Introduction and Outline of this thesis
“It is pointed out that clinical observations have shown that the harmful effect on patients with coeliac disease is not caused by all cereals but specially by wheat flour; that it is this flour which causes the acute diarrhea attacks and that when it is banished from the diet the diarrhea ceases and does not return, while the condition improves visibly, the appetite returns, the colour of the faeces improves, the patient gains weight and finally the growth in height becomes normal or more than normal.”

This quote originates from the thesis of Willem Karel Dicke, defended in 1950. Dicke was the first person who described the relationship between wheat and coeliac disease (CD). Nowadays it is known that CD is caused by the ingestion of gluten which can be found in wheat, barley, rye and some related cereals which are relatively resistant to proteolysis in the stomach. While Dicke reported the classical form of CD (i.e. children with failure to thrive and diarrhea), it is currently known that CD is a clinical chameleon with different manifestations. These vary widely with classical signs such as chronic diarrhea, weight loss and abdominal distention in approximately half of all CD patients. Less common manifestations are constipation, aphthous stomatitis, ataxia, and dermatitis herpetiformis. The prevalence of CD differs between countries and is estimated as 0.5 - 1% in the western population. It has been suggested that the majority, up to more than 80% of the CD patients, is undiagnosed and the knowledge regarding the beneficial effects of detecting and treating these undiagnosed individuals is currently sparse. Multiple studies have been performed to identify new treatment strategies for CD, however, a life-long gluten-free diet (GFD) is still the only, safe, and relatively inexpensive treatment for CD patients.

Pathophysiology
After the digestion of gluten-containing products, gluten proteins are degraded into relatively large fragments in the stomach and small intestine. Gliadin peptides, part of gluten, bind to certain types of Human Leukocyte Antigens (HLA): HLA-DQ2.5, HLA-DQ2.2 and HLA-DQ8. In certain individuals, specific T-cells react to such DQ-gliadin complexes. This causes a cascade which results in tissue damage of the small bowel and release of the enzyme transglutaminase type II (tTG): an enzyme which modifies gluten. This so-called deamination of gluten results in a much higher affinity of these gluten to the specific HLA-molecules which results in a cascade of cytokine release and ultimately villous atrophy.

Different subsets of T-cells play an important role in the pathophysiology of CD with a different composition compared to non-CD patients. The best described shift of lymphocyte populations in CD is an elevated percentage of γδ T-cell receptor positive intra-epithelial and lamina propria lymphocytes. Another lymphocyte population with a potential role in CD are CD4+CD8+ double positive T-cells. The percentage of these cells is decreased in both the small bowel epithelium and lamina propria of CD patients compared to non-CD patients. The exact role of these cell subsets is unknown, although both regulatory as well as pro-inflammatory functions have been attributed to both.

Diagnosis
Serological testing identifies most CD patients using CD-specific and -sensitive antibodies. The most important antibody is IgA anti-tTG with a high sensitivity of 98% and a specificity of 98%. In adults, the diagnosis of CD has to be completed by typical findings in duodenal biopsies: the golden (or in combination with serological testing, silver) standard. These findings are well defined by Marsh and include villous atrophy, crypt hyperplasia and intra-epithelial lymphocytosis.

In certain cases, HLA-DQ typing could make the diagnosis of CD more obvious since virtually all patients with CD are HLA-DQ2 or HLA-DQ8 positive, however, approximately 40% of the general Caucasian population carries at least one of these genes as well. This makes HLA-DQ typing suitable for excluding CD.

As previously mentioned, the majority of CD patients is yet undiagnosed. Although there is discussion whether detecting CD patients with mild or no symptoms has health-related advantages, there is evidence that undetected CD can lead to a.o. iron deficiency, osteoporosis and cancer, such as the rarely occurring enteropathy associated T-cell lymphoma (EATL). Since general practitioners play a key role in the Dutch health care system, they play a role in diagnosing and managing CD. Data regarding the daily clinical practice of CD management by general practitioners is however sparse. The same applies to the oral health of CD patients which can be useful for dentist since 80% of the general Dutch population, and consequently also a large proportion of CD patients, visits a dentist at least once a year. The best known dental anomalies are symmetric enamel defects, described by Aine.

Complications of coeliac disease
A small minority of CD patients is or becomes refractory to a GFD with an annual incidence of 0.83 / 10,000 CD patients in the Netherlands. In a subset of these patients aberrant intra-epithelial lymphocytes (IEL) are identified. This entity is called refractory CD type II (RCD II). These aberrant T-cells are lacking surface CD3 despite the presence of cytoplasmatic CD3 and are considered as a low-grade no-mass lymphoma. The identification of these cells requires flowcytometric analysis of IEL, although clonality analysis of IEL and immunohistochemistry...
could be useful as well. Once RCD II is diagnosed, the risk for developing EATL 4-6 years after diagnosis is 50% with a dismal prognosis after EATL development. Well-conducted randomized trials to investigate treatment strategies in RCD II are lacking. Current treatment consists of budesonide, cladribine and autologous stem cell transplantation.

Since symptoms alone cannot differentiate RCD II from slow responding CD and flowcytometric analysis of IEL is only available in a few centers, it can be useful to have non-invasive parameters which can differentiate these “complicated” forms from “uncomplicated” forms of CD. One of these potential parameters is the splenic volume, since a pilot study showed that RCD II and EATL patients appeared to have a smaller spleen on computed tomography than uncomplicated CD patients.

Follow-up
A challenge in the management of CD patients is how to perform the follow-up. It is known that CD patients have an elevated risk to develop osteoporosis, vitamin deficiencies and certain malignancies such as EATL and small bowel adenocarcinoma. However, good evidence-based follow-up guidelines, as well as guidelines who has to perform this follow-up, are lacking but needed since preventive care, quality of life and health care costs are becoming more and more important in daily clinical practice. For clinical guidelines, the actual risk of several complications has to be known, especially for the most feared complication of CD: EATL and small bowel adenocarcinomas. Currently known standardized incidence ratios of T-cell lymphomas (range 19-51) and small bowel adenocarcinomas (range 0-34) in CD patients compared to the general population varies widely and data regarding absolute risks are unknown.

Differential diagnosis of coeliac disease
In some situations it is difficult to diagnose CD. This may result in a diagnostic dilemma. In general, these patients can be divided in two main categories: first, patients with only serological or histological signs of CD, but not fulfilling all criteria to establish the diagnosis of CD (i.e. respectively potential and seronegative CD). For seronegative CD, other causes of villous atrophy should be excluded. These include a.o. medication-induced enteropathy, collagenous sprue, *Giardia lamblia* and Whipple disease.

Secondly, there are patients who are on a gluten-free diet and want to undergo a diagnostic work-up for CD without performing a gluten re-challenge because they develop symptoms once consuming gluten. Once CD is excluded in these patients, they are diagnosed as non-coeliac wheat (or gluten) sensitive (NCWS or NCGS) patients. The pathophysiology of NCWS is unknown although different mechanisms induced by different components of wheat could potentially be responsible, such as gluten, fermentable oligo-, di-, monosaccharides and polyols, wheat germ agglutinin and amylase-trypsin inhibitors.

This thesis focuses on the diagnosis and follow-up of CD.

*Coeliac disease: beyond villous atrophy.*
OUTLINE OF THIS THESIS

The first part of this thesis is the introduction and outline.

The second part of this thesis focuses on CD and mechanisms involved in the disease. Chapter 2 explores the distribution of gender and age at time of CD diagnosis. Chapter 3 provides data regarding γδ T-cell receptor positive IEL and aberrant IEL and how these can be used as extra diagnostic parameters in diagnosing CD including cut-off values. To investigate the role of the γδ T-cells, the cytokine profile of these cells is studied in Chapter 4. This chapter also investigates the role of CD4+CD8+ T-cells since it has previously been described that these cells are decreased in active CD patients but the exact role is still unrevealed.

The third part of this thesis focuses on the follow-up and complications of CD. Since general practitioners play a key role in the Dutch health care system, insights into the views of general practitioners on their management regarding diagnosis, treatment and follow-up of CD patients using a qualitative approach are provided as presented in Chapter 5. In Chapter 6 knowledge regarding oral health in relation to CD is reviewed and the potential role of dentists in diagnosing and follow-up of CD patients is discussed. Chapter 7 provides insights into xerostomia and oral health of diagnosed CD patients versus a control group.

Chapter 8 till 11 focuses on (pre-)malignant CD conditions. In Chapter 8, the knowledge regarding RCD is reviewed and Chapter 9 presents the results of the first randomized, double-blind-, placebo-controlled study of the treatment of RCD II (an anti-IL15 monoclonal antibody versus placebo).

Since it has been suggested that (subgroups) of CD patients are immunosuppressed, Chapter 10 focuses on splenic volume. In Chapter 11, the relative and absolute risks and their characteristics for several lymphomas and gastrointestinal carcinomas in CD patients is investigated, which could be used in daily clinical practice.

The fourth part of the thesis focuses on gluten sensitivity. Chapter 12 investigates the prevalence of self-reported gluten sensitivity in the general Dutch population.

The fifth part of the thesis consists of three chapters of clinical cases: the treatment of collagenous sprue with thioguanine [Chapter 13], losartan-induced enteropathy [Chapter 14] and fecal microbiota transfer in a patient with Clostridium difficile and RCD II [Chapter 15].

REFERENCES

Introduction


