Diet and celiac disease

Impact

Celiac disease (CD) is an auto-immune condition triggered by gluten consumption, causing intestinal damage and various health issues, such as failure to thrive, abdominal complaints and impaired bone health. Notably, the incidence of auto-immune disorders is increasing in all age groups. The related growing prevalence of CD, affecting approximately 1-2% of the population, and its chronic nature underscore the high economic and societal impact of CD. One notable distinction between CD in adults and children is the clinical presentation, and naturally, the duration of the chronic disease. The burden of CD in children is multifaceted, encompassing physical health due to nutrient deficiencies and a broader societal and psychological burden, especially from following a strict gluten-free diet (GFD) (1). Adhering to a GFD can impose a considerable financial burden on CD patients and their families. Additionally, there is also a substantial financial burden on society. Patients with CD in the US for instance experience substantially higher healthcare expenses compared to control groups matched for comorbidities and demographic factors (2). The mean annual all-cause healthcare costs of CD patients are comparable to those of patients with Crohn's disease in the US and were increased by $3776 two years after diagnosis of CD compared to matched controls (2). Consequently, the prevention of CD represents a paramount approach for alleviating this financial strain.

The exact reasons for the rising incidence of CD in children remain unclear, and the role of environmental, psychological, and societal factors contributing to this trend need further studying. The overarching goal of this thesis was to reduce the disease burden of CD in children by focusing on disease prevention on the one hand and improving treatment of patients with CD on the other hand. Thereby, this thesis specifically addresses the challenges of CD in children and underscores the necessity for a focus on the pediatric population to enhance the management and quality of life for children affected by CD.

The findings from the studies in the current thesis can provide leads, not only for scientists, healthcare providers, educators, and policymakers, but also for patients with CD and their families, offering pathways towards improved strategies for managing CD and disease prevention. The socioeconomic, seasonal, and regional disparities highlighted in the incidence of auto-immune diseases, including CD, provide indications for potentially modifiable factors in the risk of developing CD. The emphasis on prevention is paramount, and the identification of new targets and leads is crucial, not only for CD but for other intestinal diseases characterized by the disruption of barrier function. Herein, focusing on potential factors that can be targeted and harnessed in disease prevention will yield a greater impact than merely understanding disease pathophysiology. Dietary factors represent a robust

example of a potentially modifiable risk factor associated with CD. The first aim of this thesis was to investigate the role of dietary factors and barrier disruption in CD etiology.

We found, that intestinal damage could be a contributing risk factor to CD onset, as we identified different patterns in a biomarker for intestinal damage in a subgroup of children that developed CD, compared to a group that did not develop CD. Next we aimed to investigate the role of the diet on intestinal permeability in an *in vitro* cell model. We found that dietary factors associated with an increased CD risk, namely gliadin, glucose and fructose dose-dependently can lead to an increase in small intestinal permeability. Gliadin is the part of gluten, that triggers the auto-immune reaction in CD, therefore called the immunogenic component of gluten. This provides evidence for the hypothesis that high exposure to these dietary factors early in life could contribute to increased intestinal permeability, resulting in the passage of gliadin across the intestinal wall. This would enhance the contact of gliadin to the immune system and increases the risk of the CD-specific immune reaction. Surprisingly, in our study of the effects of theses sugars and gliadin on intestinal permeability, we found an altered effect when exposing the cell model to the components separately as compared to a combined exposure. This underlines, that future research should focus on studying dietary factors in realistic approximations of a meal and more physiological conditions.

The findings presented in this thesis show interesting tethering points and merit for future research focusing on nutrition, especially the impact of the Western diet and intestinal barrier damage and dysfunction as part of CD etiology.

At present, the only treatment available is GFD. Maintaining a GFD presents distinct challenges for children with CD. Key issues include the risk of nutrient deficiencies due to restricted food choices, social hurdles in environments like school lunches, and the psychological burden of constant dietary vigilance. The COVID-19 pandemic may have intensified these challenges, disrupting routines and access to gluten-free products. These factors underscore the complexity of adhering to a GFD for young patients with CD. The second aim of this thesis was to evaluate the challenges of the GFD, beyond the elimination of gluten. We evaluated the risk to develop nutrient deficiencies while following a GFD, in a review of the current literature as well as our own cohort of children with CD. Both studies showed that nutrient deficiencies such as iron and vitamin D deficiency occur frequently even after following a strict GFD for a prolonged time. Although we found these common deficiencies in our own study as well as in the literature, the full extent of the problem is still unclear. This is mainly because possible clinical relevance and implications on short-term and especially in the long-term are still not known. In our literature review we found for instance, that impaired bone

health is an important long-term consequence of CD, even when treated correctly with a GFD. The known increased risk for bone fractures and osteoporosis of patients with CD at older age could be exacerbated by (re-) occurring periods of vitamin D deficiency. A questionnaire study we conducted during the second lock-down period of the COVID-19 pandemic in the Netherlands revealed additional challenges patients and their parents are facing, which reach beyond the pandemic. Examples are the unintentional exposure to gluten when eating outdoors and the lack of knowledge on availability of gluten-free products. Our findings on the management of CD through diet and the risk to develop nutrient deficiencies, highlight the need for better patient education regarding the GFD. The evidence presented here, combined with the existing literature, can contribute to a more evidence-based approach to CD management, aiding patient, healthcare providers and other stakeholders to enhance the health and overall wellbeing of individuals with CD.

Improved education and enhanced collaboration with dietitians, General Practitioners, and all healthcare providers are pivotal in improving care for patients with CD. Herein, results such as shown in this thesis show, that dietary education must extend further than only the elimination of gluten from the diet. Examples for stakeholders outside of direct healthcare providers can be schools, but also restaurants and other establishments providing food, the food industry as well as authorities regulating them. Improvements can be made to make eating outside of the home feel safe for all patients with CD or other dietary restrictions, through good education of food workers, effective regulations and safeguarding and standardizing of appropriate food safety labels (3). This includes improvement of education and regulation concerning cross contamination leading to small traces of gluten that can trigger disease, but as important, also on the nutritional quality of gluten-free products and meals.

Working towards more evidence-based guidelines on the management and follow-up of CD for clinicians, can additionally give a basis for a part of the substantial health care costs of CD follow-up. Evidence-based decision making on for example frequency and nature of serological tests can potentially prevent unnecessary health care costs next to lowering the burden of disease follow up for patients themselves.

Addressing the broader impact of this research, it must be noted, that most research conducted so far predominantly pertains to Western society, including mainly European and Caucasian demographics. To truly understand the multifaceted nature of CD and its risk factors, incorporating a more diverse ethnic and cultural background in research is crucial. This diversity not only enriches the research but also broadens the impact of the study outcomes. This is an important limitation of

the work presented in this thesis as well as in CD research in general. For example, the disease burden is hypothesized to be substantial in Africa, where there are almost no publications on CD (4, 5). The distribution of HLA risk groups in Ethiopia is similar to Sweden, yet the prevalence of CD is not even known in large parts of the world, including Ethiopia and some of the most populous countries like China, Indonesia, Pakistan, Nigeria and Bangladesh.

It is important that research findings are widely shared with various stakeholders, e.g. explicitly including patients and their environments. In order to broaden the impact of this thesis, the studies have been presented at various national and international conferences, such as ESPGHAN, NUTRIM days, and the NCV dag of the Dutch patient society for CD, to peers, the lay public, and patients themselves. The Studium Generale lecture at Maastricht University served as a platform to articulate the findings and implications of the studies included in this thesis to a diverse audience, fostering awareness and understanding of CD and its multifaceted implications. Moreover, the commitment to open access publication ensures that the forthcoming papers of this thesis are accessible to a wide array of individuals and groups, facilitating the dissemination of knowledge and fostering an inclusive academic environment.

In conclusion, the work in this thesis contributes to the ongoing dialogue on CD, offering insights that aid significant steps forward in understanding and managing the disease. The need for more inclusive and diverse research is evident, and the contribution of this work to the global conversation on CD is a reminder of the interconnectedness of our world and the shared responsibility to enhance knowledge and understanding for the betterment of all.

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