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Gluten intake and gluten-free diet in the Netherlands

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CHAPTER 1

General introduction, aim and outline of this thesis

In the early 1930's the Dutch paediatrician W.K. Dicke discovered that the elimination of wheat from the diet was beneficial for celiac patients (1). This benefit was confirmed later during the period of food shortage in the Second World War (1944-1945), during which bread was unavailable, and Dicke observed that the clinical condition of the hospitalized children with celiac disease improved. Further studies showed that gluten and specifically its alcohol-soluble component, gliadin, was harmful for celiac patients (2). Gluten is the storage protein of wheat and wheat-related grains and can be subdivided in the gliadin and glutenin protein families, both of which are involved in celiac disease. Since then, a gluten-free diet has been the basis of the treatment of celiac patients.

In celiac patients, gluten causes histological alterations of the small bowel that may lead to disturbances in nutrient absorption and symptoms such as diarrhea, failure to thrive, abdominal pain, and extraintestinal complications such as osteoporosis, infertility and cancer (3). The treatment of celiac disease consists of a life-long gluten-free diet to heal the duodenal mucosa, improve symptoms, and protect against development of complications (4,5).

The diagnosis of celiac disease is based on characteristic histological alterations of the small bowel mucosa during gluten consumption and clear clinical remission with a gluten-free diet. In asymptomatic patients, however, a control biopsy is needed to prove mucosal recovery after treatment (6). In earlier days, a third biopsy after gluten challenge was needed to confirm the diagnosis in children (7).

Celiac disease is considered to be a life-long disorder, but there are studies describing patients diagnosed with celiac disease in childhood who seem to tolerate gluten later in life for an extended period of time (8).

Until now, the only effective treatment for the disease has consisted of a gluten-free diet in which wheat, rye, barley, spelt, kamut, and products derived from these cereals are avoided. To what extent oats belong to the list of banned cereals is still debated. Both long-term follow-up studies (9-11) and laboratory studies on oats being less toxic than wheat (12), support that oats are permitted in the gluten-free diet for adults and children. However, some patients do show mucosal damage after oat consumption, and individual differences in oat tolerance have been found (11,13). In the Netherlands, as in many other countries, fear of wheat contamination in commercially available oat products has led to a reluctance to recommend oats to celiac patients (14,15).

Wheat cereal is a staple food in many countries in Europe and is widely used in the food industry. Therefore, wheat is difficult for celiac patients to avoid; hence, the prescription to follow a gluten-free diet has a big impact on the patients' daily and social life (16), and even on the lives of family members. The availability of the gluten-free products is

limited, and consequently, celiac patients have difficulty finding gluten-free foods. Furthermore, taste as well as higher expenses can be limiting factors for compliance. For example, in the Netherlands, only a few health insurance companies contribute to the added costs of the gluten-free products. All these factors may affect the health-related quality of life of celiac patients (17,18). Furthermore, the nutritional value of gluten-free food products is lower compared to the gluten-containing equivalents, which may lead to inadequate nutrient intake (19-22).

Genetics play a role in the development of the disease: as much as 98% of the celiac patients are HLA-DQ2 (95%) or –DQ8 (3%) positive. However, the majority of people with these genetic factors do not develop celiac disease. This suggests that additional genetic and/or environmental factors play a role in disease development. Many genetic and immunological studies have been performed in an attempt to unravel the complexity of this multi-factorial disease (23-25). In addition, the possible role of environmental factors, such as early feeding, in the development or prevention of celiac disease has been studied (26-28). The Swedish ‘experiment of nature’ causing the rise and fall of ‘an epidemic’ of gluten intolerance after changes in infant feeding suggests that early feeding may be an important factor (26). Breastfeeding at the time of gluten introduction, ongoing breastfeeding while gluten is already being consumed, as well as timing and amount of gluten introduced into the diet, may play a preventive role in the development of celiac disease (27-29).

Breastfeeding and weaning influence the development of the gastro-intestinal tract, and it is possible that gradual introduction of antigens will lead to the development of oral tolerance (30,31). It is also likely that the response of the immune system to gluten is modified by breastfeeding (32,33). The presence of gluten peptides in breast milk leading to an early exposure to gluten, even before gluten is introduced into the infants’ diet, has been studied as a possible factor in the development of oral tolerance (34,35).

AIMS OF THIS THESIS

Gluten is essential for the development of celiac disease: in the absence of gluten, celiac disease will not be expressed. The aims of this thesis were to explore the relationship of celiac patients with gluten and the gluten-free diet at different ages, their ability to develop tolerance to gluten, and the impact of the gluten-free diet on health-related quality of life. Furthermore, this thesis also aims to measure some of the environmental factors such as breastfeeding and gluten intake in early life considered to play a role in the prevention of celiac disease and in the possible development of oral tolerance.

Chapter 1 consists of a general introduction and description of the aims and outline of the thesis. In chapter 2, the implication of the presence of gluten proteins in breast milk for the development of celiac disease is discussed. This relates to one of the aims of the study, i.e. to measure some of the environmental factors possibly involved in celiac disease, such as early feeding. Breastfeeding has been shown to prevent, or at least delay, the development of celiac disease (28). Breast milk contains many immunological 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. As the first contact with gluten may be important in this respect and the level of gluten peptides in breast milk may vary with intake of gluten by the mother, we studied the level of gluten peptides in breast milk of mothers on a gluten-containing diet and of mothers on a gluten-free diet. Expecting to find gluten peptides in the breast milk of mothers on a normal diet, but not in the breast milk of mothers on a gluten-free diet.

In chapter 3 we describe the development and testing of a food questionnaire to assess gluten intake, since another possible factor in the development of oral tolerance is the timing of gluten introduction and the quantity of gluten consumption in early life. However, this hypothesis is only based on observational studies. The role of gluten introduction should be confirmed by intervention studies before cause-effect conclusions can be drawn and changes in advice considering early infant feeding can be proposed. For such studies, it would be necessary to have an instrument available to assess the amount of gluten consumed. Such an instrument should be accurate, easy to use, and should be easily accessible by both researchers and parents. Since such an instrument was lacking, we developed and validated one for this purpose.

In exploring the attitude of celiac patients towards the gluten-free diet, we studied the management of the gluten-free diet by adolescent celiac patients. The results of that study are described in chapter 4. Until now, the gluten-free diet was the only effective treatment for the disease. From the perspective of the celiac patient, this treatment is quite a burden. Gluten intake is difficult to avoid since wheat is the cereal most used in staple food and widely used in the food industry. Furthermore, adherence to a gluten-free diet may have negative nutritional consequences. Dietary compliance in adolescents with celiac disease has been studied frequently and was shown to vary between 52% and 81% in European countries. In the Netherlands, however, we did not have information on this topic. Therefore, we studied the situation of dietary compliance in our country and the consequences for the nutrient intake in young celiac patients.

In an attempt to enlarge the gluten-free food choices, we studied whether the (new) naturally gluten-free cereal, tef (*Eragrostis tef*) can be safely used by celiac patients (Chapter 5). Adherence to the diet is often reported as being difficult. Next to the aforementioned aspects, the limited availability, the variety and the taste of gluten-free food products may have negative effects on the compliance with the gluten-free diet. A greater variety of tasteful products may contribute to a better compliance with the diet.

We studied the health-related quality of life (Chapter 6) in an adult population of celiac patients. Having a chronic disorder as well as having to adhere to a dietary regimen may affect quality of life. The health-related quality of life of celiac patients adhering to the gluten-free diet has been frequently studied in children as well as in adults. The adult population we studied was recruited for the study described in chapter 7 and consisted of celiac patients with strict adherence to the gluten-free diet and of celiac patients with gluten transgression or consuming a normal gluten-containing diet. This gave us the opportunity to compare the results of the health-related quality of life survey between compliers and non-compliers.

In chapter 7 we describe the results of a study on possible development of tolerance to gluten. As celiac disease is considered to be a permanent disorder, the diet has to be followed for life. However, patients consuming gluten without developing symptoms or signs of the disease have been described. Therefore, it is important to investigate which factors (genetic, immunologic or environmental) determine which patients with celiac disease remain intolerant to gluten for life and which few may regain tolerance. We studied the possible existence of adult celiac patients developing tolerance to gluten in the Netherlands and whether we could identify immunological or genetic factors that might contribute to this.

Finally, the overall results of the studies described in this thesis are discussed in chapter 8.

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