Received: 12 January 2022 | Revised: 16 February 2022 | Accepted: 28 March 2022

DOI: 10.1111/pedi.13338

CLINICAL CARE AND TECHNOLOGY

Glycated hemoglobin at diagnosis of type 1 diabetes and at follow-up in children and adolescents during the COVID-19 pandemic in Germany

Clemens Kamrath[1] | Joachim Rosenbauer[2,3] | Alexander J. Eckert[3,4] | Ute Ohlenschläger[5] | Carmen Sydlik[6] | Nicole Nellen-Hellmuth[7] | Reinhard W. Holl[3,4]

[1]Center of Child and Adolescent Medicine, Justus Liebig University, Giessen, Germany

[2]Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Dusseldorf, Dusseldorf, Germany

[3]German Center for Diabetes Research (DZD), Munich-Neuherberg, Germany

[4]Institute of Epidemiology and Medical Biometry, ZIBMT, Ulm University, Ulm, Germany

[5]Child and Adolescent Diabetology, Altonaer Kinderkrankenhaus, Hamburg, Germany

[6]Center of Child and Adolescent Medicine, Innklinikum Altötting, Altötting, Germany

[7]Center of Child and Adolescent Medicine, Leopoldina Clinic Schweinfurt, Schweinfurt, Germany

Correspondence
Clemens Kamrath, Center of Child and Adolescent Medicine, Justus Liebig University, Feulgenstr. 12, 35385, Giessen, Germany.
Email: clemens.kamrath@paediat.med.uni-giessen.de

Funding information
The DPV is supported through the German Federal Ministry for Education and Research within the German Centre for Diabetes Research (DZD, grant number: 82DZD14A02). Further financial support was received by the German Diabetes Foundation (DDS, grant number: FP-0438-2021), the German Robert Koch Institute (RKI) and the German Diabetes Association (DDG). The funding organization had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Abstract

Background: This study investigated the diagnostic delay and the subsequent quality of care during the Covid-19 pandemic among children with new-onset type 1 diabetes.

Methods: We compared the HbA_{1c} levels of 3111 children at diagnosis of type 1 diabetes and of 2825 children at a median follow-up of 4.7 months (interquartile range, 4.1–5.4) together with their daily insulin requirement during the Covid-19 pandemic with the two previous years via multivariable linear regression, using data from the German Diabetes Registry DPV.

Results: During the Covid-19 pandemic, HbA_{1c} levels were higher at diagnosis of type 1 diabetes (mean estimated difference, 0.33% [95% confidence interval, 0.23–0.43], $p < 0.001$), but not at follow-up (mean estimated difference, 0.02% [−0.02–0.07]). Children with diabetes onset during the Covid-19 pandemic had a significantly higher daily insulin requirement after initiation of therapy (mean estimated difference, 0.08 U/kg [0.06–0.10], $p < 0.001$). Both the increase in HbA_{1c} and daily insulin requirement were evident only after the first wave of the pandemic.

Conclusions: This increase in HbA_{1c} at diagnosis of type 1 diabetes during the Covid-19 pandemic may indicate a delay in seeking medical care due to the pandemic. However, this did not affect short-term glycemic control. The increased insulin

requirement at follow-up could suggest a more rapid autoimmune progression during the pandemic.

KEYWORDS
autoimmune progression, diagnostic delay, glycaemic control, insulin requirement, remission

1 | INTRODUCTION

During the coronavirus disease 2019 (Covid-19) pandemic, contacts with the health care system have markedly declined and diagnoses were delayed, leading to more advanced stages of diseases.[1,2] For children and adolescents with new-onset type 1 diabetes, this resulted in an increased rate of diabetic ketoacidosis.[3–6] However, the impact of delayed diagnosis and impaired acute care on the continued care of children and adolescents with new-onset type 1 diabetes during the Covid-19 pandemic is unknown.

The aim of this study was to quantify the diagnostic delay and its impact on subsequent quality of care during the Covid-19 pandemic in Germany by comparing the levels of glycated hemoglobin (HbA_{1c}) at diagnosis of type 1 diabetes and after initiation of therapy during the Covid-19 pandemic with those of the two previous years.

2 | METHODS

This study compared HbA_{1c} levels of children and adolescents from the German Diabetes Prospective Follow-up Registry (DPV) at diagnosis of type 1 diabetes in the year 2020, at follow-up 2–8 months later, and daily insulin requirement (units per kilogram body weight), with data from 2018 and 2019 via multivariable linear regression, adjusted for age group (<6, 6–<12, and 12–<18 years), sex, and immigrant background (patient or at least one parent born outside Germany). Adjusted differences with the corresponding 95% confidence interval (CI) were presented for the whole year, as well as for four different periods related to the Covid-19 pandemic: the pre-pandemic period (January and February 2020), the first wave of the pandemic from March to May 2020, the period from June to September 2020 with a relatively low rate of new infections, and the 2nd wave starting October 2020.[7]

The DPV registry has a nationwide coverage of more than 90% of pediatric patients with type 1 diabetes in Germany and comprises 257 pediatric diabetes centers (hospitals and practices) as of March 2021. Twice a year, locally collected longitudinal data are pseudonymized and transmitted for central plausibility checks and analyses to Ulm University, Ulm, Germany. Inconsistent data are reported back to participating centers for validation and/or correction. Data are then completely anonymized for analysis. Verbal or written informed consent for participation in the DPV registry was obtained from patients or their guardians. The ethics committee of Ulm University approved the analysis of anonymized data from the DPV registry.

Local HbA_{1c} values were mathematically standardized to the DCCT reference range (4.05–6.05%) using the "multiple of the mean" transformation method. HbA_{1c} at diagnosis was aggregated 10 days around the date of diagnosis. BMI values (calculated as weight in kilograms divided by height in meters squared) were transformed to standard deviation scores (SDS_{LMS}) based on German reference values (KiGGS [German Health Interview and Examination Survey for Children and Adolescents]) by applying the Box-Cox-transformation method.[8] Confidence intervals for estimated period-specific values were adjusted according to the Bonferroni method, and corresponding p-values according to the Holm method.

A two-sided p-value <0.05 was considered statistically significant. All analyses were performed with SAS version 9.4 (SAS Institute Inc., NC, USA).

3 | RESULTS

We obtained HbA_{1c} values at diabetes diagnosis from 3111 children and adolescents (55.5% males; median age 9.8 years [interquartile range, 5.9–12.9]) with new-onset type 1 diabetes in 2020 from 186 diabetes centers in Germany, of whom we obtained data of 2825 patients (90.8%) at a median follow-up of 4.7 months (interquartile range, 4.1–5.4). The median HbA_{1c} was 11.4% (interquartile range, 9.9–13.1 [101 mmol/mol (85–120)]) at diagnosis of type 1 diabetes and 6.7% (interquartile range, 6.1–7.3 [50 mmol/mol (43–56)]) at follow-up. The median daily insulin dose at follow-up was 0.61 IU/kg (interquartile range, 0.44–0.83) and the median BMI-SDS at follow-up was −0.27 (interquartile range, −1.09–0.54). Data from the 2020 cohort were compared with data from 5256 children and adolescents (54.7% males; median age 9.8 years [interquartile range, 6.0–13.1]) with new-onset type 1 diabetes in 2019 and 2018, and their follow-up data ($N = 4789$) after a median of 4.7 months (interquartile range, 4.1–5.4). The median HbA_{1c} of the 2019/2018 cohort was 11.1% (interquartile range, 9.6–12.81 [98 mmol/mol (82–117)]) at diagnosis and 6.6% (interquartile range, 6.1–7.3 [49 mmol/mol (43–56)]) at follow-up. The median daily insulin dose at follow-up was 0.57 IU/kg (interquartile range, 0.42–0.76) and the median BMI-SDS at follow-up was −0.29 (interquartile range, −1.10–0.55). Table 1 provides a descriptive overview of the 2020 compared to the 2018/2019 cohort.

Children and adolescents with new-onset type 1 diabetes in 2020 had higher adjusted mean HbA_{1c} at diagnosis compared to 2019 and 2018 (mean estimated difference, 0.33% [95% CI, 0.23–0.43], $p < 0.001$; Table 2A). The difference in adjusted HbA_{1c} at diagnosis between 2020 and 2019/2018 was significant in all age groups and

TABLE 1 Characteristics of patients with new-onset type 1 diabetes from 2020 and from 2018/2019

Variable	2020	2018/2019	*p*-value
At diabetes onset—number of participants	3111	5256	
Median age at diabetes diagnosis—years (interquartile range)	9.8 (5.9–12.9)	9.8 (6.0–13.1)	>0.99
Sex (male)—%	55.5	54.7	>0.99
Immigrant background—%	26.6	26.9	>0.99
Diabetic ketoacidosis—%	35.3	27.2	**<0.001**
Median HbA_{1c}—% (interquartile range)	11.4 (9.9–13.1)	11.1 (9.6–12.8)	**<0.001**
At follow-up—number of participants	2825	4789	
Median time after diabetes diagnosis at follow-up—months (interquartile range)	4.7 (4.1–5.4)	4.7 (4.1–5.4)	>0.99
Median age at diabetes diagnosis—years (interquartile range)	9.7 (6.0–12.8)	9.6 (5.8–12.8)	>0.99
Sex (male)—%	55.3	54.5	>0.99
Immigrant background—%	26.8	27.0	>0.99
Median HbA_{1c}—% (interquartile range)	6.7 (6.1–7.3)	6.6 (6.1–7.3)	>0.99
Median daily insulin dose—IU/kg (interquartile range)	0.61 (0.44–0.83)	0.57 (0.42–0.76)	**<0.001**
Median BMI—SDS (interquartile range)	−0.27 (−1.09–0.54)	−0.29 (−1.10–0.55)	>0.99

Note: For demographic and clinical data, the cohort of 2020 was compared to children and adolescents with a diagnosis of type 1 diabetes in the two previous years 2019 and 2018 in Germany. All children and adolescents were between 6 months and less than 18 years of age at the time of diabetes diagnosis. Unadjusted values were compared via Wilcoxon's rank sum test for continuous variables and χ^2-test for dichotomous variables.
The significant of bold values as results with the bold *p*-values.

both sexes (Table 2A). Analysis by periods showed that the difference in HbA_{1c} was significant after the first wave of the pandemic (Table 2B). In contrast, the HbA_{1c} during follow-up no longer differed (mean estimated difference, 0.02% [95% CI, −0.02–0.07]; Table 2C), not even in the patients who developed diabetes after the first Covid-19 wave (Table 2D). However, children with diabetes onset during the Covid-19 pandemic had a significantly higher daily insulin dose after initiation of therapy (mean estimated difference, 0.08 U/kg [95% CI, 0.06–0.10], $p < 0.001$; Table 2E). Compared to the 2 years before the pandemic, the increased insulin requirements affected those children who developed type 1 diabetes after the first wave of the Covid-19 pandemic. (Table 2F).

4 | DISCUSSION

This study found an increase in HbA_{1c} at diagnosis of type 1 diabetes after the first wave of the Covid-19 pandemic in Germany, which may indicate a delay in seeking medical care due to the pandemic. This delay is probably the main reason for the increased frequency of diabetic ketoacidosis in children with new-onset type 1 diabetes during the pandemic.[3–6]

However, this did not affect short-term treatment response, as the identical HbA_{1c} at follow-up excludes major limitations in the care of chronically ill children. This also corresponds to reports on the metabolic control of children with type 1 diabetes during the Covid-19 lockdown, which did not noticeably worsen.[9,10]

It has been demonstrated that the incidence of type 1 diabetes in children increased only a few months after the Covid-19 waves.[11,12] With this background, it is important to note that we found an increased insulin requirement in children with onset of type 1 diabetes after the first wave of the Covid-19 pandemic. This may indicate more rapid autoimmune destruction of beta cells during the pandemic. Importantly, the difference in the required daily weight-adjusted insulin amount was not due to differences in BMI and consequent differences in insulin sensitivity.

Prolonged follow-up of patients who developed new type 1 diabetes during the pandemic is needed to further analyze this phenomenon as the pandemic continues to progress and to capture longer-term potential adverse metabolic effects of more rapid progression of type 1 diabetes.

ACKNOWLEDGMENTS

Special thanks to A. Hungele and R. Ranz for support and the development of the DPV documentation software (clinical data managers, Institute of Epidemiology and Medical Biometry [ZIBMT], Ulm University, Ulm, Germany). We wish to thank all centers participating in the DPV project (a list is available at the DPV homepage: www.d-p-v.eu).

TABLE 2 Adjusted mean HbA_{1c} at diagnosis and at follow-up, and adjusted daily insulin dose at follow-up of children and adolescents with new-onset type 1 diabetes in 2020 versus 2018/2019

	In 2020—adjusted mean (95% CI)	In 2018/2019—adjusted mean (95% CI)	Absolute difference 2020 versus 2018/2019—adjusted mean (95% CI)	*p*-value
A. HbA_{1c} (in %) at diabetes diagnosis—the whole year				
All patients	11.55 (11.47–11.63)	11.22 (11.16–11.29)	0.33 (0.23–0.43)	**<0.001**
Females	11.76 (11.63–11.88)	11.49 (11.39–11.58)	0.27 (0.11–0.43)	**<0.001**
Males	11.39 (11.28–11.49)	11.01 (10.93–11.09)	0.38 (0.25–0.51)	**<0.001**
<6 years	10.43 (10.29–10.57)	10.22 (10.12–10.33)	0.21 (0.03–0.39)	**0.020**
6–11.9 years	11.76 (11.63–11.88)	11.36 (11.26–11.45)	0.40 (0.24–0.56)	**<0.001**
12–17.9 years	12.16 (12.01–12.32)	11.83 (11.71–11.94)	0.34 (0.14–0.53)	**<0.001**
B. HbA_{1c} (in %) at diabetes diagnosis—the four pandemic-related periods				
January–February	11.27 (11.01–11.53)	11.13 (10.93–11.32)	0.15 (−0.23–0.52)	>0.99
March–May	11.51 (11.28–11.74)	11.24 (11.06–11.41)	0.27 (−0.06–0.60)	0.17
June–September	11.76 (11.57–11.96)	11.40 (11.24–11.56)	0.36 (0.08–0.65)	**0.001**
October–December	11.52 (11.29–11.75)	11.08 (10.91–11.25)	0.44 (0.11–0.77)	**<0.001**
C. HbA_{1c} (in %) at follow-up[a]—the whole year				
All patients	6.77 (6.73–6.80)	6.75 (6.72–6.75)	0.02 (−0.02–0.07)	0.38
Females	6.84 (6.78–6.89)	6.80 (6.76–6.84)	0.03 (−0.03–0.10)	0.31
Males	6.71 (6.66–6.76)	6.70 (6.66–6.74)	0.01 (−0.05–0.07)	0.79
<6 years	7.13 (7.07–7.20)	7.10 (7.05–7.15)	0.03 (−0.05–0.11)	0.49
6–11.9 years	6.71 (6.66–6.76)	6.67 (6.63–6.71)	0.04 (−0.02–0.10)	0.19
12–17.9 years	6.54 (6.46–6.61)	6.55 (6.50–6.61)	−0.02 (−0.11–0.07)	0.69
D. HbA_{1c} (in %) at follow-up[a]—the four pandemic-related periods (depending on time of diabetes diagnosis)				
January–February	6.67 (6.55–6.79)	6.68 (6.59–6.76)	−0.01 (−0.17–0.16)	>0.99
March–May	6.80 (6.70–6.90)	6.69 (6.61–6.76)	0.11 (−0.03–0.26)	0.35
June–September	6.79 (6.71–6.88)	6.82 (6.75–6.89)	−0.03 (−0.15–0.10)	>0.99
October–December	6.77 (6.66–6.87)	6.77 (6.69–6.85)	0.00 (−0.15–0.14)	>0.99
E. Daily insulin dose (in IU/kg) at follow-up[a]—the whole year				
All patients	0.70 (0.68–0.71)	0.62 (0.61–0.63)	0.08 (0.06–0.10)	**<0.001**
Females	0.73 (0.71–0.75)	0.64 (0.63–0.66)	0.09 (0.06–0.12)	**<0.001**
Males	0.67 (0.65–0.69)	0.60 (0.58–0.61)	0.07 (0.05–0.09)	**<0.001**
<6 years	0.67 (0.64–0.69)	0.59 (0.57–0.60)	0.08 (0.05–0.11)	**<0.001**
6–11 years	0.70 (0.67–0.72)	0.61 (0.59–0.63)	0.09 (0.06–0.12)	**<0.001**
12–17 years	0.72 (0.70–0.74)	0.65 (0.64–0.67)	0.07 (0.04–0.10)	**<0.001**
F. Daily insulin dose (in IU/kg) at follow-up[a]—the four pandemic-related periods (depending on time of diabetes diagnosis)				
January–February	0.65 (0.60–0.69)	0.61 (0.57–0.64)	0.04 (−0.02–0.11)	0.47
March–May	0.64 (0.61–0.68)	0.60 (0.57–0.63)	0.05 (−0.01–0.10)	0.17
June–September	0.74 (0.70–0.77)	0.63 (0.61–0.66)	0.10 (0.06–0.15)	**<0.001**
October–December	0.73 (0.69–0.77)	0.63 (0.60–0.65)	0.10 (0.05–0.16)	**<0.001**

Note: Multivariable linear regression analysis, adjusted for age group (<6, 6–<12, and 12–<18 years), sex, and immigrant background (patient or at least one parent born outside Germany). Confidence intervals for estimated period-specific values were adjusted according to the Bonferroni method, and corresponding *p*-values according to the Holm method.

[a]Mean (standard deviation) time after diabetes diagnosis was 4.7 (1.0) months in both cohorts.

The significant of bold values as results with the bold *p*-values.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Clemens Kamrath conceptualized the study, interpreted the analyses, wrote the initial manuscript, and revised the manuscript. Joachim Rosenbauer analyzed the data, designed and supervised the statistical analysis, and critically reviewed and revised the manuscript. Alexander J. Eckert analyzed the data and designed the analyses, contributed to the interpretation of results, and reviewed and revised the manuscript. Reinhard W. Holl conceptualized the study, coordinated and supervised data collection, acquired funding for the study, and critically reviewed the manuscript for important intellectual content. Ute Ohlenschläger, Carmen Sydlik, and Nicole Nellen-Hellmuth collected data, contributed intellectually to the research topics of the DPV initiative, and critically reviewed the scientific content of the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

ETHICS APPROVAL STATEMENT

The ethics committee of Ulm University approved the analysis of anonymized data from the DPV registry.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13338.

DATA AVAILABILITY STATEMENT

Access to the data is possible by remote data processing upon request and approval from the DPV board.

ORCID

Clemens Kamrath https://orcid.org/0000-0002-8241-4105
Joachim Rosenbauer https://orcid.org/0000-0002-6086-2230

REFERENCES

1. Wu Y, Chen F, Wang Z, et al. Reductions in hospital admissions and delays in acute stroke care during the pandemic of COVID-19. *Front Neurol*. 2020;11:584734.
2. Aldujeli A, Hamadeh A, Briedis K, et al. Delays in presentation in patients with acute myocardial infarction during the COVID-19 pandemic. *Cardiol Res*. 2020;11(6):386-391.
3. Kamrath C, Mönkemöller K, Biester T, et al. Ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the COVID-19 pandemic in Germany. *JAMA*. 2020;324(8):801-804.
4. Kamrath C, Rosenbauer J, Eckert AJ, et al. Incidence of COVID-19 and risk of diabetic ketoacidosis in new-onset type 1 diabetes. *Pediatrics*. 2021;148(3):e2021050856.
5. Lawrence C, Seckold R, Smart C, et al. Increased paediatric presentations of severe diabetic ketoacidosis in an Australian tertiary Centre during the COVID-19 pandemic. *Diabet Med*. 2021;38(1):e14417.
6. Ho J, Rosolowsky E, Pacaud D, et al. Diabetic ketoacidosis at type 1 diabetes diagnosis in children during the COVID-19 pandemic. *Pediatr Diabetes*. 2021;22(4):552-557.
7. https://covid19.who.int/region/euro/country/de
8. Schaffrath Rosario A, 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). *Eur J Clin Nutr*. 2010;64:341-349.
9. Hammersen J, Reschke F, Tittel SR, et al. Metabolic control during the SARS-CoV-2 lockdown in a large German cohort of pediatric patients with type 1 diabetes: results from the DPV initiative. *Pediatr Diabetes*. 2022;23(3):351-361.
10. Di Dalmazi G, Maltoni G, Bongiorno C, et al. Comparison of the effects of lockdown due to COVID-19 on glucose patterns among children, adolescents, and adults with type 1 diabetes: CGM study. *BMJ Open Diabetes Res Care*. 2020;8(2):e001664.
11. Salmi H, Heinonen S, Hästbacka J, et al. New-onset type 1 diabetes in Finnish children during the COVID-19 pandemic. *Arch Dis Child*. 2021;107:180-185.
12. Kamrath C, Rosenbauer J, Eckert AJ, et al. Incidence of type 1 diabetes in children and adolescents during the Covid-19 pandemic in Germany: results from the DPV registry. *Diabetes Care*. 2022;dc210969. [published online ahead of print, 2022 Jan 17].

How to cite this article: Kamrath C, Rosenbauer J, Eckert AJ, et al. Glycated hemoglobin at diagnosis of type 1 diabetes and at follow-up in children and adolescents during the COVID-19 pandemic in Germany. *Pediatr Diabetes*. 2022;23(6):749-753. doi:10.1111/pedi.13338