Part I

Chapter 1

Introduction and outline of this thesis
Celiac disease

Between 1934 and 1941, Dr. Willem-Karel Dicke identified wheat as a causative agent for a range of abdominal and dermatological symptoms in young children. He was responsible for the recognition, the first clinical study and the first scientific publication regarding this wheat-related disease. In 1953, a protein-complex found in wheat, rye, and barley, named gluten was identified as the harmful ingredient for these children. From that day on these patients were diagnosed as having celiac disease (CD). Since this pioneering work by Dicke, major progress has been made in the understanding of the pathogenesis of CD. Today, CD is described as a chronic enteropathy caused by a state of heightened immunological responsiveness to ingested gluten in patients with a genetic predisposition. Even now the only accepted treatment of CD is a lifelong strict adherence to a gluten free diet (GFD). This interrupts the immune response triggered by gluten and restores the mucosal damage.

Until the 1980s, CD was considered a rare disease affecting mainly young children. Since then, it has been shown to occur at any age and within any race or ethnicity. Although the reported prevalence of CD in current literature seems to vary considerably, due to differences in studied populations and use of different screening methods, the estimated worldwide prevalence is 1% in the general population. The clinical presentation of CD is diverse. Classic CD patients present with diarrhea, steatorrhea, abdominal pain or bloating, weight loss, and other signs of malabsorption. As awareness increases among healthcare workers, non-classic CD patients (presenting with vague abdominal symptoms, a rash, ataxia, depression, recurrent abortions e.d.) and even asymptomatic CD patients are being diagnosed increasingly more often.

The pathogenesis of CD consists of a cascade of immune reactions, caused by partially digested gluten fragments. These immune reactions include the deamination of particular glutamine residues into glutamic acid, binding of deamidated peptides to HLA-DQ2 and/or HLA-DQ8 and a subsequent innate and adaptive immune response, eventually leading to small intestinal villous atrophy. Consequently, patients develop malabsorption in the small intestine. This activated immune response results in the production of (auto) antibodies against transglutaminase (TTG), endomysium (EMA) and/or deamidated gliadin peptides (DGP). These antibodies are therefore used to diagnose CD and serological testing is usually the first diagnostic tool for CD. When high
levels of antibodies are detected, additional genetic testing and histological evaluation of duodenal biopsies are used to confirm CD\textsuperscript{9}. Histological examination of duodenal biopsies in CD typically demonstrates an increased intraepithelial lymphocyte count, crypt hyperplasia and various degrees of villous atrophy, collectively included in the Marsh criteria\textsuperscript{13}. Generally, the combination of serology, compatible HLA-DQ haplotype, and the presence of a histological Marsh III lesion does not pose a diagnostic challenge. Some patients, however, present with clinical characteristics which raise a high suspicion of CD, yet the findings are not sufficient for a definite diagnosis. Such a scenario can be found in patients with intraepithelial lymphocytosis in the absence of villous atrophy (Marsh I), or patients who are already on a gluten-free diet (GFD) without an established diagnosis. For this category of patients additional diagnostic tests are warranted. In chapter 2 we propose to use intra-epithelial lymphocytes bearing the T cell receptor (TCR) gamma-delta chain (γδ-IEL) as an additional diagnostic test for CD and we provide a cut-off value.

**Complicated celiac disease**

A small minority of CD patients experiences persisting or recurring symptoms and villous atrophy despite strict adherence to a GFD. The most common cause is inadvertent gluten contamination\textsuperscript{14}, or a (concomitant) small intestinal bowel disorder resembling CD\textsuperscript{15}. When other causes of refractoriness have been excluded, these patients are diagnosed with complicated CD, referred to as refractory celiac disease (RCD). RCD can be divided into two types based on the absence (type I) or presence (type II) of an intra-epithelial lymphocyte (IEL) population with an aberrant phenotype\textsuperscript{16}. This phenotype is characterized by a lack of surface CD3 (sCD3) expression, but presence of intracellular CD3 complexes (iCD3). RCDII is defined by the presence of villous atrophy (Marsh III A-C) in combination with an IEL population consisting of >20% sCD3-CD7+iCD3+ IEL determined using flow-cytometry\textsuperscript{17}. RCDII is a rare condition with a cumulative incidence of 0.04\%\textsuperscript{18}. RCDII is most often diagnosed around the age of 50 or thereafter but younger patients may be observed\textsuperscript{19, 20}. Chapter 3 describes clinical characteristics of RCDI and RCDII patients, the diagnostic approach, and insights in treatment options.

RCDII has a high risk of malignant transformation to an enteropathy associated T-cell lymphoma (EATL). RCDII is therefore considered an indolent lymphoma. EATL is an intestinal T-cell Non-Hodgkin Lymphoma that arises from intraepithelial lymphocytes. RCDII and EATL patients show overlapping clinical characteristics with ‘classical’ or
untreated uncomplicated CD; ongoing weight loss, abdominal pain, diarrhea and fatty stools. Literature regarding other nutritional parameters and energy expenditure in both RCDII and EATL was lacking. Therefore we comprehensively assessed the nutritional status and intestinal absorption capacity of patients with RCDII and EATL, and compared this with newly diagnosed CD patients in chapter 4. Given the high percentage of RCDII patients that develop an EATL, the treatment goal in RCDII is to improve clinical course and prevent or delay progression to an overt EATL. Unfortunately, RCDII is, at least in part, resistant to most evaluated therapies so far. To date, there is no standardized treatment approach. In chapter 5 we describe EATL development and survival in a cohort of RCDII patients and define prognostic factors associated with EATL development in this population.

Based on its clinical presentation EATL can be divided into two subtypes; EATL can arise in patients without a proceeding history of coeliac disease (primary EATL) or EATL manifests in adult patients with previously diagnosed (refractory) coeliac disease who clinically deteriorate (secondary EATL). Treatment strategies consist of different steps, including surgery, chemotherapy and stem cell transplantation (SCT). Each step is applied depending on the eligibility of the patient. Due to the risk of bowel perforation during chemotherapy or symptomatic perforation or stenosis at diagnosis, the preferred first step in the treatment of EATL is surgical debulking. In chapter 6 we describe indications for surgery, resectability of the lymphoma and the morbidity and mortality of EATL patients who underwent surgical debulking.

There are no validated nor standardized treatment protocols for EATL due to the rarity of this disease and the difference in eligibility of the patients. In chapter 7 we retrospectively reviewed the outcome of a large multicentre-cohort of EATL patients to compare differences in treatment response, relapse rate and survival between primary and secondary EATL and between different therapy-regimens.

**Non-celiac gluten sensitivity**

Recently, there is an overwhelming interest, both in the scientific community as well as in the mass media, as to whether gluten-containing food can cause symptoms in the absence of CD. The relatively new entity presented here is named non-celiac gluten sensitivity (NCGS). NCGS manifests with intestinal (diarrhea, abdominal discomfort or pain, bloating and flatulence) and/or extra-intestinal symptoms (including fatigue,
headache, lethargy) that occur after the ingestion of gluten and improve after gluten withdrawal. Symptoms of NCGS display significant overlap with irritable bowel syndrome, the latter being one of the most common disorders in today’s society. While this concept has traditionally been encountered with skepticism, there are several recent well-conducted studies that support the concept of NCGS. In chapter 8 we have critically reviewed these studies and display an overview of the current knowledge on NCGS.

Despite this growing interest, the actual prevalence of NCGS is difficult to establish. In some countries, the number of individuals embracing a gluten-free diet is already well above 10% of the population. However, a substantial part of this group consists of people who avoid gluten-containing food in the light of a healthier lifestyle. The theory that grains by means of their composition are unhealthy, should be distinguished from the question whether gluten can cause clinically relevant symptoms in the absence of CD. Few studies have addressed the prevalence of NCGS and the outcomes vary widely. In chapter 9 we evaluate the population prevalence and the clinical characteristics of self-reported NCGS in adults in our own bread-eating country.
References


