


## REGULAR ARTICLE

# Comorbidity of inflammatory bowel disease in children and adolescents with type 1 diabetes

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## Abstract

**Aim:** To determine the prevalence of inflammatory bowel disease (IBD) in patients with type 1 diabetes (T1D) and to characterise patients with both diseases.

**Methods:** Data of 65.147 patients with T1D ≤18 years of 379 centres in Germany and Austria participating in the DPV initiative were analysed. A total of 63 children had comorbid IBD; IBD prevalence was 0.1%. Regression models were used to analyse differences in metabolic control, acute complications and steroid intake.

**Results:** Mean BMI-SDS in patients with T1D and IBD was lower ( $-0.15 \pm 0.11$ ) compared to patients with T1D only ( $0.27 \pm 0.00$ ,  $p < .001$ ). Patients with T1D and IBD had a significantly higher use of steroids ( $22\% \pm 0.05\%$  vs.  $1\% \pm 0.00$ ,  $p < .001$ ) and a significantly higher rate of severe hypoglycaemic events per patient year ( $0.33 \pm 0.07$  vs.  $0.16 \pm 0.00$ ,  $p = .001$ ). No differences were found in HbA1c levels, insulin dose and occurrence of DKA.

**Conclusion:** Although children and adolescents with T1D and IBD take steroids more often, they suffer from severe hypoglycaemia more frequently and have a lower BMI-SDS. These findings might be explained by chronic intestinal inflammation leading to malabsorption, malnutrition and increased severe hypoglycaemia.

## KEYWORDS

children, hypoglycaemia, inflammatory bowel disease, prevalence, type 1 diabetes

**Abbreviations:** BMD, bone mineral density; BMI, body mass index; BMI-SDS, body mass index standard deviation score; CD, Crohn's disease; CG, control group; DKA, diabetic ketoacidosis; DPV, diabetes patient follow-up; GFD, gluten-free diet; I. U., international units; IBD, inflammatory bowel disease; IC, indeterminate colitis; pos., positive; RR, relative risk; T1D, type 1 diabetes; T2D, type 2 diabetes; tTGA, tissue transglutaminase; UC, ulcerative colitis; vs., versus.

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## 1 | INTRODUCTION

In the last two decades, an increase in the incidence of T1D in children and adolescents<sup>1</sup> as well as a progression in the incidence of IBD in children<sup>2,3</sup> has been observed in both developed and developing countries. The incidence of T1D in Austria for children below 15 years of age increased from 12.0 to 18.4 per 100.000 children between 1999 and 2007.<sup>4</sup> A similar rise of incidence rates has been observed in Germany for children with T1D younger than 15 years (in the 1990s 13.7/100.000/year; since 2000 19.4/100.000/year).<sup>5</sup> The prevalence of T1D in Germany below the age of 15 years was 126/100.000 in 2006; the prevalence in Germany at the end of 2026 is predicted to be 265/100.000.<sup>5</sup>

In concordance with worldwide reports,<sup>3</sup> a rise in IBD has been observed in Austria and Germany.<sup>6,7</sup>

In the general population, the average annual incidence rate in the province of Styria, Austria, from 1997 to 2007 was 4.8 (95% CI 4.5–5.2) per 100.000 for ulcerative colitis and 6.7 (95% CI 6.2–7.1) per 100.000 for Crohn's disease and rose significantly during the 11 year study period.<sup>7</sup> The percentage of patients who were under 18 years of age at initial diagnosis was 5% (34/674) for ulcerative colitis and 11% for Crohn's disease (89/813). Incidence rates for patients from 0 to 19 years were 2.2 (95% CI 1.7–2.8) for ulcerative colitis and 4.8 per 100.000 (95% CI 4.0–5.7) for Crohn's disease, respectively.<sup>7</sup>

In Leipzig, province of Saxony, Germany, incidence rates for IBD in children and adolescents < 18 years of age, including not only data from the Paediatric IBD Registry of Saxony but additional data of patients who have been exclusively cared for by internists, were as follows:

11/100.000 (95% CI 7.3–14.6) for IBD; 4.4 (95% CI 2.1–6.7) for ulcerative colitis; 5.7 (95% CI 3.0–8.3) for Crohn's disease; and 0.9 (95% CI 0.0–2.0) for indeterminate colitis.<sup>8</sup>

Average prevalence for children and adolescents <18 years of age with IBD in Saxony between 2000 and 2009 is quoted as 35.8/100.000 (95% CI 34.3–37.3).<sup>9</sup>

Autoimmune comorbidities have been described in both T1D and IBD<sup>10,11</sup>; based on this evidence, correlations between both diseases could be traced down.<sup>12–14</sup> Whereas correlations between T1D and other autoimmune diseases such as coeliac disease are very well investigated,<sup>15</sup> data on correlations between T1D and IBD remain conflicting. While associations between autoimmune disorders are generally presumed, a clear relation between T1D and IBD could not be confirmed by all study groups.<sup>16</sup>

The aim of our study was to investigate whether the risk for children with T1D to develop IBD is elevated, and to compare clinical characteristics and complications of T1D patients with and without IBD, including anthropometrics and metabolic control.

## 2 | RESEARCH DESIGN AND METHODS

Diabetes patient follow-up (diabetes patient follow-up) is a prospective, observational, multicentre diabetes survey with continuous

### Key Notes

- Data on associations between type 1 diabetes (T1D) and inflammatory bowel disease (IBD) are conflicting.
- We investigated correlations between T1D and IBD with prevalence data of the German and Austrian population, using the DPV database.
- The risk for children and adolescents with T1D to develop IBD is elevated, and patients suffering from both diseases have a higher risk of severe hypoglycaemia.

data acquisition. Twice a year, anonymous longitudinal data from patients are transmitted for central validation from 419 diabetes centres in Germany ( $n = 390$ ) and Austria ( $n = 29$ ). Inconsistent data are reported back to the centres for correction and then re-entered into the database.<sup>17</sup>

According to the guidelines of the German Diabetes Association, all centres are advised to document age at diabetes manifestation, sex, weight, height, BMI, blood pressure, migration background, insulin regimen, concomitant diseases, additional medications, laboratory markers and HbA<sub>1c</sub> levels.

### 2.1 | Demographic data of study patients

From January 1995 to March 2015, data from 405.559 patients with diabetes were collected. 65.147 children and adolescents of these patients had T1D and were at/under the age of 18 years. Among this age group, we differentiated between patients with T1D and IBD ( $n = 63$ ) and patients with T1D only ( $n = 65.084$ ) (Figure 1). Patients with IBD were searched for and identified either by ICD-10 code for IBD or written diagnosis. Only patients with confirmed diagnosis of IBD were included. Demographic data of study patients are displayed in Table 1.

For analysis, data on age, age at diabetes onset, diabetes duration, insulin dose (iu/kg/day), BMI, glycaemic control (HbA<sub>1c</sub>), percentage of patients with autoimmune thyroiditis, positive tissue transglutaminase (tTGA) or endomysial antibodies, dyslipidaemia, hypertension, insulin regimen, and steroid intake were collected (table 2).

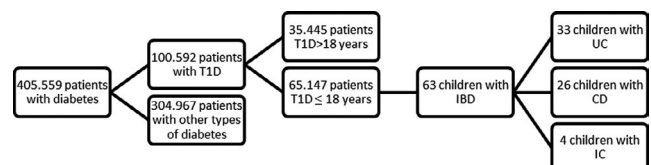


FIGURE 1 Selection of patients

**TABLE 1** Demographic data of study patients (unadjusted comparisons, presented as mean  $\pm$  SD)

	Patients with T1D and IBD (n = 63)	Patients with T1D only (n = 65.084)	p-values
Males/females (%)	50.8/49.2	52.7/47.3	0.7610
Age (years)	15.68 $\pm$ 3.08	14.0 $\pm$ 3.86	<0.0001
Age at T1D onset (years)	10.77 $\pm$ 4.32	8.59 $\pm$ 4.36	<0.0001
Diabetes duration (years)	4.91 $\pm$ 3.92	5.41 $\pm$ 4.20	0.3390
BMI SDS	-0.16 $\pm$ 1.13	0.27 $\pm$ 0.90	<b>0.0006</b>

Bold letters are used when p-values are significant ( $\leq$  0.05).

**TABLE 2** Comparison of patients after adjustment for age, sex and diabetes duration (estimated means  $\pm$  SE)

	Patients with T1D and IBD	Patients with T1D only	p-value
HbA1c (%)	8.16 $\pm$ 0.23	8.26 $\pm$ 0.01	0.656
HbA1c (mmol/mol)	65.80 $\pm$ 2.49	66.92 $\pm$ 0.08	0.656
Insulin dose (iu/kg/day)	0.90 $\pm$ 0.04	0.86 $\pm$ 0.00	0.300
BMI-SDS (kg/m <sup>2</sup> )	-0.15 $\pm$ 0.11	0.27 $\pm$ 0.00	< 0.001
Hypertension (%)	27 $\pm$ 0.06	31 $\pm$ 0.00	0.480
Dyslipidaemia (%)	30 $\pm$ 0.07	40 $\pm$ 0.00	0.207
Pump therapy (%)	32 $\pm$ 0.07	28 $\pm$ 0.00	0.481
Thyroid antibodies pos. (%)	13 $\pm$ 0.04	17 $\pm$ 0.00	0.505
tTGA positive (%)	25 $\pm$ 0.06	17 $\pm$ 0.00	0.140
Steroids (%)	22 $\pm$ 0.05	1 $\pm$ 0.00	<0.001

Bold letters are used when p-values are significant ( $\leq$  0.05).

## 2.2 | BMI

Body mass index was derived from weight in kilograms divided by squared height in metres. Age- and sex-specific BMI-reference values of 17,641 children and adolescents from the population-based German KIGGS study were used to calculate BMI-SDS.<sup>18</sup>

## 2.3 | Glycaemic control

Glycated haemoglobin A1c (HbA1c) values were measured locally. To correct for different laboratory methods, they were mathematically standardised to the Diabetes Control and Complication Trial (DCCT) reference range of 4.05–6.05% (21–43 mmol/mol).<sup>19</sup>

*Autoimmune thyroiditis* was diagnosed by positive thyroid antibodies (thyroid peroxidase and/or thyroglobulin antibodies).

*Dyslipidaemia* was defined as either taking lipid modifying drugs, or having decreased high-density lipoprotein (HDL) cholesterol values (< 35 mg/dl), or as increased values of total cholesterol (>200 mg/dl), low density lipoprotein (LDL) cholesterol (>130 mg/dl) or triglycerides (>150 mg/dl).

*Hypertension* was defined as the use of antihypertensive medication, or as increased systolic and/or diastolic arterial blood pressure, according to the KIGGS study.<sup>18</sup>

*Insulin regimen* was categorised as conventional insulin therapy (CT, two injection time-points per day), intensified insulin treatment (ICT,  $\geq$ 2 injection time-points per day) or continuous subcutaneous insulin infusion (CSII).

## 2.4 | Acute complications

Data on acute complications such as severe hypoglycaemia, hypoglycaemic coma and DKA were documented and summarised as events per patient year. Severe hypoglycaemia was defined as hypoglycaemia with the need for external help.

## 2.5 | IBD Prevalence

Published data on German IBD prevalence were used for comparison.<sup>8,9</sup> Prevalence for IBD among children and adolescents <18 years of age between 2000 and 2009 in Saxonia is 35.6/100,000 (95% CI 34.3–37.3), consisting of 11.7/100,000 with UC (95% CI 10.8–12.5), 21.3/100,000 with CD (95% CI 20.2–22.5) and 2.6/100,000 with IC (95% CI 2.2–3.0). Median age of Saxonian patients under 18 years with IBD was 13.9 years.<sup>10</sup>

## 2.6 | Statistical methods

The relative risk (RR) was calculated by MedCal, an open-access calculation program. The standardised prevalence ratio (ie the ratio of observed to expected numbers of patients with IBD in the diabetic cohort) served as a measure of RR. The expected numbers of patients with IBD were calculated as the sum of age-specific persons at risk in the type 1 diabetic cohort multiplied by corresponding national age-specific IBD prevalence rates. National data were taken from a Saxonian register.<sup>9</sup> Ninety-five per cent CIs for the RRs were estimated from the Wald test, assuming a Poisson distribution of the observed cases.

Diabetes patient follow-up data were analysed using the SAS 9.4 software (version 9.4; SAS Institute). Descriptive statistics (mean, SD and percentage) were calculated. For group comparison, Wilcoxon testing for continuous data and chi-square tests for categorical data were used. The Holm method was applied to adjust *p*-values for multiple comparisons. Multiple linear regression analysis for continuous variables (age, diabetes duration, BMI, HbA1c and insulin dose) and multiple logistic regression models for dichotomous variables (hypertension, dyslipidaemia, insulin regimen, positivity of thyroid antibodies, positivity of tTGA and steroid use) were applied for adjustment. Analysis of frequency of severe hypoglycaemia, hypoglycaemic coma and DKA was performed assuming a Poisson distribution.

Two-sided *p*-values <0.05 were considered to be statistically significant.

### 3 | RESULTS

#### 3.1 | Diabetes prevalence

The DPV pool (03/2015) contains 65.147 patients with T1D aged 18 years and below. We compared patients aged 18 years and younger than 18 years with T1D and IBD with those who had T1D only. The cohort of patients with both, T1D and IBD, consists of 63 children (33 children with ulcerative colitis, 26 children with Crohn's disease and four children with indetermined colitis, Figure 1). The percentage of patients with IBD among the patients with T1D ≤18 years is therefore 0.097%, the percentage of cases with ulcerative colitis 0.050%, Crohn's disease 0.040% and indetermined colitis 0.006%.

#### 3.2 | Relative risk for IBD

Comparing our data to IBD prevalence data from Saxony, the prevalence for IBD in T1D patients is higher than in the general population. The RR for a patient with T1D to develop any subtype of IBD until his/her 18th birthday was 3.25 (CI 95% 2.17–4.88, *p* < .001). The highest RR is related to ulcerative colitis. Therefore, a patient with T1D has a 4.67-fold risk to develop ulcerative colitis as a comorbidity. Mean age of patients with T1D and IBD was 15.7 years; mean age of patients with IBD without T1D is 13.0 years (Table 3).

#### 3.3 | Comparison of T1D patients with and without IBD

In a *linear regression model*, after adjustment for age, sex and diabetes duration, no differences between both groups (estimated means ± SE) were seen neither in glycaemic control (HbA1c 8.16% ± 0.23 vs. 8.26 ± 0.01; 65.80 mmol/mol ± 2.49 vs. 66.92 ± 0.08, *p* = .656) nor in insulin requirement (units per kg per

**TABLE 3** Relative risk for IBD among patients with T1D <18 years

Patients	Relative risk	<i>p</i> -values
All patients with IBD	3.25 (CI 95% 2.17–4.88)	<0.0010
UC	4.67 (CI 95% 2.35–9.26)	<0.0001
Crohn's disease	2.06 (CI 95% 1.17–3.65)	<0.0127
IC	1.20 (CI 95% 0.57–2.54)	0.6260

Bold letters are used when *p*-values are significant (≤ 0.05).

day 0.90 ± 0.04 vs. 0.86 ± 0.00, *p* = .300). A significant difference between both groups, however, was found in BMI-SDS (−0.15 ± 0.11 vs. 0.27 ± 0.00, *p* < .001) (Table 2).

In a *logistic regression model*, after adjustment for age, sex and diabetes duration, both groups were compared and no differences were found concerning hypertension, dyslipidaemia, insulin regimen (pump therapy), the coexistence of thyroiditis or the presence of tTGA (Table 2).

However, a significant difference was found in steroid intake. The proportion of patients who took steroids at least once was significantly higher in the group of patients suffering from both diseases (22% vs. 1%, *p* < .001) (Table 2).

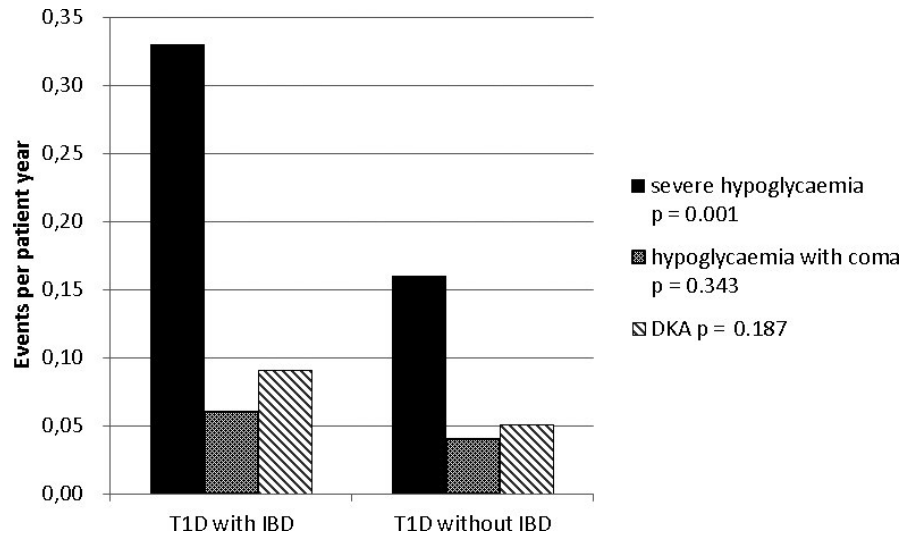
In a *Poisson regression model*, after adjustment for age, sex and diabetes duration, no differences between both groups were seen, neither in DKA nor in hypoglycaemic coma (Figure 2). However, a significant difference was found in severe hypoglycaemia. Patients with T1D and IBD reported 0.33 ± 0.22 events of severe hypoglycaemia per year, whereas patients with T1D only had 0.16 ± 0.01 events, *p* = .001 (Figure 2).

### 4 | DISCUSSION

In this study, we show that IBD occurs more frequently in patients with T1D than in the general population of the same age group (≤18 years). We see that patients with both diseases, IBD and T1D, are older at the onset of T1D than patients with T1D only. We find differences in BMI-SDS, the intake of steroids, and the frequency of severe hypoglycaemia between T1D patients with and without IBD. Patients with both diseases, T1D and IBD, have a lower BMI-SDS, take steroids more often and experience more events of severe hypoglycaemia. Although the patients with T1D and IBD take steroids more often and although a rise of glucose is a side effect of steroids, they suffer from severe hypoglycaemia more often. Our interpretation is that these effects are caused by malabsorption, due to bowel inflammation.

Our data are in consistence with most epidemiological studies showing an overlap between T1D and IBD,<sup>11–14</sup> except for an US study using patient-level medical and drug claims to trace back the diagnosis of IBD and T1D.<sup>16</sup> Kappelman et al<sup>13</sup> found an elevated risk for paediatric patients with UC to develop T1D (OR 2.7, 95% CI 1.1–6.6) but not for patients with CD.

**FIGURE 2** Acute complications (adjusted for age, sex and diabetes duration)



Recent observations suggest a rise in IBD cases by the use of dipeptidyl peptidase-4 (DPP-4) inhibitors in patients with type 2 diabetes (T2D), reaching a peak after three to 4 years of treatment.<sup>20</sup> DPP-4 inhibitors increase insulin secretion by inhibiting the degradation of glucagon-like peptide (GLP-1).<sup>21</sup> A recent nationwide cohort study from Denmark shows an increased risk of T2D in IBD.<sup>22</sup> The risk was highest the first year after a diagnosis of IBD (95% CI 4.16–4.38) and remained increased for more than 20 years following the diagnosis (95% CI 1.16–1.38).<sup>22</sup> Enzymes in the insulin secretion pathway might play a role in the pathogenesis of IBD.<sup>20</sup>

Our data indicate an increased prevalence of IBD among patients with T1D and therefore an increased risk among the patients with T1D to develop IBD. The same observation has been described for other autoimmune diseases such as juvenile arthritis<sup>23</sup> and multiple sclerosis.<sup>24</sup> Aetiological causes including genetics, epigenetics, immunological and/or environmental factors may be shared.

Type 1 diabetes and IBD, moreover its co-occurrence, have multiple life-long effects. Adult IBD patients with concomitant diabetes have been shown to have a significantly higher morbidity and mortality over a 10-year period compared to patients with IBD alone.<sup>25</sup> Some of the potential mechanisms to explain these adverse outcomes include additional alterations in the intestinal microbiome in the combined disease group, a chronic systemic inflammation and overlapping immune activity.<sup>25</sup> Inflammation of the bowel can lead to malabsorption, malnutrition, failure to thrive, a low BMI and an increased risk of hypoglycaemia, as shown in this study of children with T1D.

To summarise: As in all chronic diseases, it is important to diagnose and treat as early as possible. Although the prevalence is extremely low, we suggest to be aware of IBD in patients with T1D and screen for IBD in the presence of gastrointestinal symptoms. Faecal calprotectin represents an easy, non-invasive biomarker for an early detection of IBD in patients with T1D. By early detection and consistent treatment, adverse factors such as inflammation, malabsorption and severe hypoglycaemia may be avoided.

## ACKNOWLEDGEMENTS

We thank the German Center for Diabetes Research (DZD, grant number FKZ 82DZD01402), German Diabetes Association (DDG) and Robert Koch Institute (RKI) for their support. I thank my team at the children's hospital Graz, especially Elke Fröhlich-Reiterer and Kerstin Faninger, for their supervision and support.

We thank all centres participating in the DPV initiative and contributing their data to this study. For a full list of centres, please see the online supplementary file on our website.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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**How to cite this article:** Jasser-Nitsche H, Bechtold-Dalla Pozza S, Binder E, et al. Comorbidity of inflammatory bowel disease in children and adolescents with type 1 diabetes. *Acta Paediatr*. 2021;110:1353-1358. <https://doi.org/10.1111/apa.15643>