36.

3 Ivarsson A, Myléus A, Norström F, van der Pals M, Rosén A, Högberg L, et al. Prevalence of childhood celiac disease and changes in infant feeding. *Pediatrics* 2013;131(3):e687-94.

4 Mearin ML. Celiac disease among children and adolescents. *Curr Probl Pediatr Adolesc Health Care* 2007 Mar;37(3):86–105.

5 Ventura A, Magazù G, Gerarduzzi T, Greco L. Coeliac disease and the risk of autoimmune disorders. *Gut.* 2002 Dec;51(6):897; author reply 897-8.

6 Uenishi RH, Gandolfi L, Almeida LM, Fritsch PM, Almeida FC, Nóbrega YKM, et al. Screening for celiac disease in 1st degree relatives: a 10-year follow-up study. *BMC Gastroenterol.* 2014;14(1):36.

7 Biagi F, Corazza GR. First-degree Relatives of Celiac Patients: Are They at an Increased Risk of Developing Celiac Disease? *J Clin Gastroenterol.* 2009 Jan;43(1):3–4.

8 Catassi C, Kryszak D, Louis-Jacques O, Duerksen DR, Hill I, Crowe SE, et al. Detection of Celiac Disease in Primary Care: A Multicenter Case-Finding Study in North America. *Am J Gastroenterol.* 2007 Jul;102(7):1454–60.

9 Csizmadia CG, Mearin ML, von Blomberg BME, Brand R, Verloove-Vanhorick SP. An iceberg of childhood coeliac disease in the Netherlands. *Lancet.* 1999 Mar 6;353(9155):813–4.

10 Sapone A, Bai JC, Ciacci C, Dolinsek J, Green PH, Hadjivassiliou M, et al. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med.* 2012 Dec 7;10(1):13.

11 Tosco A, Salvati VM, Auricchio R, Maglio M, Borrelli M, Coruzzo A, et al. Natural History of Potential Celiac Disease in Children. *Clin Gastroenterol Hepatol.* 2011 Apr;9(4):320–5.

12 Norström F, Lindholm L, Sandström O, Nordyke K, Ivarsson A. Delay to celiac disease diagnosis and its implications for health-related quality of life. *BMC Gastroenterol* . 2011 Dec 7;11(1):118.

13 Rostom A, Dube C, Cranney A, Saloojee N, Sy R, Garritty C, et al. The diagnostic accuracy of serologic tests for celiac disease: a systematic review. *Gastroenterology.* United States; 2005 Apr;128(4 Suppl 1):S38-46.

14 Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). *Gastroenterology.* 1992 Jan;102(1):330–54.

15 Green PH, Jabri B. Coeliac disease. *Lancet.* 2003 Aug 2;362(9381):383–91.

16 Collin P, Kaukinen K, Vogelsang H, Korponay-Szabó I, Sommer R, Schreier E, et al. Antiendomysial and antihuman recombinant tissue transglutaminase antibodies in the diagnosis of coeliac disease: a biopsy-proven European multicentre study. *Eur J Gastroenterol Hepatol.* 2005 Jan;17(1):85–91.

17 Giersiepen K, Lelgemann M, Stuhldreher N, Ronfani L, Husby S, Koletzko S, et al. Accuracy of Diagnostic Antibody Tests for Coeliac Disease in Children. *J Pediatr Gastroenterol Nutr.* 2012 Feb;54(2):229–41.

18 Sollid LM, Markussen G, Ek J, Gjerde H, Vartdal F, Thorsby E. Evidence for a primary association of celiac disease to a particular HLA-DQ alpha/beta heterodimer. *J Exp Med.* 1989 Jan;169(1):345–50.

19 Monsuur AJ, de Bakker PIW, Zhernakova A, Pinto D, Verduijn W, Romanos J, et al. Effective detection of human leukocyte antigen risk alleles in celiac disease using tag single nucleotide polymorphisms. *PLoS One.* 2008;3(5):e2270.

20 van Belzen MJ, Koeleman BPC, Crusius JBA, Meijer JWR, Bardoel AFJ, Pearson PL, et al. Defining the contribution of the HLA region to cis DQ2-positive coeliac disease patients. *Genes Immun.* 2004 May;5(3):215–20.

21 Karell K, Louka AS, Moodie SJ, Ascher H, Clot F, Greco L, et al. HLA types in celiac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease. *Hum Immunol*. 2003 Apr;64(4):469–77.

22 Romanos J, van Diemen CC, Nolte IM, Trynka G, Zhernakova A, Fu J, et al. Analysis of HLA and non-HLA alleles can identify individuals at high risk for celiac disease. *Gastroenterology*. 2009 Sep;137(3):834–40, 840-3.

23 Zhernakova A, Stahl EA, Trynka G, Raychaudhuri S, Festen EA, Franke L, et al. Meta-Analysis of Genome-Wide Association Studies in Celiac Disease and Rheumatoid Arthritis Identifies Fourteen Non-HLA Shared Loci. Akey JM, editor. *PLoS Genet*. 2011 Feb 24;7(2):e1002004.

24 Bonamico M, Mariani P, Thanasi E, Ferri M, Nenna R, Tiberti C, et al. Patchy villous atrophy of the duodenum in childhood celiac disease. *J Pediatr Gastroenterol Nutr*. 2004 Feb;38(2):204–7.

25 Ravelli A, Villanacci V, Monfredini C, Martinazzi S, Grassi V, Manenti S. How Patchy Is Patchy Villous Atrophy?: Distribution Pattern of Histological Lesions in the Duodenum of Children With Celiac Disease. *Am J Gastroenterol*. 2010 Sep 6;105(9):2103–10.

26 Werkstetter KJ, Korponay-Szabó IR, Popp A, Villanacci V, Salemme M, Heilig G, et al. Accuracy in Diagnosis of Celiac Disease Without Biopsies in Clinical Practice. *Gastroenterology*. 2017 Oct;153(4):924–35.

27 Elitsur Y, Sigman T, Watkins R, Porto AF, Leonard Puppa EL, Foglio EJ, et al. Tissue Transglutaminase Levels Are Not Sufficient to Diagnose Celiac Disease in North American Practices Without Intestinal Biopsies. *Dig Dis Sci*. 2017 Jan 24;62(1):175–9.

28 Hopman EGD, le Cessie S, von Blomberg BME, Mearin ML. Nutritional management of the gluten-free diet in young people with celiac disease in The Netherlands. *J Pediatr Gastroenterol Nutr*. 2006;43(July):102–8.

29 Errichiello S, Esposito O, Di Mase R, Camarca ME, Natale C, Limongelli MG, et al. Celiac disease: predictors of compliance with a gluten-free diet in adolescents and young adults. *J Pediatr Gastroenterol Nutr*. 2010;50(1):54–60.

30 Jadresin O, Misak Z, Sanja K, Sonicki Z, Zizić V. Compliance with gluten-free diet in children with coeliac disease. *J Pediatr Gastroenterol Nutr*. 2008;47:344–8.

31 Black JL, Orfila C. Impact of coeliac disease on dietary habits and quality of life. *J Hum Nutr Diet*. 2011;24:582–7.

32 Öhlund K, Olsson C, Hernell O, Öhlund I. Dietary shortcomings in children on a gluten-free diet. *J Hum Nutr Diet*. 2010;23:294–300.

33 Thompson T, Dennis M, Higgins L a., Lee a. R, Sharrett MK. Gluten-free diet survey: Are Americans with coeliac disease consuming recommended amounts of fibre, iron, calcium and grain foods? *J Hum Nutr Diet*. 2005;18:163–9.

34 Alvarez-Jubete L, Arendt EK, Gallagher E. Nutritive value and chemical composition of pseudocereals as gluten-free ingredients. Int *J Food Sci Nutr*. 2009 Jan 21;60 Suppl 4(sup4):240–57.

35 do Nascimento AB, Fiates GMR, Dos Anjos A, Teixeira E. Analysis of ingredient lists of commercially available gluten-free and gluten-containing food products using the text mining technique. *Int J Food Sci Nutr*. 2013 Mar 5;64(2):217–22.

36 Thompson T. Thiamin, riboflavin, and niacin contents of the gluten-free diet: is there cause for concern? *J Am Diet Assoc*. 1999 Jul;99(7):858–62.

37 Hall NJ, Rubin G, Charnock A. Systematic review: Adherence to a gluten-free diet in adult patients with coeliac disease. *Aliment Pharmacol Ther*. 2009;30(April):315–30.

38 See J, Murray J a. Gluten-free diet: the medical and nutrition management of celiac disease. *Nutr Clin Pr*. 2006;21(February 2006):1–15.

39 Zanchi C, Ventura A, Martelossi S, Di Leo G, Di Toro N, Not T. Rapid anti-transglutaminase assay and patient interview for monitoring dietary compliance in celiac disease. *Scand J Gastroenterol*. 2013 Jun 5;48(6):764–6.

40 Biagi F, Bianchi PI, Marchese A, Trotta L, Vattiato C, Balduzzi D, et al. A score that verifies adherence to a gluten-free diet: a cross-sectional, multicentre validation in real clinical life. *Br J Nutr.* 2012;1–5.
41 Monzani A, Rapa A, Fonio P, Tognato E, Panigati L, Oderda G. Use of Deamidated Gliadin Peptide Antibodies to Monitor Diet Compliance in Childhood Celiac Disease. *J Pediatr Gastroenterol Nutr.* 2011 Jul;53(1):55–60.
42 Moet CBO Richtlijn coeliakie en dermatitis herpetiformis. Haarlem: Nederlandse Vereniging van MaagDarm-Leverartsen; http://www.diliguide.nl/document/2073/coeliakie-en-dermatitis-herpetiformis.html. 2008. Ref Type: Online Source.
43 Elias J, Hoorweg-Nijman JJG, Balemans WA. Clinical relevance and cost-effectiveness of HLA genotyping in children with Type 1 diabetes mellitus in screening for coeliac disease in the Netherlands. *Diabet Med.* 2015 Jun ;32(6):834–8.
44 Mitchell RT, Sun A, Mayo A, Forgan M, Comrie A, Gillett PM. Coeliac screening in a Scottish cohort of children with type 1 diabetes mellitus: is DQ typing the way forward? *Arch Dis Child*. 2016;101(3).
45 O. Kordonouri, A. M. Maguire MK. ISPAD Clinical Practice Consensus Guidelines 2006-2007. Other complications and associated conditions. *Pediatr Diabetes.* 2007;8(3):171–176.
46 Kraai IH, Luttik MLA, De Jong RM, Jaarsma T, Hillege HL. Heart failure patients monitored with telemedicine: Patient satisfaction, a review of the literature. *Journal of Cardiac Failure.* 2011.
47 NIH consensus development conference on celiac disease. *NIH Consens State Sci Statements.* 2004;21(1):1–23.
48 Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes.* 2008;32(supplement 1):22–35.
49 Castellaneta S, Piccinno E, Oliva M, Cristofori F, Vendemiale M, Ortolani F, et al. High Rate of Spontaneous Normalization of Celiac Serology in a Cohort of 446 Children With Type 1 Diabetes: A Prospective Study. *Diabetes Care.* 2015 May;38(5):760–6.
50 Vécsei A, Arenz T, Heilig G, Arenz S, Bufler P, Koletzko S. Influence of age and genetic risk on antitissue transglutaminase IgA titers. *J Pediatr Gastroenterol Nutr.* 2009 May;48(5):544–9.