Gluten intake and gluten-free diet in the Netherlands

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Summary

Chapter 1 contains a general introduction on celiac disease and its treatment and a description of the aims and outline of the thesis. Celiac disease is the result of a sensitivity to dietary gluten in genetically predisposed individuals. The diagnosis of celiac disease is based on characteristic histological alterations of the small bowel mucosa during gluten consumption and clear clinical remission on avoidance of gluten. The treatment of celiac disease consists of a life-long, gluten-free diet to heal the duodenal mucosa, improve symptoms and protect from development of complications. The aims of this thesis were to measure some of the environmental factors (e.g. breastfeeding and gluten introduction) considered to play a role in the prevention of celiac disease and in the development of oral tolerance. Furthermore, to explore the relationship of celiac patients with gluten and the gluten-free diet at different ages, their ability to develop gluten tolerance and the impact of the gluten-free diet on health-related quality of life.

Breastfeeding has been shown to prevent, or at least delay the development of celiac disease. Breast milk contains many immunologic factors that stimulate the infant's immune system, but its exact role in the prevention of celiac disease is not known. Furthermore, breast milk contains small amounts of food antigens, like gluten peptides that may contribute to tolerance induction. In chapter 2 we describe the results of a study on the presence of T cell stimulatory epitopes originating from dietary gluten in the breast milk of 23 mothers on a normal diet and of 13 mothers on a gluten-free diet. T cell stimulatory epitopes of both gliadin and glutenin were detected in breast milk but no correlation with the gluten intake of the mother was found. We conclude that infants are exposed to small levels of gluten through breast milk. These small levels may be one of the factors responsible for the induction of oral tolerance to gluten.

Another possible factor in the prevention of celiac disease or the development of oral tolerance is the timing and amount of gluten introduced into the infants' diet. An easy and reliable instrument that can be used to assess the gluten intake in young infants was lacking until now. In chapter 3 we describe the development and validation of a food questionnaire to assess gluten intake in young infants. Eighty-seven parents of healthy infants aged 0-12 months completed the newly developed food questionnaire and a 2-day food record as a reference. We found that up to the age of 10 months the gluten intake assessed with the food questionnaire was comparable with that of the food record, but in the older children it was higher when assessed with the food record. This difference was probably caused by a greater variety of food products in the older children that could not be detected by our food questionnaire: all of the gluten-containing products that were reported in the food of the children aged 3-6 months by using the food record, were contained in the food questionnaire for this age category, but for children aged 7-12 months this was the case for 95% of the gluten delivering products reported in the food

record. For future use among the older children, the food questionnaire can easily be improved. We conclude that this new, short, standardized, validated and easy to use food questionnaire may be a useful instrument to assess gluten intake in infants. After necessary translation, adaptation and validation the food questionnaire can be used to assess gluten intake of young infants across countries and can be used in collaborative studies.

In chapter 4 we present the results of a study on the nutritional state and the management of the gluten-free diet by young Dutch celiacs. Of all 395 celiac patients aged 12 to 25 years who were members of the Dutch Celiac Society, 219 responded to the invitation letter and 132 gave informed consent to participate. Strict dietary compliance was reported by 75% of them, which was comparable with the percentage of dietary compliance in adolescents in other European countries. The young celiac patients had a higher consumption of saturated fat and a lower consumption of fiber and iron than recommended, but similar to the general population. Most of these young patients (61%) found the diet easy to follow. Eighty six percent of the patients reported regular medical controls, but only 7% had regular dietary controls. The mean standard deviation score for body mass index was -0.3±0.8. We conclude that the dietary compliance in this group is high, and that the nutritional state is adequate but the nutrient intake has to be improved. We believe that adequate medical and dietary support will be necessary for this group of young celiac patients to maintain this self-reported good management of the gluten-free diet and to prevent long-term complications.

Gluten-free food products usually have a lower nutritional value and thus patients adhering strictly to a gluten-free diet are at risk for nutrient deficiencies. Furthermore, the compliance with the gluten-free diet may, among others, depend on the variability and possibilities within the gluten-free food package. We wanted to assess whether the naturally gluten-free cereal *Eragrostis tef* (tef), having a nutritional value comparable with that of wheat, is associated with health problems when used by celiac patients. The results of this study can be found in chapter 5. All 7990 members of the Dutch Celiac Disease Society were invited to complete a 2-step questionnaire on tef use and the development of symptoms after tef consumption. Thirty-six percent responded to the first questionnaire of whom 53% consumed tef and 15% reported complaints. For the second more detailed questionnaire on the use of commercially available tef products suitable for a gluten-free diet, on previous symptoms during regular gluten-free diet without tef and on symptoms after tef consumption, 1828 were willing to complete it. 1545 had biopsy proven celiac disease, 66% of them used tef and 17% reported symptoms after tef consumption. This percentage of symptoms was significantly lower than patients without tef consumption reported in their regular gluten-free diet (17%

versus 61%; p=0.0001). We conclude that tef is frequently used by Dutch celiac patients and a wide majority can consume tef without clinical symptoms. Celiac patients using tef reported a significant reduction in symptoms, possibly related to a reduction in gluten intake or to an increase in fiber intake. We believe that tef can be a valuable addition to the gluten-free diet of celiac patients.

Chapter 6 contains the results of the study on whether health-related quality of life of celiac patients assessed with the SF-36 is associated with dietary compliance. This study was performed among the patients participating in the study described in chapter 7. We found that compared with the general population celiac patients scored significantly worse on general health perception, but significantly better on bodily pain and limitations due to physical problems. We conclude that strict adherence to a gluten-free diet is not associated with a lower health-related quality of life of celiac patients.

Celiac disease is believed to be a permanent intolerance to gluten. However, a number of patients discontinue the gluten-free diet without developing symptoms or signs. The aim of our study described in chapter 7 was to investigate whether celiac patients are capable of developing tolerance to gluten. We defined tolerance as no immunological or histological signs of celiac disease while consuming gluten. We found that of the 53 patients from our hospital known to have biopsy confirmed celiac disease for more than 10 years, 12 (23%) consumed a gluten-containing diet, 8 (15%) admitted gluten transgression and 33 (62%) followed a gluten-free diet. Twenty-two patients consented to small bowel biopsy. A normal small bowel mucosa (Marsh 0-1) was found in 4 of 8 patients on a gluten-containing diet, in all 4 patients with gluten transgression and in 9 of 10 patients adhering to a gluten-free diet. Marsh 3a-c lesions, suggestive of active celiac disease, were found in 4 patients on a gluten-containing diet and in 1 following a gluten-free diet. The patient on a gluten-free diet with Marsh 3a lesion is now being studied for possible refractory celiac disease. In contrast to expectations, we found osteoporosis only in the patients on a gluten-free diet, possibly explained by their significant older age and significant higher age at diagnosis or by the fact that some patients started to adhere to the gluten-free diet with a delay of 6 years after diagnosis of celiac disease.
From the 53 patients, 2 were considered to have developed tolerance to gluten. One of them was HLA-DQ2/DQ8 negative. We conclude that development of tolerance to gluten is possible in some exceptional patients with celiac disease. However, further follow-up will be necessary to find out whether this tolerance is permanent or only a long-term return to latency. This feature may be associated with genetic characteristics, especially with HLA genotypes that differ from DQ2 or DQ8. More insight into the mechanisms of the development of gluten tolerance may help to distinguish those celiac patients that might not require life-long treatment with a gluten-free diet.

Chapter 8 contains the general discussion and the conclusions of this thesis. In an effort to develop methods to prevent celiac disease, we have measured some of the environmental factors that are considered to play a role in the development or prevention of celiac disease. We have measured the presence of gliadin and glutenin in breastfeeding, and we have developed an instrument to assess the gluten intake in young infants. Both methods are applied in a recently started prospective collaborative European study on breastfeeding and gluten intake in newborns from high-risk families which explores the possibilities of primary prevention of celiac disease. The information resulting from that study may possibly lead to changes in the actual European guidelines for infant feeding, concerning the introduction of gluten after 6 months of age.

In the literature there is an ongoing discussion about the question whether celiac disease is a permanent condition, or can return to latency. We made an attempt to find patients who have become tolerant to gluten. We found 2 of these exceptional patients and found that one of them had HLA typing different from HLA-DQ2/DQ8, suggesting that genetic factors may play a role in the development of tolerance. However, the underlying mechanisms leading to prevention or development of celiac disease, or leading to tolerance to gluten once celiac disease has been diagnosed are complex and need to be further studied.
In the near future more patients will be diagnosed with celiac disease and professionals involved in their treatment have to be prepared to take care of the increasing number of patients. Therefore, new methods for treating and supporting this increasing number of patients need to be explored. Combined consultation of the doctor and the dietitian and the use of facilities like telephone and the internet in supporting the patients are ways to provide efficient and adequate support.

The only available treatment of celiac disease is adherence to the gluten-free diet. Attention to the adequacy of the nutrient intake within the gluten-free diet is necessary to prevent celiac patients from health risks. However, new possibilities in the treatment are promising and may decrease the burden of the treatment and positively influence the nutrient intake and the health-related quality of life. This may prevent the patients from cessation with the gluten-free diet, and thus protect them from the potential risk of complications.