Bone Fractures in Children and Young Adults With Type 1 Diabetes: Age Distribution, Fracture Location, and the Role of Glycemic Control

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ABSTRACT

Type 1 diabetes (T1D) is a known risk factor for fractures, but the underlying pathophysiology is still not fully understood. This study aims to define age peaks and frequent fracture sites of children and young adults with T1D. Additionally, associations of fractures with metabolic and lifestyle factors as well as with additional complications in individuals with T1D were analyzed. A total of 750 individuals with T1D aged ≤25 years with fractures were matched to 3750 patients with T1D without fractures by demographics and insulin regimen. Hemoglobin A1c (HbA1c) values were compared using linear regression, and logistic regression was used to calculate odds ratios (OR) for fractures in individuals with acute complications and diseases. Median (Q1–Q3) age was 12.7 (9.9 to 14.9) years in individuals with fractures and 16.3 (12.6 to 17.8) years in the entire control group with 65% versus 53% males. Peak age for fractures was 7 to <15 years in males and 9 to <11 years in females, which is earlier than reported for the general population. HbA1c (%) was significantly higher in individuals with fractures than in controls (difference of estimated means: 0.26%; 95% confidence interval [CI] 0.07–0.46), especially in postpubertal females (0.68; 0.10–1.26). Significantly higher odds for fractures were observed in individuals with severe hypoglycemia (OR = 1.90; 95% CI 1.47–2.47), especially in prepubertal females (OR = 2.81; 1.21–6.52) and postpubertal males (2.44; 1.11–5.38), celiac disease (2.02; 1.35–2.93), and with a history of smoking (1.38; 1.02–1.88). The peak age of fractures appears to be earlier in T1D than in the general population. Poor glycemic control is related to fractures, even before puberty. Associations of HbA1c and severe hypoglycemia with fractures highly depend on age and sex. © 2021 The Authors. Journal of Bone and Mineral Research published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

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Introduction

Bone fractures are common injuries in children and occur most frequently at about 10 to 14 years of age, with boys having more fractures and a slightly later peak than girls. Risky behavior, bone remodeling during puberty, and growth are main reasons for fractures in children. Most fractures during childhood occur at play or sports, and the upper limb is affected most frequently, followed by the lower limb. Other fracture sites are rare in healthy children. Additionally, previous fractures are an important risk factor for further fractures and therefore some children seem to be at higher risk. This might be attributable to differences in bone development during puberty.

Type 1 diabetes (T1D) can alter or delay pubertal development, especially in those with poor glycemic control, which may lead to increased fracture risk due to lower bone mineral density (BMD), lower trabecular volume, and higher bone turnover than in healthy children. Altered pubertal development could also influence the behavior of children with T1D. However, it is less clear whether children with T1D sustain fractures at other ages or fracture sites.

In adults with T1D, worse glycemic control reflected by high hemoglobin A1c (HbA1c) is a reason for impaired bone quality and higher fracture risk. In children, there are some studies reporting an association between high HbA1c and reduced BMD, and one very recent study demonstrated altered microarchitecture of bones even before decreased BMD. However, only a few studies investigated the association with fracture risk, especially in prepubertal children, in whom diabetes duration is short and other mechanisms might have a stronger effect on fractures risk.

Severe hypoglycemia was described previously as a potential risk factor for fractures in adults with T1D, but data on the relation between severe hypoglycemia or diabetic ketoacidosis (DKA) and fracture risk in children are lacking. Further, the associations of body mass index (BMI) or concomitant pathology such as celiac disease with fracture risk in children with T1D is still controversial.

The aim of this study was to evaluate the age distribution and most common fracture sites in children and young adults with T1D. Additionally, associations of fractures with metabolic control, physical activity, and smoking, as well as diabetes complications and comorbidity among children and young adults with T1D were investigated.

Materials and Methods

Data collection and participants

This analysis is based on data from the prospective, multicenter diabetes patient follow-up registry Diabetes Prospective Follow-up (DPV; Diabetes-Patienten-Verlaufsdokumentation), which is a standardized electronic health record developed at the Institute of Epidemiology and Medical Biometry, Ulm University, Germany. The initiative and the analysis of anonymized data were approved by the Ethics Committee of Ulm University (approval number 202/09) as well as by local review boards.

Five hundred one diabetes centers from Germany, Austria, Switzerland, and Luxembourg provided pseudonymized data on diabetes treatment and outcome until March 2020, representing an estimated coverage of more than 80% of children with diabetes in Germany, Austria, and Luxembourg. Twice a year, participating centers report de-identified data for central analysis at Ulm University. The transferred data are checked for inconsistency or implausibility and reported back to the respective centers for correction, if necessary.

Individuals recorded in the DPV initiative were included if they had a clinical diagnosis of T1D, were aged ≤25 years, and were ≥0.5 years at diabetes onset. Children and young adults who had a documented fracture that occurred more than 12 months ago or that was documented as “status post” fracture with unknown time lag were excluded because in those cases no reliable association between the fracture and actual diabetes-related outcomes was possible. Additionally, individuals without current data on HbA1c or insulin regimen were excluded (Fig. 1).

Group selection and evaluation period

Individuals in the study population were allocated to the fracture group if they had at least one documented fracture at any site with documented time of occurrence within the last 12 months. Children and young adults who had no documented fracture were allocated to the control group.

For the control group, the evaluation period included the last documented year of treatment, whereas for the fracture group, data for 1 year before the most recent fracture were evaluated. Data were aggregated if the subject had more than one visit during the evaluation period.

Age distribution and fracture sites compared with the general population

The age-related distribution of fractures is presented as proportion of individuals with fractures during the respective age category. Based on a previous study on healthy children from New Zealand, age categories were defined as ≤5, 5 to ≤7, 7 to ≤9, 9 to ≤11, 11 to ≤13, 13 to ≤15, 15 to ≤18, 18 to ≤21, and ≥21.

The distribution of fracture sites is presented as percentage of all fractures within the respective group. Because some individuals had multiple fractures at different sites, the absolute number of documented fractures was 794 among 750 individuals. We divided three age groups representing different stages of development: female (prepubertal ≤11; pubertal >11 to 15; postpubertal >15 to 25 years) and male (≤12; pubertal >12 to 16; postpubertal >16 to 25 years). Patients with documented Tanner staging were assigned to the corresponding groups regardless of age. Patients without Tanner staging were classified by age only.

Propensity score matching

A total of 85,734 individuals fulfilled the inclusion criteria; 750 of them had a documented fracture and were assigned to the fracture group (Fig. 1). Individuals with fractures differed largely from controls in demographic characteristics (Table 1). For this reason, we matched the 750 children and young adults with fractures to the control group based on age, sex, diabetes duration, migration background, and insulin regimen. The variables sex, migration background, and insulin regimen were matched exactly. Age and diabetes duration were included continuously as well as categorized (age ≤11, >11 to 15, >15 years; diabetes duration ≤2, >2 to 6, >6 years) into the non-parsimonious propensity score. One-to-five matching was conducted (greedy-matching algorithm) with a caliper width of 0.2. Standardized differences were assessed before and after matching to evaluate balancing of covariates between the matched cohorts. A standardized difference of less than 10% for a baseline covariate reveals a
negligible imbalance.\textsuperscript{(20,21)} Five separate controls could be identified for each of the 750 individuals, resulting in a final study cohort of 3750 individuals for further analyses.

Patient data

For descriptive comparison between fracture group and control group (entire and matched), the matching variables sex,
Table 1. Description of Study Population Before and After Matching, Fracture Group Versus Control Group

| Matching variables                      | Entire control group | Fracture group | Matched control group | Standardized difference before matchinga | Standardized difference after matchinga |
|-----------------------------------------|----------------------|----------------|-----------------------|------------------------------------------|------------------------------------------|
| Sex (% male)                            | 53.1, n = 84,984     | 64.7, n = 750  | 64.7, n = 3750        | 0.23744*                                 | 0.00000                                  |
| Migration background (%)                | 17.6, n = 84,984     | 15.2, n = 750  | 15.2, n = 3750        | 0.06545                                  | 0.00000                                  |
| Insulin regimen (% pump)                | 38.0, n = 84,984     | 29.2, n = 750  | 29.2, n = 3750        | 0.18651*                                 | 0.00000                                  |
| Age (years)                             | 16.3 (12.6–17.8), n = 84,984 | 12.7 (9.9–14.9), n = 750 | 12.7 (9.8–14.9), n = 3750 | -0.69243*                              | -0.00754                                  |
| Diabetes duration (years)               | 5.5 (2.4–9.3), n = 84,984 | 3.2 (0.8–6.7), n = 750 | 3.0 (0.9–6.0), n = 3750 | -0.44771*                              | 0.05074                                  |
| Other characteristics                   |                      |                |                       |                                          |                                          |
| Age at diabetes onset (years)           | 9.1 (5.3–12.4), n = 84,984 | 8.1 (4.9–11.3), n = 750 | 8.4 (5.1–11.5), n = 3750 | <0.001**                                | 1.00                                     |
| Height-SDS (–0.68–0.73), n = 78,429    | 0.24 (–0.54–0.94), n = 722 | 0.12 (–0.57–0.84), n = 3624 | <0.001**                                | 0.535                                    |
| Weight-SDS (–0.30–1.00), n = 78,429    | 0.26 (–0.39–0.90), n = 722 | 0.23 (–0.41–0.88), n = 3624 | 0.043**                                  | 1.00                                     |
| BMI-SDS (–0.29–0.96), n = 78,429       | 0.21 (–0.44–0.83), n = 722 | 0.22 (–0.40–0.83), n = 3624 | 0.002**                                  | 1.00                                     |
| HbA1c (%)                               | 7.9 (7.1–9.1), n = 84,984 | 7.9 (7.1–9.2), n = 750  | 7.8 (6.9–8.9), n = 3750 | 1.00                                    | 0.017**                                  |
| HbA1c (mmol/mol)                        | 7.9 (54–76), n = 84,984 | 7.9 (54–77), n = 750  | 7.8 (52–74), n = 3750 |                                          |                                          |
| % doing sports                          | 69.8, n = 55,949     | 77.0, n = 525   | 73.8, n = 2510        | 0.002**                                  | 1.00                                     |
| % smoking                               | 13.3, n = 84,984     | 7.5, n = 750    | 5.5, n = 3750         | <0.001**                                 | 0.456                                    |
| % with severe hypoglycemia              | 7.1, n = 84,862      | 11.5, n = 750   | 6.4, n = 3746         | <0.001**                                 | <0.001**                                 |
| % with DKA                              | 3.5, n = 84,899      | 4.5, n = 750    | 5.6, n = 3746         | 0.435                                   | 1.00                                     |
| % with celiac disease                   | 15.9, n = 84,984     | 24.1, n = 750   | 13.6, n = 3750        | <0.001**                                 | <0.001**                                 |

BMI = body mass index; HbA1c = hemoglobin A1c; SDS = standard deviation score (according to KiGGS reference data for individuals aged <18 years; according to AGA reference data for individuals aged ≥18 years); CG = control group; migration background = the participant or one of his/her parents were born outside of Germany, Austria, Switzerland, or Luxembourg. Data are presented as median (lower quartile; upper quartile) or as proportion (%) with number of individuals. *Standardized difference of fracture group minus control group before and after matching. **p value between fracture group and entire control group (left column) or matched control group (right column). *Significantly different (p < 0.001) before matching. **Significantly different (p < 0.05) after matching.

migration background, age, diabetes duration, and insulin regimen, as well as further baseline characteristics such as age at diabetes onset, height, weight, body mass index (BMI) and HbA1c (% and mmol/mol) were analyzed.

For height, weight, and BMI, standard deviation scores (SDS) based on KiGGS reference data (individuals aged <18 years)\(^{22}\) or AGA reference data (individuals aged ≥18 years)\(^{23}\) were used. HbA1c values were standardized to the Diabetes Control and Complications Trial (DCCT) reference range of 4.05% to 6.05% (20.7 to 42.6 mmol/mol) using the multiple of the mean transformation method to account for different laboratory methods.\(^{24}\) Severe hypoglycemia was defined as a state in which the patient required help by another person and severe hypoglycemia with coma as loss of consciousness.\(^{25}\) DKA was defined as pH <7.3 and/or bicarbonate <15 mmol/L.\(^{26}\) Migration background was determined as the participant itself or on if his/her parents were born outside of Germany, Austria, Switzerland, or Luxembourg. Smoking was defined as reported current or previous smoking yes/no. Sport per week was defined as club sports (individual exercise at home was not documented).\(^{27}\) If no information on sport was available, we considered this as no sports. Celiac disease was defined as a documented diagnosis in the DPV registry or as positive transglutaminase antibodies.

Statistical analysis

All statistical analyses were generated using SAS (SAS Institute Inc., Cary, NC, USA) version 9.4, build TS1M5, on a Windows Server 2016 mainframe. Descriptive statistics were performed for matching variables and baseline characteristics. The results are shown as median with quartiles for continuous variables using the Kruskal-Wallis test to compute unadjusted p values and as proportions for binary variables using the chi-square test. Standardized differences between the fracture group and the entire control group or the matched control group are additionally shown.
HbA1c (%) was analyzed using linear regression calculating the difference of estimated means (LSMeans) together with lower (LCI) and upper (UCI) 95% confidence intervals between the fracture group and the matched control group. These models were stratified by sex and age groups.

For the parameters BMI category, sports, smoking, severe hypoglycemia, severe hypoglycemia with coma, DKA, and celiac disease, logistic regression models were implemented to calculate odds ratios (OR) with 95% CI for fractures (yes/no) among matched samples. BMI was divided into three groups: normal...
weight (reference group) with BMI 20 to <25 or standardized BMI (BMI-SDS) –1.28 to <1.28, underweight (BMI <20 or BMI-SDS <–1.28), and overweight (BMI ≥25 or BMI-SDS ≥1.28). Sports was categorized as no sports (reference group), 1 to 2 times per week, and >2 times per week. Severe hypoglycemia, severe hypoglycemia with coma, and DKA were defined as at least one event during the evaluation period (yes/no). Smoking and celiac disease were also binary variables. Logistic regression models for severe hypoglycemia and celiac disease were additionally implemented stratified by age categories and sex.

For all regression models, the observed margin option was used for calculation of least-squared means. Two-sided \( p < 0.05 \) indicated a significant difference.

### Results

#### Study population

Among all individuals registered in DPV, 85,734 were aged ≤25 years, had a diagnosis of T1D, and fulfilled the inclusion criteria. Within the study population, 750 (0.9%) had at least one recent fracture (Fig. 1).

Among this entire cohort, in the fracture group, the proportion of males was higher than in the control group (65% versus 53%), individuals with fractures were younger, younger at diabetes onset, taller, had lower weight-SDS and BMI-SDS, had a shorter diabetes duration, and used pump therapy less often compared with the control group (Table 1).

### Age distribution and fracture sites compared with the general population

A total of 794 fractures at different sites in 750 individuals were documented. In males, the proportion of fractures increased with age up to 7 to <9 years as a first peak (Fig. 2A). The proportion of fractures then stayed relatively constant and rose slightly to a second peak at 13 to <15 years and declined subsequently. In females, the proportion of fractures revealed one clear peak at 9 to <11 years and then a decline up to <21 years (Fig. 2A).

Fig. 2B shows the age distribution of fractures in healthy children from New Zealand, who were followed from birth to the age of 18 years, with identical age groups. For males, there was only one clear peak at 13 to <15 years. In females, the curve was similar to our curve, but the age peak was about 2 years later.

The most frequent fracture site among all age groups in our cohort was the upper limb (50.0% to 65.3%) with the highest proportion in prepubertal children, followed by the lower limb (21.0% to 29.2%). Face fractures stayed relatively constant at 5% to 6.5% over all age groups. Spine and pelvis fractures were extremely rare in prepubertal and pubertal children but represented 7.2% (spine) and 5.0% (pelvis) of all fractures in postpubertal individuals (Supplemental Fig. S51).

### Results of matched cohort

All matching variables in the matched control group did not differ significantly from individuals with fractures and all standardized differences were <0.1 (Table 1). Height-SDS, weight-SDS,
Celiac disease increased the chance for fractures in prepubertal and in pubertal children for both sexes.

**Discussion**

In the present study, we detected associations between higher HbA1c values and fractures, depending on age and sex: In females with poor metabolic control, fracture rate was increased for all age groups; in males, this effect was restricted to prepuberty. Severe hypoglycemia, severe hypoglycemia with coma, concomitant celiac disease, and smoking were associated with higher odds for fractures. Age distribution of fractures was similar to data from the general population, but the peak age was slightly earlier. Localization of fracture sites in children with type 1 diabetes was similar to healthy children, with few exceptions: More hip, spine, and skull/face fractures were observed in children and young adults with T1D.

The proportion of males with fractures was 65% and therefore slightly higher than in healthy children with a reported proportion between 55% and 63%. In the entire cohort, individuals with fractures were slightly taller than controls. Because of the considerable difference in mean age and multiple effects of type 1 diabetes on growth, this must be interpreted with caution.

The peak age for fractures in our cohort was 9 to <11 years for females and 7 to <15 years for males, which is slightly earlier (females) or longer with an earlier start (males) compared with healthy children and depicts that fractures might occur slightly earlier in children and adolescents with T1D. Because we were not able to match our cohort to the population on healthy children from New Zealand in terms of pubertal status, the fact that diabetes can alter or delay pubertal development could

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**Table 2. OR for Fractures Associated With Acute Complications, Comorbid Conditions, and Lifestyle**

| Outcome | No. of matched sets | OR (95% CI) | p Value |
|---------|---------------------|-------------|---------|
| BMI (ref = normal weight) | 670 | 1.29 (0.87–1.90) | 0.277 |
| Underweight | | 1.06 (0.79–1.42) | 0.886 |
| Overweight | | 1.38 (1.02–1.88) | 0.039* |
| Smoking | 750 | 1.21 (0.97–1.52) | 0.104 |
| Sports (ref = no sports) | 750 | 1.21 (0.97–1.52) | 0.104 |
| 1–2×/week | | 1.18 (0.93–1.48) | 0.239 |
| >2×/week | | 1.18 (0.93–1.48) | 0.239 |
| SH | 746 | 1.90 (1.47–2.47) | <0.001* |
| Female prepuberteral | 99 | 2.81 (1.21–6.52) | 0.016* |
| Female pubertal | 113 | 1.91 (1.02–3.58) | 0.044* |
| Female postpubertal | 53 | 1.41 (0.54–3.69) | 0.481 |
| Male prepuberteral | 156 | 1.59 (0.87–2.91) | 0.135 |
| Male pubertal | 240 | 1.90 (1.23–2.94) | 0.004* |
| Male postpubertal | 85 | 2.44 (1.11–5.38) | 0.027* |
| SH with coma | 746 | 2.80 (1.90–4.12) | <0.001* |
| DKA | 746 | 0.80 (0.55–1.15) | 0.229 |
| Celiac disease | 750 | 2.02 (1.67–2.45) | <0.001* |
| Female prepuberteral | 99 | 2.40 (1.47–3.92) | <0.001* |
| Female pubertal | 113 | 1.70 (1.03–2.81) | 0.040* |
| Female postpuberteral | 53 | 1.55 (0.75–3.21) | 0.233 |
| Male prepuberteral | 157 | 2.63 (1.76–3.94) | <0.001* |
| Male pubertal | 241 | 2.06 (1.46–2.92) | <0.001* |
| Male postpuberteral | 87 | 1.30 (0.69–2.46) | 0.423 |

OR = odds ratio; CI = confidence interval; BMI = body mass index; SH = severe hypoglycemia; DKA = diabetic ketoacidosis; ref = reference group.

Shown are the estimated odds ratios with 95% CI. Results from logistic regression models, matched for age, sex, diabetes duration, migration background, and insulin regimen.

*Significantly different (p < 0.05).

BMI-SDS, and age at onset were not significantly different either, but HbA1c was slightly higher in individuals with fractures.

**Metabolic control**

Fig. 3 shows differences in HbA1c between the matched cohorts. HbA1c was significantly higher in children and young adults with fractures than in matched controls (8.4 [8.3–8.5] versus 8.1 [8.1–8.2] %, p < 0.001). Stratified by sex and age categories, significant differences were observed in prepuberteral (8.2 [7.8–8.5] versus 7.8 [7.6–7.9] %, p = 0.035), pubertal (8.6 [8.3–9.0] versus 8.2 [8.0–8.4] %, p = 0.031), and in postpubertal females (9.1 [8.6–9.7] versus 8.5 [8.2–8.7] %, p = 0.023) as well as in prepubertal males (8.1 [7.9–8.4] versus 7.7 [7.6–7.9] %, p = 0.028). No significant differences were observed in pubertal and postpubertal males.

BMI, lifestyle, and complications

No significant differences could be found either for underweight or for overweight subjects compared with the normal-weight group (Table 2).

Previous or current smoking enhanced the odds for fractures significantly, while no association between sport and fractures was observable (Table 2).

In terms of complications, no association between DKA and fractures was observable, but severe hypoglycemia (OR = 1.90 [1.47–2.47]), severe hypoglycemia with coma (OR = 2.80 [1.90–4.12]), and celiac disease (OR = 2.02 [1.67–2.45]) increased the odds for fractures significantly (all p values < 0.001; Table 2). In females, severe hypoglycemia resulted in significantly higher odds for fractures in prepuberteral and pubertal stages, whereas males had higher odds for fractures during puberty and postpuberty. Celiac disease increased the chance for fractures in prepuberteral and in pubertal children for both sexes.
have contributed to different age peaks of fractures between healthy children and children with T1D. Most fractures were located at the upper and lower limb. However, the proportion of other fracture sites especially of the skull/face, spine, and hip was higher compared with children in the general population. A Norwegian study on 15- to 18-year-old healthy adolescents reported 66.2% of fractures being located at the upper limb and 29.4% at the lower limb, which left 4.3% at other sites. In another study on healthy Lebanese children between 8 and 18 years of age, the proportion of upper (71.3%) and lower limb (26.1%) fractures together was even higher with only 2.6% of other fracture sites. In contrast, we observed fractures that were not located at the upper or lower limb in 9.5% of pubertal children and in 21.1% of postpubertal adolescents. This could implicate that diabetes-related effects on bone quality enhance the risk for fractures in unusual sites in children and young adults. This is supported by a recent study that found an altered bone microarchitecture in young patients with T1D compared with healthy controls. In young children, skull and facial fractures, as well as spine fractures, could be related to child abuse, which is known to be more prevalent in children with chronic conditions such as T1D. Hip fractures are very rare in healthy children (<1%) and mostly the result of accidents with high-energy trauma. Insulin-treated diabetes carries the risk for hypoglycemia, a complication that can lead to high-energy trauma due to falls. However, falls on plane surfaces normally should not entail fractures in children. We could detect 15 fractures that resulted from hypoglycemia and led to hospitalization, but most of them were fractures of the upper limb. It must be assumed that not all hypoglycemic events and fractures were documented and not all of them led to inpatient stays. Another explanation for the unexpected high proportion of hip fractures in our cohort might be that serious and uncommon fractures such as hip fractures were documented more frequently compared with common fractures (for example, at the forearm).

Some studies report a relation between high HbA1c and BMD in pediatric T1D, but little is known about the direct association of glycemic control with fracture risk in children and adolescents with T1D. One study followed individuals with newly diagnosed T1D (age at diagnosis 0 to 60 years) over 20 years and found a significant relationship between HbA1c and fractures, especially in those who were between 0 and 10 years of age (hazard ratio with 95% CI per 1-unit increase of HbA1c (%) 1.86 [1.35–2.56], p < 0.001) or between 10 and 20 years of age (1.67 [1.22–2.29], p = 0.001) at diagnosis. However, no information on age at time of fracture occurrence was provided; therefore, many of these individuals could have been adults when fractures occurred. Our results indicated that in females at all stages (especially postpubertal) and in prepubertal males, high HbA1c is associated with fractures. In postpubertal adolescents, this is in line with other findings on worse glycemic control increasing fracture risk. Associations between HbA1c and fractures in prepubertal children implicate that even in very young individuals, optimal glycemic control is crucial to prevent fractures. The ISPAD (International Society for Pediatric and Adolescent Diabetes) clinical consensus guidelines reported a higher risk for fractures in children and adolescents with T1D and elevated HbA1c as a potential risk factor. However, the authors analyzed children and adolescents aged 0 to 19 years without further age stratification and the effect was smaller than in adults with T1D. The relation between glycemic control and fractures already in prepubertal children with T1D in our cohort is therefore an important, novel finding. In male children and adolescents, risky behavior, especially in pubertal and postpubertal stages, might have a higher influence on fracture risk than in females, and therefore good glycemic control could be more important in females than in males, which is in line with a study from the UK that reported a higher hazard ratio for fractures related to elevated HbA1c in females than in males with T1D.

It must be mentioned that other aspects could have contributed to fracture risk, especially in prepubertal children, such as genetics, nutrition, or maternal diabetes, as suggested in a recent study. We could not detect differences in parental T1D between the fracture and control group, but the proportion of children being diagnosed with T1D within the first year of life (2.0% versus 1.0%) and the first 3 years of life (13.3% versus 12.0%) was higher in the fracture group than in controls. This could support the assumption that early manifestation of T1D can affect bone accrual. Additionally, a recent meta-analysis found lower bone mineral density in youths with T1D independently from diabetes duration and HbA1c, which could be another reason for fracture risk in children with T1D, but underlying reasons are still not completely understood.

Another aspect that must be kept in mind is that eating disorders are related to fractures in adolescents, especially in girls, and T1D is known to be associated with disturbed eating behavior. Even in our cohort, the proportion with fractures, with versus without eating disorders, was 60 (38 to 79) % versus 16 (14 to 18) %, p < 0.001 in females, whereas no significant difference could be found in males (31 [12 to 59] % versus 17 [15 to 18] %, p = 0.183). However, these results should be interpreted with caution as only 33 (20 female, 13 male) individuals with eating disorders were documented in our matched cohort.

Previous results on BMI and fracture risk in healthy children are controversial. There is evidence that overweight and obese children have higher risk for upper and lower limb fractures, whereas another study reported decreased fracture risk in obese children and increased fracture risk in children with underweight. In our cohort of children and young adults with T1D, no significant relation between BMI and fractures could be detected.

Frequency of physical activity was not associated with fractures in the present study. Normally, most fractures during childhood occur at sports. Snowboarding as well as playing handball or soccer are especially associated with fractures. This could be a hint that diabetes-related aspects such as high HbA1c or hypoglycemia might be more important in children, adolescents, and young adults with diabetes than doing sports. On the other hand, moderate physical activity can also lead to a higher muscle mass and a better bone structure, which would lower the fracture risk. Perhaps fewer children with T1D perform those high-risk sports and the positive and negative influences of physical activity on fracture risk neutralize in young individuals with T1D.

Smoking, active or passive, was reported to impair the development of peak bone mass in children. This is in line with our results on current or previous smoking. We found higher odds for fractures in individuals with at least one event of severe hypoglycemia or severe hypoglycemia with coma but not with DKA. Another study reported higher odds for fractures in adults with T1D and hypoglycemia compared with individuals with T1D but no history of hypoglycemia (OR = 1.58, 95% CI 1.27–1.97). No study could be found on the association of severe hypoglycemia or DKA with fracture risk in children with T1D. These results together with our findings on children and young adults suggest that severe hypoglycemia,
but not DKA, is a risk factor for fractures in people with T1D independently from age. However, in females, the odds for fractures associated with severe hypoglycemia were highest prepubertal, whereas in males, opposite results were found. Together with our findings on HbA1c, this could implicate that in male children and young adults with T1D, poor glycemic control is the most important factor in the very young, but prevention of hypoglycemia becomes more important with higher age, whereas in females, these effects are inverse. Celiac disease is known to affect bone health,[43] but results on fracture risk are controversial.[18,44] Even in children with T1D, one study did not find an association between celiac disease and fracture risk.[45] In the present study, we could confirm that children and young adults with T1D and concomitant celiac disease have higher odds for fractures, especially prepubertal, and therefore at least the combination of these two diseases is associated with fracture risk. Unfortunately, we were not able to investigate the vitamin D status, but vitamin D deficiency could be a reason for the higher odds of fractures in individual with celiac disease.[46]

This study was based on real-life data from more than 80% of the pediatric patients with T1D from Germany, Austria, and Luxembourg and provides new insights into the relationship between glycemic control and fracture risk in children, adolescents, and young adults, stratified by age and sex. Similar data have not been reported before. Additionally, representative results on age distribution and location of fracture sites among 794 documented fractures in children and young adults with T1D could be presented and compared with healthy children. However, in this diabetes registry, injuries at the locomotor system might be incompletely documented, which could have affected the distribution of age at fracture and fracture sites. Therefore, no assumption on prevalence of fractures was made. Because we used data from a diabetes registry, classification of prepubertal, pubertal, and postpubertal period could not be based on Tanner stages in all children; age groups were used as a proxy when pubertal development was not documented.[47] It must be kept in mind that pubertal development can differ largely between individuals. As we compared unequal groups (fracture and control) in terms of group size and baseline characteristics, we matched the cohort to homogenize confounders such as age, sex, migration background, diabetes duration, and insulin regimen. The number of parameters available in a registry is limited, and the DPV registry is focused on diabetes-related parameters. When evaluating the data on fractures, information on general physical activity as well as on parameters of bone metabolism, especially on 25-OH(D) concentrations, would be desirable. Unfortunately, this information could not be taken from the register. For most fractures, we could not ascertain whether they were directly caused by hypoglycemic events and therefore the reason for the association between hypoglycemia and fractures in this young T1D cohort remains in large part unclear.

Results of the present study implicate that good glycemic control and avoidance of acute complications is crucial to reduce the risk of fractures in children and adolescents with T1D. This is especially true for early childhood and seems to be more important in females than in males.

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Research data are not shared.

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Disclosures

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