Research Article

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Increased risk of non-alcoholic fatty liver disease after diagnosis of celiac disease

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Background & Aims: Non-alcoholic fatty liver disease is a common cause of chronic liver disease. Celiac disease alters intestinal permeability and treatment with a gluten-free diet often causes weight gain, but so far there are few reports of non-alcoholic fatty liver disease in patients with celiac disease.

Methods: Population-based cohort study. We compared the risk of non-alcoholic fatty liver disease diagnosed from 1997 to 2009 in individuals with celiac disease (n = 26,816) to matched reference individuals (n = 130,051). Patients with any liver disease prior to celiac disease were excluded, as were individuals with a lifetime diagnosis of alcohol-related disorder to minimize misclassification of non-alcoholic fatty liver disease. Cox regression estimated hazard ratios for non-alcoholic fatty liver disease were determined.

Results: During 246,559 person-years of follow-up, 53 individuals with celiac disease had a diagnosis of non-alcoholic fatty liver disease (21/100,000 person-years). In comparison, we identified 85 reference individuals diagnosed with non-alcoholic fatty liver disease during 1,488,413 person-years (6/100,000 person-years). This corresponded to a hazard ratio of 2.8 (95% CI 2.0–3.8), with the highest risk estimates seen in children (HR = 4.6; 95% CI 2.3–9.1). The risk increase in the first year after celiac disease diagnosis was 13.3 (95% CI 3.5–50.3) but remained significantly elevated even beyond 15 years after the diagnosis of celiac disease (HR = 2.5; 95% CI 1.0–5.9).

Conclusion: Individuals with celiac disease are at increased risk of non-alcoholic fatty liver disease compared to the general population. Excess risks were highest in the first year after celiac disease diagnosis, but persisted through 15 years after diagnosis with celiac disease.

Keywords: Autoimmune; Steatohepatitis; Gluten; NASH; NAFLD; Celiac disease.
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Abbreviations: CD, celiac disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SIBO, small intestinal bacterial overgrowth; VA, villous atrophy; ICD, international classification of disease (codes); CI, confidence Interval; HR, hazard ratio; OR, odds ratio; BMI, body mass index.

Introduction

Celiac disease (CD) is associated with both acute and chronic liver diseases, especially autoimmune liver disease [1,2]. Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in children and adolescents in Western nations [3], it is estimated to be present in 20% of the population [4], and some individuals may progress to fibrosis and cirrhosis [4,5]. Yet, data establishing whether individuals with CD may be at risk of NAFLD are nascent [1,6]. Metabolic risks as well as those altering intestinal permeability found in CD can also be potential triggers for NAFLD.

Obesity and metabolic syndromes are accepted as major accessory complications of NAFLD [7], though not all patients with NAFLD are obese [8]. A high-fat diet and sedentary lifestyle are adaptable risks, modifications to these can yield improvements in NAFLD [9], and recovery after weight loss may be related to reduced insulin resistance [10]. Many adults and children with CD are overweight or obese at diagnosis, or become overweight after treatment [11,12], consequently increasing the risk to develop NAFLD. Children [13] and adults [14] with CD may have increased cardiovascular risks which overlap with those associated with NAFLD.

The gut-liver axis via the portal system has been implicated as a potential route of inflammatory cytokines, which may trigger the onset of non-alcoholic steatohepatitis (NASH). Levels of endotoxin (lipopolysaccharide), derived from intestinal Gram-negative microbiota, are elevated in the sera of adults [15] and children [16] with NAFLD, suggesting these individuals have increased intestinal permeability. Small intestinal bacterial overgrowth (SIBO) is more common among patients with NAFLD than healthy individuals [17] and is associated with higher TNF-α levels, independent of increases in gut permeability markers [18]. Individuals with CD have altered intestinal permeability due to the disturbance of mucosal integrity induced by gluten and the associated inflammatory response [19]. Additionally,

SIBO is common among individuals with CD [20], which may further impair mucosal barriers and may have other links to the pathogenesis of NAFLD [18]. Whether a compromised intestinal barrier is a cause or effect of NAFLD requires additional study, though the prevailing theory is that bacteria-derived endotoxin and related cytokines may serve as a "second hit" among certain patients with hepatic steatosis leading to the development of NASH [21].

In this population-based study, we aim to investigate the frequency with which NAFLD is identified among individuals with CD.

Materials and methods

Study participants

In 2006–2008 we collected small intestinal biopsy record data from all 28 pathology departments in Sweden. The biopsies had been performed between 1969–2008 and collected data included date of biopsy, biopsy site (duodenum or jejunum), morphology codes consistent with villous atrophy (VA), (Marsh grade III) (see Supplementary Table 1A), and personal identity number (PIN) [22]. In this paper we equated VA with CD (details of the data collection have been published before) [23]. While we did not require positive CD serology for a CD diagnosis, patient chart validation in a random subset of individuals with VA found 88% were positive for transglutaminase, endomysium or gliadin antibodies at the time of biopsy [22].

We then matched each individual with CD with up to five reference individuals matching; age, sex, calendar year and county of residence at the time of biopsy. Reference individuals were sampled from the Swedish Total Population Registry maintained by the government agency Statistics Sweden. Through this matching procedure, for example, a woman born in 1963 with a CD diagnosis in 1998 living in the county Dalarna was matched to up to five other women, born in 1963, living in that county in 1998. After removal of duplicates and potential data irregularities, our remaining study participants (29,096 CD patients and 144,522 reference individuals) were identical to that of our mortality study in CD [24].

NAFLD, other liver disease, and alcohol use

Patients with our outcome measure, NAFLD, were identified using a search for the ICD-10 (International Classification of Disease) code K76.0 in the Swedish Patient Registry, a registry of patient diagnoses initiated in 1964 which became nationwide in 1987. More than 99% of all somatic care is registered in the registry and most disorders have a positive predictive value of 85–95% [25]. Prior to the year 2000, the patient registry only contained inpatient data, but since 2000 has included both inpatient and hospital-based outpatient data. We restricted our follow-up to 1997–2009 since the Swedish ICD-10 began in 1997 (before that, NAFLD could not be distinguished from other liver disease).

Initially, to rule out that CD had been diagnosed due to prior liver disease (e.g. misclassified NAFLD), we excluded individuals with any liver disorder diagnosed before a first intestinal biopsy with VA (n = 948; 3.3%) or before the corresponding date in reference individuals (n = 3217; 2.2%). Hence, all study participants were free of a diagnosis of liver disease at study entry.

Since alcohol is a predominant cause of fatty liver disease, we also identified all individuals with a lifetime diagnosis of alcohol-related disease (see Supplementary Table 2 for relevant ICD codes) (CD: n = 812, 2.8%; and reference individuals: n = 3845; 2.7%). These ICD codes represent both somatic and psychiatric disorders where alcohol use has been implicated and did, in some circumstances, overlap with individuals who had a prior diagnosis of liver disease. Swedish National Registries do not otherwise record alcohol use in healthy people. At this stage we also excluded study participants with a follow-up that ended before 1997 (CD: n = 723 (2.5%); reference: n = 2899 (2.1%)) since they could not potentially be diagnosed with fatty liver since that diagnosis was only introduced in 1997.

Finally, our analyses were carried out stratum-wise. We compared each CD individual only with his/her matched reference individuals and thereafter calculated a summary estimate for NAFLD, excluding reference individuals in strata where the CD individual had been excluded for any reason. The final dataset therefore consisted of 26,816 individuals with CD and 130,051 reference individuals (Table 1).

Main covariates

The government agency Statistics Sweden delivered data on the following potential confounders: country of birth (Nordic *vs.* not Nordic), educational level, and socioeconomic status at the time of biopsy. When a child did not have data on socioeconomic status or education, parental data were used. Crude and adjusted risk estimates were limited to individuals with complete data on socioeconomic status and education (72.0% of CD patients and 72.5% of reference individuals had complete data on these covariates). We categorized education into four groups (⩽9 years of primary school, 2 years of high school, 3–4 years of high school, college/university) while socioeconomic status was categorized into six groups (in accordance with the European Socioeconomic Classification, ESeC: levels 1, 2, 3+6, 7, 8, and 9). (For additional details see our previous paper [26]).

Statistics

Hazard ratios (HRs) for NAFLD were estimated using internally stratified Cox regression, with all comparisons made within a stratum of matched individuals as in a conditional logistic regression. The proportional hazards assumption was tested using log-minus-log curves (Supplementary Fig. 1). Although we found that the assumption of proportional hazards was not violated, we calculated follow-up specific HRs since the HR for NAFLD was substantially higher in the first year after CD diagnosis. We began follow-up on the date of first biopsy with VA (equivalent to CD in our study) and on the corresponding date in matched reference individuals or on Jan 1, 1997, whichever occurred latest. Follow-up time ended with NAFLD diagnosis, December 31, 2009, emigration, or death, whichever occurred first.

In pre-defined analyses, we calculated HRs for NAFLD in males-females, different age strata (e.g. ⩽19 years, see also Table 1), and calendar year (Table 1). Potential effect modification was tested by entering interaction terms in the statistical models. We also carried out separate analyses adjusting for country of birth, level of education, and socioeconomic status.

In a post hoc analysis, we also examined the risk of NAFLD in 11,121 CD patients with Marsh 1–2 lesions (inflammation but no VA). The data collection of these individuals has been described before [27] and was identical to that of CD, except that other SnoMed codes were used (see Supplementary material).

In a sensitivity analysis we tested if the association between CD and NAFLD changed using attained age instead of time since biopsy as the time scale. Finally, we examined if adjustment for a type 2 diabetes, autoimmune thyroid disease, lipid-lowering drugs (as proxy for dyslipidemia) or drugs linked to NAFLD would influence the association between CD and NAFLD. Drug treatment was identified using relevant ATC codes in the Swedish Prescribed Drug Registry (Supplementary material). Type 2 diabetes and autoimmune thyroid disease were identified according to relevant ICD codes in the Swedish Patient Registry (Supplementary material). This latter registry started on July 1, 2005 and hence we restricted this last analysis to individuals who had not died or emigrated prior to this date.

Prior NAFLD and later CD

To investigate if a positive association with NAFLD was present before CD diagnosis, we performed a case-control study of 16,865 individuals with CD diagnosed in 1997 or later, and 83,767 matched controls. Data were analyzed using a conditional logistic regression model which eliminated the influence of the matching criteria (age, sex, birth year, and county). In *a priori* analyses we stratified for time between NAFLD and later CD (<1 year, 1–5 years, and >6 years).

Statistical analyses were performed using SPSS 22 (SPSS Statistics, Version 22.0, Armonk, NY). p values <0.05 were considered to be statistically significant.

Ethics

This study was approved by the Regional Ethical Review Board in Stockholm (2006/633-31/4). Because this was a registery-based study, no participant was contacted and all data were anonymized prior to data analyses.