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Title: Coeliac disease : prevention and improvement of care
Issue Date: 2016-12-07
Parts of this chapter have been published as
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Is it time for mass screening for celiac disease?
Coeliac disease is a common condition with a variable presentation, and is frequently not recognized by physicians. Although a gluten-free diet has a positive effect on the health of the coeliac patient, prevention would be even more beneficial. Accordingly, the first aim of this thesis was to investigate the influence of infant feeding on the prevention and development of childhood coeliac disease.

Primary prevention of coeliac disease means that tolerance for gluten needs to be achieved or maintained. As mentioned in the introduction of this thesis, results from previous retrospective studies suggested that the introduction of gluten between the age of 4 months and 6 months represents a window of opportunity for preventing coeliac disease. Based on these results both Dutch and European guidelines recommended introducing gluten not before the age of 17 weeks and not after the age of 26 weeks, preferably during a period of breastfeeding. However, the results of the PreventCD study, which are presented in chapter 2, did not show the hypothesized benefit of early exposure to small quantities of gluten with regard to reducing the incidence of coeliac disease among children from high risk families. In addition, maintenance of breastfeeding at the time of gluten introduction, and breastfeeding in general, did not reduce the risk of this disorder. Although we want to underscore the overall importance of breastfeeding for child health, our results may alleviate the stress that is placed on mothers, especially those from coeliac families, who are unable to breastfeed their baby: it will not increase their baby’s risk for coeliac disease.

Our results are in agreement with those of other recent prospective studies (CELIPREV, Generation R, MoBa, and TEDDY). CELIPREV is a prospective multicenter intervention study with Italian children who have a familial risk for coeliac disease, followed from birth and randomized to gluten introduction at the age of 6 months or 12 months. Delaying gluten introduction and breastfeeding did not modify the risk of coeliac disease, although gluten introduction at 12 months was associated with a delay in disease onset. The HLA genotype was an important predictor of disease. Furthermore, the results of the Dutch ‘GenerationR Study’, a Rotterdam population-based prospective cohort study from foetal life until young adulthood, showed that the risk of coeliac disease autoimmunity is not influenced by introducing gluten after the age of 6 months, or by breastfeeding during the first 6 months of life. The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study, conducted by the Norwegian Institute of Public Health. Introducing gluten after the age of 6 months and breastfeeding past the age of 1 year were associated with a modest increase in the clinical diagnosis of coeliac disease. Gluten introduction during the period of breastfeeding was not protective. The Environmental Determinants of Diabetes in the Young (TEDDY) is a multinational study with children at high risk for type 1 diabetes and a genetic predisposition of coeliac disease (HLA-DQ2/DQ8). Gluten introduction before the age of 17 weeks or after the age of 26 weeks was
not associated with an increased risk of coeliac disease. Finally, a systematic review that included the aforementioned prospective studies concluded that breastfeeding and timing of gluten introduction have no effect on the risk of developing coeliac disease during childhood, necessitating for an update of the current European guidelines.[7] These guidelines were prepared by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) in collaboration with the PreventCD group, and recommend that gluten can be introduced into the infant’s diet between the ages of 4 and 12 months, but state that the age of gluten introduction in infants in this age range does not seem to influence the absolute risk of developing coeliac disease during childhood.[8] Furthermore, according to the guideline, introducing gluten while the infant is being breastfed cannot be recommended as a means of reducing the risk of developing coeliac disease.[8]

While prevention of coeliac disease is not possible at this moment, diagnosing the disease in its earliest stage – secondary prevention – may be a realistic alternative. One way to pursue this is by case-finding: actively seeking for symptoms associated with coeliac disease (see box 1 in chapter 1) and a low threshold use of further examinations. Because of the variable presentation of coeliac disease, this will not resolve its underdiagnosis. Therefore, the current evidence-based guidelines recommend screening for coeliac disease in high-risk groups (see box 2 in chapter 1). This screening involves determination of coeliac disease specific antibodies against tissue transglutaminase (TG2A) or endomysium (EMA) in serum.[9] As presented in chapter 2, TG2A are reliable predictors of coeliac disease, also in very young children.[10] First-degree relatives of coeliac patients have an elevated risk for coeliac disease of 2-20%, depending on sex and HLA-genotype.[10] Furthermore, coeliac disease appears at a very young age (<3 years old) in children with a first-degree relative with coeliac disease: In children diagnosed with coeliac disease and a positive family history, 50% had developed the disease by age 3 years, implying that one should start with screening prior to this age.[10] In addition, coeliac disease has a female preponderance of 2-3:1 by 3 years of age, with in an incidence of 7.2% in girls with a positive family history versus 3.4% in boys.[10] Children homozygous for HLA-DQ2 clearly have a higher risk of coeliac disease (14.9%) than HLA-DQ2 heterozygous (3.9%) and HLA-DQ8 positive (hetero- and homozygous) children (0.9%), \( p<0.001 \).[10]

Would mass screening for coeliac disease be a sensible alternative to case-finding? Ten years ago, when Wilson and Junger’s criteria for mass screening were applied to coeliac disease, there was controversy over whether the general population would accept mass screening and whether the health status of minimally symptomatic or asymptomatic patients identified by mass screening improved after treatment.[11, 12] Furthermore, the natural course of the disease and cost-effectiveness of mass screening were unclear.[11, 12] Results of recent prospective studies allow for re-opening of this discussion. The Swed-
ish ETICS-PreventCD study has shown that mass screening for coeliac disease in 13,279 children aged 12-year old was feasible and well-accepted.[1] Results from the ‘GenerationR Study’ among 6-year old children from the general population provided information about the natural course of coeliac disease. Undiagnosed coeliac disease was found in 1.3% (57/4442 screened children was positive for TG2A) and was associated with important health problems, such as a reduced bone mineral density and a delayed growth in weight.[13] In addition, children of women with undiagnosed and thus untreated coeliac disease had a reduced fetal growth and a lower birth weight.[14] Concerning the costs of mass screening, the results of a study concerning coeliac disease screening in adults showed that screening has a cost-effectiveness ratio of 48,960 USD per QALY. Based on this outcome, the authors suggest that mass screening for coeliac disease is indeed cost-effective.[15] Confirming the diagnosis in asymptomatic patients still requires obtaining small bowel biopsies according to the current evidence-based guideline of the ESPGHAN.[9] This in contrast to patients with coeliac disease associated symptoms, TG2A titres of more than 10 times the upper limit of normal, a positive EMA in a new blood sample and HLA-DQ2/DQ8 positivity. Results from the Swedish ETICS screening study show that this also applies to children diagnosed after screening.[16] The prospective and international PRoCeDe study will provide information about this as well.[17] It would make the process of diagnosing coeliac disease in children identified by screening simpler, less invasive and cheaper. An argument that is frequently used against mass screening is that minimally symptomatic or asymptomatic patients will not adhere to the gluten free diet. However, long-term follow-up of young Dutch children and the results of the study with 12-year old Swedish children disprove this argument: the children were compliant with their diet.[18, 19] Furthermore, a prospective study showed that treatment of coeliac disease diagnosed based on mass screening yields health gains, both for adults and children.[18] In Dutch children with coeliac disease identified by mass screening, chronic symptoms of diarrhoea, abdominal pain, constipation, fatigue, irritability, oral aphthous ulcers and growth failure, improved after diagnosis and treatment.[18] In adult Finnish coeliac patients who were diagnosed after screening, chronic health problems as indigestion, gastro-oesophageal reflux and anxiety improved significantly after treatment with a gluten-free diet.[20] Furthermore, dietary adherence was excellent after screening and there were no significant differences between screening-detected and symptom-detected patients with regard to coeliac disease-health related quality of life.[18, 20, 21] Consequently, secondary prevention may only be achieved on large scale by mass screening of the general population.

Traditional medical care for patients with treated coeliac disease consists of regular physician visits to evaluate their health, weight, height (in children), gluten-free diet adherence and coeliac-specific serum antibodies.[22, 23] Although important, these measures can be time-consuming. Moreover, many patients do not visit their physician for regular follow-
Time constraints during outpatient follow-up also typically restrict comprehensive assessments of a patient's health-related quality of life (HRQOL) and dietary adherence. Accordingly, the second aim of this thesis was to explore new strategies for the improvement of care for children and young adults with coeliac disease.

While coeliac disease-specific HRQOL is an accepted outcome within a research environment, insufficient time during actual follow-up visits may prevent the physician from specifically measuring it, and therefore only general assessments can be provided. It has been established that in patients with other chronic diseases, the physician overestimates the patient's HRQOL [25-27]. We are the first to have compared the self-reported coeliac disease-specific HRQOL in a group of children and young adults with the physician's report provided during a regular outpatient follow-up visit for coeliac disease (chapter 3). Our results indicate that there is an important discrepancy between these reports since in 57% of the patients, the physician had a different perception of the patients' HRQOL than the patient him/herself. What raises concern is that this occurred among patients considered to be especially vulnerable: those with a "bad" self-reported HRQOL. Our data show that this problem occurs significantly more frequently in those who received the diagnosis within the past 9 years and in female patients, possibly due to their significantly poorer self-reported HRQOL, especially for the "communication" subscale, compared to their male counterparts (p<0.014). Our results concerning the discrepancy between the self-reported and physician-reported HRQOL are consistent with previous studies with children affected by other chronic diseases [25-27]. Our study supports the implementation of a self-reported coeliac disease-specific HRQOL measurement in the clinical follow-up of the patients. Sharing the results of the questionnaire may improve the patient/parent-doctor communication and the physicians' understanding of the needs and priorities of children and young adults with coeliac disease. As the standard consultation time allotted for follow-up visits is limited, the outpatient clinic of the department of paediatric gastroenterology of Leiden University Medical Centre will ask the patient to complete the CDDUX questionnaire prior to physician appointments. If our results are successful, we will advise other hospitals caring for patients with coeliac disease to follow-up on our example.

Previous studies in adults with other chronic diseases suggest that an online self-management e-health system can encourage patients to improve health care participation and the decision-making process. [28] Patients are able to deal with their symptoms, treatment, physical and psychosocial consequences and lifestyle changes that are inherent in living with a chronic condition through successful disease self-management. [29] In chapter 4, we presented the results of an online consultation replacing outpatient consultations in the follow-up of coeliac children and young adults (CoelKids). We hypothesized that disease control in the course of the study would be similar in patients using the online consultation
and traditional outpatient follow-up. To the best of our knowledge, this is the first study investigating a self-management intervention in this specific population on a physical, psychological, nutritional and economic level. Our results indicate that the online consultation for children and young adults with coeliac disease is an effective and satisfactory instrument for self-management of their disease. Symptoms were recognized significantly more often in the online than the outpatient consultations, possibly because the online consultation initiated a conversation about symptoms between parent and child that was not restricted by the limited time available for an outpatient consultation. Abnormal growth was similarly recognized through both approaches. Additionally, online consultations increased the coeliac disease-specific HRQOL while its mean costs were lower compared with the costs of traditional care. Results from the POC self-test for TG2A assessment showed the used test is unfit for the population under study. The used self-test has been validated for coeliac disease screening, with reported sensitivities and specificities of $\geq 94\%$ and $\geq 93\%$, respectively. [30, 31] However, its efficiency or that of the other POC self-tests for monitoring treated coeliac disease had not yet been prospectively evaluated when this study commenced in 2011. These patients usually have less high titers of TG2A than untreated patients.[32] Before implementing online consultations in the follow-up of coeliac patients, a POC self-test that is sensitive enough to detect low positive TG2A levels is required, as these are common in patients with treated CD secondary to dietary transgressions.

Triggered by the inadequate performance of the POC self-test used in the CoelKids study (chapter 4), we compared the performance of three commercially available POC tests against the serum TG2A of coeliac disease-affected children treated with a gluten free diet (chapter 5). Our results show that the sensitivity of one of these three tests was acceptable (95% confidence interval excluded values <90%) if the reading time was prolonged from 10 minutes to 1 day. For all three POC tests, we find lower sensitivities than previous studies using these tests in screening for coeliac disease. This could be explained by the fact that antibody titres in treated CD are typically lower than in untreated CD cases identified by screening or case-finding. Another explanation for their difference in performance may be attributed to the varying principles of each of them: one only tests for IgA TG2A, one for IgA and IgG TG2A and the other for IgA, IgG and IgM TG2A. However, the added value of IgG and IgM antibody measurement in our cohort is questionable since IgA TG2A was present in all samples that yielded false-negative results. Implementation of a POC test for TG2A in a clinical setting may reduce the frequency of venepuncture for conventional TG2A testing in children (and probably also in adults) with treated coeliac disease and could improve self-management of their disease. An important advantage of a POC test is the potential of being a more rapid alternative to conventional serologic testing. To accommodate the longer reading time that is required to obtain an acceptable sensitivity, well instructed patients could do the test at home on the day prior to their outpatient clinic visit and bring the
test for evaluation by their physician. This allows for an on-the-spot management decision in case of a positive result, for example: conventional serologic testing, dietetic counselling regarding the adherence to the gluten free diet and discussion with the physician on the harmful effects of gluten ingestion. Furthermore, as shown in chapter 4, the use of a POC test instead of conventional TG2A testing may have health cost-saving implications. [33] and a finger prick is experienced to be less invasive than a venepuncture, particularly for children. For implementation of POC tests in the follow-up of treated coeliac patients we recommend to use tests that have been validated in this specific group of patients. To rule out the risk of observer variability, a ‘reader’ that automatically interprets the result of the POC self-test should be developed and prospectively tested in the follow-up of patients with treated coeliac disease. This could, for example, be a smartphone application that interprets a photograph of the test result.

In conclusion, new developments with respect to prevention and management of coeliac disease are taking place at a fast pace. The results presented in this thesis have altered the conceptual landscape of coeliac disease[34] and increased our understanding of the risk factors associated with this disease (chapter 2). Furthermore, they call for an update of the current national and international guidelines on infant feeding. A recommendation for improvement of patient/parent-doctor communication on patients’ HRQOL is presented in chapter 3 and a self-management e-health system for coeliac patients is evaluated in chapter 4. Finally, we presented a POC test that may be suitable for follow-up of treated coeliac disease in chapter 5.

**Future perspectives**

The lack of an association between the timing of gluten introduction, the duration and presence of breastfeeding, and the development of coeliac disease keeps us guessing for an explanation for the striking increased incidence of this disease in the Western world during the recent decades. It remains likely that other environmental factors play an important role, such as the gut microbiome. It has been suggested that intestinal dysbiosis is associated with coeliac disease.[35] It is however unknown whether the alterations are cause or consequence of the disease. To answer questions such as “Who will develop coeliac disease?” and “When will this happen?” it is crucial to prospectively collect and study the blood, faeces and duodenal biopsies (‘biobanking’) from patients at high-risk for developing coeliac disease (see the appendix for a letter to the medical ethical committee of the Leiden University Medical Centre concerning biobanking). In a subproject of the PreventCD study, we plan to annually collect faeces of the participating children to establish the relationship between the composition of the gut microbiome and coeliac disease.
Is it time to start with mass screening for coeliac disease instead of only screening people from coeliac families? Perhaps we are nearly there, but a couple of questions remain unanswered. Such as: what is the optimal screening method and frequency and at what age should we screen? It also needs to be clarified whether the costs of screening and treatment are acceptable when compared with the total costs of healthcare. Recent advances in the diagnostics of coeliac disease, such as the POC tests for TG2A, will lower the costs of mass screening and will increase cost-effectiveness. Future studies should take these features into account but also focus on the ethical aspects of mass screening with the different available diagnostic tools in different age categories.

In the coming years, e-health is envisaged to play an increasing role in the care for patients with a chronic disease. This thesis (chapters 4 and 5) showed that also in treated coeliac disease, an online consultation is a satisfactory alternative for an outpatient follow-up visit. Before implementing online consultations in these patients' health care, it is necessary to validate the POC self-test for TG2A in this specific population. Recently, a new option for the assessment of gluten free diet adherence has been described: detection of gluten immunogenic peptides in urine.[36] This may be a less invasive, cheaper and possibly even more reliable alternative to conventional blood testing or POC testing for TG2A. However, studies that validate the relevance of this method in clinical practice are required. To maintain participant engagement with e-health, we suggest adjusting to the increased popularity of medical applications on smartphones and tablets. Furthermore, efforts should be made to arrange reimbursement of online consultations as part of the treatment plan for coeliac patients.
REFERENCE LIST


