A Population-Based Study of the Risk of Diabetic Retinopathy in Patients With Type 1 Diabetes and Celiac Disease

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OBJECTIVE—Celiac disease (CD) is associated with type 1 diabetes (T1D). In the current study, we examined whether CD affects the risk of diabetic retinopathy (DRP) in patients with T1D.

RESEARCH DESIGN AND METHODS—This was a population-based cohort study. Through the Swedish National Patient Register, we identified 41,566 patients diagnosed with diabetes in 1964–2009 and who were ≤30 years of age at diagnosis. CD was defined as having villous atrophy (Marsh stage 3) according to small intestinal biopsies performed between 1969 and 2008, with biopsy reports obtained from Sweden's 28 pathology departments. During follow-up, 947 T1D patients had a diagnosis of CD. We used Cox regression analysis with CD as a time-dependent covariate to estimate adjusted hazard ratios (aHRs) for DRP in patients with T1D and CD and compared them with patients with T1D but no CD.

RESULTS—Duration of CD correlated with the risk of DRP. When results were stratified by time since CD diagnosis, individuals with T1D and CD were at a lower risk of DRP in the first 5 years after CD diagnosis (aHR 0.57 [95% CI 0.36–0.91]), followed by a neutral risk in years 5 to <10 (1.03 [0.68–1.57]). With longer follow-up, coexisting CD was a risk factor for DRP (10 to <15 years of follow-up, aHR 2.83 [95% CI 1.95–4.11]; ≥15 years of follow-up, 3.01 [1.43–6.32]).

CONCLUSIONS—Having a diagnosis of CD for >10 years is a risk factor for the development of DRP in T1D. Long-standing CD in patients with T1D merits intense monitoring of DRP.

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Diabetic retinopathy (DRP) is a common microvascular complication of diabetes that is characterized by vascular changes in the retinal circulation (1). Although the severest form of DRP leading to blindness is less common, the rising incidence of T1D means that more people will develop DRP (2). The major risk factor for DRP development is hyperglycemia (increased HbA_{1c}) (3). Other risk factors include the duration of diabetes, hypertension, hyperlipidemia, and nephropathy (3). Some research indicates that inflammatory and autoimmune mechanisms may be involved in pathogenesis of DRP (4–7).

Celiac disease (CD) is a common immune-mediated enteropathy affecting ~1% of the Western population. CD is associated with other autoimmune diseases, including T1D. The prevalence of CD in T1D ranges from 3 to 12% (8,9). Although the link between CD and T1D is well established, few studies have examined the role of CD in T1D complications such as DRP. Such studies are warranted to clarify the need for screening routines in T1D patients. A recent study (10) addressing T1D complications in the presence of CD found no retinal abnormalities in T1D patients with CD (10). However, that study only enrolled 13 patients with CD and T1D, and there was no follow-up after the diagnosis of CD (10). We previously found a higher prevalence of advanced DRP in patients with T1D and CD than in T1D control subjects without CD (11), but that study was limited in size (T1D and CD: $n = 12$), and follow-up ended after 1 year. Despite its limitations, this study suggests that microvascular complications may be more frequent in T1D patients with CD (11). The aim of this population-based study was to examine the risk of DRP in patients with T1D and biopsy-proven CD versus patients with only T1D.

RESEARCH DESIGN AND METHODS

—In summary, we linked T1D and DRP data from the Swedish National Patient Register (NPR) (12) with nationwide CD data from small intestinal biopsy reports.

T1D

Individuals with T1D were identified by the Swedish NPR. This register contains data on inpatient health care since 1964 (nationwide coverage since 1987) and hospital-based outpatient care since 2001 (12). T1D was defined as having a relevant ICD code: ICD-7, 260; ICD-8, 250; ICD-9, 250; and ICD-10: E10). In earlier ICD versions (ICD-7, -8, and -9) the Swedish NPR did not distinguish between T1D and type 2 diabetes. Therefore, in this study, we restricted our study sample to individuals diagnosed with diabetes who were ≤30 years of age. This TID definition has been used before and has a high positive predictive value (13).

Initially, the Swedish National Board of Health and Welfare identified 42,806 individuals with a diagnosis of T1D. The government agency Statistics Sweden could confirm the identity of 42,578 of these individuals. We then excluded 31 individuals because of data irregularities. Finally, we excluded 981 individuals (2.3%)

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who had a diagnosis of DRP before the first recorded diagnosis of T1D.

Our final sample consisted of 41,566 individuals with T1D. Of these, 947 (2.3%) had a diagnosis of CD before 31 December 2009 (hence, 40,619 were not diagnosed with CD).

CD

CD was defined as duodenal/jejunal villous atrophy (Marsh stage 3) (14) according to biopsy reports from all 28 pathology departments in Sweden. The biopsies had been performed from 1969 to 2008 (15), but our data collection took place 2006–2008. We originally had data on 29,096 individuals with biopsy-verified CD (15). Some 95% of individuals with villous atrophy have CD (16), and non-CD diagnoses seldom explain villous atrophy (0.3% of individuals with villous atrophy had indications of concomitant inflammatory bowel disease) (16).

Outcome measure

DRP was defined based on relevant ICD codes in the Swedish NPR (inpatient and hospital-based outpatient data) (ICD-7, 388.22; ICD-8, 250.02; ICD-9, 250E and 362A; and ICD-10, H36). Severe DRP was defined as having a DRP code and requiring retinal laser therapy (surgical codes 1600, 1637, CKC10, and CKC15).

Statistical analyses and covariates

We used Cox regression analysis with CD modeled as a time-dependent covariate to examine the risk of DRP in patients with T1D and CD versus those with only T1D. Follow-up began on the date of first T1D diagnosis and ended with the diagnosis of DRP, emigration, death, or end of the study period (31 December 2009)—whichever occurred first.

The risk of DRP was evaluated by years since CD diagnosis (<5 years, 5 to <10 years, 10 to <15 years, and ≥15 years). Other predefined subgroup analyses included stratification by sex, calendar year at T1D diagnosis (1964–1975, 1976–1987, 1988–1999, and 2000–2009), and age at T1D diagnosis (0–9, 10–19, and 20–30 years). We chose this age categorization (i.e., 0–9, 10–19, and 20–30 years) because puberty in Swedish children seldom starts before age 10 years. The risk of DRP in the above subgroups was analyzed in two time strata: <10 years since CD diagnosis and ≥10 years since CD diagnosis (Table 2). Stratification for time since CD diagnosis was deemed necessary because the proportional hazards assumption was not fulfilled (hence, no overall HR for DRP in individuals with T1D and CD was calculated in this study).

The incidence rates (absolute risk) of DRP in T1D and CD were estimated by dividing the number of first DRP events with the number of person-years at risk in the cohort. The number of expected events was calculated as the number of observed events divided by the HR. In all adjusted analyses, the following covariates were considered: age at T1D onset (three categories), calendar period (four categories), and sex. In a separate analysis, we adjusted for country of birth (Nordic versus non-Nordic country) because CD (17) and T1D (18) may vary by geographic origin.

In a first sensitivity analysis, we excluded individuals with a record of oral antidiabetic medication (ATC codes A10B +A10×) in the prescribed drug register (19) (such patients may have type 2 diabetes even though they have an ICD-10 code consistent with insulin-dependent diabetes [E10]). In a second analysis, we excluded women who received their first diagnosis of T1D 0–9 months before giving birth because these women may have suffered from gestational diabetes mellitus rather than T1D (data on pregnancy duration were obtained from the Medical Birth Register [20]). In a third sensitivity analysis, we restricted study participants to those with an inpatient diagnosis of T1D (n = 39,612; 95.3%). We also performed a subanalysis in which we restricted the outcome to severe DRP requiring retinal laser therapy.

Ethics

This project (2011/841-31/3) was approved on 15 June 2011 by the ethics review board, Stockholm, Sweden.

RESULTS

—Table 1 shows descriptive characteristics of the study participants.

DRP risk relative to duration of CD

The risk of DRP correlated with duration of CD. With adjustment for age, sex, and calendar period, individuals with T1D and CD were initially at a lower risk of DRP during the first 5 years after CD diagnosis (adjusted hazard ratio [aHR] 0.57), followed by a neutral risk during years 5 to <10 (1.03) (Supplementary Table 1). The aHR then increased substantially 10 to <15 years after CD diagnosis (2.83), followed by a threefold increased risk of DRP >15 years after CD diagnosis (3.01) (Supplementary Table 1).

Table 1—*Characteristics of the study participants*

	T1D and CD	T1D	*P*
Total	947	40,619	
Age at T1D diagnosis (years)*,[a]	9 (9)	16 (15)	<0.001
Age at T1D diagnosis (years)			<0.001
0–9	566 (59.8)	11,855 (29.2)	
10–19	261 (27.6)	14,347 (35.3)	
20–30	120 (12.7)	14,417 (35.5)	
Age at end of study (years)*	21 (12)	31 (23)	<0.001
Entry year, median (range)	1997 (1964–2009)	1990 (1964–2009)	<0.001
Follow-up (years)*,[b]	12 (10)	15 (18)	<0.001
Age at CD diagnosis (years)*	12 (12)	No data	
Females (%)	522 (55.1)	19,228 (47.3)	<0.001
Males (%)	425 (44.9)	21,391 (52.7)	<0.001
Calendar year			<0.001
1964–1975	96 (10.1)	9,476 (23.3)	
1976–1987	150 (15.8)	10,445 (25.7)	
1988–1999	342 (36.1)	8,553 (21.1)	
2000–2009	359 (37.9)	12,145 (29.9)	
Country of birth (Nordic)	940 (99.3)	38,837 (96.0)	<0.001
Gestational diabetes mellitus	14 (1.5)	2,204 (5.4)	<0.001
Oral antidiabetes medication	19 (2.0)	2,336 (5.8)	<0.001
DRP events	102 (10.8)	4,497 (11.1)	0.771

Data are n (%) or *median (interquartile range) unless otherwise indicated. [a]Ages rounded to the nearest year. [b]Follow-up time until diagnosis of DRP, death from other cause, emigration, or 31 December 2009 (whichever occurred first).

The absolute risk of DRP during the first 5 years of follow-up in patients with T1D and CD was 289/100,000 person-years (compared with 507/100,000 person-years in the T1D cohort) (excess risk: −218/100,000 person-years). The absolute risk increased over time, and after >15 years of follow-up the absolute risk of DRP was 2,769/100,000 person-years in patients with T1D and CD versus 920/100,000 person-years in the T1D cohort (excess risk of 1,849/100,000 person-years) (Supplementary Table 1). Adjusting for country of birth did not change our risk estimates (data not shown).

Stratified analyses

The overall aHR for DRP during the first 10 years after CD diagnosis was low (0.75) (Table 2), and in this time stratum there were no interactions between CD and sex, age, or calendar period at T1D diagnosis (data not shown). Because of a lack of DRP events in patients with T1D and CD aged 20–30 years at T1D diagnosis, we were unable to calculate a hazard ratio (HR) in this group (only 120 patients with T1D and CD had T1D onset between 20 and 30 years of age) (Tables 1 and 2).

The overall aHR for DRP beyond 10 years of CD diagnosis was increased (2.87) (Table 2), and DRP risks did not differ according to sex, age, or calendar period at T1D diagnosis (data not shown). We were not able to estimate HR for the last calendar period (2000–2009) because no study participant had ≥10 years of follow-up before the end of the study (31 December 2009).

Sensitivity analyses

Excluding women who had their first T1D diagnosis during pregnancy (these women could potentially have gestational diabetes mellitus) or those with a record of oral antidiabetes medication did not influence the HRs (Supplementary Table 2). The risk estimate also did not change when we restricted our dataset to inpatients with T1D (Supplementary Table 2).

By restricting the outcome to severe DRP (DRP requiring retinal laser therapy), we found the same pattern of low initial risk followed by an increased HR after 10 years with CD (<5 years with CD, HR 0.56 [95% CI 0.18–1.74]; 5–9.99 years, 0.43 [0.11–1.73]; 10–14.99 years, 2.49 [1.18–5.25]; and ≥15 years, 2.01 [0.50–8.06]).

CONCLUSIONS—In this large population-based cohort study, duration of CD proved to be a strong predictor of future DRP development. The association between T1D and CD is well recognized and may be due to shared risk factors (21). Research has largely focused on studying the prevalence of CD in T1D (8,9), as well as the benefits of starting a gluten-free diet in asymptomatic CD within the T1D population (9,22). Few studies have examined the risk of complications in patients with both conditions (10,11,23), and none have thus far been able to determine time-specific risks for T1D complications.

The present findings are consistent with those of our earlier study (U.K. study) (11) in which advanced retinopathy was seen in 58.3% of patients with T1D and CD versus in 25% of patients with T1D without CD (11). The high prevalence of DRP, neuropathy, and nephropathy in the U.K. study could mirror different patient characteristics and T1D-management traditions in Sweden and the U.K. Case and control subjects in the U.K. study were selected from a tertiary diabetes center (possibly with higher rates of complications because of selecting patients with severe T1D), whereas the current (Swedish) study was based on all patients with a recorded diagnosis of T1D. The higher prevalence of DRP in the U.K. study could also be due to malnutrition in the CD plus T1D group, since they were thinner than the T1D-only group.

Research evidence suggests that patients with T1D screened for CD and subsequently prescribed a gluten-free diet improve in their clinical parameters, including growth and metabolic control, compared with T1D patients untreated for CD (9,22). However, in our U.K. study on retinopathy a 1-year gluten-free diet did not influence the prevalence of retinopathy (11). Although the majority of young patients with CD seem to adhere well to a gluten-free diet (24), we cannot rule out that the addition of yet another condition (i.e., T1D) affected dietary adherence negatively. In a random subset of patients with CD in our dataset, 83% adhered to a gluten-free diet (16). In the current study, we lack individual-based information on gluten-free diet, but one can speculate that the highest degree of dietary adherence was noted just after diagnosis, when the risk of DRP is lower.

In a recent multicenter study (25), the effect of biopsy-proven CD on metabolic control in patients with T1D was examined over time. After 5 years of follow-up, patients with T1D and CD had lower weight and height than patients with only T1D (25). However, no differences in BMI and HbA_{1c} levels were observed between the groups after the 5-year follow-up. If patients with T1D and CD have worse nutritional status than T1D patients without CD, the former's risk of DRP development could be increased (26).

One explanation for the lower risk of DRP at baseline in patients with T1D and CD is the lower levels of cholesterol and blood pressure found in CD patients (27). Hypercholesterolemia and hypertension increase the risk of DRP (3). Recently, Picarelli et al. (10) demonstrated that patients with T1D and CD had lower levels of HbA_{1c}, triglycerides, and cholesterol than patients with only T1D. These researchers (10) found no signs of retinal or renal abnormalities in patients with T1D and CD (10), but the study was cross-sectional without follow-up.

Inflammatory and autoimmune mechanisms may be involved in DRP development (4). In fact, anti-inflammatory drugs have been suggested as potential new therapies against DRP (7). When the carotid intima-media thickness was examined in Italian patients with T1D and CD (23) (as a measure of subclinical atherosclerosis), these patients had greater carotid intima-media thickness than patients with only T1D (23). The positive association between CD and subclinical atherosclerosis could signal microvascular damage (DRP). Patients with CD are at increased risk of cardiovascular death (15) and incident ischemic heart disease (28). Another possible mechanism for the increased risk of DRP seen over time is that of persistent low-grade inflammation. The intestinal mucosa in patients with CD can take a long time to fully recover, even after initiation of a gluten-free diet. Studies show that chronic, low-grade inflammation plays an important role in the pathogenesis of DRP (29). Having low-grade intestinal inflammation or CD with little symptoms might also affect the patient's adherence to a strict gluten-free diet, which in turn could potentially affect the risk of future DRP.

The pattern of increasing risk of DRP seen over time was also present in our subgroup analyses in which we found lower risk estimates for DRP during <10 years' duration of CD diagnosis and higher risk during ≥10 years' CD duration. The nonsignificant differences in DRP risk across calendar periods may be due to longer T1D duration before the end

of follow-up in patients diagnosed in earlier calendar periods (many years at risk for DRP in each patient). In contrast, patients diagnosed in the latest calendar period were (for study design reasons) only at risk just after T1D diagnosis, and because the follow-up time was short, most patients did not develop DRP. The number of DRP events after 2000 was low, with a wide 95% CI (0.11–1.80). The differences in calendar period–specific risk estimates may also reflect the changes made in T1D care and management in Sweden over time as well as the diagnostic methods used for identification of CD.

The major strengths of this study are the population-based design, the definition of CD (all cases were biopsy verified), and that our study included all patients with T1D in Sweden. The nationwide identification of CD from all pathology departments in Sweden (16) minimized the risk of selection bias. Although we did not use positive CD serology for the diagnosis of CD, 88% of those with available data on CD serology had positive antibodies before biopsy (16). Another strength is the large number of participants and statistical power: because >900 patients had T1D and CD, we could perform stratified analyses. Additional data on pregnancy and medication allowed us to conduct sensitivity analyses and minimize potential misclassification. Even when we restricted our outcome to DRP requiring retinal laser therapy, we found the same pattern of low HR in early CD followed by an increased HR over time (longer duration of CD). Because of fewer positive events in this subanalysis, only the HR in patients with CD for 10–14.99 years was statistically significant.

This study is limited by the absence of information on metabolic control (HbA_{1c}, insulin dosage, and BMI) in patients with T1D. In addition, the 41,566 patients with T1D were not screened for CD specifically for this study; therefore, the clinical presentation may vary among our CD patients. Today, all Swedish children and adolescents with T1D are screened for CD (routine care), but that may not have been the case in the beginning of the study period. In the 1990s, two-thirds (29 of 44) of all pediatric departments regularly screened all T1D patients for CD, with the remaining departments opting for CD testing on clinical suspicion (30). Hence, we cannot dismiss the possibility that there are individuals with undiagnosed CD in our T1D-only cohort. Still, their presence will not affect our risk

Table 2—*Subgroup analyses in relation to risk of DRP according to duration of CD*

	0–9 years after CD diagnosis					≥10 years after CD diagnosis				
Subgroup	Observed events	Expected events	HR (95% CI) adjusted	Absolute risk/ 100,000 PYAR	Excess risk/ 100,000 PYAR	Observed events	Expected events	HR (95% CI) adjusted	Absolute risk/ 100,000 PYAR	Excess risk/ 100,000 PYAR
Overall	30	40	0.75 (0.55–1.03)	485	−162	45	16	2.87 (2.06–4.02)	2,540	1,655
Sex										
Males	13	19	0.70 (0.42–1.17)	469	−201	17	6	2.76 (1.66–4.61)	2,471	1,576
Females	17	22	0.79 (0.53–1.18)	499	−131	28	9	2.99 (1.92–4.66)	2,583	1,719
Age at T1D diagnosis (years)										
0–9	23	31	0.74 (0.50–1.08)	583	−205	33	21	1.56 (1.08–2.25)	3,837	1,377
10–19	7	6	1.07 (0.62–1.85)	488	32	12	5	2.51 (1.12–5.61)	2,243	1,349
Calendar period										
1964–1975	1	1.3	0.76 (0.11–5.38)	155	−49	1	0.2	4.70 (0.66–33.46)	373	294
1976–1987	12	16	0.76 (0.43–1.35)	1,044	−330	21	9	2.23 (1.45–3.43)	3,918	2,161
1988–1999	16	18	0.91 (0.61–1.36)	602	−60	22	14	1.55 (0.90–2.70)	2,941	1,044
2000–2009[a]	1	2	0.44 (0.11–1.80)	58	−74					

Because there were no individuals in the T1D+CD group who developed DRP in the 20–30 years age-group, it was not possible to calculate an HR. PYAR, person-years at risk. [a]Because the study ended 31 December 2009, we were not able to calculate an HR in the 2000–2009 period for individuals who had a CD diagnosis for ≥10 years.

estimate more than marginally because patients with T1D and undiagnosed CD are unlikely to make up more than a small percentage of our reference category (T1D only). Furthermore, if undiagnosed CD would have any effect, it would probably dilute existing associations.

Our results indicate that CD is a strong predictor for simplex and severe laser-treated DRP in patients with T1D. We suggest that the lower effect of DRP in early CD is due to DRP-protective characteristics of patients with CD (lower cholesterol and BMI). Long-standing CD, however, increased the risk of DRP by >200% (aHR 3.01) and thus merits closer monitoring of DRP in patients with T1D.

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K.M. helped assure that International Committee of Medical Journal Editors (ICMJE) criteria for authorship were read and met, agreed with the manuscript's RESULTS and CONCLUSIONS, designed the experiments and the study, analyzed data, wrote the first draft of the manuscript, contributed overall to the writing of the manuscript, contributed to the design of the study and interpretation of the data analyses, gave guidance regarding the development of statistical models and interpretation of data, approved the final version of the manuscript, and was responsible for data integrity. M.K. helped assure that ICMJE criteria for authorship were read and met, agreed with the manuscript's RESULTS and CONCLUSIONS, contributed to the writing of the article, contributed to the design of the study and interpretation of the data analyses, gave guidance regarding the development of statistical models and interpretation of data, approved the final version of the manuscript, and obtained funding. S.M.M., D.S.S., and J.L. helped assure that ICMJE criteria for authorship were read and met, agreed with the manuscript's RESULTS and CONCLUSIONS, contributed to the writing of the article, contributed to design of the study and interpretation of the data analyses, gave guidance regarding the development of statistical models and interpretation of data, and approved the final version of the manuscript. J.F.L. helped assure that ICMJE criteria for authorship were read and met, agreed with the manuscript's RESULTS and CONCLUSIONS, designed the experiments and the study, collected data and performed experiments for the study, contributed to the writing of the article, contributed to the design of the study and interpretation of the data analyses, gave guidance regarding the development of statistical models and interpretation of data, approved the final version of the manuscript, was responsible for data integrity, and obtained funding. K.M. and J.F.L. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Henricsson M, Nyström L, Blohmé G, et al. The incidence of retinopathy 10 years after diagnosis in young adult people with diabetes: results from the nationwide population-based Diabetes Incidence Study in Sweden (DISS). Diabetes Care 2003;26:349–354
2. Forlenza GP, Rewers M. The epidemic of type 1 diabetes: what is it telling us? Curr Opin Endocrinol Diabetes Obes 2011;18:248–251
3. Nordwall M, Arnqvist HJ, Bojestig M, Ludvigsson J. Good glycemic control remains crucial in prevention of late diabetic complications—the Linköping Diabetes Complications Study. Pediatr Diabetes 2009;10:168–176
4. Adamis AP, Berman AJ. Immunological mechanisms in the pathogenesis of diabetic retinopathy. Semin Immunopathol 2008;30:65–84
5. Kastelan S, Zjacić-Rotkvić V, Kastelan Z. Could diabetic retinopathy be an autoimmune disease? Med Hypotheses 2007;68:1016–1018
6. Baudouin C, Gordon WC, Fredj-Reygrobellet D, et al. Class II antigen expression in diabetic preretinal membranes. Am J Ophthalmol 1990;109:70–74
7. Zhang W, Liu H, Rojas M, Caldwell RW, Caldwell RB. Anti-inflammatory therapy for diabetic retinopathy. Immunotherapy 2011;3:609–628
8. Murray JA. Celiac disease in patients with an affected member, type 1 diabetes, iron-deficiency, or osteoporosis? Gastroenterology 2005;128(Suppl. 1):S52–S56
9. Hansen D, Brock-Jacobsen B, Lund E, et al. Clinical benefit of a gluten-free diet in type 1 diabetic children with screening-detected celiac disease: a population-based screening study with 2 years' follow-up. Diabetes Care 2006;29:2452–2456
10. Picarelli A, Di Tola M, Sabbatella L, et al. Type 1 diabetes mellitus and celiac disease: endothelial dysfunction. Acta Diabetol. 21 June 2011 [Epub ahead of print]
11. Leeds JS, Hopper AD, Hadjivassiliou M, Tesfaye S, Sanders DS. High prevalence of microvascular complications in adults with type 1 diabetes and newly diagnosed celiac disease. Diabetes Care 2011;34:2158–2163
12. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450
13. Miao J, Brismar K, Nyrén O, Ugarph-Morawski A, Ye W. Elevated hip fracture risk in type 1 diabetic patients: a population-based cohort study in Sweden. Diabetes Care 2005;28:2850–2855
14. Marsh MN; MN M. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992;102:330–354
15. Ludvigsson JF, Montgomery SM, Ekbom A, Brandt L, Granath F. Small-intestinal histopathology and mortality risk in celiac disease. JAMA 2009;302:1171–1178
16. Ludvigsson JF, Brandt L, Montgomery SM, Granath F, Ekbom A. Validation study of villous atrophy and small intestinal inflammation in Swedish biopsy registers. BMC Gastroenterol 2009;9:19
17. Ji J, Ludvigsson JF, Sundquist K, Sundquist J, Hemminki K. Incidence of celiac disease among second-generation immigrants and adoptees from abroad in Sweden: evidence for ethnic differences in susceptibility. Scand J Gastroenterol 2011;46:844–848
18. Söderström U, Aman J, Hjern A. Being born in Sweden increases the risk for type 1 diabetes - a study of migration of children to Sweden as a natural experiment. Acta Paediatr 2012;101:73–77
19. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 2007;16:726–735
20. Cnattingius S, Ericson A, Gunnarskog J, Källén B. A quality study of a medical birth registry. Scand J Soc Med 1990;18:143–148
21. Smyth DJ, Plagnol V, Walker NM, et al. Shared and distinct genetic variants in type 1 diabetes and celiac disease. N Engl J Med 2008;359:2767–2777
22. Sanchez-Albisua I, Wolf J, Neu A, Geiger H, Wäscher I, Stern M. Coeliac disease in children with type 1 diabetes mellitus: the

effect of the gluten-free diet. Diabet Med 2005;22:1079–1082
23. Pitocco D, Giubilato S, Martini F, et al. Combined atherogenic effects of celiac disease and type 1 diabetes mellitus. Atherosclerosis 2011;217:531–535
24. Mayer M, Greco L, Troncone R, Auricchio S, Marsh MN. Compliance of adolescents with coeliac disease with a gluten free diet. Gut 1991;32:881–885
25. Frohlich-Reiterer EE, Kaspers S, Hofer S, et al. Anthropometry, metabolic control, and follow-up in children and adolescents with type 1 diabetes mellitus and biopsy-proven celiac disease. *J Pediatr* 2011;158:589–593
26. Kaur H, Donaghue KC, Chan AK, et al. Vitamin D deficiency is associated with retinopathy in children and adolescents with type 1 diabetes. Diabetes Care 2011; 34:1400–1402
27. Lewis NR, Sanders DS, Logan RF, Fleming KM, Hubbard RB, West J. Cholesterol profile in people with newly diagnosed coeliac disease: a comparison with the general population and changes following treatment. Br J Nutr 2009;102:509–513
28. Ludvigsson JF, James S, Askling J, Stenestrand U, Ingelsson E. Nationwide cohort study of risk of ischemic heart disease in patients with celiac disease. Circulation 2011;123:483–490
29. Noda K, Nakao S, Ishida S, Ishibashi T. Leukocyte adhesion molecules in diabetic retinopathy. J Ophthalmol 2012;2012: 279037
30. Danielsson L, Stenhammar L, Ascher H, et al. Gluten intolerance in children—diagnostic routines in Sweden 1996. Great variations in celiac disease studies. Lakartidningen 1997; 94:3165–3168 [in Swedish]