diabetesresearchandclinicalpractice192(2022)110110

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Diabetes-related antibody-testing is a valuable screening tool for identifying monogenic diabetes – A survey from the worldwide SWEET registry

Catarina Limbert [a,b,*], Stefanie Lanzinger [c,d], Carine deBeaufort [e], Violeta Iotova [f], Julie Pelicand [g], Mariana Prieto [h], Riccardo Schiaffini [i], Zdeněk Šumnik [j], Danièle Pacaud [k,l], the SWEET Study Group

[a] Hospital Dona Estefânia, Unit of Paediatric Endocrinology and Diabetes, Lisbon, Portugal
[b] Nova Medical School, Universidade Nova de Lisboa, Lisbon, Portugal
[c] Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Ulm, Germany
[d] German Centre for Diabetes Research (DZD), Miünchen-Neuherberg, Germany
[e] Department of Paediatric Diabetes and Endocrinology, Centre Hospitalier Luxembourg, Luxembourg, Luxembourg
[f] Department of Paediatrics, Medical University of Varna, Varna, Bulgaria
[g] San Camilo Hospital-Medicine School, Universidad de Valparaíso, San Felipe, Chile
[h] Servicio de Nutrición, Hospital de Pediatría SAMIC J. P. Garrahan, 1245 Buenos Aieres, Argentina
[i] Diabetes Unit, Bambino Gesù Children's Hospital, Rome, Italy
[j] Department of Paediatrics, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic
[k] Alberta Children's Hospital Research Institute, University of Calgary, Calgary, AB, Canada
[l] Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

ARTICLE INFO

Keywords:
Paediatric
Diabetes
Monogenic
Diagnosis

ABSTRACT

Aims: To evaluate access to screening tools for monogenic diabetes in paediatric diabetes centres across the world and its impact on diagnosis and clinical outcomes of children and youth with genetic forms of diabetes.
Methods: 79 centres from the SWEET diabetes registry including 53,207 children with diabetes participated in a survey on accessibility and use of diabetes related antibodies, c-peptide and genetic testing.
Results: 73, 63 and 62 participating centres had access to c-peptide, antibody and genetic testing, respectively. Access to antibody testing was associated with higher proportion of patients with rare forms of diabetes identified with monogenic diabetes (54 % versus 17 %, $p = 0.01$), lower average whole clinic HbA1c (7.7[Q1,Q2: 7.3–8.0]%/61[56–64]mmol/mol versus 9.2[8.6–10.0]%/77[70–86]mmol/mol, $p < 0.001$) and younger age at onset (8.3 [7.3–8.8] versus 9.7 [8.6–12.7] years $p < 0.001$). Additional access to c-peptide or genetic testing was not related to differences in age at onset or HbA1c outcome.
Conclusions: Clinical suspicion and antibody testing are related to identification of different types of diabetes. Implementing access to comprehensive antibody screening may provide important information for selecting individuals for further genetic evaluation. In addition, worse overall clinical outcomes in centers with limited diagnostic capabilities indicate they may also need support for individualized diabetes management.
Trial Registration: NCT04427189.

1. Introduction

Monogenic forms of diabetes are caused by a pathogenic variant of a single gene which is inherited in an autosomal dominant or recessive manner. Monogenic diabetes is clinically classified in three main groups (1) Maturity Onset Diabetes of the Young (MODY), (2) Neonatal diabetes (NDM) presenting before 6 months of life and (3) other subtypes that include multisystem syndromes (eg. Wolfram or Alström syndrome), mitochondrial diabetes caused by mutations in maternal mitochondrial DNA, severe insulin resistance and lipodystrophy [1]. Epidemiologic

* Corresponding author at: Unit of Paediatric Endocrinology and Diabetes, Hospital Dona Estefânia, Nova Medical School, Lisboa, Portugal.
E-mail address: catarina.limbert@nms.unl.pt (C. Limbert).

https://doi.org/10.1016/j.diabres.2022.110110
Received 19 August 2022; Received in revised form 19 September 2022; Accepted 25 September 2022
Available online 30 September 2022

studies report a frequency of 1–6,5% of MODYs in paediatric diabetes populations [2–7], which is similar [3] or even higher than the frequency of type 2 diabetes (T2D) [2,4]. Nevertheless, monogenic forms of diabetes are frequently underdiagnosed in most diabetic centres probably because clinical and laboratory findings may overlap with other types of diabetes [7,8] and genetic testing is not available. In several monogenic diabetes, a precise diagnosis and subsequent etiology-based treatment has a drastic impact on patient care with improvement of glycemic control and better quality of life [9–11]. The switch from insulin to oral agents (sulphonylureas) is indicated in *HNF1a / HNF4A*-MODY and in neonatal diabetes due to *ABCC8* and *KCNJ11* mutations, which affect the K-ATP channel components [9]. Indeed, early treatment with sulfonylurea may induce long -lasting remission of diabetes in patients with K-ATP channel mutations associated with PND [12]. Furthermore, remission of transient neonatal diabetes without adopting hypoglycemic therapy should not preclude genetic analysis. In patients with *GCK*- mutation diagnosis, no pharmacological treatment is indicated [13].

Referral to specialized centres for the diagnosis of rare forms of diabetes varies across regions, mainly because of differences in awareness and differences in access to appropriate screening testing [5,14]. Inequalities in access to antibodies or genetic testing are particularly evident between the industrialized world and certain regions in South America, Asia and Africa where testing is not offered by the state health system and not covered by private insurance companies.

Registries such as the worldwide SWEET project and networks such as eNDO-ERN aim to harmonize care and promote knowledge sharing and research on rare forms of diabetes [15,16]. In this study, our aim is to assess the screening tests available for the diagnosis of monogenic diabetes in a large number of paediatric diabetes centres across the world and to examine the relationship between access to c-peptide, antibody and genetic testing on diagnosis and clinical outcomes of children and youth with genetic forms of diabetes.

2. Material and methods

This analysis was based on data from the international, prospective, multicentre diabetes SWEET registry [16,17]. SWEET (NCT04427189) was approved by the ethical committee of Hannover Medical School and is associated with the AUF DER BULT Diabetes Centre for Children and Adolescents, Hannover, Germany, which coordinates the SWEET collaboration. The local institutional review boards of the participating centres approved the pseudonymized data collection.

As of 2020, SWEET included 105 participating centres (65 % from Europe) with 806,599 visits in 74,613 people with diabetes. Criteria for inclusion in the analysis were centres with data from individuals diagnosed with T1D, T2D and monogenic forms of diabetes that included MODY and neonatal diabetes, other genetic defects of β-cell function and genetic defects of insulin action, aged $\leq$ 18 years. Within the database, type and subtypes of diabetes are determined by their treating physician and reported in the database according to the ISPAD classification [17]. Excluded were patients with diabetes associated with cystic fibrosis (CFRD), other disease of the exocrine pancreas, endocrinopathies, drug or chemically induced, infections, uncommon forms of immune-mediated disease and other genetic syndromes sometimes associated with diabetes as well as individuals with no data entered in the past 5 years, missing gender, age, diabetes duration or diabetes type, diagnosed after the age of 18 years, and patients with glucose intolerance not yet diagnosed with diabetes. In total, 53,207 youth with diabetes remained. Data from visits of the last year of observation were aggregated so that every individual was represented only once. For centre level data, aggregated results for centres were provided.

The clinical information available for this paper include age at onset (years), gender, type and, for non T1D and T2D, subtype of diabetes and from their last recorded visit height (cm), weight (kg), body mass index (BMI, kg/m^2), BMI z-scores (according to the WHO growth charts [18], hemoglobin A1c (HbA1c, % and mmol/mol), use of insulin (yes/no), and total daily insulin dose (units per kg). In order to adjust for differences between laboratories for HbA1c measurements, multiple of the mean (MOM) method [19] was used to mathematically standardize A1C values to the reference range of the Diabetes Control and Complications Trial (DCCT, 4.0–6.0 %).

A survey was developed to assess access to, and clinical practice use of diabetes related antibody, c-peptide, HLA typing and monogenic diabetes genetic testing. The initial version was first circulated for feedback to all co-authors as content experts. It was then piloted in a group 10 of paediatric endocrinologists for comments on clarity and ability to be completed in an acceptable time frame. It was approved by the SWEET Data, Presentation and Publication Committee and was distributed to the SWEET members attending the SWEET meeting in October 2019 and through an email link for online completion to all centres. Two further reminders were sent over the next 3 months.

2.1. Statistical analysis

Results are presented as median with lower and upper quartile for continuous variables or as number and percentage for binary or categorical variables. Wilcoxon test was used to compare continuous variables between groups and chi-square test for categorical variables. Linear regression models compared differences between patients from centres with access to AB testing at diagnosis and those without access for aged at onset, HbA1c, BMI-SDS and insulin daily dose per kilogram. Age at onset was adjusted for sex; while HbA1c, BMI-SDS and insulin daily dose per kilogram were adjusted for sex, age group, and diabetes duration. Results are presented as adjusted mean and standard error (SE).

All analyses were performed with Statistical Analysis Software 9.4 (SAS, SAS Institute Inc., Cary, North Carolina). Two-sided p-value $<$ 0.05 was considered as significant.

3. Results

A total of 79 of 105 SWEET centres responded to the survey and contributed valid data to the database. The centres came from all continents and can be grouped according to the World bank list of economies as 71 % high income countries, 11 % upper middle, 15 % lower middle income, and 3 % low-income countries. The participating centres take care of 53,207 individuals with paediatric diabetes and the prevalence of genetic defects of β-cell function resemble the data that was recently published [16] for the total SWEET database **(Suppl Table)**. Table 1 presents the main results of the survey demonstrating that 92 % of the centres had access to c-peptide levels, 84 % to any pancreatic antibody determination and 78 % genetic testing for monogenic diabetes, respectively. The clinical characteristics of the 53,207 individuals with type 1, type 2 or diagnosed having monogenic diabetes (MODY, neonatal diabetes, genetic defects of insulin action) are presented in Table 2.

3.1. Access to testing: Survey analysis

Sixty-six centres had access to diabetes-related antibody testing (66 to GAD, 29 to ZnT8, 23 to islet cell, 15 to insulin (IAA) and 13 to IA-2A antibodies). Fifty-six centres routinely tested all newly diagnosed patients for diabetes related antibodies. The other 10 (15 %) centres tested patients' antibodies based on clinical suspicion of type 2 or other forms of diabetes. Seventy-three centres had access to c-peptide testing, but only 44 centres measured c-peptide on all newly diagnosed patients. From the 45 centres having access to HLA typing, only 11 centres routinely performed HLA typing in newly diagnosed patients. Sixty-two centres had access to genetic testing for monogenic forms of diabetes (either locally or through send-out nationally or internationally) (Table 1). Genetic testing for monogenic diabetes is done based on

Table 1
Survey results.

	Total number of responses	Yes N (percentages) *
Do you have access to diabetes related antibody testing in your centre?	79	66 (84 %)
When do you test for diabetes related antibody in your patients?		
On all children with new onset diabetes	66	56 (85 %)
Only if clinical suspicion of type 2 diabetes	65	13 (20 %)
Only if clinical suspicion of rare forms of diabetes	66	14 (21 %)
Do you have access to C-peptide measurement?	79	73 (92 %)
When do you have access to C-peptide measurement?		
On all children with new onset diabetes	73	44 (60 %)
Only if clinical suspicion of type 2 diabetes	73	29 (40 %)
Only if clinical suspicion of rare forms of diabetes	73	25 (34 %)
Do you have access to genetic testing for HLA typing?	79	45 (57 %)
When do you test for HLA susceptibility typing?		
On all children with new onset diabetes	45	11 (24 %)
Only if clinical suspicion of type 2 diabetes	45	2 (4 %)
Only if clinical suspicion of rare forms of diabetes	45	18 (40 %)
Do you have access to genetic testing for monogenic forms of diabetes?	79	62 (78 %)
When do you test for monogenic diabetes?		
According to clinical suspicion	61	61 (100 %)
According to family history	61	55 (90 %)
According to laboratory results	61	47 (77 %)

*Percentages were calculated based on the number of responses to each question listed.

clinical suspicion, family history and/or laboratory findings. Funding for genetic testing is a diverse mix of public/private funds and with about 20 % of costs covered by research funds. Eighteen centres from upper middle to low-income countries have used one of the international reference laboratories offering testing free of charge (Table 1).

3.2. Centres comparison: Survey and data base analysis

Although the proportion of type 1, type 2 and other forms of diabetes did not differ between centres based on access to antibody testing, there was a difference in the subcategorization of other rare forms of diabetes with 17 % of patients being identified as monogenic diabetes in those without access to antibody testing versus 54 % in centres with access to antibody testing (Wilcoxon test, p = 0.01).

There was no difference between centres with (n = 62) or without (n = 17) access to genetic testing for the proportion of type 1, 2 or rare forms of diabetes. Furthermore, access to genetic testing was not associated with a difference in proportion of patients subcategorized with specific rare forms of diabetes (Wilcoxon test, p = 0.21). However, centres without access to genetic testing reported patients with a monogenic diabetes diagnosis based on clinician diagnosis and without genetic confirmation in 54 % of cases while this proportion was 29 % in centres with access to genetic testing.

Similarly, there was no difference between centres with (n = 47) and without (n = 6) access to c-peptide testing for the proportion of type 1, 2 or rare forms of diabetes. Those centres without access to c-peptide testing reported patients with a monogenic diabetes diagnosis based on clinical information without genetic confirmation in 97 % of cases while this proportion was 30 % in centres with access to c-peptide (statistical analysis not performed due to small numbers).

Table 3
Association between testing availability and diagnosis of different types of diabetes and metabolic outcomes.

	Centers with Access to AB +Access GT N = 61	Centers with Access to AB No access to GT N = 5	Centers with No access to AB and No access to GT N = 13	P
Type 1 %	94	96	95	NS
Type 2 %	3	2	3	NS
Rare forms of diabetes %	3	2	2	NS
Monogenic genetically confirmed %	71	58	35	
Clinical suspicion of Monogenic diabetes %	29	42	65	
Whole Center Median HbA1c [Q1-Q3]	7.7 [7.3–8.0]% 61[56–64] mmol/mol	7.9 [7.5–8.8]% 63[58–73] mmol/mol	9.2 [8.6–10.0]% 77[70–86] mmol/mol	AB + GT vs No access P = 0.0006
Patients with monogenic diabetes*: Median HbA1c [Q1-Q3] *	6.3 [6.0–6.7]% 63[42–50] mmol/mol	6.3 [5.8–7.6]% 63[40–60] mmol/mol	7.4 [6.1–9.8]% 57[43–73] mmol/mol	Wilcoxon test P < 0.0001
Patients age at onset [Q1-Q3] of monogenic diabetes *	9.2 [5.0–12.4] year	10.5 [6.6–14.4] year	11.1 [9.1–13.6] year	Wilcoxon test P = 0.0006

AB: antibody, GT: genetic testing.
*Includes only those with confirmed genetic testing monogenic diabetes.

Table 2
Clinical characteristics (median [Q1-Q3]) presented as aggregated data per centres based on the type of diabetes*.

	Whole clinic population	Type 1 diabetes	Type 2 diabetes	Monogenic diabetes (MODY, neonatal diabetes and insulin action defects)
Sex (male %)	51	51	41	53
Age at onset	8.4 [7.7–9.2]	8.2 [7.6–9.0]	13.8 [12.8–14.6]	9.1 [6.7–11.3]
Diabetes duration	4.8 [3.8–5.7]	5.0 [3.8–5.8]	2.0 [1.4–3.2]	3.7 [2.0–5.7]
BMI SD	0.5 [0.3–0.7]	0.5 [0.3–0.7]	2.3 [2.0–2.8]	0.3 [-0.1–0.7]
HbA1c (%)	7.8 [7.3–8.6]%	7.8 [7.4–8.6]%	6.9 [6.3–7.8]%	6.4 [6.2–7.3]%
mmol/mol	62[56–70]mmol/mol	62[57–70]mmol/mol	52[45–62]mmol/mol	46[44–56]mmol/mol
Proportion with HbA1c < 7.5 %/58 mmol/mol	41	40	64	69
Daily insulin dose per kg	0.8 [0.8–0.8]	0.8 [0.8–0.9]	0.5 [0.4–0.7]	0.7 [0.6–0.8]
Proportion on pump therapy (%)	34	35	5	21

Data reported as median with lower and upper quartile or percentage.
*Reported by clinicians using the ISPAD classification.

Percentage of patients presenting with DKA at onset was identical (51 %) in centres with access and those without access to antibody, c-peptide or genetic testing.

At a center level, those institutions with better availability of testing also appear to have better overall clinical outcomes in children and youth with and without monogenic diabetes (Table 3).

On the patient level, clinical characteristics differences between patients from centres with access to AB testing at diagnosis and those without access were found. First, age at onset adjusted for sex was significantly associated with access to AB testing: centres with access to AB 8.3 [95 %CI: 0.8] years versus 9.5 [0.4] years in centres without access to AB ($p < 0.001$). In a linear regression adjusted for sex, age and diabetes duration, average whole clinic HbA1c was significantly higher in centres without access to antibody testing: 9.3 [0.03]%/78[0.25] mmol/mol versus 8.2 [0.01]%/66[0.08]mmol/mol; $p < 0.0001$. BMI-SDS was significantly higher in centres with access to AB testing compared to those without access: adjusted for sex, age and diabetes duration (0.65 [0.01] versus 0.15 [0.02]; $p < 0.0001$). A regression of insulin daily dose adjusted for sex, age group and diabetes duration also found similar results with dosages being lower in centres with access to AB testing: (0.80 [0.00] units/kg/day versus 0.93 [0.00] units/kg/day; $p < 0.001$).

4. Discussion

In world-wide specialized paediatric diabetes centres member of the SWEET registry, the majority have access to antibodies testing (84 %), C-peptide determination (73 %), and genetic testing (57 %). Access to antibody testing was associated with a higher proportion of rare forms of diabetes subclassified as monogenic diabetes by clinicians: 54 % compared to 17 % of cases in centres without access to antibody testing. The survey showed that clinical suspicion and antibody testing are related to the identification of the different sub-types of diabetes in the SWEET database. Access to genetic testing increases the percentage of genetic confirmation of monogenic diabetes in SWEET centers. Thus, availability of screening parameters and particularly testing of new-onset cases for diabetes-related antibodies improved identification of different types of diabetes in children allowing better implementation of international guidelines for children and adolescents with diabetes [20].

Indeed, according to the International Society for Paediatric and Adolescents Diabetes (ISPAD) recommendations [20], genetic testing is mandatory immediately after NDM diagnosis. In children and youth, monogenic diabetes testing should be performed in cases of diabetes with a positive family history of diabetes, absence of pancreatic antibodies or evidence of preserved beta cell- function. The present study reveals varying worldwide screening practices used for the diagnosis of diabetes among large paediatric centres. There was a difference between access to screen tests and routine use in all newly diagnosed patients with diabetes. From 66 centres with access to antibody testing, 15 % use antibody testing only in case of suspicion of non-type 1 diabetes. In addition, most centers will only test for one diabetes related auto-antibody, mostly GAD antibodies. This approach may erroneously lead to a non-type 1 diabetes diagnosis, especially in younger children in which IA-2A and IAA are more common [21,22]. Close to half of the centres with access to C-peptide, do not measure it at new-onset diabetes. C-peptide reflects insulin secretion capacity and can be used at diagnosis to differentiate between insulin insufficiency and insulin resistance. Finally, 76 % of centres with access to HLA genotyping, do not routinely evaluate this gene in newly diagnosed children. Identification of HLA and non-HLA risk loci allow for calculation of diabetes genetic risk score (GRS), which has been considered of help to discriminate diabetes subtypes, including monogenic diabetes [23,24]. From our data, however, in real-world diabetes care the use of GRS is still not implemented among pediatric diabetes centres of SWEET.

Such distinct diagnostic approaches among SWEET centres may be due to differences in the incidence of diabetes in each country, number of patients per centre, economic resources of each centre and degree of clinicians' knowledge on testing rationales [25,26]. Diagnosis of T1D in the paediatric age group is usually based on typical clinical features and glycemic levels. (17, 27) While genetic screening is universally recommended in neonatal diabetes forms, comparable recommendations on minimal or mandatory screening parameters to rule out monogenic diabetes by antibodies or genetic testing are not available, which certainly contributes to heterogeneous approaches among centres.

The latest analysis of the SWEET registry classifying 2789 patients as rare forms of diabetes indicate that this category includes 22 % of MODY patients and 18 % with neonatal diabetes [16], which corresponds well to the current survey data. In all participating centres in the survey, genetic testing for monogenic diabetes is performed based on clinical suspicion, family history and/or laboratory findings, which is in line with the current international guidelines [20,27]. The percentage of DKA at onset in centres with and without access to genetic or antibody testing does not change, which indirectly reflects a similar level of clinical suspicion of other forms of diabetes among SWEET centres, independently of the available screening diagnostic tools.

When evaluating the access to screening tools for diagnosis of subtypes of diabetes, genetic testing does not seem to influence the diagnosis rate of monogenic diabetes in paediatric centres differently from a recent study suggesting that genetic screening has an impact on the prevalence of monogenic forms [11]. Our results may be due to the low prevalence of monogenic diabetes in the studied centres and the high level of clinical suspicion required to perform genetic testing even in centres with access to molecular diagnosis. In an ideal world, all suspected cases of rare forms of diabetes should be confirmed with genetic testing for proper diagnosis. However, in the SWEET registry, the classification of monogenic forms of diabetes does not require a mandatory genetic confirmation, in accordance with existing pediatric diabetes guidelines.

Access to antibody testing seems to contribute to a higher rate of identification of monogenic diabetes in the participating centres. Five to 10 % of individuals with T1D are expected to be antibody negative before the era of molecular diagnosis [27]. Conversely, in monogenic forms of diabetes, pancreatic antibodies are normally negative [20,28]. Thus, a negative antibody testing at diabetes onset should prompt suspicion of other types of diabetes rather than being interpreted as antibody negative T1D.

Inequities in access to antibody testing are related to clinical outcomes among centres of SWEET. From the 79 centres participating in our study, 23 are middle- and low-income countries according to the World Bank list. The link between higher mean A1C and no access to antibody testing may reflect overall gaps in technology, education, or basic resources in diabetes management and consequently worse diabetes outcomes [29–31]. The older age at onset, higher insulin requirements, and lower BMI in centres without access to AB testing also suggest a shortage of human and technological resources in diabetes management.

Interestingly, in a previous report of SWEET registry on type 2 and other non-type 1 diabetes, MODY 2 also accounted for the most frequent monogenic diabetes form reported in the database [15]. Of the 53,207 individuals registered in SWEET, 27,013 (50.8 %) are from Europe. Because European centres represent a large percentage of centres among SWEET it is unclear if the high proportion of MODY 2 identified in this population of mainly European descent would be found once more data becomes available from other continents.

There are several limitations to this study. First, the lack of genetic confirmation for all patients with diagnosis of monogenic diabetes included in the study is certainly a limitation of our results. It highlights the issue that, worldwide, several pediatric diabetes centers of reference still rely only on clinical diagnosis for the diagnosis of monogenic diabetes. A second limitation is the predominance of European centres in SWEET which may not reflect clinical practices in other parts of the world. Third, the relatively low number of centers from low-income countries limits their input to better understand the influence of

access to screening tools/genetic testing in the prevalence of different forms of monogenic diabetes.

5. Conclusions

This real-world analysis provides evidence that different screening and diagnostic practices and diverse genetic backgrounds may have an impact on the prevalence of genetically confirmed monogenic diabetes. The 100,000 Genomes Pilot project on rare disease diagnosis in the U.K. demonstrates how such advanced approaches help to elucidate previously unknown disease entities [32] leading to personalized therapeutic intervention. Implementing access to comprehensive antibody screening evaluation in children and youth with new-onset diabetes may provide important information for further genetic evaluation [33] and represent a major step towards an approach using precision medicine to improve paediatric diabetes outcomes.

Contribution statement

All authors contributed to the study concept and design. DP and CL supervised the study. SL analysed the data. All authors participated in data interpretation. CL and DP drafted the first version of the manuscript. The final manuscript was reviewed and approved by all. SL is the guarantor of the study data and analysis. CL and DP take full responsibility for the work including the study design, access to data and the decision to submit and publish the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

SWEET is a registered non-profit charity in Hannover, Germany. It is financed through membership fees of the participating centres (based on income of country of residence according to the World Bank) and corporate members. We acknowledge with gratitude the support from the following SWEET e.V. corporate members – in alphabetical order: Abbott, Boehringer Ingelheim, DexCom Inc., Insulet, Eli Lilly & Co., Medtronic Europe, Sanofi.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.110110.

References

[1] Riddle MC, Philipson LH, Rich SS, Carlsson A, Franks PW, Greeley SAW, et al. Monogenic diabetes: from genetic insights to population-based precision in care. reflections from a diabetes care editors' expert forum. Diabetes Care 2020;43(12):3117–28.

[2] Fendler W, Borowiec M, Baranowska-Jazwiecka A, Szadkowska A, Skala-Zamorowska E, Deja G, et al. Prevalence of monogenic diabetes amongst Polish children after a nationwide genetic screening campaign. Diabetologia 2012;55(10):2631–5.

[3] Neu A, Feldhahn L, Ehehalt S, Hub R, Ranke MB, Dg B-W. Type 2 diabetes mellitus in children and adolescents is still a rare disease in Germany: a population-based assessment of the prevalence of type 2 diabetes and MODY in patients aged 0–20 years. Pediatr Diabetes 2009;10(7):468–73.

[4] Mozzillo E, Salzano G, Barbetti F, Maffeis C, Lombardo F, Franzese A, et al. Survey on etiological diagnosis of diabetes in 1244 Italian diabetic children and adolescents: impact of access to genetic testing. Diabetes Res Clin Pract 2015;107(3):e15–8.

[5] Delvecchio M, Mozzillo E, Salzano G, Iafusco D, Frontino G, Patera PI, et al. Monogenic Diabetes Accounts for 6.3% of Cases Referred to 15 Italian Pediatric Diabetes Centers During 2007 to 2012. J Clin Endocrinol Metab. 2017;102(6):1826-34.

[6] Johansson BB, Irgens HU, Molnes J, Sztromwasser P, Aukrust I, Juliusson PB, et al. Targeted next-generation sequencing reveals MODY in up to 6.5% of antibody-negative diabetes cases listed in the Norwegian Childhood Diabetes Registry. Diabetologia 2017;60(4):625–35.

[7] Johnson SR, Carter HE, Leo P, Hollingworth SA, Davis EA, Jones TW, et al. Cost-effectiveness Analysis of Routine Screening Using Massively Parallel Sequencing for Maturity-Onset Diabetes of the Young in a Pediatric Diabetes Cohort: Reduced Health System Costs and Improved Patient Quality of Life. Diabetes Care 2019;42(1):69–76.

[8] Irgens HU, Molnes J, Johansson BB, Ringdal M, Skrivarhaug T, Undlien DE, et al. Prevalence of monogenic diabetes in the population-based Norwegian Childhood Diabetes Registry. Diabetologia 2013;56(7):1512–9.

[9] Pearson ER, Pruhova S, Tack CJ, Johansen A, Castleden HA, Lumb PJ, et al. Molecular genetics and phenotypic characteristics of MODY caused by hepatocyte nuclear factor 4alpha mutations in a large European collection. Diabetologia 2005;48(5):878–85.

[10] Shepherd M. Transforming lives: transferring patients with neonatal diabetes from insulin to sulphonylureas. European Diabetes Nursing 2006;3(3):137–42.

[11] Johnson SR, Ellis JJ, Leo PJ, Anderson LK, Ganti U, Harris JE, et al. Comprehensive genetic screening: The prevalence of maturity-onset diabetes of the young gene variants in a population-based childhood diabetes cohort. Pediatr Diabetes 2019;20(1):57–64.

[12] Bonfanti R, Iafusco D, Rabbone I, Diedenhofen G, Bizzarri C, Patera PI, et al. Differences between transient neonatal diabetes mellitus subtypes can guide diagnosis and therapy. Eur J Endocrinol. 2021;184(4):575-85.

[13] Stride A, Shields B, Gill-Carey O, Chakera AJ, Colclough K, Ellard S, et al. Cross-sectional and longitudinal studies suggest pharmacological treatment used in patients with glucokinase mutations does not alter glycaemia. Diabetologia 2014;57(1):54–6.

[14] Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): how many cases are we missing? Diabetologia 2010;53(12):2504–8.

[15] Pacaud D, Schwandt A, de Beaufort C, Casteels K, Beltrand J, Birkebaek NH, et al. A description of clinician reported diagnosis of type 2 diabetes and other non-type 1 diabetes included in a large international multicentered pediatric diabetes registry (SWEET). Pediatr Diabetes 2016;17(Suppl 23):24–31.

[16] Reschke F, Rohayem J, Maffei P, Dassie F, Schwandt A, de Beaufort C, et al. Collaboration for rare diabetes: understanding new treatment options for Wolfram syndrome. Endocrine 2021;71(3):626–33.

[17] Mayer-Davis EJ, Kahkoska AR, Jefferies C, Dabelea D, Balde N, Gong CX, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Definition, epidemiology, and classification of diabetes in children and adolescents. Pediatr Diabetes 2018;19:7–19.

[18] Organization 2007 [29/04/2016].. Available from: http://www.who.int/growthref/who2007_bmi_for_age/en/index.html.

[19] American Diabetes Association; European Association for the Study of Diabetes; International Federation of Clinical Chemistry and Laboratory Medicine; International Diabetes Federation. Consensus statement on the worldwide standardisation of the HbA1c measurement. Diabetologia 2007;50(10):2042–3.

[20] Hattersley AT, Greeley SAW, Polak M, Rubio-Cabezas O, Njølstad PR, Mlynarski W, et al. ISPAD Clinical Practice Consensus Guidelines 2018: The diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes 2018;19:47–63.

[21] Ross C, Ward ZJ, Gomber A, Owais M, Yeh JM, Reddy CL, et al. The Prevalence of Islet Autoantibodies in Children and Adolescents With Type 1 Diabetes Mellitus: A Global Scoping Review. Front Endocrinol (Lausanne) 2022;13:815703.

[22] Ziegler AG, Rewers M, Simell O, Simell T, Lempainen J, Steck A, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA 2013;309(23):2473.

[23] Patel KA, Oram RA, Flanagan SE, De Franco E, Colclough K, Shepherd M, et al. Type 1 Diabetes Genetic Risk Score: A Novel Tool to Discriminate Monogenic and Type 1 Diabetes. Diabetes 2016;65(7):2094–9.

[24] Redondo MJ, Gignoux CR, Dabelea D, Hagopian WA, Onengut-Gumuscu S, Oram RA, et al. Type 1 diabetes in diverse ancestries and the use of genetic risk scores. Lancet Diabetes Endocrinol 2022;10(8):597–608.

[25] Green A, Hede SM, Patterson CC, Wild SH, Imperatore G, Roglic G, et al. Type 1 diabetes in 2017: global estimates of incident and prevalent cases in children and adults. Diabetologia 2021;64(12):2741–50.

[26] Sumnik Z, Szypowska A, Iotova V, Bratina N, Cherubini V, Forsander G, et al. Persistent heterogeneity in diabetes technology reimbursement for children with type 1 diabetes: The SWEET perspective. Pediatr Diabetes 2019;20(4):434–43.

[27] Holt RIG, DeVries JH, Hess-Fischl A, Hirsch IB, Kirkman MS, Klupa T, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2021;64(12):2609–52.

[28] Carlsson A, Shepherd M, Ellard S, Weedon M, Lernmark Å, Forsander G, et al. Absence of Islet Autoantibodies and Modestly Raised Glucose Values at Diabetes Diagnosis Should Lead to Testing for MODY: Lessons From a 5-Year Pediatric Swedish National Cohort Study. Diabetes Care 2020;43(1):82–9.
[29] Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016–2018. Diabetes Technol Ther 2019;21(2):66–72.
[30] Gerhardsson P, Schwandt A, Witsch M, Kordonouri O, Svensson J, Forsander G, et al. The SWEET Project 10-Year Benchmarking in 19 Countries Worldwide Is Associated with Improved HbA1c and Increased Use of Diabetes Technology in Youth with Type 1 Diabetes. Diabetes Technol Ther 2021;23(7):491–9.
[31] Cardona-Hernandez R, Schwandt A, Alkandari H, Bratke H, Chobot A, Coles N, et al. Glycemic Outcome Associated With Insulin Pump and Glucose Sensor Use in Children and Adolescents With Type 1 Diabetes. Data From the International Pediatric Registry SWEET. Diabetes Care 2021;44(5):1176–84.
[32] Smedley D, Smith KR, Martin A, Thomas EA, McDonagh EM, Cipriani V, et al. 100,000 Genomes Pilot on Rare-Disease Diagnosis in Health Care - Preliminary Report. N Engl J Med 2021;385(20):1868–80.
[33] Eggermann T, Elbracht M, Kurth I, Juul A, Johannsen TH, Netchine I, et al. Genetic testing in inherited endocrine disorders: joint position paper of the European reference network on rare endocrine conditions (Endo-ERN). Orphanet J Rare Dis 2020;15(1).