Increased Risk of Systemic Lupus Erythematosus in 29,000 Patients with Biopsy-verified Celiac Disease

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ABSTRACT. ***Objective.*** To investigate a possible association between celiac disease (CD) and systemic lupus erythematosus (SLE). Case series have indicated a possible association, but population-based studies are lacking.

Methods. We compared the risk of SLE in 29,048 individuals with biopsy-verified CD (villous atrophy, Marsh 3) from Sweden's 28 pathology departments with that in 144,352 matched individuals from the general population identified through the Swedish Total Population Register. SLE was defined as having at least 2 records of SLE in the Swedish Patient Register. We used Cox regression to estimate hazard ratios (HR) for SLE.

Results. During followup, 54 individuals with CD had an incident SLE. This corresponded to an HR of 3.49 (95% CI 2.48–4.90), with an absolute risk of 17/100,000 person-years and an excess risk of 12/100,000. Beyond 5 years of followup, the HR for SLE was 2.54 (95% CI 1.57–4.10). While SLE was predominantly female, we found similar risk estimates in men and women. When we restricted our outcome to individuals who also had a dispensation for a medication used in SLE, the HR was 2.43 (95% CI 1.22–4.87). The HR for having 2 records of SLE diagnoses, out of which at least 1 had occurred in a department of rheumatology, nephrology/dialysis, internal medicine, or pediatrics, was 2.87 (95% CI 1.97–4.17).

Conclusion. Individuals with CD were at a 3-fold increased risk of SLE compared to the general population. Although this excess risk remained more than 5 years after CD diagnosis, absolute risks were low. (J Rheumatol First Release Aug 1 2012; doi:10.3899/jrheum.120493)

Key Indexing Terms:
AUTOIMMUNE CELIAC GLUTEN SYSTEMIC LUPUS ERYTHEMATOSUS

Celiac disease (CD) is characterized by small intestinal inflammation and is triggered by gluten exposure in genetically sensitive individuals[1]. CD occurs in 1%–2% of the Western population[2,3] and has been linked to a number of disorders including type 1 diabetes[4], sepsis[5], lymphoproliferative malignancy[6], and excess mortality[7].

Systemic lupus erythematosus (SLE) is an immune-mediated disease with a prevalence of about 40/100,000 in Northern Europeans[8]. It is a multisystem disease with protean manifestations including rash, arthritis, cytopenias, and renal disease. It occurs predominantly in women and is associated with high morbidity and mortality from renal disease or central nervous system lupus[9,10].

Several case reports and case series have suggested a possible association between CD and SLE[11,12,13,14,15,16,17,18,19], but earlier research has suffered from low statis-

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tical power. At least 2 studies have also reported a high prevalence of antigliadin antibodies in SLE but with substantially lower rates of histologically verified CD[17,19], and because of their lack of a control group with non-SLE individuals, these studies were unable to estimate relative risks of SLE in CD. Connective tissue disorders as a group seem to be more frequent among patients with CD, but the small number of cases affected by each specific connective tissue disorder has been a limitation to estimate disease-specific risk[20]. For example, 19% of 924 patients with CD from France developed an autoimmune disease, but only 2 patients had a subsequent diagnosis of SLE[21].

Our aim was to investigate the risk of SLE in a nationwide cohort of patients with biopsy-verified CD compared to individuals matched from the general population.

MATERIALS AND METHODS

We linked nationwide data on biopsy-verified CD from Swedish pathology registers to inpatient and hospital-based outpatient data on SLE obtained from the Swedish Patient Register[22] as well as to the Prescribed Drug Register[23].

Study participants. Reports on duodenal and jejunal biopsies performed between 1969 and 2008 were collected from all 28 Swedish pathology departments between October 2006 and February 2008 (Table 1). Data were available on date of biopsy, topography (duodenum or jejunum), morphology codes consistent with villous atrophy (VA; Table 2), and personal identity number[24]. Each individual with CD (as defined below) was matched with up to 5 reference individuals from the Total Population Register on age, sex, calendar year, and county[25]. After removal of data irregularities, we had information on 29,096 individuals with CD and 144,520 reference individuals.

Celiac disease. CD was defined as VA (Marsh stage 3)[26], according to the biopsy report. We did not request a positive CD serology for the diagnosis of CD, but in a subset of individuals with available data, 88% had a positive serology at the time of biopsy. A detailed account of the data collection, including a validation of CD, has been published elsewhere[27]. Each biopsy report was based on an average of 3 tissue specimens[28].

SLE. SLE was defined as having at least 2 records of the following calendar-year-specific international classification of disease (ICD) discharge diagnoses in the National Patient Register: ICD-7: 456.2; ICD-8: 734.1; ICD-9: 710A; ICD-10: M32 (minus drug-induced M32.0).

Table 1. Characteristics of participants, presented as n (%).

Characteristics	Reference Individuals	Celiac Disease
Total	144,352	29,048
Age at study entry, yrs		
0–19	58,846 (40.8)	11,800 (40.6)
20–39	26,356 (18.3)	5306 (18.3)
40–59	32,198 (22.3)	6455 (22.2)
60+	26,952 (18.7)	5487 (18.9)
Sex		
Women	89,403 (61.9)	17,965 (61.8)
Men	54,949 (38.1)	11,083 (38.2)
Calendar period		
1989	20,356 (14.1)	4102 (14.1)
1990–1999	59,818 (41.4)	12,045 (41.5)
2000–	64,178 (44.5)	12,901 (44.4)

Table 2. A comparison of different histopathological classification systems.

Classification Used in This Project	Villous Atrophy		
Marsh classification[26]	Type IIIa	Type IIIb	Type IIIc
Marsh description	Flat destructive		
Corazza classification[52]	Grade B1	Grade B2	
SnoMed codes	M58, D6218, M58005	M58, D6218, M58006	M58, D6218, M58007
KVAST/Alexander classification	III Partial VA	IV Subtotal VA	IV Total VA
Characteristics			
Villous atrophy	+	++	++
IEL	+	+	+
Crypt hyperplasia	+	++	++

IEL: intraepithelial lymphocytosis.

We then excluded 48 CD individuals and 80 reference individuals with a discharge diagnosis of SLE before CD or study entry. An additional 88 reference individuals were excluded from the study population because their index individual with CD had been excluded and analyses were performed retaining stratum.

Other covariates. Data on the following potential confounding factors were also collected from the government agency Statistics Sweden: country of birth (Nordic vs not Nordic), education level, and socioeconomic status. Education was defined according to 4 *a priori* categories (≤ 9 years of primary school, 2 years of high school, 3–4 years of high school, college/university) and socioeconomic status according to 6 categories (according to the European Socioeconomic Classification: levels 1, 2, 3+6, 7, 8, and 9; Olén, *et al*[29]). Education was missing in 4% (n = 1150), and 31% lacked data on socioeconomic status (n = 8901). These individuals were fitted into separate categories for the statistical analyses. Using the Patient Register, type 1 diabetes and autoimmune thyroid disease (Table 3) were identified because both CD and SLE have been linked to those diseases.

Statistics. Through internally stratified Cox regression we estimated hazard ratios (HR) for SLE. The internal stratification means that the Cox regression resembles a conditional logistic regression in the way that all comparisons are made within the same stratum (defined by the matching), and then a summary HR is calculated. The proportional hazards assumption was examined by visual inspection of log-minus-log curves (Figure 1). The attributable risk percentage (the proportion of all SLE in patients with CD that could be explained by the underlying CD) was estimated by the formula 1 − 1/HR.

Followup began at first biopsy with CD and on the corresponding index date in the matched reference individuals. Followup ended at the first of the following: first SLE diagnosis, December 31, 2009, emigration, or death.

Table 3. International Classification of Disease (ICD) codes.

Type 1 diabetes mellitus: Before 1997, the ICD coding for diabetes (ICD-7: 260, ICD-8: 250, ICD-9: 250) did not distinguish between type 1 and type 2 diabetes. We defined individuals with type 1 diabetes as those who were ≤ 30 years of age at their first hospitalization for diabetes (ICD-7-ICD-10). ICD-10: E10.
Autoimmune thyroid disease: Defined as follows: ICD-7: 252.00, 252.01, 252.02, 253.10, 253.19, 253.20, 253.29, 254.00; ICD-8: 242.00, 242.09, 244, 245.03; ICD-9: 242A, 242X, 244X, 245C, 245W; ICD-10: E03.5, E03.9, E05.0, E05.5, E05.9, E06.3, E06.5.

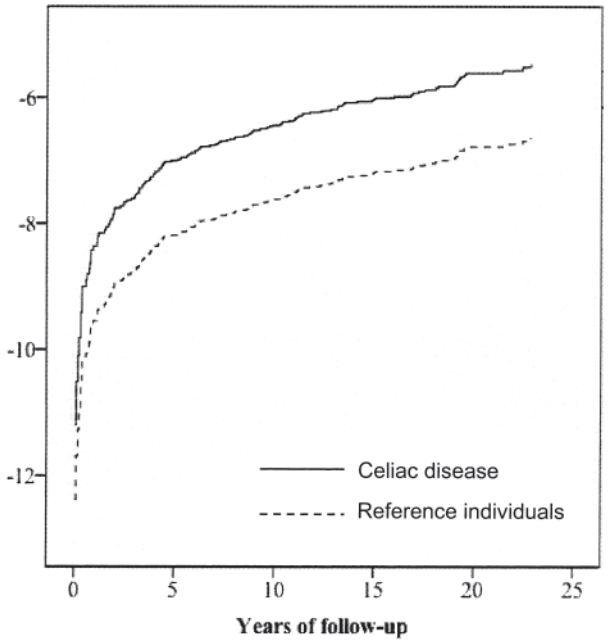

Figure 1. Log-minus-log curve: celiac disease and systemic lupus erythematosus.

In predefined analyses, we estimated the risk of SLE according to time since CD diagnosis overall and stratified by sex, age at CD diagnosis, and calendar period. In separate analyses we adjusted for country of birth, education level, socioeconomic status, type 1 diabetes, and autoimmune thyroid disease.

In sensitivity analyses we further restricted the definition of SLE in 4 ways: (1) include that at least 1 SLE discharge diagnosis at some stage occurred in an internal medicine, rheumatology, nephrology/dialysis, or pediatrics department; (2) require at least 12 months between the first and last SLE record, allowing other visits in between; (3) require that the 2 first discharges with SLE-specific ICD codes occurred within 12 months; and (4) require at least 1 dispensing of a medication common in the treatment of SLE from the Prescribed Drug Register (Table 4). The Prescribed Drug Register provides data only on medication dispensations from the pharmacy, therefore any medication administered at an infusion center could not be identified. This analysis was restricted to individuals with followup beyond July 1, 2005, because that was when the Swedish Prescribed Drug Register started (this analysis included both prevalent and incident CD).

In a subanalysis we compared the risk of future SLE in women according to whether they were diagnosed with CD before or after assumed menopause (≤ 50 years; ≥ 51 years)[30]. Several studies have indicated that sex hormones may play a role in SLE etiology[31].

A posthoc power analysis using a 0.05 level of significance and 80% power showed that our study could detect an HR of 1.90 for SLE.

We used SPSS 20 to calculate statistics. P values < 0.05 were considered statistically significant.

Ethics. This study was approved by the Regional Ethical Review Board in Stockholm. Because this was a register-based study, no participant was contacted and all data were anonymized prior to data analyses.

Table 4. Anatomical therapeutic chemical codes for systemic lupus erythematosus medication.

H02AB06 (prednisolone); H02AB04 (methylprednisolone); P01BA01 (chloroquine); L0AX01 (azathioprine); L04AD01 (cyclosporine); L04AA06 (mycophenolic acid); L04AX03 (methotrexate); L01AA01 (cyclophosphamide); V03AF01 (mesna).

RESULTS

The median age at first biopsy with CD was 30 years (range 0–95 yrs). Most patients entered the study after 1990 (Table 1), and the median year of study entry was 1998 (range 1969-2008). The majority of study participants were women (Table 1). The median age at first SLE diagnosis was 52 years in individuals with CD, and 48 years in reference individuals.

Overall risk of future SLE. During followup, there were 54 cases of SLE during 325,770 person-years of observation in individuals with CD [crude incidence rate (IR) = 17 cases/100,000 person-years]. In the general population comparator we observed 81 cases during 1,640,669 person-years (IR = 5 cases/100,000 person-years), yielding an excess risk of 12/100,000 person-years. This corresponded to an HR of 3.49 (95% CI 2.48–4.90). Adjustment for socioeconomic status, education, and country of birth did not appreciably alter the results (HR 3.51; 95% CI 2.49–4.96). The proportion of all SLE in patients with CD that could be explained by the underlying CD (attributable fraction) was 71%. Individuals with CD had an 8-fold increased risk of SLE in the first year of followup, and 5 years after CD diagnosis, the HR decreased to 2.54 (Table 5). Excluding the first year of followup, the HR was 3.05 (95% CI 2.11–4.41), and was generally similar when the first 2 years were excluded (HR 2.88; 95% CI 1.94–4.28).

The HR for SLE in individuals with CD diagnosed in childhood or adolescence (< 20 years old at CD diagnosis) was 2.31, and 5.81 in patients diagnosed with CD after age 60 years; this difference was not statistically significant (p = 0.096). In a posthoc analysis restricting followup to < 20 years of age, 6 individuals with CD had an incident diagnosis of SLE, corresponding to an HR of 2.27 (95% CI 0.86–5.97).

Individuals with CD were at a 2.43-fold increased risk of having a later diagnosis of SLE confirmed by medication against SLE (95% CI 1.22–4.87).

Results were similar across the numerous sensitivity analyses considering alternative definitions of SLE. When further requiring an SLE diagnosis from a department of rheumatology, nephrology/dialysis, internal medicine, or pediatrics, 44 individuals with CD had a later diagnosis of SLE (HR 2.87; 95% CI 1.97–4.17). When we restricted our outcome to having at least 2 records of SLE with at least 12 months between the first and the last visit with SLE, the HR was 3.12 (95% CI 2.06–4.71). Examining instead the risk of having SLE with the first and second diagnosis occurring within 12 months, the HR was 3.37 (95% CI 2.34–4.84).

There was no statistically significant difference by sex (p = 0.571; Table 6). We found no difference in HR between women diagnosed with CD before and after assumed menopause (p for interaction = 0.138).

Table 5. Risk of SLE in patients with celiac disease, according to followup.

Followup	HR; 95% CI	p	Person-yrs	No. SLE Events in CD	Incidence Rate* CD	Ref
All	3.49; 2.48–4.90	< 0.001	325,770	54	17	5
< 1 yr	8.85; 3.41–22.98	< 0.001	28,729	10	35	5
1–5 yrs	3.87; 2.17–6.89	< 0.001	107,807	19	18	5
> 5 yrs	2.54; 1.57–4.10	< 0.001	189,233	25	13	5
Beyond 1 yr followup	3.05; 2.11–4.41	< 0.001	297,041	44	15	5

* SLE cases per 100,000 person-years of CD. SLE: systemic lupus erythematosus; CD: celiac disease; Ref: reference individuals; HR: hazard ratio.

Table 6. Risk of SLE in patients with celiac disease. Analyses are stratified.

Subgroup	HR; 95% CI	p	Person-yrs	No. SLE Events in CD	Incidence Rate* CD	Ref
Age, yrs						
< 20	2.31; 1.05–5.06	0.037	147,194	9	6	3
20–39	2.69; 1.35–5.36	0.005	60,110	12	20	8
40–59	3.91; 2.21–6.91	< 0.001	74,790	20	27	7
≥ 60	5.81; 2.69–12.58	< 0.001	43,676	13	30	4
Sex						
Women	3.47; 2.42–4.98	< 0.001	203,448	48	24	7
Men	3.55; 1.27–9.91	0.016	122,323	6	5	1
Calendar period						
–1989	2.82; 1.35–5.87	0.008	85,781	11	13	5
1990–99	3.91; 2.40–6.35	< 0.001	161,554	28	17	5
2000–	3.35; 1.78–6.28	< 0.001	78,435	15	19	6

* SLE cases per 100,000 person-years. CD: celiac disease; Ref: reference individuals; SLE: systemic lupus erythematosus.

DISCUSSION

To our knowledge, this is the largest population-based study of CD and risk of future SLE to date. We found a 3-fold increased risk of SLE in CD compared to the general population. However, that still translates into a low absolute risk — we estimated that at most 2 individuals with CD out of 1000 would develop SLE in the 10 years following CD diagnosis.

Several case reports of patients with both CD and SLE were published in the 1980s and 1990s[11,12,13,14,15,16]. In a report by Rensch, *et al*, 24 of 103 patients (23.3%) with SLE tested positive for antigliadin antibodies but none were positive for endomysial antibodies nor had small intestinal changes consistent with CD[17]. Given the lower specificity of gliadin antibodies[32], the association with gliadin antibodies but not with endomysial antibodies is less supportive of an association between SLE and CD. In 2008, Freeman described 6 individuals with CD who developed SLE (out of 246 individuals with CD seen at the University of British Columbia Hospital during a period of 25 years)[18]. Among 24 patients with SLE screened for CD in Tunisia, Ben Abdelghani, *et al* found a high prevalence of antigliadin antibodies but also 2 patients (8%) with positive tissue transglutaminase antibodies; of them, CD was confirmed by histopathology in 1 patient (4%)[19]. However, these 3 studies[17,18,19] were performed within patient groups with no general population comparator and none included children.

Of 54 CD patients with future SLE, 48 were women (89%), consistent with the well-known predominance of SLE in women[33]. We observed an increased risk of SLE in both men and women with CD, and the HR were independent of sex. Sex-specific risk factors are otherwise likely to play an important role in the development of immune-mediated diseases, because a female predominance has been shown for a number of diseases (including both CD and SLE)[34]. We found no evidence that the risk of SLE differed in women diagnosed before or after age 50 years (a proxy for menopause).

The increased use of CD serology in the clinical laboratory investigations toward CD diagnosis means that more patients with only minor symptoms of CD are identified and subsequently undergo biopsy to confirm a diagnosis of CD. We found no evidence that the change in diagnostic routines has resulted in a lower risk of SLE, using the last decade of observation as a proxy for changing diagnostic procedures. The HR for SLE in patients diagnosed with CD in the last 10-year period was 3.35 (95% CI 1.78–6.28).

Apart from the nationwide ascertainment of cases, the main strength of our study is the high positive predictive value of our CD diagnosis. We used biopsy report data from all of Sweden's pathology departments to identify individuals with histopathology Marsh stage 3, equal to VA[26]. A validation of 114 randomly selected patient charts found that 95% of patients with VA in Sweden have CD[27]. Some 79% of patients with CD had gastrointestinal symptoms, and when 2 independent researchers manually reviewed > 1500 biopsy reports with either VA or inflammation[27], diagnoses other than CD were uncommon (inflammatory bowel disease was mentioned in 0.3% of the biopsy reports, and *Helicobacter pylori* in 0.2%)[27]. Biopsy reports also have a high sensitivity for CD because 96%–100% of all Swedish gastroenterologists and pediatricians perform biopsies on their patients before CD diagnosis[27].

Although the study population was large, the statistical power was limited by the relatively small number of incident SLE cases observed during followup. We are unaware of any large-scale validation of the SLE diagnosis in Sweden. Investigations within nested case-control studies suggest low positive predictive value when a single inpatient ICD code is used to define SLE[35]. Therefore, we restricted our outcome (in all analyses) to individuals with at least 2 diagnoses of SLE, and considered both inpatient and outpatient care. Four additional sensitivity analyses restricting the definition of SLE found similar statistically significant associations between CD and SLE. Although only a subanalysis, we included both prevalent and incident cases of CD when we examined the risk of having SLE confirmed by a medication used for SLE. A better approach for this subanalysis would have been to include only individuals with CD and their reference individuals whose biopsy and study entry occurred after July 1, 2005. However, we had insufficient power for that, given the short followup after 2005 and the limited number of SLE events. We lacked data on clinical features in SLE, HLA, and laboratory markers including autoantibodies to further confirm the SLE diagnosis or consider specific phenotypes. Although we lacked data on smoking, this is unlikely to explain the positive association between CD and SLE, because smoking seems to be positively associated with SLE[36], but negatively associated[37,38] with CD (or not associated at all[39]). Finally, no information was available on dietary adherence in CD, limiting our ability to evaluate the risk of SLE according to gluten intake. In a subset of individuals with CD, patient chart data showed indications of poor compliance in 17% of individuals with CD[27].

Potential mechanisms. The underlying mechanism for the positive association between CD and SLE may be multifactorial, related to shared genetic risk factors, involvement of the innate immune system, especially Toll-like receptors (TLR), as well as several cytokine and chemokine pathways. Thus, the association of CD and SLE could be part of the spectrum of "shared autoimmunity," a concept also used to explain overlaps between SLE and other autoimmune rheumatic diseases (e.g., "rhupus")[40]. Shared patterns of altered gene expression that may lead to immune dysregulation have been observed among unrelated individuals with systemic autoimmune diseases regardless of specific disease diagnosis[41,42]. Many HLA and non-HLA risk genes are shared between CD and SLE and may act independently or synergistically in disease pathophysiology. Ninety percent of patients with CD carry the DQ2 allele, which is often present with the DR3 haplotype, and two-thirds of patients with SLE carry DR2 or DR3 haplotypes[43]. The ancestral haplotype B8-DR3-DQ2 is also strongly associated with immunoglobulin A (IgA) deficiency, which is commonly seen in both diseases[44]. Similarly, single-nucleotide polymorphism in the *TNFAIP3*[45,46], *UBE2L3*, and *CLEC16A* region may be associated with both CD and SLE, and IgA deficiency. *ETS1*, a susceptibility gene common to both CD and SLE, codes for a transcription factor that is a negative regulator of Th17 cell differentiation and terminal differentiation of B cells[47]. Involvement of the innate immune system through activation of dendritic cells through TLR (TLR7 and TLR9 for SLE and TLR7 and TLR8 for CD) and consequent production of type I interferon is another postulated mechanism. In a study of autoantigen profiling, healthy controls with high antinuclear antibody titers showed upregulation of the *TGM2* gene, which encodes for the CD autoantigen transglutaminase 2[48]; thus gliadin autoreactivity may be associated with incomplete forms of lupus and some early events in development of lupus may arise in the skin. UV light is a known trigger for lupus flares and induces apoptosis of keratinocytes with expression of self-antigens on the surface of apoptotic blebs that drives the autoimmune response in SLE[49,50]. It can be speculated that skin lesions of dermatitis herpetiformis, frequently seen in patients with CD, and consequent local inflammatory response may link the immune system to self-antigens and predispose a susceptible individual to lupus autoimmunity.

Finally, nutritional factors may influence the association between CD and SLE. Vitamin D deficiency is common especially in undiagnosed CD and may be a sign of malnutrition, but does also occur in diagnosed CD[51]. Such deficiency may be a risk factor for SLE[52].

Both genetic predisposition and malnutrition in CD could hence contribute to the positive association between CD and SLE in our study. Surveillance bias also may have contributed to the association, especially to the 8-fold increased risk of SLE observed in the first year after CD diagnosis. But when we excluded the first year of followup, individuals with CD were still at a 3-fold increased risk of future SLE.

Individuals with CD seem to be at an increased risk of SLE compared to the general population, but absolute risks are low.

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