Microvascular Complications in Childhood-Onset Type 1 Diabetes and Celiac Disease: A Multicenter Longitudinal Analysis of 56,514 Patients From the German-Austrian DPV Database

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OBJECTIVE

To investigate whether celiac disease (CD) associated with type 1 diabetes increases the risk of microvascular complications.

RESEARCH DESIGN AND METHODS

Patients (*n* = 56,514) aged >10 years with diabetes duration <20 years from 392 centers in Germany and Austria were assigned to one of three categories (*n*): no CD (50,933), biopsy-confirmed CD (812), or suspected CD (4,769; clinical diagnosis or positive antibodies). The confirmed and suspected groups were combined and analyzed for retinopathy or nephropathy. Cox proportional hazards regression was used to adjust for potential confounders (glycated hemoglobin [HbA_{1c}], age at diabetes onset, sex, smoking, dyslipidemia, and hypertension).

RESULTS

Kaplan-Meier analysis revealed that retinopathy and nephropathy occurred earlier in the presence versus absence of CD: retinopathy at age 26.7 years (95% CI 23.7–30.2) in 25% of patients with CD vs. age 33.7 years (33.2–34.4) in 25% without CD, and microalbuminuria at age 32.8 years (29.7–42.5) vs. 42.4 years (41.4–43.3). The adjusted risk for both retinopathy (hazard ratio 1.263 [95% CI 1.078–1.481]) and nephropathy (1.359 [1.228–1.504]) was higher in patients with diabetes and CD versus those without CD. Cox regression revealed CD as an independent risk factor for microvascular complications after adjustment for confounders.

CONCLUSIONS

CD is an independent risk factor for retinopathy and nephropathy in patients with type 1 diabetes. Our study therefore supports the recommendation for regular serologic testing for CD, even in the absence of clinical CD. Further prospective studies are required to investigate whether a gluten-free diet might reduce the risk of microvascular disorders in patients with diabetes and CD.

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Current international pediatric guidelines recommend screening for microvascular complications (diabetic retinopathy and nephropathy) as well as for associated diseases (celiac disease [CD], autoimmune thyroiditis, hypertension, and disturbances of lipid metabolism) (1–3). CD is frequently associated with T1D, as both disorders have a common genetic background (4–6).

Two newer studies brought into discussion the question of whether CD itself is a risk factor for the development of microvascular complications. A case-control study conducted by Leeds et al. (7) in the U.K. found that adult patients with type 1 diabetes and newly diagnosed CD had a higher glycated hemoglobin (HbA_{1c}) and a higher prevalence of retinopathy, nephropathy, and neuropathy than patients without CD. A population-based cohort study of the Swedish National Patient Register reported coexisting CD to be a risk factor for retinopathy (8). Against this background we conducted the current study to determine whether this potential association could be confirmed in a large cohort of German and Austrian patients with type 1 diabetes. As the consequences would be serious if this association proved causal, it is important to verify it in different populations using different methods.

Current guidelines recommend screening patients with type 1 diabetes for CD at diabetes onset and subsequently at regular intervals as there is an increased incidence of CD in these patients (1,2,9). Current guidelines for the diagnosis of CD emphasize the strong prognostic value of the newer-generation antibody tests so that biopsy confirmation is no longer needed in patients with typical clinical signs but is recommended in mild or atypical cases (10).

RESEARCH DESIGN AND METHODS

DPV Database

The German-Austrian DPV Initiative collects prospective, longitudinal, anonymized data from patients with diabetes using standardized documentation software (11). The database includes anthropometric parameters, type of diabetes, age at diabetes onset, insulin dose, treatment regimen, autoantibodies, and HbA_{1c}. Implausible data are reported back to the treatment center for verification or correction every 6 months.

Ethics Approval

Analysis of anonymized routine data within the DPV Initiative was approved by the Ethics Committee of the Medical Faculty of the University of Ulm and the institutional review boards at the participating centers.

Patients

The current study encompassed 56,514 patients with type 1 diabetes from 392 centers participating in the DPV Initiative prior to March 2013. Inclusion criteria were age >10 years at the last follow-up visit and age <20 years at diabetes onset. Patients were assigned to one of the following three categories, based on their CD status:

1. no CD (no clinical signs of CD; normal duodenal biopsy result, if performed; and no antibodies detected against endomysium, transglutaminase, or gliadin-IgA, if tested);
2. suspected CD (clinical diagnosis; positive antibody result for endomysium, transglutaminase, or gliadin-IgA; recommendation of or adherence to a gluten-free diet; and biopsy result graded as Marsh 0, 1, or 2 without positive antibodies [12]); or
3. confirmed CD (duodenal mucosal biopsy performed, graded as Marsh 2 with positive antibodies, or as Marsh ≥3 [12]).

Included in the analysis were all patients with one or more ophthalmologic examinations (42,063 patients) and/or one urine albumin examination (44,303 patients).

Data Analysis and Statistics

Anonymized follow-up data were aggregated using SQL statements and analyzed using SAS 9.3 (SAS Institute Inc., Cary, NC). Group comparisons used the Wilcoxon test for continuous variables and the χ^2 test for binary variables. *P* values were corrected for multiple comparisons according to the Holm method. Time-to-event analyses for retinopathy and nephropathy were carried out using Kaplan-Meier curves. Patients with no occurrence of retinopathy or nephropathy during their individual observation time were censored. Comparisons of groups were made using the log-rank test. Multivariable Cox proportional hazards models with duration of diabetes as the underlying time metric were used to model factors influencing the occurrence of retinopathy or nephropathy. Presence or absence of CD, sex, smoking, dyslipidemia, and hypertension were each included as dichotomous variables in the model; HbA_{1c} and age at diabetes onset were included as categorical variables. HbA_{1c} was categorized into two groups (≤7.5 or >7.5%); age at diabetes onset was categorized into four groups (≤5, >5 to ≤10 , >10 to ≤15, and >15 years). The Breslow method was applied to adjust for ties. *P* values <0.05 were considered statistically significant.

Retinopathy

All patients with one or more documented eye examinations performed and graded by a local ophthalmologist were included in the analysis (13); 42,063 patients met this criterion. Nonproliferative retinopathy and advanced retinopathy were defined in accordance with international guidelines (1,2,3,9).

Nephropathy

All patients with one or more urine albumin tests during the most recent year of treatment were included in the analysis (44,303 patients). Microalbuminuria was defined as two or more positive microalbuminuria tests (spot urine, overnight collection, or 24-h urine samples) within 1 year. Kaplan-Meier analysis was based on the 1st year with microalbuminuria according to this definition.

CD

Patient data were analyzed with regard to clinical diagnosis of CD or the presence of antibodies to gliadin-IgA, endomysium, or transglutaminase. Due to low specificity, the presence of antigliadin-IgG antibodies alone was not considered sufficient to suspect CD. All antibody findings during follow-up were included in the analysis. For confirmed CD, duodenal biopsies had to be grade ≥3 according to the Marsh classification or grade 2 plus positive antibodies (10) (12). Antibody testing and histology studies were performed locally at the participating centers.

HbA_{1c}

To document long-term metabolic control, HbA_{1c} levels were determined at the participating centers in compliance with national quality requirements (14). Measurements from

different laboratories were mathematically standardized to the Diabetes Control and Complications Trial (DCCT) reference range of 4.05–6.05% (20.77–42.62 mmol/mol) using the multiple of the mean method (15).

Hypertension

Arterial hypertension was diagnosed if the mean blood pressure in the most recent year exceeded 140 mmHg for systolic or 90 mmHg for diastolic blood pressure as defined by the European Society of Hypertension (16).

Dyslipidemia

In accordance with international standards (17) and an earlier analysis of DPV data (18), dyslipidemia was defined as the presence of at least one of the following: total cholesterol >5.2 mmol/L (>200 mg/dL), HDL cholesterol <0.9 mmol/L (<35 mg/dL), LDL cholesterol >3.4 mmol/L (>130 mg/dL), and triglycerides >1.7 mmol/L (>150 mg/dL) (18). All lipid determinations were done at the local laboratories. Total cholesterol and triglycerides were determined in compliance with national quality requirements (14).

Smoking

Patients were asked about their smoking habits at each visit and classified as smokers if they reported smoking one or more cigarettes per day.

BMI and Height Standard Deviation Scores

BMI and height data, adjusted for age and sex and expressed as standard deviation scores (SDS), were compared with reference values for German children and adolescents, using Cox-Box transformation and the least mean squares method (19). BMI-SDS and height-SDS values in adult patients were extrapolated based on coefficients for age 18 years.

RESULTS

Patient Characteristics

Table 1 summarizes the demographic and clinical characteristics of the study population of 56,514 patients with childhood-onset type 1 diabetes (52.1% males). At the most recent visit, mean age in the study population was 19.5 years, and mean age at diabetes onset was 9.7 years, as was mean diabetes duration. Of all patients, 23,998 (42.5%) were antibody negative with no evidence of CD, for 26,935 (47.7%) there was no evidence of CD or no documented antibody test, 4,769 (8.4%) had suspected CD, and 812 (1.4%) had confirmed CD.

Of 42,063 patients with eye examinations, 30,638 (72.8%) had two or more eye examinations, whereas the remaining 11,425 (27.2%) had one. Of 31,185 patients with data for both retinopathy and nephropathy, 684 (2.2%) had both types of microvascular complications. This small subgroup was not further analyzed.

Retinopathy

Age

Kaplan-Meier analysis (Fig. 1, top) revealed that the age by which 25% of patients had developed retinopathy was 33.7 years (95% CI 33.2–34.4) for those without CD and 26.7 years (23.7–30.2) for those with suspected or confirmed CD. The difference between the curves was statistically significant by log-rank test ($P < 0.0001$). At age 25 years, 11.1% of patients without CD and 21.8% of patients with suspected or confirmed CD had retinopathy.

Diabetes Duration

As shown in Table 2, retinopathy developed in 25% of patients without CD and 25% of patients with suspected or confirmed CD after diabetes durations of 23.4 years (95% CI 22.8–24.1) and 18.6 years (17.3–20.8), respectively. The difference was not statistically significant by the log-rank test ($P = 0.2453$).

Other Influencing Factors

Multivariable analysis using Cox proportional hazards modeling as shown in Table 3 demonstrated that CD remained a statistically significant factor even after adjusting for long-term median HbA_{1c}, age of onset, sex, blood pressure, lipid status, and smoking. The hazard ratio (HR) for CD was 1.263 (95% CI 1.078–1.481) ($P = 0.0039$), the HR for HbA_{1c} >7.5% (58.5 mmol/mol) was 1.298 (1.273–1.324) ($P < 0.0001$), and the HR for smoking was 1.193 (1.095–1.300) ($P < 0.0001$). Diabetes onset during puberty (age-group 10–15 years) was associated with the highest age-related HR of 1.969 (1.779–2.179) compared with diabetes onset at age <5 years ($P < 0.0001$). Dyslipidemia (HR 0.928 [0.867–0.994], $P = 0.0329$)

Table 1—Demographic and clinical characteristics, including the incidence of CD, in 56,514 patients with type 1 diabetes from 392 centers in Germany and Austria

Patients	All	No CD	Suspected/confirmed CD	*P* (Holm)
n	56,514	50,933	5,581	
Males, %	52.1	52.2	51.0	0.180
Mean age at most recent visit, years	19.5	**19.8**	**16.4**	**<0.0001**
Median age (IQR) at most recent visit, years	17.2 (14.4–19.3)	17.3 (14.5–19.6)	16.4 (13.7–18.1)	
Mean age at diabetes onset, years	9.7	9.9	8.3	**<0.0001**
Median age (IQR) at diabetes onset, years	10.0 (6.5–12.9)	10.1 (6.7–13.0)	8.4 (4.9–11.6)	
Diabetes duration, years	9.7	9.9	8.0	0.683
Median diabetes duration (IQR), years	7.2 (3.7–11.9)	7.2 (3.6–12.1)	7.6 (4.5–10.9)	
BMI-SDS	0.62	**0.63**	**0.55**	**<0.0001**
Height-SDS	−0.15	−0.15	−0.12	0.180
HbA_{1c}, %	8.3	8.3	8.3	0.108
HbA_{1c}, mmol/mol	67.3	67.3	67.3	0.108
Smoking, cigarettes/day	1.5	**1.6**	**0.9**	**<0.0001**

Bold type indicates statistical significance. IQR, interquartile range.

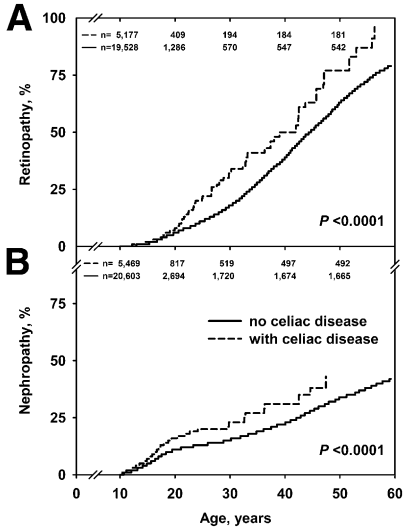

Figure 1—Kaplan-Meier analysis of retinopathy (*A*) and nephropathy (microalbuminuria) (*B*) by age in patients with type 1 diabetes and suspected or confirmed CD (dashed line) and without CD (solid line).

was not a risk factor, and hypertension (HR 1.046 [0.967–1.131], $P = 0.2603$) and sex (HR 1.040 [0.971–1.113], $P = 0.2624$) also showed no significant effects.

Nephropathy

Age

As shown in Fig. 1 (bottom), the age by which 25% of patients had developed microalbuminuria was 42.4 years (95% CI 41.4–43.3) in those without CD and 32.8 years (29.7–42.5) in those with suspected or confirmed CD. The differences were statistically significant by the log-rank test ($P < 0.0001$). At age 25 years, 13.2% of patients without CD had nephropathy compared with 19.9% of patients with suspected or confirmed CD.

Diabetes Duration

Table 2 shows that diabetes duration after which 25% of patients developed nephropathy was 30.2 years (95% CI 29.6–30.9) in the absence of CD and 24.1 years (19.6 –34.5) in suspected or confirmed CD. The differences were statistically significant by log-rank test ($P < 0.0001$).

Other Influencing Factors

Table 3 shows the Cox proportional hazards model, which included CD, long-term HbA_{1c}, smoking, hypertension, dyslipidemia, male sex, and three subgroups of age at diabetes onset.

In this model, statistically significant factors for nephropathy were as follows: suspected or confirmed CD (HR 1.359 [95% CI 1.228–1.504], $P < 0.0001$), HbA_{1c} >7.5% (58.5 mmol/mol) (1.058 [1.036–1.080], $P < 0.0001$), hypertension (1.353 [1.267–1.444], $P < 0.0001$), dyslipidemia (1.138 [1.069–1.212], $P < 0.0001$), and age >5 years at diabetes onset (5–10 years, 1.753 [1.600–1.921], $P < 0.0001$; 10–15 years, 2.378 [2.167–2.611], $P < 0.0001$; and >15 years, 1.279 [1.128–1.450], $P = 0.0001$; reference, diabetes onset at age <5 years). Male sex and smoking did not significantly increase the risk of nephropathy in this model.

CONCLUSIONS

Published estimates on the prevalence of biopsy-confirmed CD in patients with diabetes vary considerably. For instance, recent studies reported 12.3% for Denmark (5), 3.9% for Germany (20), and 1.3% for Germany and Austria (21). A study by Holmes (6) calculated a multistudy mean of 4.5% (0.97–16.4%) based on data from different regions, and Camarca et al. (4) reported a prevalence of 4.4–11.1% in patients with type 1 diabetes vs. 0.5% in the general population.

Thus, the prevalence of 1.4% biopsy-proven CD patients observed in the current study population of 56,514 patients with diabetes from 392 centers in Germany and Austria is comparable to most studies. When comparing our work with earlier DPV studies by Fröhlich-Reiterer et al. (21) (investigating CD), Galler et al. (22) (microalbuminuria), Hammes et al. (13) (retinopathy), and Raile et al. (23) (nephropathy), the following should be borne in mind. Although the same DPV database was used, the analyses were performed at different times, used different inclusion criteria, and therefore involved different numbers of patients. The combined total prevalence of biopsy-proven and clinically suspected cases of CD in our cohort at the time of the present analysis was 9.9%, which is within the range of prevalences for patients with type 1 diabetes reported from other European countries.

Epidemiological studies frequently use different definitions of nephropathy. In our analysis, microalbuminuria was defined as two or more positive urine tests during the most recent year. Intermittent and spontaneous or pharmacologically induced regression of albuminuria, as frequently occurs in children and adolescents, was not taken into account (22).

We stratified patients as having no (evidence of) CD, clinical/serological CD (suspected CD), or (biopsy) confirmed CD. This accounted for changes occurring during the long observation period, including changes in diagnostic criteria for CD, the introduction of (more) specific antibodies into the diagnostic repertoire, and increased screening rates. Various definitions of CD (e.g., asymptomatic, subclinical, and classical) are discussed in a recent consensus paper (24). However, it must be taken into account that the DPV database is a long-term, multicenter registry that is subject to different and changing definitions of CD.

Two very recent studies are of particular interest in relation to our study. A population-based study with a very long observation period (1964–2009) and a high prevalence of CD (2.3% biopsy-confirmed cases of CD) observed that the risk of retinopathy depended on time

Table 2—CD status and diabetes duration in years before developing microvascular complications (no CD vs. suspected/confirmed CD)

	Retinopathy		Nephropathy	
	No CD	Suspected or confirmed CD	No CD	Suspected or confirmed CD
Lower quartile (25%)	23.4 (22.8–24.1)	18.6 (17.3–20.8)	30.2 (29.6–30.9)	24.1 (19.6–34.5)
Median (50%)	33.1 (32.4–33.7)	28.9 (21.7–33.3)	56.5 (53.5–60.3)	54.1 (34.6–54.1)
Upper quartile (75%)	44.1 (43.3–45.3)	34.6 (33.3–44.0)	n.e. (n.e.)	54.1 (n.e.)

All data in years; 95% CIs in parentheses. n.e., nonestimable.

Table 3—Influencing factors for retinopathy and nephropathy in a Cox proportional hazards model

	Retinopathy	Nephropathy
CD	**1.263 (1.078–1.481)**	**1.359 (1.228–1.504)**
HbA_{1c} >7.5% (58.5 mmol/mol)*	**1.298 (1.273–1.324)**	**1.058 (1.036–1.080)**
Smoking	**1.193 (1.095–1.300)**	0.927 (0.854–1.006)
Hypertension	1.046 (0.967–1.131)	**1.353 (1.267–1.444)**
Dyslipidemia	**0.928 (0.867–0.994)**	**1.138 (1.069–1.212)**
Male sex	1.040 (0.971–1.113)	1.006 (0.945–1.070)
Age at diabetes onset ≤5 years	1.000	1.000
Age at diabetes onset >5 to ≤10 years	**1.613 (1.460–1.782)**	**1.753 (1.600–1.921)**
Age at diabetes onset >10 to ≤15 years	**1.969 (1.779–2.179)**	**2.378 (2.167–2.611)**
Age at diabetes onset >15 years	**1.449 (1.291–1.626)**	**1.279 (1.128–1.450)**

Values are HR (95% CI) for no CD vs. suspected or confirmed CD. Bold type indicates statistical significance (probability $>\chi^2$). *Long-term HbA_{1c}, standardized to the DCCT reference range using the multiple of the mean method (15).

since diagnosis of CD (8). Sex, age, and calendar period were not found to be independent risk factors, and blood pressure, HbA_{1c}, and lipid status were not included in the analysis. By comparison, our study did not investigate time since diagnosis of CD but did include cases of "probable" CD and had a shorter observation period. The other, cross-sectional study focused on patients with a long history of diabetes and untreated, newly diagnosed CD (7). The fact that the findings from all three studies with very different approaches were comparable strongly suggests that CD plays a relevant role in increasing the risk of developing microvascular complications in type 1 diabetes.

Recommendations for serologic screening for CD in patients with type 1 diabetes still vary considerably between countries. Serologic screening is recommended by the current guidelines of the German Diabetes Association (1), the International Diabetes Foundation/International Society for Pediatric and Adolescent Diabetes (IDF/ISPAD) (2), and the ISPAD Clinical Practice Consensus Guidelines (9), whereas the American Diabetes Association's Standards of Medical Care in Diabetes—2014 only recommends to "consider screening" (3). Of note, these recommendations are all based exclusively on the increased prevalence of CD in type 1 diabetes. However, the known complications of CD affect patients with and without diabetes alike, for instance with regard to the risk for lymphomas and colon cancer (25–29). The now-established association between concomitant CD and microvascular complications in type 1 diabetes is another independent argument in favor of screening for CD.

Overall, our work confirms the above-mentioned studies by Mollazadegan et al. (8) and Leeds et al. (7) and adds a new argument to the discussion about the pros and cons of screening for CD in patients with type 1 diabetes because CD is an independent risk factor for diabetes-related microvascular complications. Moreover, CD also carries an increased risk of macrovascular complications (25), especially an increased intima-medial thickness of the carotid arteries (30,31). CD alone is associated with an increased intima-medial thickness, which is further increased in combination with type 1 diabetes, although adult patients with CD have a lower rate of hypertension and hypercholesterolemia (32). A 2013 study by Mollazadegan et al. (33) showed that patients with type 1 diabetes diagnosed with CD for ≥15 years had a 2.8-fold increased risk of death, independently of the cause of death. The independent risk of end-stage renal disease in patients with CD has recently been reported to be approximately threefold (HR 2.87), with adjustment for diabetes having only a marginal effect (34).

Taken together, these aspects support the above-mentioned guideline recommendations to screen patients with diabetes for CD in contradistinction to screening the general population for CD, which most experts oppose (25). Patients with type 1 diabetes should be made aware of the increased risks associated with concomitant CD to encourage and motivate them to effectively reduce other risk factors that can be controlled, such as HbA_{1c}, hypertension, and dyslipidemia.

Whether or not a gluten-free diet can help to reduce the risk of complications in patients with type 1 diabetes and CD remains to be investigated. Although beneficial for growth (5,21), a gluten-free diet, according to most studies, has no beneficial effect on HbA_{1c} and the frequency of hypoglycemia (5,21,35). A marked benefit of a gluten-free diet in terms of a protective effect against malignancies also appears unlikely, at least in subclinical cases discovered by screening (25). CD with no or only mild symptoms is probably not associated with an increased risk of lymphoproliferative malignancy (25). The positive and negative effects of a gluten-free diet on the quality of life of asymptomatic patients should be considered (4,36,37,38,39). Screening for CD therefore may contribute to identifying patients with type 1 diabetes whose quality of life could be improved by reducing intestinal inflammation.

Opinions differ on the effect of a gluten-free diet in preventing vascular complications. A gluten-free diet has been suggested to have a beneficial effect on renal function due to low dietary levels of advanced glycosylation end products (40). Whereas some authors postulate that a gluten-free diet may negatively impact quality of life, we attach greater importance to the long-term consequences of undiagnosed and untreated CD.

In summary, our study demonstrates that CD increases the risk of microvascular complications in patients with type 1 diabetes. We conclude from this evidence and the recent literature that screening for CD is to be recommended in pediatric patients with type 1 diabetes.

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Author Contributions. T.R.R. and J.Wo. conceived and designed the study, interpreted data, wrote the draft manuscript, and prepared the final manuscript. S.L., K.-P.Z., E.F.-R., N.S., and M.S. classified patients into CD categories. W.M. categorized clinical data and decided on the use of references for the calculation of anthropometric *z* score (SDS) values. T.M.K., B.P.H., and J.Wö. categorized clinical data and decided on the use of references for the calculation of anthropometric *z* score (SDS) values. R.W.H. conceived and designed the study, performed statistical analysis, and interpreted data. All authors participated in data collection and reviewed, revised, and approved the final manuscript. R.W.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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