Increased risk of end-stage renal disease in individuals with coeliac disease

Adina Welander,1 Karl-Göran Prütz,2 Michael Fored,1 Jonas F Ludvigsson1,3

ABSTRACT

Objective The prevalence of end-stage renal disease (ESRD) is increasing worldwide. Although increased levels of coeliac disease (CD) autoantibodies are often seen in renal disease, the importance of biopsy-verified CD for the risk of future ESRD is unclear. The aim of this study was therefore to investigate the risk of future ESRD in individuals with CD.

Methods This was a population-based prospective cohort study. 29 050 individuals with CD (Marsh III) were identified through small-intestinal biopsy reports obtained between July 1969 and February 2008 in Sweden’s 28 pathology departments. ESRD was defined as the need for renal dialysis or renal transplant in accordance with the international classification of disease and procedure codes in Swedish patient registers. Using Cox regression, the risk of ESRD in individuals with CD compared with age- and sex-matched reference individuals was estimated.

Results During follow-up, 90 individuals with CD developed ESRD (expected count 31). This corresponded to a HR for ESRD of 2.87 (95% CI 2.22 to 3.71, p<0.001). Adjusting for diabetes mellitus had only a marginal effect on the risk estimate (HR 2.52, 95% CI 1.80 to 3.40). Excluding individuals with any urinary/renal disorder before study entry, the HR for ESRD in CD was 2.47 (95% CI 1.80 to 3.40). When restricting the outcome measure to ESRD confirmed by independent data from the Swedish Renal Registry (SRR), the risk estimate increased to 3.20 (95% CI 2.39 to 4.28).

Conclusion This study indicates that individuals with biopsy-verified CD suffer increased risk of subsequent ESRD.

INTRODUCTION

Coeliac disease (CD) is an immune-mediated disorder with a worldwide prevalence approaching 1%.1–3 In genetically susceptible individuals the ingestion of gluten leads to a T cell-mediated inflammatory process of the small intestine and subsequent villous atrophy (VA).4 Individuals with CD are at an increased risk of both autoimmune and non-autoimmune co-morbidities, including certain cancers,5 type 1 diabetes mellitus6 and Addison’s disease.7

The prevalence of end-stage renal disease (ESRD), defined as the need for renal replacement therapy such as dialysis or kidney transplant, is increasing worldwide.8 Although the underlying reasons are poorly understood, increased prevalence of diabetes mellitus is an important contributor.9 The Swedish prevalence of ESRD was 867 per million people in 2008, with an incidence of 125 per million person-years.10 In Sweden, diabetic nephropathy is the most common reason for incident ESRD, whereas primary glomerulonephritis is the most common underlying disorder of ESRD.10

Individuals with primary glomerulonephritis often display an activated mucosal immune system,11 increased gut permeability12 13 and an increased number of mucosal intraepithelial T lymphocytes,12 suggesting impaired oral tolerance in the pathophysiology of glomerulonephritis.14 Several studies have demonstrated increased levels of CD autoantibodies in individuals with renal disease.15 16 In addition, some renal diseases will improve on a low-antigenic diet lacking in gluten.17

Previous studies have suggested an association between CD and renal disease. For instance, Collin et al showed an increased prevalence of CD in individuals with immunoglobulin A (IgA) nephropathy.18 In a recent study from our group, an increased risk of dialysis (HR 3.48, 95% CI 2.26 to 5.57) and renal transplant (HR 3.15, 95% CI 1.29 to 7.71) was seen in individuals with CD.19
Additionally, Peters et al found an increased mortality rate of nephritis in individuals with CD (standardised mortality ratio (SMR) 5.4). These studies, however, were limited to hospital-based CD. We know of no previous study assessing the risk of ESRD in biopsy-verified CD identified from the general population. We therefore performed a population-based cohort study to investigate the risk of ESRD in individuals with biopsy-verified CD.

METHODS

Data sources

Intestinal biopsy data

Data from biopsies performed between July 1969 and February 2008 were collected through registry searches of all 28 pathology departments in Sweden. CD was defined as VA (Marsh stage III, see Supplementary table 1) of the duodenum or jejunum. We excluded individuals with records of ESRD prior to study entry (time of small-intestinal biopsy).

ESRD data

ESRD data were obtained from the Swedish Renal Registry (SRR) and patient registers (the Swedish Hospital Discharge Register and the Swedish Outpatient Register). ESRD is defined as the need for renal dialysis or renal transplant according to the International Classification of Disease (ICD) and procedure codes in Swedish patient registers (Supplementary table 2). The National Board of Health and Welfare has collected information on individual hospital discharges in Sweden since 1964, with complete national coverage by the Swedish Hospital Discharge Register since 1987. Since 2001, all diagnoses from hospital-based outpatient visits are reported to the Swedish Outpatient Register. The SRR was founded in 1991. In a validation study, >95% of all Swedish patients with chronic renal disease with either dialysis treatment or a renal transplantation were reported to the SRR. Data on underlying renal disease causing ESRD were obtained through the SRR.

Covariates

Diabetes mellitus type 1 is positively associated with both ESRD and CD, and thus a potential confounder. In ICD7–9 the Swedish patient registers did not discriminate between diabetes mellitus type 1 and type 2. We defined diabetes as diabetes mellitus occurring before 31 years of age in the Swedish Hospital Discharge Register (for relevant ICD codes, see Supplementary table 2). Data on country of birth (Nordic vs non-Nordic) were collected from the Total Population Register. From Statistics Sweden, we obtained data on education level.

Reference individuals

All Swedish residents are assigned a 10-digit personal identity number (PIN), a unique personal identifier referred to in all medical records and official registers. The PIN was used by Statistics Sweden to link data from the different data sources. All data were deidentified prior to analysis to protect patient privacy. For each individual with intestinal biopsy, Statistics Sweden identified up to five reference individuals without any prior duodenal/jejunal biopsy. Reference individuals were matched for age, sex, calendar period and county. We excluded reference individuals for which the SRR or patient registers indicated ESRD before study entry.

We identified 29,096 individuals with CD and 144,522 reference individuals. After excluding individuals with prior ESRD or data irregularities, 29,050 individuals with CD and 144,565 reference individuals were included in the main analysis.

Statistics

We used Cox regression to estimate the risk of ESRD in individuals with CD compared with reference individuals without CD. Follow-up began at the time of first biopsy result (or corresponding time in matched reference individuals) and ended at first diagnosis of ESRD, emigration, death or 31 December 2008. Censoring data were obtained through the Total Population Register. Analyses were performed stratum wise (ie, each individual was compared only with his or her matched reference individuals), thereby controlling for age, sex, calendar period and county. Primary analyses included analyses stratified by age, sex, calendar period and follow-up. In secondary analyses we adjusted for diabetes mellitus, education and country of birth (Nordic country vs rest of the world). In additional analyses we adjusted for any renal disease prior to study entry, excluding all individuals with a prior diagnosis of any renal disease (for relevant ICD codes, see Supplementary material). Statistical significance was defined as 95% CIs for risk estimates not including 1. At this significance level (0.05), we had 80% power to detect a 1.71-fold increased risk of subsequent ESRD in CD. PASW Statistics V.18.0 (SPSS) was used to perform the analyses.

RESULTS

Characteristics of study participants

Sixty-two per cent of the participants were female (table 1). The median age at study entry was 30 years (range 0–99 years). A majority of the study participants entered the study in adulthood. Diabetes was found in 920 (3.2%) individuals with CD.

Table 1 Characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Matched reference individuals</th>
<th>Coeliac disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>144,365</td>
<td>29,050</td>
</tr>
<tr>
<td>Age at study entry, years (median, range)</td>
<td>30.0 (0–95)</td>
<td>30.0 (0–95)</td>
</tr>
<tr>
<td>Attained age, years (median, range)</td>
<td>40.6 (8.0–105.4)</td>
<td>40.7 (9.0–100.3)</td>
</tr>
<tr>
<td>Age 0–19 (%)</td>
<td>58,836</td>
<td>11,797</td>
</tr>
<tr>
<td>Age 20–39 (%)</td>
<td>26,374</td>
<td>5,070</td>
</tr>
<tr>
<td>Age 40–59 (%)</td>
<td>32,206</td>
<td>6,646</td>
</tr>
<tr>
<td>Age ≥60 (%)</td>
<td>26,974</td>
<td>5,462</td>
</tr>
<tr>
<td>Follow-up,* years (median, range)</td>
<td>9.1 (0.0–39.6)</td>
<td>9.0 (0.0–39.5)</td>
</tr>
<tr>
<td>Follow-up,* years (mean±SD)</td>
<td>10.4±6.4</td>
<td>10.3±6.4</td>
</tr>
<tr>
<td>Females (%)</td>
<td>89,487</td>
<td>17,987</td>
</tr>
<tr>
<td>Males (%)</td>
<td>54,876</td>
<td>11,063</td>
</tr>
<tr>
<td>Calendar year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 1989 (%)</td>
<td>20369</td>
<td>4101</td>
</tr>
<tr>
<td>1990–1999 (%)</td>
<td>59795</td>
<td>12037</td>
</tr>
<tr>
<td>2000 onwards (%)</td>
<td>64199</td>
<td>12912</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>531</td>
<td>920</td>
</tr>
</tbody>
</table>

*Follow-up time until diagnosis of ESRD, death, emigration or 31 December 2008.
and in 531 (0.4%) matched reference individuals (table 1). Data on education level were obtained in 94% of participating individuals.

**CD and future ESRD**

Of 29,050 individuals with CD, 90 (0.3%) developed subsequent ESRD (table 2). In reference individuals, 152 individuals developed ESRD (0.1%). The incidence of subsequent ESRD in individuals with CD was 50 per 100,000 person-years, and 10 per 100,000 person-years in reference individuals. The median age at ESRD diagnosis was 41 years in both reference individuals and individuals with CD. The median length of follow-up from CD diagnosis to ESRD diagnosis was 9 years (table 1). In individuals (patients with CD and reference individuals) reported to the SRR the most common underlying renal disorder causing ESRD was diabetes nephropathy (table 3).

We found a positive association between CD and future ESRD (HR 2.87, 95% CI 2.22 to 3.71) (table 2). The risk increase remained statistically significant after adjusting for diabetes mellitus (HR 2.52, 95% CI 1.92 to 3.31). Adjusting for education level did not significantly alter risk estimates, nor did the estimates change after adjusting for birth outside the Nordic region (data not shown). We excluded the first year of follow-up in a separate analysis. This, however, had little effect on the risk estimate (HR 2.70, 95% CI 2.05 to 3.55). Further, when we excluded individuals with records of any renal disease prior to study entry (for ICD codes, see Supplementary table 2), a statistically significant association remained between CD and later ESRD (HR 2.47, 95% CI 1.30 to 4.40).

In a final model we defined ESRD as having both a diagnosis of ESRD in a Swedish patient register and an independent recording of ESRD in the SRR. In this analysis patients with CD were at a 5.20-fold increased risk of ESRD (95% CI 2.59 to 4.28). Regarding modality of treatment, we found an increased risk of later renal dialysis (HR 3.06, 95% CI 2.34 to 4.01) but not of later renal transplant (HR 1.55, 95% CI 0.67 to 3.62) in individuals with CD.

**DISCUSSION**

We used two separate data sources (patient registers and the SRR) to identify individuals with ESRD. The Swedish Hospital Discharge Register has been extensively validated and most diagnoses have a positive predictive value (85–95%). The SRR has been extensively used and, when validated, the authors found that >95% of persons with ESRD were reported to the SRR. By restricting our analysis to ESRD reported in a patient register and the SRR, we were able to reduce possible misclassification and increased the specificity of ESRD. Applying this restriction, the risk estimate increased slightly (HR 3.20, 95% CI 2.04 to 4.01), suggesting that the positive association between CD and ESRD is unlikely to be explained by misclassification.

One limitation of our study is that we did not have any data on the occurrence of tobacco use. Smoking seems to be negatively correlated with CD, but it is an established independent risk factor for chronic renal disease, including diabetic nephropathy. Given these associations, the positive correlation between CD and ESRD cannot be explained by smoking.

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**Table 2** Risk of ESRD in CD according to follow-up

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Observed events</th>
<th>Expected events</th>
<th>HR (95% CI)</th>
<th>p Value</th>
<th>Absolute risk/100 000 PYAR</th>
<th>Excess risk/100 000 PYAR</th>
<th>Attributable percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>90</td>
<td>31</td>
<td>2.87 (2.22 to 3.71)</td>
<td>&lt;0.001</td>
<td>30</td>
<td>20</td>
<td>65</td>
</tr>
<tr>
<td>Year &lt;1</td>
<td>12</td>
<td>3</td>
<td>4.73 (2.27 to 9.84)</td>
<td>&lt;0.001</td>
<td>42</td>
<td>33</td>
<td>79</td>
</tr>
<tr>
<td>1–4.99</td>
<td>24</td>
<td>10</td>
<td>2.41 (1.49 to 3.88)</td>
<td>&lt;0.001</td>
<td>23</td>
<td>14</td>
<td>59</td>
</tr>
<tr>
<td>5+</td>
<td>54</td>
<td>19</td>
<td>2.86 (2.04 to 4.01)</td>
<td>&lt;0.001</td>
<td>32</td>
<td>21</td>
<td>65</td>
</tr>
</tbody>
</table>

The reference is the general population comparator cohort. CD, coeliac disease; ESRD, end-stage renal disease; PYAR, person-years at risk.

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**Table 3** Underlying renal disease in patients with ESRD

<table>
<thead>
<tr>
<th>Matched reference individuals, n (%)</th>
<th>Coeliac disease, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>12 (9.9)</td>
</tr>
<tr>
<td>Diabetes nephropathy</td>
<td>33 (27.3)</td>
</tr>
<tr>
<td>Cystic kidney disease</td>
<td>12 (9.9)</td>
</tr>
<tr>
<td>Nephrosclerosis</td>
<td>17 (14.0)</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>8 (6.6)</td>
</tr>
<tr>
<td>Unspecified chronic failure</td>
<td>14 (11.8)</td>
</tr>
<tr>
<td>Other</td>
<td>25 (20.7)</td>
</tr>
<tr>
<td>Total</td>
<td>121 (100)</td>
</tr>
<tr>
<td></td>
<td>72 (100)</td>
</tr>
</tbody>
</table>

*Data reported to the Swedish Renal Registry. ESRD, end-stage renal disease.
This was a study of clinical CD and not a screening study. Hence, we were unable to examine the risk of ESRD in undiagnosed CD. We cannot rule out that some individuals with undiagnosed CD are present in the reference population. Yet, such misclassification (the existence of false-negative controls) will have little effect on risk estimates in that undiagnosed CD cannot represent >1–2% of the control group.46

Another limitation is our lack of data on dietary adherence. Poor adherence to a gluten-free diet may lead to persistent inflammation and malnutrition. In a subset of individuals with CD, 17% showed signs of low dietary adherence.27

Our results are in line with those of Peters et al, who found an increased mortality caused by nephritis in individuals with CD (SMR 5.4: 95% CI 1.4 to 13.8). That study, however, was earlier study were younger at study entry (median age 3 vs 39 years 15 3 4.31 (1.70 to 3.87) <0.001 48 29 61

Age and calendar period

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Observed events</th>
<th>Expected events</th>
<th>HR (95% CI)</th>
<th>p Value</th>
<th>Absolute risk/100 000 PYAR</th>
<th>Excess risk/100 000 PYAR</th>
<th>Attributable percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>59</td>
<td>20</td>
<td>2.98 (2.16 to 4.10)</td>
<td>&lt;0.001</td>
<td>53</td>
<td>35</td>
<td>66</td>
</tr>
<tr>
<td>Females</td>
<td>31</td>
<td>11</td>
<td>2.71 (1.76 to 4.16)</td>
<td>&lt;0.001</td>
<td>17</td>
<td>10</td>
<td>63</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 years</td>
<td>5</td>
<td>1</td>
<td>3.52 (1.13 to 10.96)</td>
<td>0.03</td>
<td>4</td>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>20–39 years</td>
<td>15</td>
<td>3</td>
<td>4.31 (2.16 to 8.60)</td>
<td>&lt;0.001</td>
<td>28</td>
<td>21</td>
<td>77</td>
</tr>
<tr>
<td>40–59 years</td>
<td>33</td>
<td>13</td>
<td>2.57 (1.70 to 3.87)</td>
<td>&lt;0.001</td>
<td>48</td>
<td>29</td>
<td>61</td>
</tr>
<tr>
<td>60+ years</td>
<td>37</td>
<td>14</td>
<td>2.71 (1.81 to 4.05)</td>
<td>&lt;0.001</td>
<td>91</td>
<td>58</td>
<td>63</td>
</tr>
<tr>
<td>Calendar period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 1989</td>
<td>30</td>
<td>8</td>
<td>3.63 (2.26 to 5.84)</td>
<td>&lt;0.001</td>
<td>37</td>
<td>27</td>
<td>72</td>
</tr>
<tr>
<td>1990–1999</td>
<td>42</td>
<td>17</td>
<td>2.52 (1.74 to 3.65)</td>
<td>&lt;0.001</td>
<td>28</td>
<td>17</td>
<td>60</td>
</tr>
<tr>
<td>2000 onwards</td>
<td>18</td>
<td>6</td>
<td>2.85 (1.64 to 4.95)</td>
<td>&lt;0.001</td>
<td>27</td>
<td>18</td>
<td>65</td>
</tr>
</tbody>
</table>

The reference is the general population comparator cohort. ESRD, end-stage renal disease; PYAR, person-years at risk.

In conclusion, we found a threefold increased risk of ESRD in individuals with CD. Because ESRD is common, especially in elderly populations, our findings have important implications for persons with CD. If others replicate our findings, we suggest an increased awareness of renal disease in patients with CD.

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Competing interests None.

Ethics approval This study was approved by the Research Ethics Committee of the Karolinska Institutet (dnr 2006/633-31/4).

Contributors AW, main investigator and wrote the first draft of the manuscript; KGP, acquisition of data and critical revision of the manuscript; MF, study concept and design, analysis and interpretation of the data, critical revision of the manuscript; JFL, study concept and design, supervision of the study, statistical analysis, revision of the manuscript. JFL is the study guarantor.

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REFERENCES

Coeliac disease


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