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Enhanced monitoring and screening in pediatric coeliac disease

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PART III

DISCUSSION

CHAPTER 7

General discussion and conclusion

Although coeliac disease (CD) is a frequent, but still underdiagnosed disease, focus in research should not only be on diagnostics and novel therapies, but also on best ways to take care of and monitor patients once they are on a gluten-free diet (GFD). In addition, evidence based screening policies in populations at risk in order to diagnose CD as early as possible should be developed as secondary prevention of the disease. The questions formulated at the start of this thesis with regard to these 2 domains are presented in **Table 1**, together with the assembled recommendations.

Table 1 *Main conclusions of this thesis*

Questions	Findings	Recommendations
Do nutritional deficiencies persist or develop in coeliac children after start of a GFD?	Nutritional deficiencies recover within 1 year of GFD.	Standard blood-investigations besides CD specific serology are not necessary after one year of follow-up.
Do short GFD questionnaires detect infrequent dietary transgressions in coeliac children?	The short dietary questionnaire developed by Biagi does not provide more information than CD-specific serology.	The standardized dietary interview, especially if completed before a face-to-face consultation, provides detailed information on dietary (non-) compliance.
What is the impact of HLA-screening in children at risk for coeliac development?	Parents of young children from coeliac families support HLA-typing and would repeat it in future children.	HLA-typing should be offered to children from risk families with the associated information provided.
What is the best screening method in FDRs of newly diagnosed coeliac patients?	One time screening could be enough in adolescent siblings and parents of newly diagnosed coeliac patients.	Regular screening by means of CD-specific serology should be offered to all HLA-DQ2 and/or DQ8 positive pediatric FDRs <10 years of age.
When should duodenal biopsies be performed in children with T1DM and elevated TG2A serology, since serology is often found to be false positive and/or declining spontaneously in these children?	In asymptomatic children with T1DM, 12% of the children have normal duodenal mucosa when biopsied in case of a TG2A titer of >3xULN.	Follow-up of serology instead of performing endoscopy to retrieve biopsies in these patients seems safe and appropriate.

In-depth discussion of the findings and recommendations

Until present, the GFD is the only treatment of CD. Although it has a proven positive effect on the health of the coeliac patient, effective long-term management programs are lacking for children as well as for adults. The need for effective long-term follow-up to improve compliance with the diet and outcome of coeliac patients has been recognized by many expert groups[1–5], since delay of the GFD appears to lead to an increased risk of co-morbidity, mortality and tendency to a lower quality of life[6,7]. Therefore, in

2016, evidence-informed expert recommendations were published for the management of CD in children by pediatric gastroenterologists from the United States of America[8], in which the shortage of good quality data regarding this matter was emphasized. At present, standard medical care for CD children consists of regular visits to the pediatrician or pediatric gastroenterologist to evaluate overall health, anthropometrics, GFD adherence and laboratory investigations including CD specific antibodies and additional tests to rule out deficiencies and co-morbidity. With this in mind, it is important to acknowledge earlier reports that have indicated that follow-up care is not being provided to all patients, both in the pediatric as adult population[9-12]. In a pediatric cohort in Israel, it was shown that patients lost to follow-up have a poorly controlled disease with more non-adherence to the diet and positive CD-specific serology[13]. One can only speculate whether this non-compliance leads to more long-term complications, since follow-up data are lacking, both in adults as well as in children, and in untreated as well as treated patients. It is therefore indeed relevant for the establishment of evidence based follow-up care of CD patients treated with a GFD.

This was the reason to study eventual nutritional deficiencies that may occur in CD patients and that are usually checked during follow-up. These alterations, although often present at diagnosis, disappear within one year of GFD, as we have shown in **Chapter 2**. This means that standard blood-investigations besides CD specific serology are not necessary after one year of follow-up. This outcome is important, due to its consequences for the organization of the health care for children with CD, because blood tests are time-consuming and expensive, and in a few children also painful and frightening. The percentages of nutritional deficiencies found in our study were comparable with previous studies, with the exception of vitamin B12, which was much lower in our cohort (2%) in comparison to earlier studies in adolescents and adults (12-41%)[14-17]. Our findings on the frequency of thyroid dysfunction (nearly 4%) are similar to the ones from previous studies, with the prevalence of thyroid autoimmunity (elevated thyroid stimulating hormone (TSH) or presence of thyroperoxidase (TPO) antibodies), hypothyroidism and hyperthyroidism varying from 10-26%, 2-6% and 1%, respectively[18,19]. The rationale behind thyroid function testing as part of a CD patient's follow up is based on the high frequency of thyroid autoimmunity in CD[20], but there is conflicting evidence about the GFD's protective effect in the development of auto-immune thyroid disease[21-23]. Based on our results, routine testing of TSH, commonly used to screen for thyroid disease, should be discouraged, since (temporarily) abnormal results occur often without abnormal FT4 levels and thyroid disease. This can lead to overdiagnosis and anxiety in patients and parents. Thyroid testing should therefore be reserved for symptomatic children, presenting with abnormal growth or pubertal development, fatigue, altered defecation and appetite, muscle aches or tremor, ophthalmopathy, thermodysregulation and altered school performance. If tested, FT4 levels should be determined. Since

mucosal healing after start of a GFD tends to behave similarly in adults and children, we hypothesize that the same advice could be given to coeliac adults, but there is no current evidence to support this.

The next step enabling us to evaluate the management and follow-up of children with CD is defining the best way to assess dietary adherence, which is the only available treatment. Since the diet is not always easy to follow, identifying the patients who do and do not comply to the diet is vital. While an extensive dietary evaluation by a trained dietitian is considered the best method to evaluate GDF adherence, this method is time-consuming, taking 20-30 minutes per patient, and requires expert personnel. In **Chapter 3**, we have shown that a standardized dietary questionnaire is a good alternative to the face-to-face contact with a dietitian. A short questionnaire developed and tested in adults[24], did not provide more information on diet adherence than anti-tissue transglutaminase type 2 antibodies (TG2A). Both do not detect all errors in children and adolescents with CD. We have pointed out a decreased dietary compliance in adolescents, an established fact in CD populations[25-27]. Sex, age at CD diagnosis and the presence of other family members with CD did not influence compliance, nor did being on another diet besides the GFD or the presence of complaints after gluten ingestion. Despite our efforts, we were unable to reduce the length of the dietary interview. However, with the increasing use of electronic patient records and eHealth tools, completing questionnaires before or during a medical consultation should be easily implemented in the health care for children and young adults with CD. The routine use of this dietary questionnaire especially when completed before the face-to-face contact, in combination with TG2A determination, will facilitate the communication between patients/parents and doctors, with a better focus on pitfalls and problems with the GFD. It will help the doctor to have an insight into possible dietary transgressions and reasons why and when they occur. This will provide the opportunity to anticipate on possible educational counselling and support. We expect that this will contribute to improvement of care for CD patients by, on the short term, empowering them leading to a better diet adherence, and possibly on the long-term, by avoiding complications of their disease. Not only will it be a useful tool in daily practice, but the dietary interview can also be used in prospective studies looking at long-term outcome of CD patients on a GFD. Novel methods of measuring gluten immunogenic peptides (GIP) in urine and in faeces can add value to diet monitoring[28,29]. GIP enables direct and quantitative assessment of gluten intake. It can help to detect incidental dietary transgressions that are not detected by CD specific serology and to identify patients non-compliant with the diet. However, because GIP analysis only detects gluten ingested a few days prior to testing, gluten ingestion before this time may remain undetected. GIP determinations might also be helpful in patients who adhere to the diet, but who have persistent elevated TG2A. If TG2A is still declining and GIP is negative on repetitive basis, reassurance of patients and their parents is probably justified.

Another step forward to improve health and quality of life in coeliac patients is to diminish the level of under diagnosis. To be able to do so, awareness of the disease and an increased level of suspicion, both among doctors and the general public, is important. In addition, secondary prevention by early diagnosis and treatment should be further improved by developing screening programs for risk groups. When addressing screening for CD, it is important to look at the benefits of the outcome first of all. Looking at the literature, there is some evidence for screening strategies as a method of preventing complications and reducing medical costs[30-32]. However, benefits and cost-effectiveness of screening remain controversial[33,34]. Active case finding can be considered, albeit well known that the use of symptoms to identify CD patients has its limits. As it happens symptoms associated with CD are as prevalent in individuals with and without the disease[35]. However, case finding programs in children based on symptoms are an alternative for general screening programs, which is opposed to by the Medical Ethical Committees in the Netherlands. Since health benefits after diagnosis and treatment are expected in symptomatic children, permission to perform the GLUTENSCREEN study in the youth health care in the province North-Holland in the Netherlands was granted. Screening for CD in certain high risk groups is recommended both by the Dutch and European CD guidelines[2,36], as individuals with other autoimmune diseases such as type 1 diabetes mellitus (T1DM), autoimmune thyroid and liver disease, individuals with syndromes like Down, Turner and Williams syndrome and with selective IgA deficiency and also first degree relatives (FDRs) of coeliac patients have a higher risk of getting the disease. In order to achieve better care for high risk groups, involvement of general practitioners in the Netherlands is imperative when updating coeliac guidelines, since their own current guideline on CD does not advice to screen FDRs[37], who mostly are under medical attention of the general practitioner.

Because of the high negative predictive value of HLA-typing for CD, unnecessary investigations in HLA-DQ2 and DQ8 negative individuals can be avoided. This given forms the basis for the advice in the ESPGHAN CD Guidelines to use HLA-typing as the first step of screening in risk-groups[2]. However, in FDRs the percentage of HLA-Q2/DQ8 negative individuals is low, in the cohorts we have studied for this thesis 12.5% (**Chapter 4**) and 15% (**Chapter 5**), quite comparable to what was found in other cohorts[38,39]. The same applies for diabetic patients, in whom several studies have demonstrated that absence of HLA-DQ2 and/or DQ8 haplotypes is scarce[40-42]. Together with the fact that HLA-typing is at present quite expensive and the difficulty for people to interpret the results, should prompt us to question this advice. On the other hand, in this day and age of shared decision making, it is not only up to the doctor to decide whether this absolute risk is something to know or not. We have demonstrated that parents of young children from coeliac families support HLA-typing and would repeat it in future children (**Chapter 4**). They would even be prepared to pay for the screening of their offspring[43]. In order to judge whether parents can actually be involved in such decisions, it is important not

only to know their opinion but also whether they are able to understand the background of genetics, which is notorious for its complexity and related cognitions. Despite the good knowledge that parents in coeliac families have with regard to HLA-typing on its own, misinterpretation of HLA negative results occurred in 48% of cases (**Chapter 4**). Parents who knew that presence of HLA-DQ2/DQ8 was necessary for individuals to be able to develop CD, thought that there was still a chance for their HLA-DQ2/DQ8 negative child to become a coeliac. Possibly, it is hard for them to adjust to a favourable outcome if the disease scenario disappears. It should however prompt physicians to make sure that parents understand the results and to improve the way of giving information. The information brochure that has been developed for this purpose in Dutch is attached as **Supplemental material appendix D** in this thesis. It can be helpful, especially since we found that parents who received favourable results were less inclined to look for additional information on HLA-genotyping and CD by themselves.

In addition, in the case of FDRs, HLA-typing can contribute to predict the individual risk to develop CD, which may have consequences for screening. Unfortunately, primary prevention by dietary interventions with breastfeeding and early or delayed introduction of gluten has proven not to be possible in at risk children[39,44]. In **Chapter 5**, we have presented the results of a retrospective analysis of CD screening in FDRs. We found a high prevalence of CD of 15%, even higher than earlier studies[45-47]. Several prospective studies have demonstrated the natural occurrence of CD in genetically at risk individuals[39,44,48], with a high prevalence ranging from 5 to 40% depending of the cohort, sex and genotype. Extrapolation of these data to older children and adults who are confronted with a family member being diagnosed with CD is however not straight forward. In this **Chapter 5**, we have shown that individual risk depends on the HLA-genotype, with HLA-DQ2 homozygosity resulting in the highest risk, therefor warranting closer surveillance. Our results suggest that the timing of CD specific antibody testing could be individualized depending on the relationship of the FDR with the index patient, the age of the FDR at time of the index diagnosis and HLA-type of the FDR. Prospective studies with regular screening intervals are needed to further address this issue, especially with regard to the adolescent age group. A proposal for a screening algorithm can be found in **Chapter 5** of this thesis (**Figure 3**).This would mean, although costly, that HLA-typing has its benefits even in this group, not only to rule out (future) CD, but mainly to estimate the risk of developing the disease.

Like FDRs, HLA-typing is also advised to be performed in children with T1DM as part of the coeliac screening process. Similar to FDRs, the vast majority of diabetic children is HLA-DQ2 and/or DQ8 positive (86%)[40]. About 7% of them have CD[40,49]. However, the diabetic children seem different than other risk groups, since there is a substantial group of children with T1DM who have fluctuating and/or normalizing CD specific antibodies[50-52]. On the other hand, like FDRs, older age at time of T1DM diagnosis has a

protective effect with regard to CD diagnosis[53]. In **Chapter 6**, we have shown the tendency in our cohort of diabetic children with CD as well to be younger than the diabetic children without CD. The usual female predominance of CD does not appear to be seen in other cohorts with T1DM and CD[53,54], even though in general there appears to be no gender difference in incidence of childhood T1DM[55]. Maybe the male preponderance is by part caused by a higher incidence of males in specific diabetic subgroups, like adolescents older than 13 years of age from European origin[55,56]. In our cohort however, we did not witness this male dominance, maybe due to relatively young age of our cohort (mean age 9.7 years).

In **Chapter 6**, we have demonstrated that when complying with the current ESPGHAN guidelines in asymptomatic children with T1DM, 12% of the children have normal duodenal mucosa when biopsied after ascertaining a TG2A titer of >3xULN. In accordance with our own results and other studies, repetition of serology instead of performing endoscopy to retrieve biopsies in these patients seems appropriate[50,51]. Current follow-up protocols for children with T1DM include CD specific serology at diagnosis and every 1-2 years thereafter[57]. In order to gather evidence on the length and interval of screening after diagnosis of T1DM prospective studies are needed. The international TEDDY (The Environmental Determinants of Diabetes in the Young) birth cohort study, studies factors influencing the development of T1DM, but also CD, because of the shared genetic background. It has been shown, that T1DM autoimmunity precedes coeliac autoimmunity in early childhood in children at high genetic risk of both diseases and that preceding islet autoantibodies (IA) significantly increase the risk of subsequent TG2A generation[58]. Data from the PreventCD cohort, shows a higher incidence of CD especially in multiple IA[59]. However, the time from IA seroconversion to clinical manifestation of T1DM shows a big variation between individuals, ranging from weeks to decades with individuals with different types of IAs having the highest risk in the shortest time[60], so CD can also precede T1DM. One can argue, that screening for IA could be done in coeliac children, since it was shown in the TEDDY cohort that genetically susceptible children who were diagnosed with T1DM diagnosed due to screening/surveillance have a better diabetes quality of life and lower parenting stress post-diagnosis compared to children diagnosed with T1DM in the community[61].

Future directions

In order to improve health-related quality of life of children with CD, it is important to find other ways to achieve early diagnosis and to optimize treatment and follow-up. In the next few years, special attention should be given to transition from pediatric to adult coeliac care. Ideally, this transition should be a collaborative process involving patients,

their parents or caregivers, the physician and the dietician[62]. Currently, the majority of coeliac patients in their twenties and forties who are diagnosed during childhood receive no medical or dietary supervision after transition to adulthood, with dietary non-compliance and complications such as iron deficiency anaemia and osteopenia as a result[63]. In 2016, the Prague consensus report on this matter was published[64], focussing on transfer of full responsibility for the adolescent, discussing dietary adherence and consequences of non-adherence and advising adult gastroenterologist on the approach for patients diagnosed during childhood based on the ESPGHAN[2] or NASPGHAN[3] criteria. Efforts should be made to endorse transition programs together with adult gastroenterologists. A better collaboration could also mean family programs by organising family outpatient clinics where within one family multiple FDRs could get their annual check-up whilst the others could be screened at the same time. Both knowledge on CD, self-management, family/risk group screening and transition could benefit from deploying medical applications and robots. Humanoid robots have been introduced in the health care domain for both adults[65,66] and children[67]. They could generate a continuous awareness of the chronicity of a disease whilst offering the support that is needed at any time and at any age. In this respect lessons will be learned from the PAL (Personal Assistant for healthy Lifestyle) 4U Project that started in 2015 as part of EU Horizon 2020 Program to improve child's diabetes regimen by assisting the child, health professional and parent. Another promising innovative example is the MyCyF-app, also funded by Horizon 2020, for patients with cystic fibrosis. Its goal is to enable them to monitor the disease, change enzyme-treatment and diet if needed and educate patients, caregivers and health professionals. Like these chronic illnesses, coeliac follow-up programs could also benefit from similar self-management programs. For example, online self-management systems can encourage patients to improve participation in their own health care by dealing with their symptoms, treatment and lifestyle changes. It can contribute to shared decision making between doctor and patient[68,69]. In CD, moving from traditional medical care with annual face-to-face 15-20 minutes visits focussing on complaints, growth and blood results to online consultations with questionnaires that also address quality of life and dietary adherence might be the way forward. Our research group has shown that implementation of eHealth is feasible for children with CD. It is cost saving, increases CD-specific health-related quality of life and is satisfactory in the majority of patients and parents[70]. Introducing robots or apps into coeliac care should incorporate several domains: 1. Education and information on the disease and treatment, not only for the patient and his/her family but also for use at school, restaurants etc, 2. Real-time diet evaluation, for example by using barcodes, with regard to gluten content and nutritional value, 3. Chat function with peers and/or professionals if needed (medical doctor, dietician, psychologist). Alliance with health science and technology together with the national coeliac association is needed in order to complement the needs of patients and to find the best eHealth solution.

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