This is the peer reviewed version of the following article: Comparing clinical characteristics of pediatric patients with pancreatic diabetes to patients with type 1 diabetes – a matched case-control study, which has been published in final form at <https://doi.org/10.1111/pedi.12894>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

Comparing clinical characteristics of pediatric patients with pancreatic diabetes to patients with type 1 diabetes – a matched case-control study

Running title: pancreatic diabetes in pediatric patients

S. Lanzinger^{1,2}, A. Welters³, A. Thon⁴, K. Konrad⁵, T. Kapellen⁶, J. Grulich-Henn⁷,
D. Raddatz⁸, R. W. Holl^{1,2}

¹Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Ulm, Germany

²German Center for Diabetes Research (DZD), München-Neuherberg, Germany

³Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

⁴Clinic for Pediatric Pneumology and Neonatology, Hannover Medical School, Hannover, Germany

⁵Department of Pediatric and Adolescent Medicine, Elisabeth-Hospital Essen, Essen, Germany

⁶Department of Pediatrics, University of Leipzig, Hospital for Children and Adolescents, Leipzig, Germany

⁷Department of Pediatrics, University of Heidelberg, Heidelberg, Germany

⁸Clinic for Gastroenterology und Gastrointestinal Oncology, University Medical Center Goettingen, Germany

Corresponding Author:

Stefanie Lanzinger, PhD

Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm

Albert-Einstein-Allee 41

89081 Ulm, Germany

Telephone: 0731 50-25483

Fax: 0731 50-25309

Email: stefanie.lanzinger@uni-ulm.de

Acknowledgements

The authors thank all participating centers of the DPV initiative, especially the collaborating centers in this investigation. Special thanks to Andreas Hungele and Ramona Ranz for support and the development of the DPV documentation software and Katharina Fink and Esther Bollow for the DPV data management (in each case clinical data manager, Ulm University).

Abstract

Background: Only few studies have been conducted on pancreatic diabetes and data from large epidemiological studies are missing. Our main objective was to study the most important differences and similarities between pediatric individuals with pancreatic diabetes and type 1 diabetes.

Methods: Patients <20 years of age were identified from the diabetes patient follow-up registry (DPV). Data of the most recent treatment year between January 2000 and March 2018 was aggregated. Propensity score was used to match individuals with pancreatic diabetes to individuals with type 1 diabetes. Matching was conducted one to one by sex, age, diabetes duration, BMI-SDS and migration background.

Results: We studied 731 individuals with pancreatic diabetes and 74,460 with type 1 diabetes. In the matched cohort of 631 pairs, HbA1c was significantly lower in pancreatic diabetes (7.4% [95%-confidence interval: 7.2; 7.5%]) compared to type 1 diabetes patients (8.7% [8.5; 8.8%]). Daily insulin dose (0.80 IU/kg [0.77; 0.84] vs. 0.86 IU/kg [0.82; 0.90]) and insulin pump use (13.3% [10.7; 16.4] vs. 22.1% [19.0; 25.6%]) were lower in patients with pancreatic diabetes. However, event rates of severe hypoglycemia were similar between pancreatic and type 1 diabetes patients (8.8 [5.4; 14.2] vs. 9.6 [5.9; 15.6] events per 100 patient years).

Conclusions: With the use of robust epidemiological data our study improves the knowledge on clinical characteristics in pediatric individuals with pancreatic diabetes. Moreover, our results serve as a basis to reconsider treatment options and for discussing clinical practice guidelines for patients with this rare medical condition.

Key words: pancreatic diabetes, type 1 diabetes, cystic fibrosis, propensity score matching

Introduction

Pancreatic diabetes is a form of secondary diabetes that is associated with disorders of the exocrine pancreas (1). Thus far, few studies have been conducted on pancreatic diabetes and data from large and robust epidemiological studies are missing. Due to the rarity and heterogeneity of the disease, individuals with pancreatic diabetes are often excluded from large epidemiological analyses. To our knowledge, there are no prevalence data available on pancreatic diabetes in children and adolescents so far. In adult patients the prevalence of pancreatic diabetes was estimated from 1.8% in newly diagnosed patients in England (2) up to 8% in a German hospital (3).

Pancreatic diabetes is regarded as a heterogeneous disease due to different pathogenic subgroups. In children and adolescents the most common pathogenesis of pancreatic diabetes is cystic fibrosis. Moran and colleagues reported that pancreatic diabetes is present in around 20% of adolescents with cystic fibrosis (4). Other pathogenic subgroups, which play a minor role in pediatric patients, are hereditary or chronic pancreatitis, pancreatectomy for trauma or congenital hyperinsulinism, iron overload due to thalassemia and hemochromatosis (5). Specific subgroups of pancreatic diabetes, such as congenital hyperinsulinism and hereditary chronic pancreatitis, were investigated in a small number of studies, which have been limited by small sample sizes (6-10).

Development of diabetes means a further treatment burden in addition to other treatment needed for the underlying condition in patients with diseases of the exocrine pancreas and therefore, has a great impact on quality of life (11). Hence, the prevention of diabetes associated complications such as severe hypoglycemia, is of great importance in this patient group (11,12). So far clinical practice guidelines for pediatric individuals with diabetes cover a short section on rare types such as pancreatic diabetes

(13). It is important to improve the knowledge on clinical characteristics in individuals with pancreatic diabetes. This can be achieved by studying the differences or similarities of patients with pancreatic diabetes to pediatric individuals with type 1 diabetes. In a previous study, Konrad and colleagues compared children and adolescent with cystic fibrosis related diabetes with type 1 diabetes patients (14). The authors reported that with progression of cystic fibrosis related diabetes the treatment modalities and metabolic control became similar between both diabetes types (14).

The objectives of our analyses were to describe the prevalence of pathogenic subgroups of pancreatic diabetes in patients <20 years of age, which were documented in the comprehensive German/Austrian/Swiss/Luxemburg diabetes patient follow-up registry (DPV) (15). Moreover, we aimed at comparing the clinical course and long-term treatment of pancreatic diabetes with type 1 diabetes in order to elucidate the most important differences and similarities between these two diabetes types.

Methods

Participants and Data

Within the multicenter, prospective DPV registry, data on demographic and anthropometric characteristics, diabetes therapy and diabetes related comorbidities are collected during routine examination for all types of diabetes using an electronic documentation software. Anonymized data are sent to Ulm University regularly for data validation and analyses. Data collection and analysis were approved by the ethics committee of Ulm University as well as by the local review boards of the participating centers.. As of March 2018, the DPV data base comprised a total of 471 centers (425 in Germany, 42 in Austria, 3 in Switzerland and 1 center in Luxemburg).

Individuals documented in DPV with type 1 diabetes or pancreatic diabetes <20 years of age were included into the analyses. For each patient, data of the most recent treatment year between January 2000 and March 2018 was aggregated. Demographic and clinical data under investigation were sex, age at most recent treatment year, age at diabetes onset, diabetes duration, migration background (at least one parent or patient born outside the DPV countries), body mass index standard deviation score (BMI-SDS), HbA_{1c} (% or mmol/mol), daily insulin dose (IU/kg), type of insulin treatment (conventional insulin therapy (CT, ≤ 3 injection time-points per day), intensive insulin therapy (ICT, 4-8 injection time-points per day) or insulin pump), use of continuous glucose monitoring systems (CGMS), number of self-monitoring blood glucose measurements per day (SMBG), number of hospital admissions, event rates of severe hypoglycemia or diabetic ketoacidosis (DKA).

National reference data of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS study) was used in order to derive BMI-SDS values

(16). A BMI-SDS <10th percentile was defined as underweight, BMI-SDS between the 10th and the 90th percentile was classified as normal weight and a BMI-SDS >90th percentile as overweight. HbA_{1c} values were standardized to the Diabetes Control and Complications Trial (DCCT) reference range of 4.05–6.05% (20.7–42.6 mmol/mol) using the multiple of the mean transformation method to account for different laboratory methods (17). Severe hypoglycemia (with or without coma) was defined as an event associated with seizure, convulsion or loss of consciousness according to guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD) (18). DKA was defined as venous pH <7.3 or bicarbonate < 15 mmol/L (19).

When comparing individuals with pancreatic diabetes to type 1 diabetes our outcomes of primary interest were HbA_{1c}, SMBG, daily insulin dose, insulin pump usage, use of CGMS, number of hospital admissions, rates of severe hypoglycemia and rates of diabetic ketoacidosis (DKA) of the most recent treatment year.

Subgroups of pancreatic diabetes

Free text fields of the DPV software were searched in order to identify patients with pancreatic diabetes. Terms associated with pancreatic diabetes were searched for and patients were categorized into the following subgroups: pancreatic diabetes due to 1) chronic pancreatitis or pancreas insufficiency, 2) pancreatectomy for trauma, for congenital hyperinsulinism or for other reasons, 3) thalassemia or hemochromatosis and 4) cystic fibrosis. Other pathogenic subgroups which are very rare in pediatric patients such as pancreatic cancer were not considered.

Statistical analyses

In a first step, descriptive statistics were conducted to compare characteristics between different subgroups of pancreatic diabetes as well as between pancreatic diabetes and type 1 diabetes patients. Continuous variables are presented as median (of the most recent treatment year) with lower and upper quartiles, categorical variables as percentages, severe hypoglycemia and DKA as event rates per 100 patient years (PYs) and number of hospital admissions per 1 PY. Unadjusted comparisons were conducted using Kruskal-Wallis test for continuous variables, Chi-squared test for categorical variables and negative binomial regression models with individual observation time as offset for event rates, respectively.

In a second step, we used the concept of propensity score matching (20) to compare pancreatic diabetes with type 1 diabetes. Individuals were matched one to one by sex, age, diabetes duration, BMI-SDS and migration background using a greedy matching algorithm (21). Propensity score was calculated using multivariable logistic regression with pancreatic diabetes as the dependent variable and sex, age, diabetes duration, BMI-SDS and migration background as covariates. Age, diabetes duration and BMI-SDS were included continuously as well as categorized into age <16 years, 16-<18 years and ≥18 years; diabetes duration ≤2 years and >2 years; BMI-SDS <-1.282 (<10th percentile), -1.282 – 1.282 (10th to 90th percentile) and >1.282 (>90th percentile).

A standardized difference was calculated as described by Austin (20) to evaluate similarity of the covariates between the matched groups. A standardized difference less than 0.1 was considered as a negligible difference between the means (continuous covariate) or proportions (categorical covariate) of the two groups (20). Linear, logistic and negative binomial regression were then conducted to study differences in HbA_{1c}, SMBG, daily insulin dose, insulin pump usage, CGMS usage, number of hospital

admissions, rates of severe hypoglycemia and DKA between matched pairs of pancreatic diabetes and type 1 diabetes patients. Results of regression models are presented as least-square means or event rates together with 95%-confidence intervals (CI) estimated using observed marginal distribution of covariates.

Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary,NC). A two-sided p-value <0.05 was considered as statistically significant.

Results

The prevalence of pancreatic diabetes in patients <20 years, which were registered in DPV as of January 2000, was 0.9% (94.0% type 1 diabetes, 2.2% type 2 diabetes, 2.9% other types of diabetes). We investigated 731 individuals with pancreatic diabetes and 74,460 individuals with type 1 diabetes <20 years of age.

Table 1 shows characteristics of individuals with pancreatic diabetes stratified by the pathogenic subgroup. Cystic fibrosis related diabetes was the most common subgroup of pancreatic diabetes in DPV patients <20 years ($n = 597$, 81.6%). Other subgroups played a minor role with 42 (5.8%) having pancreatic diabetes following chronic pancreatitis or pancreas insufficiency, 64 (8.8%) with pancreatectomy for trauma or for congenital hyperinsulinism and 28 (3.8%) individuals with pancreatic diabetes due to thalassemia or hemochromatosis. Large differences were found between the subgroups, for example mean age at diabetes onset ranged from 8.4 years in the pancreatectomy group to 13.8 years in the cystic fibrosis group ($p\text{-value} < 0.001$). BMI-SDS was lowest in individuals with cystic fibrosis (-1.1) and highest in individuals with thalassemia or hemochromatosis (0.3, $p < 0.001$). Moreover, the proportion of males was highest in people with thalassemia or hemochromatosis (54%), whereas lowest in individuals with chronic pancreatitis or pancreas insufficiency (31%, $p = 0.162$). Figure 1 shows treatment of individuals with pancreatic diabetes by subgroup. In all subgroups the majority of individuals were treated with insulin only (69% to 92%, $p = 0.020$) followed by lifestyle therapy only (5% to 19%, $p = 0.147$) (Figure 1).

Comparing pancreatic diabetes with type 1 diabetes

In table 2 characteristics of pancreatic diabetes are compared with type 1 diabetes. In the unmatched entire study cohort individuals with pancreatic diabetes were older

(mean age 16.5 years vs. 14.6 years, $p<0.001$), predominantly female (59% vs. 47%, $p<0.001$) and underweight (mean BMI-SDS -0.9 vs. 0.3, $p<0.001$) compared to individuals with type 1 diabetes. The proportion of individuals with a migration background was similar between pancreatic and type 1 diabetes ($p=0.792$). After conducting propensity score matching by sex, age, diabetes duration, BMI-SDS and migration background, 631 patients with pancreatic patients were matched to 631 individuals with type 1 diabetes. 10 patients with pancreatic diabetes had to be excluded as no type 1 diabetes matching partner was found. The standardized difference of all covariates was <0.1 , demonstrating a negligible difference between the two groups (Table 2).

Linear regression of the matched cohort showed a significantly lower HbA1c in individuals with pancreatic diabetes (7.4% [95%-CI: 7.2; 7.5%]) compared to type 1 diabetes (8.7% [8.5; 8.8%], $p<0.001$) (Figure 2 A). SMBG was lower in pancreatic diabetes (3.5 [3.4; 3.7]) compared to type 1 diabetes (4.5 [4.3; 4.7], $p<0.001$) (Figure 2 B). Moreover, insulin requirement was lower in pancreatic diabetes with an insulin dose of 0.80 IU/kg [0.77; 0.84], whereas insulin dose was 0.86 IU/kg [0.82; 0.90] ($p=0.028$) in type 1 diabetes (Figure 2 C). Insulin pump was used by 13.3% [10.7; 16.4] of pancreatic diabetes patients and by 22.1% [19.0; 25.6%] of type 1 diabetes patients ($p<0.001$, Figure 2 D). Moreover, CGMS was used less often by individuals with pancreatic diabetes (6.0% [4.4; 8.1%]) compared to individuals with type 1 diabetes (11.5% [9.2; 14.2%], $p<0.001$) (Figure 2 E).

Figure 3 presents event rates of hypoglycemia, DKA and number of hospital admissions from binomial regression models of the matched cohort. We observed similar event rates of severe hypoglycemia (8.8 [5.4; 14.2] and 9.6 [5.9; 15.6] events per 100 PY, $p=0.800$) as well as of hypoglycemic coma (1.5 [0.6; 3.3] and 2.0 [1.0; 4.2] events per

100 PY, $p=0.559$) between individuals with pancreatic diabetes and individuals with type 1 diabetes (Figure 3 A and B). Event rates of DKA were lower in pancreatic diabetes (2.5 [1.5; 4.1] per 100 PY) compared to type 1 diabetes (8.2 [6.2; 10.9] per 100 PY, $p<0.001$) (Figure 3 C). However, pancreatic diabetes was associated with a non-significantly higher number of hospital admissions (1.1 [0.9; 1.2] per PY) compared to type 1 diabetes (0.9 [0.7; 1.0] per PY, $p=0.100$) (Figure 3 D).

Discussion

Cystic fibrosis related diabetes was the most common subgroup of pancreatic diabetes in patients <20 years of age (81.6%). In the unmatched entire study cohort, pancreatic diabetes patients were older, predominantly female and underweight in comparison to type 1 diabetes patients. Results of the matched cohort showed that HbA1c and SMBG were lower in pancreatic diabetes compared to type 1 diabetes. Insulin requirement and proportion of insulin pump as well as CGMS use was significantly lower in pancreatic diabetes. Moreover, pancreatic diabetes was associated with lower event rates of DKA and higher number of hospital admissions compared to type 1 diabetes. Event rates of severe hypoglycemia as well as hypoglycemic coma were similar between individuals with pancreatic diabetes and type 1 diabetes.

The prevalence of pancreatic diabetes in patients <20 years (0.9%) was lower compared to the reported prevalence in adult patients with pancreatic diabetes (2,3). We observed large differences between the pathogenic subgroups of pancreatic diabetes. The proportion of patients with a migration background was highest in individuals with thalassemia or hemochromatosis (46.4%) compared to the other subgroups (14.1-31.3%). This might be one explanation for the high HbA1c and BMI-SDS in this subgroup (22). However, other factors such as changes in diet and socio-economic status might also play a role.

Our results of lower HbA1c in pancreatic diabetes compared to type 1 diabetes was expected as our group of pancreatic diabetes was dominated by cystic fibrosis related diabetes, that means patients with residual beta cell function and endogenous insulin release. It was shown that HbA1c is often spuriously low in individuals with cystic fibrosis (23). Moreover, our results showing lower SMBG in pancreatic diabetes

compared to type 1 diabetes are consistent with a previous study conducted by Konrad and colleagues (14). The authors compared pediatric patients up to 21 years of age with cystic fibrosis-related diabetes to type 1 diabetes. According to the current ISPAD guidelines a successful intensive diabetes management requires 6 to 10 SMBG (24). Hence, in our study both pancreatic diabetes patients (3.5 SMBG) and type 1 diabetes patients (4.5 SMBG) were below this recommendation.

In contrast to our study, Konrad et al. (14) found a higher daily insulin dose in cystic-fibrosis related diabetes (0.83 IU/kg) compared to type 1 diabetes (0.79 IU/kg) after adjustment for age, sex and diabetes duration. Whereas in our matched cohort estimated insulin dose from linear regression was slightly lower in pancreatic diabetes (0.80 IU/kg) compared to type 1 diabetes (0.86 IU/kg). One explanation might be that we included 134 (18.4%) individuals having pancreatic diabetes due to other reasons than cystic fibrosis. Whereas in the study of Konrad and colleagues only patients with cystic fibrosis related diabetes were studied. In general, treatment was heterogeneous between the different pathogenic subgroups of pancreatic diabetes. Insulin requirement ranged from 0.70 (IU/kg) to 1.0 (IU/kg) between the pathogenic subgroups. Treatment with insulin only ranged from 69% in the chronic pancreatitis or pancreas insufficiency subgroup to 92% in the pancreatectomy group. In general, the frequency of insulin pump usage increased in comparison to a previous study by Scheuing et al. (25) where 4.1% of cystic fibrosis-related diabetes patients and 17.7% of type 1 diabetes patients used an insulin pump. In accordance to the previous study we observed a less frequent use of insulin pump therapy in individuals with pancreatic diabetes (13.3%) than in individuals with type 1 diabetes (22.1%). Moreover, use of CGMS was also lower in pancreatic diabetes (6.0%) compared to type 1 diabetes (11.5%). Consistent to previous results, in our analysis event rates of DKA were low (2.5 per 100 PY) in pancreatic

diabetes possibly due to the impaired glucagon secretion and the fact that insulin secretion is also impaired, but not completely absent (11,14).

Previous literature reviews emphasized the high variability in blood glucose levels in pancreatic diabetes (11,12), therefore, blood glucose monitoring is very important. Individuals with pancreatic diabetes might benefit from the use of insulin pumps or CGMS, especially in child- and young adulthood (24). Blood glucose monitoring is also important with regard to the prevention of severe hypoglycemia (24,26). We observed similar event rates of severe hypoglycemia and hypoglycemic coma in individuals with pancreatic diabetes (severe: 8.8 events per 100 PY, coma: 1.5 events per 100 PY) and type 1 diabetes (9.6 events per 100 PY, 2.0 events per 100 PY). Due to the impaired glucagon response in addition to the impaired insulin secretion, patients with pancreatic diabetes are at high risk for severe hypoglycemia (11,12,26).

Overall, our results indicate that diabetes treatment needed in pancreatic diabetes is similar to treatment of type 1 diabetes. However, insulin pump and CGMS is less frequently used by patients with pancreatic diabetes. One reason might be limited access of both pancreatic diabetes patients and gastroenterologists to treatment modalities such as insulin pump and CGMS. Moreover, pancreatic diabetes patients might be less compliant due to the high treatment burden. Diabetes education and support for pancreatic diabetes should be similar to the support of type 1 diabetes patients (23). Current ISPAD guidelines recommend that patients with cystic fibrosis related diabetes should be examined regularly by a specialized multidisciplinary team with expertise in diabetes and cystic fibrosis (23). Therefore, interdisciplinary cooperation between diabetologists and gastroenterologists is very important.

Limitations and strengths

Our study was limited by the fact that we identified patients with pancreatic diabetes by searching free text fields of the DPV software. However, individuals with unclear text entries were excluded from the analysis. Therefore, the number of individuals with pancreatic diabetes might be underestimated rather than overestimated in our analysis. Lifestyle, social factors and dietary habits are challenging to measure in registries and were not assessed. Therefore, residual confounding cannot be ruled out. The novelty of our study is that we investigated pancreatic diabetes as a rare diabetes type using data of the large DPV registry, and hence provided results based on a meaningful number of patients. Whereas previous studies in this context were often limited in sample size. Moreover, we used the innovative method of propensity score matching to compare individuals with pancreatic diabetes to individuals with type 1 diabetes. In contrast to traditional regression analysis, propensity score matching is similar to a randomized controlled trial which allows the separation of the study design from the outcome analysis (20).

Conclusions

Pancreatic diabetes is rare and needs to be investigated further using robust epidemiological studies, which are so far missing in this context. Results from registry data may serve as a basis for discussing guidelines and to reconsider treatment options for rare diabetes types in pediatric individuals such as pancreatic diabetes. Our results indicate that diabetes treatment, education and support for patients with pancreatic diabetes should be similar to type 1 diabetes patients. Therefore, interdisciplinary cooperation between diabetologists and gastroenterologists is very important. Moreover, international collaboration may also provide additional insight.

Funding

The study was funded by German Diabetes Association (DDG).

Additional support was provided by the Federal Ministry of Education and Research within the German Competence Network Diabetes Mellitus (grant 01GI1106), which was integrated into the German Center for Diabetes Research (DZD) as of January 2015. This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115797 (INNODIA). This Joint Undertaking receives support from the Union's Horizon 2020 research and innovation programme and "EFPIA", "JDRF" and "The Leona M. and Harry B. Helmsley Charitable Trust".

Sponsors were not involved in data acquisition or analysis.

Conflict of interest

The authors declare that there is no duality of interest associated with this manuscript.

References

1. Gudipaty L, Rickels MR. Pancreatogenic (Type 3c) Diabetes. Pancreapedia: The Exocrine Pancreas Knowledge Base 2015;.
2. Woodmansey C, McGovern AP, McCullough KA, et al. Incidence, Demographics, and Clinical Characteristics of Diabetes of the Exocrine Pancreas (Type 3c): A Retrospective Cohort Study. Diabetes care 2017; 40:1486-1493.
3. Hardt PD, Brendel MD, Kloer HU, Bretzel RG. Is pancreatic diabetes (type 3c diabetes) underdiagnosed and misdiagnosed? Diabetes care 2008; 31 Suppl 2:S165-9.
4. Moran A, Becker D, Casella SJ, et al. Epidemiology, pathophysiology, and prognostic implications of cystic fibrosis-related diabetes: a technical review. Diabetes care 2010; 33:2677-2683.
5. Petrov MS. Diabetes of the exocrine pancreas: American Diabetes Association-compliant lexicon. Pancreatology 2017; 17:523-526.
6. Arya VB, Senniappan S, Demirbilek H, et al. Pancreatic endocrine and exocrine function in children following near-total pancreatectomy for diffuse congenital hyperinsulinism. PloS one 2014; 9:e98054.
7. Bowman P, Sulen A, Barbetti F, et al. Effectiveness and safety of long-term treatment with sulfonylureas in patients with neonatal diabetes due to KCNJ11 mutations: an international cohort study. The lancet.Diabetes & endocrinology 2018; 6:637-646.
8. Demirbilek H, Hussain K. Congenital Hyperinsulinism: Diagnosis and Treatment Update. Journal of clinical research in pediatric endocrinology 2017; 9:69-87.

9. Rosendahl J, Bodeker H, Mossner J, Teich N. Hereditary chronic pancreatitis. Orphanet journal of rare diseases 2007; 2:1-1172-2-1.
10. Welters A, Meissner T, Grulich-Henn J, et al. Characterization of diabetes following pancreatic surgery in patients with congenital hyperinsulinism. Orphanet Journal of Rare Diseases 2018; [Epub ahead of print].
11. Czako L, Hegyi P, Rakonczay Z,Jr, Wittmann T, Otsuki M. Interactions between the endocrine and exocrine pancreas and their clinical relevance. Pancreatology : official journal of the International Association of Pancreatology (IAP) ...[et al.] 2009; 9:351-359.
12. Meier JJ, Giese A. Diabetes associated with pancreatic diseases. Current opinion in gastroenterology 2015; 31:400-406.
13. Mayer-Davis EJ, Kahkoska AR, Jefferies C, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Definition, epidemiology, and classification of diabetes in children and adolescents. Pediatric diabetes 2018; 19:7-19.
14. Konrad K, Thon A, Fritsch M, et al. Comparison of cystic fibrosis-related diabetes with type 1 diabetes based on a German/Austrian Pediatric Diabetes Registry. Diabetes care 2013; 36:879-886.
15. Hofer SE, Schwandt A, Holl RW, Austrian/German DPV Initiative. Standardized Documentation in Pediatric Diabetology: Experience From Austria and Germany. Journal of diabetes science and technology 2016; 10:1042-1049.
16. Rosario AS, Kurth BM, Stolzenberg H, Ellert U, Neuhauser H. Body mass index percentiles for children and adolescents in Germany based on a nationally

representative sample (KiGGS 2003-2006). European journal of clinical nutrition 2010; 64:341-349.

17. Rosenbauer J, Dost A, Karges B, et al. Improved metabolic control in children and adolescents with type 1 diabetes: a trend analysis using prospective multicenter data from Germany and Austria. Diabetes care 2012; 35:80-86.

18. Ly TT, Maahs DM, Rewers A, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatric diabetes 2014; 15 Suppl 20:180-192.

19. Wolfsdorf JI, Allgrove J, Craig ME, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Pediatric diabetes 2014; 15 Suppl 20:154-179.

20. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate behavioral research 2011; 46:399-424.

21. Parsons L. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. 2001;.

22. Scheuing N, Wiegand S, Bächle C, et al. Impact of maternal country of birth on type-1-diabetes therapy and outcome in 27,643 children and adolescents from the DPV registry. PloS one 2015; 10:e0135178.

23. Moran A, Pillay K, Becker DJ, Acerini CL. Management of cystic fibrosis-related diabetes in children and adolescents. Pediatric diabetes 2014; 15:65-76.

24. DiMeglio LA, Acerini CL, Codner E, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes. *Pediatric diabetes* 2018; 19:105-114.
25. Scheuing N, Badenhoop K, Borkenstein M, et al. Why is insulin pump treatment rarely used in adolescents and young adults with cystic fibrosis-related diabetes? *Pediatric diabetes* 2015; 16:10-15.
26. Abraham MB, Jones TW, Naranjo D, et al. Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatric diabetes* 2018;.

Figure Legends

Figure 1. Treatment of individuals with pancreatic diabetes stratified by subgroup.

Figure 2. Comparison of A) HbA1c, B) SMBG, C) daily insulin dose per kg, D) frequency of insulin pump use and E) frequency of CGMS use between matched pairs of type 1 diabetes and pancreatic diabetes (least-square means together with 95%-CI estimated from linear and logistic regression).

T1D, type 1 diabetes; PD, pancreatic diabetes

Figure 3. Comparison of A) severe hypoglycemia , B) hypoglycemic coma, C) DKA and D) number hospital admissions between matched pairs of type 1 diabetes and pancreatic diabetes (event rates together with 95%-CI estimated from negative binomial regression).

T1D, type 1 diabetes; PD, pancreatic diabetes

Table 1. Patient characteristics of the most recent treatment year of patients with pancreatic diabetes <20 years (n = 731), stratified by subgroup.

	Subgroups of pancreatic diabetes			
	Chronic pancreatitis/pancreas insufficiency n = 42	Pancreatectomy for trauma/ congenital hyperinsulinism n = 64	Thalassemia/ hemochromatosis n = 28	Cystic fibrosis n = 597
	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Age (years)	15.1 (3.8)	15.6 (3.6)	16.3 (3.0)	16.7 (2.7)
Age at diabetes onset (years)	11.1 (5.5)	8.4 (5.7)	13.3 (4.1)	13.8 (3.4)
Diabetes duration (years)	4.1 (4.1)	7.2 (6.1)	3.0 (3.6)	2.9 (2.8)
BMI-SDS	0.1 (1.4)	0.2 (1.3)	0.3 (1.0)	-1.1 (1.2)
HbA1c (mmol/mol)	59.4 (24.3)	60.9 (21.4)	66.5 (27.5)	55.2 (22.1)
HbA1c (%)	7.6 (2.2)	7.7 (2.0)	8.2 (2.5)	7.2 (2.0)
Daily insulin dose (IU/kg)	0.7 (0.4)	0.7 (0.4)	1.0 (0.4)	0.8 (0.6)
SMBG	3.5 (2.3)	4.1 (1.7)	3.8 (2.1)	3.4 (1.7)
	percent	percent	percent	percent
Male sex	31.0	48.4	53.6	40.4
CT (1-3 injection time- points/day)	28.1	21.3	29.2	30.0

ICT (4-8 injection time-points/day)	40.6	62.3	62.5	59.3
Insulin pump	31.3	16.4	8.3	10.7
Migration background	19.0	31.3	46.4	14.1
	event rates (95%-CI)	event rates (95%-CI)	event rates (95%-CI)	event rates (95%-CI)
Hospital admissions per 1 PY	0.6 (0.5; 0.7)	0.3 (0.3; 0.4)	0.7 (0.6; 0.9)	1.0 (1.0; 1.1)
Severe hypoglycemia per 100 PYs	11.6 (8.6; 15.7)	14.5 (11.7; 17.9)	9.8 (6.1; 15.7)	6.8 (6.1; 7.6)
Hypoglycemic coma per 100 PYs	0.0 (0.0; 0.0)	1.4 (0.7; 2.8)	4.9 (2.5; 9.6)	1.3 (0.9; 1.6)
DKA per 100 PYs	0.0 (0.0; 0.0)	2.9 (1.8; 4.7)	9.8 (6.1; 15.7)	0.9 (0.7; 1.2)

Table 2. Description of covariates of the entire and matched study cohort.

	Entire study cohort			Matched study cohort		
	Type 1 diabetes	Pancreatic diabetes	Standardized	Type 1 diabetes	Pancreatic diabetes	Standardized
	n = 74,460	n = 731	difference	n = 631	n = 631	difference
	mean (SD) or %	mean (SD) or %		mean (SD) or %	mean (SD) or %	
Age (years)	14.6 (4.1)	16.5 (2.9)	0.539	16.5 (2.8)	16.4 (2.9)	-0.017
<16 years	50.7	30.0	-0.432	33.0	32.5	-0.010
16-<18 years	30.7	35.7	0.106	34.7	35.5	0.016
≥18 years	18.6	34.3	0.362	32.3	32.0	-0.007
Diabetes duration (years)	5.9 (4.3)	3.3 (3.6)	-0.632	3.6 (3.4)	3.6 (3.6)	-0.001
≤2 years	23.5	45.6	0.478	42.3	42.8	0.009
>2 years	76.5	54.4	-0.478	57.7	57.2	-0.009
BMI-SDS	0.3 (0.9)	-0.9 (1.3)	-1.026	-0.7 (1.2)	-0.7 (1.1)	-0.020

<-1.282	5.0	35.9	0.829	31.6	30.8	-0.017
-1.282 - 1.282	80.9	59.8	-0.476	64.9	64.5	-0.010
>1.282	14.1	4.3	-0.341	3.5	4.7	0.064
Male sex	53.0	41.0	-0.241	42.0	42.1	0.003
Migration background	17.6	17.1	-0.013	17.3	17.0	-0.008