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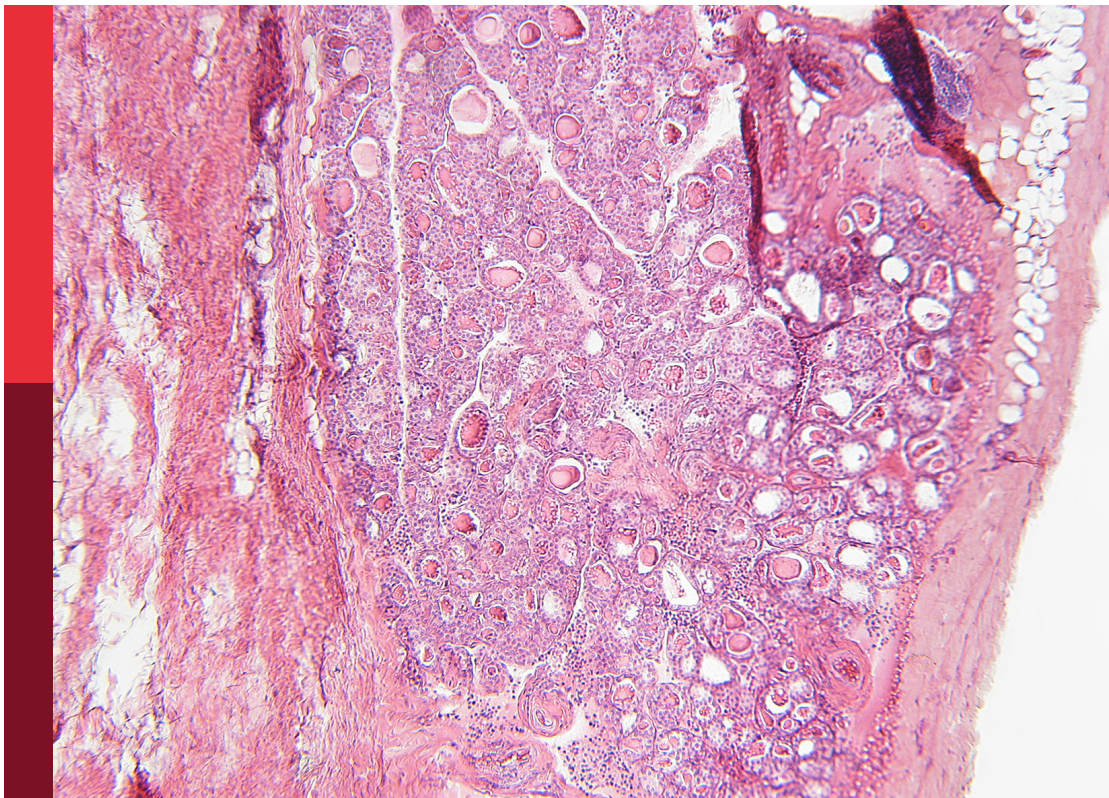

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Technologies for diabetes, volume II

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Table of contents

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Advanced Hybrid Closed Loop users' satisfaction of telemedicine and telenursing in pediatric and young adult type 1 diabetes

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Background and aims: The aim of the study was to evaluate the satisfaction of the use of telemedicine and telenursing in children and young adults with Type 1 Diabetes (T1D) using Advanced Hybrid Closed Loop systems (AHCL) with a focus on the role of connectivity, data download and the ease of technical steps in the set and sensor change procedures.

Methods: An online anonymous survey was administered to AHCL users. The questionnaire consisted of five Clusters: Cluster A-B-C included questions related to the general satisfaction in the use of telemedicine, Cluster D was focused on the role of data download and connectivity, Cluster E was related to satisfaction in telenursing and Cluster F to the perception of ease of execution of the technical steps like changing the infusion set and the sensor.

Results: We collected 136 completed questionnaires. 83.8% of AHCL users were overall satisfied with the quality of the telemedicine service. 88.2% of patients downloaded AHCL data before visits and the overall quality of televisits (data sharing, connectivity, ease of use) was satisfactory for 85.3% of users. Telenursing support during set and sensor change procedures was considered effective by 98% of AHCL users. The sensor and insulin infusion set change procedure is perceived as different for the two systems: set change simpler for Medtronic ($p = 0.011$) users, while sensor change was simpler for Tandem users ($p = 0.009$).

Conclusion: Telemedicine and telenursing have an essential role in diabetology and are highly appreciated in AHCL users. The nurse support in the education of the use of AHCL systems is effective and must be implemented. Unfortunately, not all patients have the technological tools needed for downloading data at home and using telemedicine services; this represents an important challenge for the future of diabetology and for the equity in accessibility to care.

KEYWORDS

type 1 diabetes mellitus, telemedicine, telenursing, Advanced Hybrid Closed Loop, insulin infusion set, continuous glucose monitoring

1. Introduction

Telemedicine refers to a set of innovative technologies and processes useful to allow remote communication between healthcare professionals and patients (1, 2). This method of visit was implemented and accelerated during the Covid-19 pandemic, where it was essential to continue regular follow-up of chronic diseases, respecting the standards of distance required at the time. Social isolation highly influenced patient care around the world, favoring remote consultation through telehealth/telemedicine as an option to maintain assistance to patients with chronic disease (3). The pandemic accelerated the development of telenursing as a part of telemedicine that focuses on the delivery of care services in the nursing field (4). Digital transformation is already ongoing in pediatrics (5, 6) and many studies have reported the usefulness and the satisfactions of patients in the various fields of pediatrics (7).

Type 1 Diabetes (T1D) is one of the most suitable chronic diseases for this innovation of care thanks to advanced technology systems and innovative devices such as continuous glucose monitoring (CGM) and advanced hybrid closed-loop systems (AHCLs) that allow online data sharing (8). The sharing of the data remotely makes it possible to monitor the patient's glycemic control and to make any changes to insulin therapy via telehealth services. During Covid-19 pandemic many pediatric diabetes centers adapted to the pandemic by resorting to telemedicine (9, 10). In the last few years, telenursing services dedicated to patients with T1D have increased, to support both correct glycemic monitoring and correct use of advanced insulin pumps (11, 12).

Telemedicine proved to be effective and not inferior to face-to-face visits in maintaining or improving glycemic control in pediatric patients affected by T1D (13–16). Despite the barriers encountered in implementing this service, telemedicine is essential as an alternative follow-up tool for a chronic disease such as diabetes (17–21). Many healthcare professionals of the diabetes teams have been satisfied with the use of telemedicine in patients with T1D and consider it a clinical practice to be strengthened in the future (22). Above all, the patients and their families were satisfied with the use of telemedicine (22, 23).

In a previous work we evaluated the satisfaction of patients and their families in the use of telemedicine through a questionnaire already validated and adapted to T1D patients (12, 24). It was the first survey focused on pediatric and young population affected by type 1 diabetes. The results of the survey demonstrated that telemedicine and telenursing have a positive impact on the daily life of T1D patients and their parents. Data collected showed excellent satisfaction of the service provided, especially in pump users and in patients who live furthest from the center. Furthermore, telenursing service resulted in an effective and appreciated tool to provide education and practical support in the management of insulin pumps and sensors. However, a limitation of the previous study was the absence of questions related to some fundamental aspects in the use of telemedicine, such as device connectivity, data download, quality of video-call and internet connection. After the Covid-19 pandemic we continued to use telemedicine in the Regional Pediatric Diabetes Center of IRCCS Istituto Giannina Gaslini as an alternative follow-up tool in patients who wanted to and for whom remote data sharing was possible. In recent years, the telemedicine service has been officially recognized by the Hospital and the Region and the platforms have been implemented. To date, our Center performs half of the outpatient visits via telemedicine (about 100–150 visits per month) and provides telenursing education in the first week after starting the insulin pump for the support in set and sensor change procedure.

To implement the previous study and to overcome the limitations we decided to investigate fundamental aspects omitted in the previous study such as connectivity and data download. Furthermore, we considered it essential to further investigate patient AHCL systems users of satisfaction in telenursing.

2. Methods

2.1. Aims and study design

The primary aim of the study was to evaluate the satisfaction of the use of telemedicine and telenursing in children and young adults with T1D using AHCL systems and followed by the Regional Pediatric Diabetes Center of IRCCS Istituto Giannina Gaslini, Genoa, Liguria, Italy. The secondary aims were to assess satisfaction of nursing support in sensor and infusion set change procedures and to assess patients' perception of ease of performing these procedures, also in relation to the type of AHCL system used.

AHCL initiation training program conducted by healthcare professionals of our Center consists of a theoretical part on the correct use and functioning of the advanced insulin pump (conducted by the diabetologist and the dietician) and a practical part on the correct preparation and placement of infusion set and sensor (conducted by the nurse). In the days following the placement of AHCL system, the first change of CGM sensor and the first change of the infusion set can be assisted by the nursing staff through the telenursing service. Telenursing support is offered to all patients, but those who perform the first sensor change in telenursing aren't many, because many patients already have the sensor in use from onset and are already able to perform the replacement independently.

The study was conducted from September to December 2022 and consisted of two different phases: the creation and validation of the questionnaire, and its administration to the patients and their families.

2.2. Validation of the questionnaire

A new questionnaire was created starting from the one used in the previous study (12), which has been better adapted to AHCL users and implemented to create a new evaluation tool more focused on connectivity, data download and set and sensor change procedures. Content validation of the new questionnaire was performed by a group of six experts in the field of diabetes working at IRCCS Istituto Giannina Gaslini (a pediatric diabetologist, a resident in pediatrics, a psychologist and three pediatric nurses). The content validity was completed after one round only: after the first round, all items had a 100% item-content validity index (I-CVI) for the relevance. Regarding the comprehensibility, two items reached 83.3% of I-CVI, while the remaining 37 had 100% I-CVI (scale-content validity index, S-CVI = 94.9%) (25).

The validated questionnaire consisted of six sections (Supplementary Table S1):

- *Cluster A – Adequacy of medical care*
- *Cluster B – Psychological impact of telemedicine*
- *Cluster C – Possible advantages and future use of telemedicine*
- *Cluster D (**new**) – Connectivity and data download*
- *Cluster E – Telenursing* (satisfaction with the telenursing service was assessed in patients who performed the first nurse-assisted infusion set change)
- *Cluster F (**new**) – Infusion set and glucose sensor replacement*

In all the clusters, responses were given on a 10-point Likert scale ranging either from "strongly disagree" to "strongly agree" or from "extremely difficult" to "extremely easy," subsequently divided into three sections: 0 to 6 (neutral or dissatisfied/neutral or difficult), 7 to 8 (satisfied/easy) and 9 to 10 (extremely satisfied/extremely easy). A 10-level index of the overall ease of infusion insulin set change was obtained averaging the related answers to the corresponding items in cluster F (rounded to the nearest whole number). Cluster D and Cluster E included some multiple-choice questions (Yes or No). The answers of Cluster A-B-C were also compared based on the age of the patient, the answers of Cluster D and E were also compared based on the type of AHCL used by the patient.

2.3. Study population

Participation in the study was voluntary, and completing the survey implied a participant's consent. The inclusion criteria were: T1D according to the American Diabetes Association (ADA) criteria, age between 1 and 25 years, use of AHCL system for at least 1 month, use of the telemedicine service at least once. Patients and caregivers who were unable to understand, read or write in Italian were excluded. The two AHCL systems used by our patients at the time of the study were Tandem Control-IQ (Tandem Diabetes Care, San Diego, CA, United States) and Minimed 780G (Medtronic, Northridge, CA, United States) (7). The Italian national health system allows AHCL to be prescribed and reimbursed to all patients with T1D. Therefore, our center proposes the use of these advanced systems regardless of the socio-economic situation of the family.

The study was proposed to patients (and their parents/caregivers) who met inclusion criteria during the scheduled visits. The questionnaire was administered online and anonymously. One individual per family answered the questionnaire based on the age or the child's level of independence: a parent/caregiver answered for patients <12 years of age, while the patient answered for children and young adults ≥12 years of age.

2.4. Data analysis

Content validation of the questionnaire was performed using the Content Validity Index for each item (I-CVI) and for the whole questionnaire ("scale validity index," S-CVI) and then calculated as the proportion of experts providing a positive judgment about both the relevance and the comprehensibility of each item. An item was considered as validated if an I-CVI > 83% was assigned for both the relevance and the comprehensibility, while the corresponding cut-offs for S-CVI were set at 90% (25).

The validated questionnaire was analyzed using absolute frequencies and percentages to summarize qualitative variables. Ten-level Likert scales were aggregated into three categories (0–6, 7–8, and 9–10). The comparison between groups was performed by the Pearson chi-square test or the Fisher exact test when appropriate. All analyses were carried out using the software STATA for Windows, version 13.1 (Stata Corporation, College Station, Texas, United States).

3. Results

The survey was administered to 180 patients. We collected 136 completed questionnaires: 41 (30.1%) were filled out by parents or caregivers since the age of the patients was <12 years and 95 (69.9%) by the patients ≥12 years of age. Eighty patients (58.8%) used Tandem Control-IQ and 56 (41.2%) used Minimed 780G. Data related to the responses of Clusters A, B, and C are shown in Table 1.

3.1. Cluster A—adequacy of medical care

Most patients felt comfortable or very comfortable (respectively 26.5 and 62.5%) to explain their medical problems during televisits. Patients <12 years seem to be able to express their medical problems better than patients ≥12 years (80.5% vs. 54.7%, $p = 0.017$). The absence of physical contact was not a relevant problem for most of the participants (73.5% of score > 6) even if adolescents and young adults ≥12 years suffered the distance more than parents/caregivers (31.6% vs. 14.6% of score 0–6). In conclusion, 83.8% of the population was overall satisfied with the quality of the service provided. Regardless of age, 56.6% was highly satisfied (score 9–10) and 27.2% satisfied (score 7–8) (Table 1).

3.2. Cluster B—psychological impact of telemedicine

Most of the population was able to speak easily to the diabetes medical team during the televisits: 52.2% report that they were able to communicate very well (score 9–10) and 34.6% well (score 7–8). 86.8% of responders felt psychologically comfortable when communicating with the medical team (65.4% of them felt very comfortable, score 9–10). There were no significant differences by age in both items B1 and B2. 64.7% were extremely satisfied with the attentions received during telemedicine follow-up visits (score 9–10), even if parents/children <12 years of age were more satisfied than adolescents (75.6% vs. 60.0%, $p = 0.026$). Finally, a large part of the participants perceived telemedicine as an attention toward themselves (Table 1).

3.3. Cluster C—possible advantages and future use of telemedicine

Telehealth is not uniformly considered as an appropriate modality of care in young T1D patients: 27.2% of them do not consider it appropriate, 31.6% consider it a moderately appropriate modality (score 7–8) and 41.2% very appropriate (score 9–10), but statistical significance was borderline ($p = 0.064$). 48.5% of responders strongly agree on continuing to be followed via telemedicine (score 9–10),

TABLE 1 Participants responses to questions of Cluster A (adequacy of medical care), Cluster B (psychological impact of telemedicine), and Cluster C (possible advantages and future use of telemedicine).

	>12 years			<12 years			*p*	Total		
	Score 0–6 *N* (%)	Score 7–8 *N* (%)	Score 9–10 *N* (%)	Score 0–6 *N* (%)	Score 7–8 *N* (%)	Score 9–10 *N* (%)		Score 0–6 *N* (%)	Score 7–8 *N* (%)	Score 9–10 *N* (%)
A1. I was able to explain my medical problems well enough via televisit	13 (13.68)	30 (31.58)	52 (54.74)	2 (4.88)	6 (14.63)	33 (80.49)	**0.017**	15 (11.03)	36 (26.47)	85 (62.5)
A2. The absence of physical contact during televisit was not a relevant problem	30 (31.58)	27 (28.42)	38 (40)	6 (14.63)	15 (36.59)	20 (48.78)	0.120	36 (26.47)	42 (30.88)	58 (42.65)
A3. Overall, I am satisfied with the quality of the service provided via televisit	16 (16.84)	26 (27.37)	53 (55.79)	6 (14.63)	11 (26.83)	24 (58.54)	0.938	22 (16.18)	37 (27.21)	77 (56.62)
B1. I was easily able to talk with the medical team during the televisit	14 (14.74)	37 (38.95)	44 (46.32)	4 (9.76)	10 (24.39)	27 (65.85)	0.127	18 (13.24)	47 (34.56)	71 (52.21)
B2. I felt at ease when communicating with my medical team	13 (13.68)	24 (25.26)	58 (61.05)	5 (12.20)	5 (12.20)	31 (75.61)	0.195	18 (13.24)	29 (21.32)	89 (65.44)
B3. I received adequate attention during televisit	9 (9.47)	29 (30.53)	57 (60.00)	6 (14.63)	4 (9.76)	31 (75.61)	**0.026**	15 (11.03)	33 (24.26)	88 (64.71)
B4. I perceived telemedicine as an attention toward me	16 (16.84)	24 (25.26)	55 (57.89)	5 (12.20)	7 (17.07)	29 (70.73)	0.367	21 (15.44)	31 (22.79)	84 (61.76)
C1. I think that televisits are an adequate modality of assistance for my disease	28 (29.47)	34 (35.79)	33 (34.74)	9 (21.95)	9 (21.95)	23 (56.10)	0.064	37 (27.21)	43 (31.62)	56 (41.18)
C2. I am willing to continue some of my follow-up visits via videocall, keeping appointments in person at longer intervals	26 (27.37)	22 (23.16)	47 (49.47)	6 (14.63)	16 (39.02)	19 (46.34)	0.100	32 (23.53)	38 (27.94)	66 (48.53)
C3. Televisits allow me and my family to save time/money/time off work and/or school	12 (12.63)	18 (18.95)	65 (68.42)	3 (7.32)	12 (29.27)	26 (63.41)	0.376	15 (11.03)	30 (22.06)	91 (66.91)

Bold values = statistically significant.

27.9% seems to want it even if less strongly (score 7–8), while 23.5% prefer face-to-face visits (score 0–6): this desire emerged particularly in the population of adolescents and young adults ≥12 years old (27.4% vs. 14.6%), although the results are not statistically significant ($p = 0.100$). Most of the participants (89% of score > 6) affirmed that televisits allow them to save money and time, avoiding taking time off work and/or school (Table 1).

3.4. Cluster D—connectivity and data download

Data of the responses of Cluster D are shown in Table 2. Approximately 88% of patients download data or verify that they are available to the diabetes team before televisits, with no significant differences between the two AHCL systems used (88.75% of Tandem users and 87.50% of Minimed users). Nearly 38.8% of patients using Tandem Control-IQ found downloading data difficult before televisits compared to 16.1% of patients using Minimed 780G ($p = 0.003$). Most of the participants found it easy to share the data and discuss it with the medical team during televisits. Connectivity during televisits was very satisfactory for 41.2% of the population, satisfactory for 38.2% and unsatisfactory for 20.6%. The global quality of the service (data sharing, connection, ease of use) was positively perceived and more than 80% of responders were satisfied with this service.

3.5. Cluster E—telenursing

48 (35%) of 136 patients participating on the survey made the first sensor change assisted via telenursing, of whom 25 (31.2%) were Tandem Control-IQ users and 23 (41.1%) were Minimed 780G users. 63 (46.3%) of 136 patients made the first change of the insulin infusion set assisted via telenursing, of whom 40 (50.0%) were Tandem Control-IQ users and 23 (41.1%) were Minimed 780G users. The support of the nurse was globally considered effective by almost all patients (87.3% score of 9–10, 11% score of 7–8). 54 (85.7%) out of 63 patients considered (score 9–10) the skills acquired during the first infusion set change more than enough and only 2 patients reported that they needed other appointments to learn how to change sets on their own.

3.6. Cluster F—infusion set and glucose sensor replacement

Data regarding the perception of the difficulty in performing the single steps of the infusion set change and the sensor change are shown in Table 3. 47.8% of the patients found filling the tank very easy, however the procedure was simpler in Minimed 780G users than in Tandem Control-IQ users (66.1% vs. 35.0% score 9–10, $p < 0.001$). Connecting the reservoir to the catheter, catheter filling

TABLE 2 Participants responses to questions of Cluster D (connectivity and data download).

	Score 0–6 *N* (%)	Score 7–8 *N* (%)	Score 9–10 *N* (%)	*p*	
D2. It was easy to download the daùta or check data availability before the televisit	31 (38.75)	22 (27.50)	27 (33.75)	**0.003**	Tandem
	9 (16.07)	13 (23.21)	34 (60.71)		Medtronic
	40 (29.41)	35 (25.74)	61 (44.85)		Total
D3.It was easy to share the data and discuss it with the diabetes team during the televisit	19 (23.75)	25 (31.25)	36 (45.00)	0.266	Tandem
	9 (16.07)	14 (25.00)	33 (58.93)		Medtronic
	28 (20.59)	39 (28.68)	69 (50.74)		Total
D4. The connectivity during the televisit was satisfactory	16 (20.00)	29 (36.25)	35 (43.75)	0.761	Tandem
	12 (21.43)	23 (41.07)	21 (37.50)		Medtronic
	28 (20.59)	52 (38.24)	56 (41.18)		Total
D5. The overall quality of the televisit (data sharing, connection, ease of use) was satisfactory	15 (18.75)	30 (37.50)	35 (43.75)	0.216	Tandem
	5 (8.93)	27 (48.21)	24 (42.86)		Medtronic
	20 (14.71)	57 (41.91)	59 (43.38)		Total

Bold values = statistically significant.

and following the steps indicated by the pump were very easy for most of the patients (respectively 73.5, 77.2, and 73.5%), regardless the insulin pump used. Data showed that the insertion of the cannula subcutaneously was much easier for those who used Minimed 780G rather than Tandem Control-IQ (71.4% vs. 35.0% of score 9–10, $p < 0.001$). Combining the scores of the single steps the infusion set change is globally considered very easy by 67.7% of the patients, with a significant difference between Tandem Control-IQ and Minimed 780G users (57.7% vs. 82%, $p = 0.011$). On the other hand, the glucose sensor replacement is globally considered very easy by 52.9% of patients, with a significant difference between Tandem Control-IQ and Minimed 780G users (62.5% vs. 32.3%, $p = 0.025$). Figure 1 shows the overall ease of infusion set and sensor replacement perceived by the patients.

4. Discussion

The use of telemedicine in the care of T1D pediatric patients has undergone a strong implementation since the Covid-19 pandemic.

A cross-sectional electronic survey distributed through a global network during the pandemic showed that the proportion of people with diabetes receiving telemedicine visits increased from <10 to >50% (21). Even before the pandemic, Wood et al. had shown that telehealth improved adherence to ADA recommendations increasing the number of follow-up visits (2.0 ± 1.3 times per year in the year prior to starting telemedicine and 2.9 ± 1.3 times, in the year after starting telemedicine, $p < 0.0001$), proving to be equivalent to in-person visits to maintain glycated hemoglobin (HbA1c) levels (13). To date, telemedicine continues to be used effectively on glycemic control and satisfactory for the patient in many countries (12, 22, 23). Several studies have demonstrated an improvement in CGM parameters in patients followed with telemedicine service during or after the pandemic (15, 16). In a recent study 28 children with T1D and their caregivers have carried out remote visits for 6 months. After 3 and 6 months of remote visits, Time in Range and Time Above Range significantly improved just as their psychological health (19). However, in low-middle income countries and in rural areas telemedicine services where used, have proved useful in maintaining regular patient follow-up but not always effective in maintaining a good glycemic control (17, 18). The role of telehealth, in these areas where technology is less used, may be fundamental to decrease clinical costs through the prompt diagnosis of decompensation, fewer visits to the emergency room for complications like ketoacidosis and severe hypoglycemia, and healthier lifestyle behaviors (26).

The barriers in the use of telemedicine in T1D care have been extensively analyzed and the aspect of connectivity and access to technology represents one of the essential points for the correct use of this service (19–21). Starting from this consideration, we wanted to evaluate the satisfaction in the use of telemedicine, with a particular focus on the aspect of connectivity, missing in the previous study but fundamental in evaluating the patient experience. Patients using AHCL systems were the most satisfied of the telemedicine service in our previous study (12). In a country like Italy, patients treated with highly technological instruments can benefit most from remote visits thanks to the possibility of comprehensive glycemic and insulin pump data sharing via dedicated cloud platforms.

A patient followed up at our center has an average of two televisits and two in-person visits per year. We also decided to include in the study the patients who have used it less (at least once), in order to avoid the bias of excluding those who have discontinued using the service even after only one visit due to dissatisfaction with the telemedicine. Despite the general satisfaction with the telemedicine service in AHCL users, parents or caregivers seem to be more satisfied than the patients in some aspects of the adequacy of care and psychological impact. Data showed that both young patients ≥12 years and parents/caregivers of patients <12 years were able to express their medical problems during televisits, but it seems easier for parents than for young T1D patients. Most of the participants declared that they receive adequate attention from the healthcare professionals, but the parents perceive more attention than the children and young patients. Patients and parents speak easily with the medical team, felt comfortable during televisits, perceived remote visits as an attention toward them and an adequate

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TABLE 3 Patients' perception of the difficulty of performing the glucose sensor and the infusion set change steps.

	Score (0–6) *N* (%)	Score (7–8) *N* (%)	Score (9–10) *N* (%)	*p*	
F1. How do you rate the ease of replacing the glucose sensor?	13 (16.25)	17 (21.25)	50 (62.50)	**0.025**	Tandem
	17 (30.36)	17 (30.36)	22 (39.29)		Medtronic
	30 (22.06)	34 (25.00)	72 (52.94)		Total 136
F2. How easy did you find filling the tank?	24 (30.00)	28 (35.00)	28 (35.00)	**<0.001**	Tandem
	2 (3.57)	17 (30.36)	37 (66.07)		Medtronic
	26 (19.12)	45 (33.09)	65 (47.79)		Total 136
F3. How easy did you find it to connect the reservoir to the catheter?	6 (7.50)	19 (23.75)	55 (68.75)	0.332	Tandem
	2 (3.57)	9 (16.07)	45 (80.36)		Medtronic
	8 (5.88)	28 (20.59)	100 (73.53)		Total 136
F4. How easy did you find catheter filling?	6 (7.50)	16 (20.00)	58 (72.50)	0.338	Tandem
	2 (3.57)	7 (12.50)	47 (83.93)		Medtronic
	8 (5.88)	23 (16.91)	105 (77.21)		Total 136
F5. How easy did you find the placement of the cannula subcutaneously?	18 (22.50)	34 (42.50)	28 (35.00)	**<0.001**	Tandem
	1 (1.79)	15 (26.79)	40 (71.43)		Medtronic
	19 (13.97)	49 (36.03)	68 (50.00)		Total 136
F6. How easy did you find it to follow the steps given by the pump?	6 (7.50)	20 (25.00)	54 (67.50)	0.171	Tandem
	2 (3.57)	8 (14.29)	46 (82.14)		Medtronic
	8 (5.88)	28 (20.59)	100 (73.53)		Total 136
FF. Ease of replacing the infusion set (calculated)	7 (8.75)	27 (33.75)	46 (57.50)	**0.010**	Tandem
	2 (3.57)	8 (14.29)	46 (82.14)		Medtronic
	9 (6.62)	35 (25.74)	92 (67.65)		Total 136

Bold values = statistically significant.

modality of assistance for T1D. The absence of physical contact was not a relevant problem for most of the participants even if adolescents and young adults suffered the distance more than parents (14.6% vs. 31.6% of disagreement scores), although this data was not statistically significant. Most of the participants will continue to use telemedicine, but the preference for in-person visits emerged particularly in the patients (27.4% vs. 14.6% of disagreement scores). Saving time and money are confirmed factors of satisfaction, even if this aspect seems less important for the patient (12.6% vs. 7.3% of disagreement score). Globally and regardless of age, 83.8% of the population was overall satisfied with the quality of the service provided.

These discrepancies between the perception of children and parents or caregivers is not surprisingly both because they are in line with the results of the previous study and because of the well-known importance of the relationship between healthcare professional and patient in chronic diseases, especially in the pediatric age (12, 27, 28). We therefore believe it is normal that an adolescent or young adult, even if largely satisfied with the telemedicine service, suffers more from the lack of physical contact, has more difficulty explaining their problems and perceives to receive less attention from the healthcare professional remotely. In the light of these results and considering outdated the limitations relating to the pandemic period, we believe it is essential to evaluate the benefits and critical issues in the use of telemedicine patient by patient. In fact, only by evaluating all the characteristics and needs of the patient (i.e., age, psychological and therapeutic situation, distance from the clinic, economic conditions of the family, ability to use data sharing platforms) it is possible for the diabetes team to choose the best modality of assistance for each patient and in every moment of his therapeutic path. Data relating to the distance from the diabetes center had already been collected in the previous study which demonstrated the greater satisfaction of those who lived further away from the clinic. Given that AHCLs are used by our patients regardless of socio-economic status, we suppose that the results relating to the study population of the previous study are representative of that of AHCL users.

Data download and sharing are fundamental aspects of the success of the televisit at our Center, which consists of a face-to-face remote visit on the company's online videocall platform during which glycemic and insulin pump data are discussed, sharing in real-time the data download screen. Despite most patients (88.8%) declare that they download data before the visit, 11.2% of them do not, declaring to encounter various kinds of technical or connection problems. This percentage is not negligible, because it means that 1 out of 10 patients is unable to carry out a complete and effective televisit according to our standards. It would be important to understand whether the failure to download and share data is due to forgetfulness or negligence of the patient or to the lack of suitable technological tools to carry it out.

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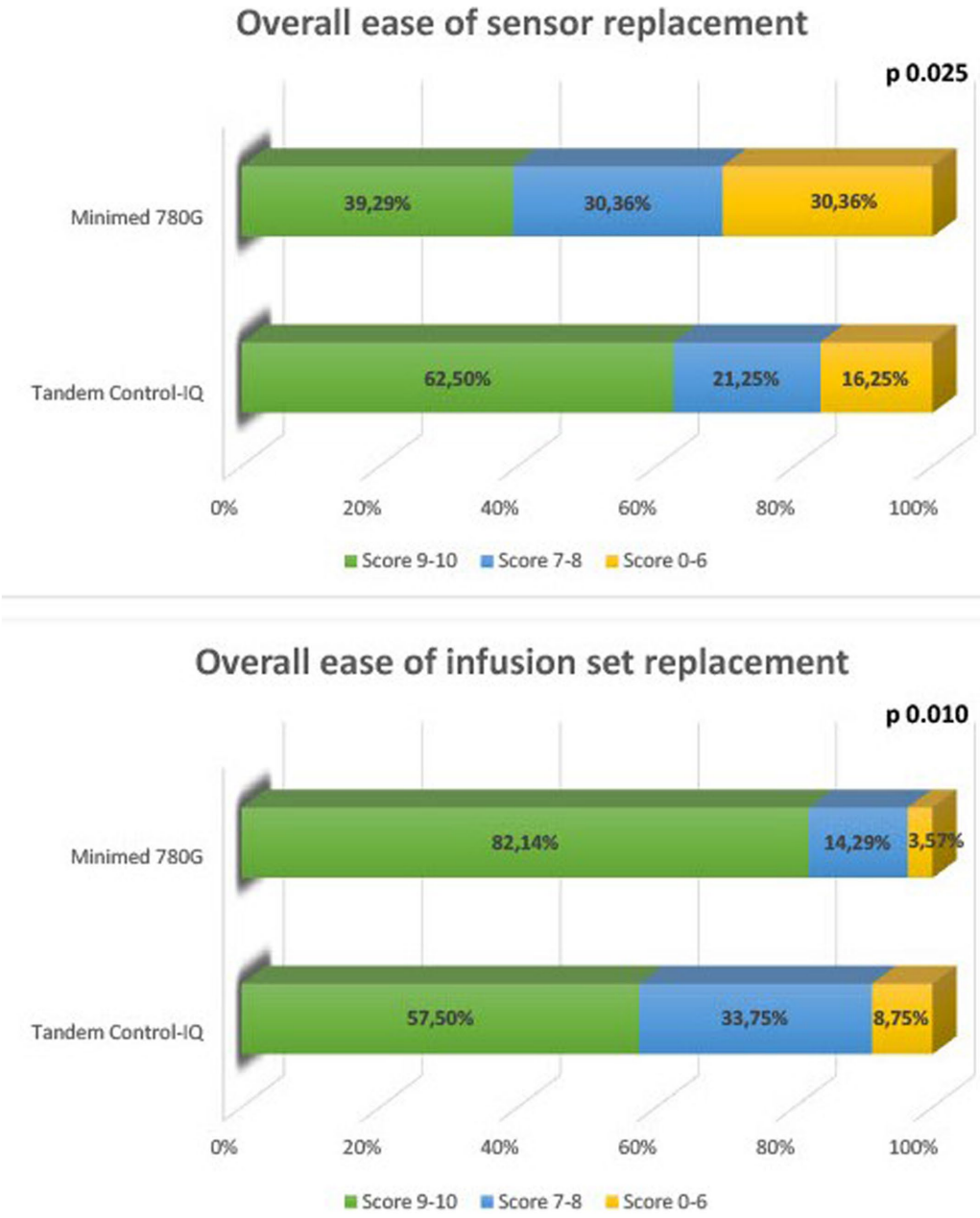

FIGURE 1
Overall ease of infusion set, and sensor replacement perceived by the patients.

Comparing the two AHCL systems, Minimed 780G users download data more easily than Tandem Control-IQ users. This is an obvious result since the download on the Minimed 780G platform (Carelink®) is based on an automatic update while the download on the Tandem Control-IQ platform (Glooko®) requires the connection of the insulin pump to a suitable electronic device. A further aspect to underline is 20.6% of patients are dissatisfied with the quality of the connection during the televisits. This is a significant percentage that highlights how much work still needs to be done in improving the telehealth platforms and the connections made available by the Institutions.

Thanks to the support of the regional Association for families of T1D patients (ADG Genova Onlus), our center is implementing the use of technology and telemedicine providing free technological devices and connection to families who are not economically able to buy them independently. However, we believe that much more can still be done in both our center and in other centers of high-income countries, also with the support of companies producing systems that require advanced technological tools available for the best T1D care without discrimination.

Telenursing was confirmed to be effective for patients and parents/caregivers also in this second survey dedicated to AHCL users. We chose to evaluate telenursing satisfaction only in patients who made their first infusion set change remotely, because it is a procedure that requires many steps and it allows a better evaluation of the efficacy of the nurse's support. The support of the nurse is

considered effective by 98.4% of patients and 96.8% of patients did not need other appointments to learn how to do the insulin set change. Given the excellent results relating to its use, our diabetes team is strongly motivated to implement and improve the telenursing service.

In the survey, we decided to evaluate in detail the difficulty of the single steps of the insulin infusion set change to identify the problematic issues and implement the nursing support in the most critical steps for each AHCL system. According to the results of the survey, the filling of the tank and the placement of the cannula emerge as the most critical steps. The greatest difficulties in these two steps were encountered by the Tandem Control-IQ Users (difficulty of filling the tank 28.7% vs. 3.3%, $p < 0.001$; difficulty of placement of the cannula 20.7% vs. 1.6%, $p < 0.001$). These results are consistent with the technical characteristics of the two instruments. In fact, filling the tank of the Tandem Control-IQ requires the air to be aspired from the tank before refilling as an additional step. Even the placement of the subcutaneous set of Tandem Control-IQ (Autosoft 90 or 30) requires some additional steps compared to Minimed 780G (unwinding the catheter and manual loading of the needle). In the case of the glucose sensor, as expected, the multi-step replacement of the Guardian sensor of Minimed 780G is perceived as more complicated than the single-step procedure of the Dexcom sensor of Tandem Control-IQ. Since it is obvious that multi-step procedures can be more complicated to perform by the patient, it is essential that the nurse gives more support to the patients during these most critical steps.

A limitation of this study is that we included only AHCL users in the survey, thus selecting the study population and encouraging the participation of patients and families who are more inclined and capable with technology. Furthermore, the restriction of the survey to a cohort of T1D patients followed by a single center of a high-income country limits the reproducibility of the results. Another limitation is related to the anonymous online administration which was not a guarantee of completion by all patients/parents who had consented to participate and did not allow the collection of clinical data of the study population. Furthermore, the number of televisits performed by the participants, the number of patients discontinuing early the service were not available for evaluation. Although AHCL are used by our patients regardless of socioeconomic status, the lack of these data can also be considered a limitation of this study. The strength of our study is that, to our knowledge, it is the first survey on satisfaction of telemedicine with a dedicated focus on connectivity and data download, which are well recognized as barriers and key factors in the use of telemedicine (21). Moreover, this is the first survey that evaluates in detail the difficulties encountered by patients in using AHCL in terms of set and sensor replacement, allowing diabetes teams to identify the critical steps to better direct the support to the patient.

5. Conclusions and future perspectives

This study showed once again the satisfaction of T1D patients and their parents assisted with telemedicine service. The survey also assessed the download and sharing of data and the connectivity as critical elements for the effective use of televisits. To perform a successful televisit, the patient must download and share the glycemic and pump data from his/her own device. The results of the study show that a minority of patients do not download data and are not satisfied with the quality of connectivity during the visit. These data underline the need for continued efforts by diabetes centers, patients' associations, manufacturers of technological device for T1D therapy, hospitals or institutions and healthcare systems to ensure equitable access to technologies and treatments for T1D patients. Data show great satisfaction in telenursing and suggest the importance of implementing this service, dedicating nursing support where the sensor and infusion set replacement multi-step procedures are more difficult for patients. Finally, we hope that this work will be an inspiration for companies that produce AHCL to improve the steps that are considered more critical by patients. The connection of the insulin pump data with phones seems to have become mandatory in order to be able to manage the data with the help of the referring doctors. The simplicity of the steps in positioning the infusion sets and sensors is highly appreciated by patients and could be further simplified in order to reduce errors that could lead to clinical consequences.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MB and FD designed the study and wrote the manuscript. MFS reviewed the manuscript and contributed to the discussion. DF wrote the manuscript and designed the tables. MS wrote the manuscript and designed the figures. BL and GS researched data and wrote the manuscript. FR designed the study. PS researched data. EC contributed to the creation and validation of the questionnaire. SP performed statistical analyses. Gd'A reviewed the manuscript. NM designed the study and contributed to the discussion.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1249299/full#supplementary-material

References

1. WHO Group Consultation on Health Telematics (1997, Geneva, Switzerland). *A health telematics policy in support of WHO's health-for-all strategy for global health development: Report of the WHO Group consultation on health telematics, 11–16 December, Geneva, 1997* World Health Organization (1998).

2. Italian Ministry of Health (2020). Indicazioni nazionali per l'erogazione di prestazione in telemedicina. 27 ottobre. V 4.4. Allegato A Accordo Stato-Regioni. Available at: https://www.statoregioni.it/media/3221/p-3-csr-rep-n-215-17dic2020.pdf.

3. Esposito S, Rosafio C, Antodaro F, Argentiero A, Bassi M, Becherucci P, et al. Use of telemedicine healthcare Systems in Children and Adolescents with chronic disease or in transition stages of life: consensus document of the Italian Society of Telemedicine (SIT), of the Italian Society of Preventive and Social Pediatrics (SIPPS), of the Italian Society of Pediatric Primary Care (SICuPP), of the Italian Federation of Pediatric Doctors (FIMP) and of the syndicate of family pediatrician doctors (SIMPeF). *J Pers Med*. (2023) 13:235. doi: 10.3390/jpm13020235

4. Isidori V, Diamanti F, Gios L, Malfatti G, Perini F, Nicolini A, et al. Digital technologies and the role of health care professionals: scoping review exploring Nurses' skills in the digital era and in the light of the COVID-19 pandemic. *JMIR Nurs*. (2022) 5:e37631. doi: 10.2196/37631

5. Strehle EM, Shabde N. One hundred years of telemedicine: does this new technology have a place in paediatrics? *Arch Dis Child*. (2006) 91:956–9. doi: 10.1136/adc.2006.099622

6. Esposito S, Rosafio C, Antodaro F, Argentiero A, Bassi M, Becherucci P, et al. Use of telemedicine healthcare Systems in Pediatric Assistance at territorial level: consensus document of the Italian Society of Telemedicine (SIT), of the Italian Society of Preventive and Social Pediatrics (SIPPS), of the Italian Society of Pediatric Primary Care (SICuPP), of the Italian Federation of Pediatric Doctors (FIMP) and of the syndicate of family pediatrician doctors (SIMPeF). *J Pers Med*. (2023) 13:198. doi: 10.3390/jpm13020198

7. Shah AC, Badawy SM. Telemedicine in pediatrics: systematic review of randomized controlled trials. *JMIR Pediatr Parent*. (2021) 4:e22696. doi: 10.2196/22696

8. Bassi M, Franzone D, Dufour F, Strati MF, Scalas M, Tantari G, et al. Automated insulin delivery (AID) systems: use and efficacy in children and adults with type 1 diabetes and other forms of diabetes in Europe in early 2023. *Life (Basel, Switzerland)*. (2023) 13:783. doi: 10.3390/life13030783

9. Negreiros FDDS, Araújo AL, Mattos SM, Moreira TR, Cestari VRF, Silva LMSD, et al. Digital technologies in the care of people with diabetes during the COVID-19 pandemic: a scoping review. *Revista da Escola de Enfermagem da U S P*. (2021) 55:e20210295. doi: 10.1590/1980-220x-reeusp-2021-0295

10. Elbarbary NS, Dos Santos TJ, de Beaufort C, Agwu JC, Calliari LE, Scaramuzza AE. COVID-19 outbreak and pediatric diabetes: perceptions of health care professionals worldwide. *Pediatr Diabetes*. (2020) 21:1083–92. doi: 10.1111/pedi.13084

11. Kotsani K, Antonopoulou V, Kountouri A, Grammatiki M, Rapti E, Karras S, et al. The role of telenursing in the management of diabetes type 1: a randomized controlled trial. *Int J Nurs Stud*. (2018) 80:29–35. doi: 10.1016/j.ijnurstu.2018.01.003

12. Bassi M, Strati MF, Parodi S, Lightwood S, Rebora C, Rizza F, et al. Patient satisfaction of telemedicine in pediatric and young adult type 1 diabetes patients during Covid-19 pandemic. *Front Public Health*. (2022) 10:857561. doi: 10.3389/fpubh.2022.857561

13. Wood CL, Clements SA, McFann K, Slover R, Thomas JF, Wadwa RP. Use of telemedicine to improve adherence to American Diabetes Association standards in pediatric type 1 diabetes. *Diabetes Technol Ther*. (2016) 18:7–14. doi: 10.1089/dia.2015.0123

14. Raymond JK, Berget CL, Driscoll KA, Ketchum K, Cain C, Fred Thomas JF. CoYoT1 clinic: innovative telemedicine care model for young adults with type 1 diabetes. *Diabetes Technol Ther*. (2016) 18:385–90. doi: 10.1089/dia.2015.0425

15. Kaushal T, Tinsley L, Volkening LK, Ambler-Osborn L, Laffel L. Improvement in mean CGM glucose in young people with type 1 diabetes during 1 year of the COVID-19 pandemic. *Diabetes Technol Ther*. (2022) 24:136–9. doi: 10.1089/dia.2021.0258

16. Cobry EC, Reznick-Lipina T, Pyle L, Slover R, Thomas JF, Alonso GT, et al. Diabetes technology use in remote pediatric patients with type 1 diabetes using clinic-to-clinic telemedicine. *Diabetes Technol Ther*. (2022) 24:67–74. doi: 10.1089/dia.2021.0229

17. Santana YELiberatore RDR Junior. Teleconsultation for pediatric patients with type 1 diabetes mellitus during the COVID-19 pandemic: experience of a university hospital in Brazil. *J Pediatr*. (2022) 98:587–9. doi: 10.1016/j.jped.2022.02.001

18. Evin F, Er E, Ata A, Jalilova A, Demir G, Atik Altınok Y, et al. The value of telemedicine for the follow-up of patients with new onset type 1 diabetes mellitus during COVID-19 pandemic in Turkey: a report of eight cases. *J Clin Res Pediatr Endocrinol*. (2021) 13:468–72. doi: 10.4274/jcrpe.galenos.2020.2020.0160

19. Braune K, Boss K, Schmidt-Herzel J, Gajewska KA, Thieffry A, Schulze L, et al. Shaping workflows in digital and remote diabetes care during the COVID-19 pandemic via service design: prospective, longitudinal, open-label feasibility trial. *JMIR Mhealth Uhealth*. (2021) 9:e24374. doi: 10.2196/24374

20. Lee JM, Carlson E, Albanese-O'Neill A, Demeterco-Berggren C, Corathers SD, Vendrame F, et al. Adoption of telemedicine for type 1 diabetes care during the COVID-19 pandemic. *Diabetes Technol Ther*. (2021) 23:642–51. doi: 10.1089/dia.2021.0080

21. Giani E, Dovc K, Dos Santos TJ, Chobot A, Braune K, Cardona-Hernandez R, et al. ISPAD Jenious group. Telemedicine and COVID-19 pandemic: the perfect storm to mark a change in diabetes care. Results from a world-wide cross-sectional web-based survey. *Pediatr Diabetes*. (2021) 22:1115–9. doi: 10.1111/pedi.13272

22. Frielitz FS, Dördelmann J, Lemke S, Lange K, Hiort O, Katalinic A, et al. Assessing the benefits and challenges of video consultations for the treatment of children with type 1 diabetes - a qualitative study among diabetes professionals. *Exp Clin Endocrinol Diab Off J Ger Soc Endocrinol German Diab Assoc*. (2021) 129:831–6. doi: 10.1055/a-1149-8814

23. Ruiz de Adana MS, Alhambra-Expósito MR, Muñoz-Garach A, Gonzalez-Molero I, Colomo N, Torres-Barea I, et al. Diabetes group of SAEDYN (Andalusian Society of Endocrinology, diabetes, and nutrition). Randomized study to evaluate the impact of telemedicine Care in Patients with Type 1 diabetes with multiple doses of insulin and suboptimal HbA_{1c} in Andalusia (Spain): PLATEDIAN study. *Diabetes Care*. (2020) 43:337–42. doi: 10.2337/dc19-0739

24. Palandri F, Bartoletti D, Giaquinta S, D'Ambrosio F, Auteri G, Sutto E, et al. Telemedicine in patients with haematological diseases during the coronavirus disease 2019 (COVID-19) pandemic: selection criteria and patients' satisfaction. *Br J Haematol*. (2021) 192:e48–51. doi: 10.1111/bjh.17208

25. Polit DF, Beck CT. The content validity index: are you sure you know What's being reported? Critique and recommendations. *Res Nurs Health*. (2006) 29:489–97. doi: 10.1002/nur.20147

26. Hirschler V, Molinari C, Figueroa Sobrero A, Pelicand J, Pinto Ibárcena P, Del Aguila Villar CM, et al. Influence of telemedicine on the number of visits and HbA1c determinations in Latin American children with type 1 diabetes. *Diabetes Technol Ther*. (2021) 23:731–6. doi: 10.1089/dia.2021.0189

27. Lindholm Olinder A, DeAbreu M, Greene S, Haugstvedt A, Lange K, Majaliwa ES, et al. ISPAD clinical practice consensus guidelines 2022: diabetes education in children and adolescents. *Pediatr Diabetes*. (2022) 23:1229–42. doi: 10.1111/pedi.13418

28. de Wit M, Gajewska KA, Goethals ER, McDarby V, Zhao X, Hapunda G, et al. ISPAD clinical practice consensus guidelines 2022: psychological care of children, adolescents and young adults with diabetes. *Pediatr Diabetes*. (2022) 23:1373–89. doi: 10.1111/pedi.13428

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A systematic bibliometric analysis on the clinical practice of CGM in diabetes mellitus from 2012 to 2022

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Background: Continuous glucose monitoring (CGM) has revolutionized diabetes management, but a comprehensive analysis of its clinical implementation is lacking. This study aims to explore CGM in diabetes practice over the past decade using bibliometric analysis. It will identify trends, research focal points, and provide a framework for future investigations.

Materials and methods: The Web of Science Core Collection (WOSCC) was utilized to acquire literature pertaining to the employment of continuous glucose monitoring (CGM) in diabetes that was published between the years 2012 and 2022, and to conduct a comprehensive analysis of the associated citation data. To achieve bibliometric visualization and analysis of the collated data, the bibliography package in the Rstudio(v.4.2.2), Citespace 6.2.R4, and VOS viewer were employed.

Results: A total of 3024 eligible publications were extracted from 91 countries, with the United States being the leading country in terms of the number of issued articles. Furthermore, the annual publication rate has shown a gradual increase during the past decade. Among the various journals in this field, DIABETES TECHNOLOGY & THERAPEUTICS was identified as the most highly cited one. Keyword clustering analysis of the extracted publications indicates that the research hotspots in the past decade have primarily focused on "continuous glucose monitoring", "glycemic variability", "type 1 diabetes", "hypoglycemia", and "glycemic control". Moreover, the analysis of keyword emergence reveals that "Time In Range" and "Young Adult" represent the current research frontiers for the years 2012-2022.

Conclusion: The concept of Time in Range (TIR) has garnered considerable attention as a significant area of inquiry and an emerging research trend in the clinical practice of Continuous Glucose Monitoring (CGM) for Diabetes Mellitus. Moreover, recent investigations have demonstrated a growing focus on young adults with type 1 diabetes as the research population of interest. In the foreseeable future, research endeavors will persist in the pursuit of improving

glycemic management among young adults through the utilization of continuous glucose monitoring (CGM) technology, while also delving into the examination of the Time in Range metric via supplementary clinical investigations.

KEYWORDS

diabetes mellitus, continuous glucose monitoring, bibliometric analysis, Citespace, VOSviewer

1 Introduction

Diabetes, a chronic non-communicable disease, ranks third after cardiovascular and cerebrovascular diseases and tumors in posing a serious risk to human health. With the accelerating pace of urbanization, lifestyle modifications, and the aging of the population, the prevalence of diabetes is escalating rapidly. According to the International Diabetes Federation (IDF), the global prevalence of diabetes among individuals aged 20 to 79 years is estimated to be 10.5% (536.6 million people) in 2021, and this figure is projected to reach 12.2% (783.2 million people) by 2045. The global health expenditure associated with diabetes is also projected to rise continuously (1, 2). Blood glucose serves as the fundamental source of energy in the body and plays a pivotal role in maintaining normal physiological functions. Abnormal fluctuations in blood glucose levels are closely linked to the onset and progression of numerous diseases, such as diabetes mellitus and hypoglycemia. Consequently, blood glucose monitoring has emerged as a crucial and indispensable tool in clinical management. Moreover, with the growing focus on health, an increasing number of individuals are becoming aware of their blood glucose levels and adopting corresponding measures to safeguard their well-being. Continuous glucose monitoring (CGM) is a non-invasive technique that enables the continuous monitoring of the concentration of glucose in subcutaneous interstitial fluid through the use of a glucose sensor. This technology facilitates the recording of the trend and characteristics of blood glucose fluctuations in real time (3, 4). Scanning CGMs, in particular, can provide continuous glucose monitoring for up to 14 days, with the sensor measuring glucose levels every minute and storing readings every 15 minutes. Scanning allows for the presentation of continuous and reliable information on blood glucose fluctuations throughout the day. The CGM system is factory-calibrated, eliminating the need for frequent finger-stick blood calibrations during use. This feature reduces the discomfort of blood collection, promotes patient compliance and initiative in blood glucose monitoring (5), and facilitates ease of operation. With the proliferation of continuous glucose monitoring (CGM) in clinical practice, it has emerged as a widely utilized tool for ambulatory glucose monitoring, facilitating the monitoring of blood glucose levels and the identification of uncontrolled hyperglycemia, hypoglycemia, and fluctuations in blood glucose (6). Consequently, prospective clinical studies have increasingly adopted CGM devices to gather data and evaluate the blood glucose profiles of study participants, in conjunction with HbA1c findings, in order to further assess the efficacy of therapeutic interventions on HbA1c (7). Given the expanding evidence supporting the efficacy of CGM in diabetes treatment and its rising demand in primary care, it is imperative to attend to its clinical use for diabetes (8). In light of these contextual factors, this research delves comprehensively into the clinical practice of Continuous Glucose Monitoring (CGM) within the domain of diabetes. This includes investigating its impact on glycemic control, the utilization of CGM-related metrics, remote monitoring and telemedicine applications, artificial pancreas(closed-loop systems), as well as integration with insulin pump mechanisms, among other facets (9).The vast quantity of research-related literature currently being produced presents a challenge for traditional literature analysis in obtaining comprehensive and pertinent information. Bibliometric analysis, however, enables both quantitative and qualitative information contained within journal articles to be analyzed (10). This approach has been proven effective in identifying emerging topics and research frontiers across a wide range of disciplines (11, 12). Accordingly, in this study, we employ scientific bibliometric analysis to systematically examine published works, with the aim of revealing annual publication outputs, identifying leading countries, regions, journals, and institutions, and evaluating research impact. We further report on the research impact of countries, regions, institutions, and journals through analysis of keywords and co-cited literature. Finally, we explore current research hotspots and future trends in the use of CGM in clinical practice for diabetes.

2 Materials and methods

2.1 Extraction of citation data

On the 1st of August 2023, a comprehensive search was conducted on the Web of Science Core Collection (WOSCC) to retrieve all citations published from the 1st of January 2012 to the 31st of December 2022. The search was executed using the following formula: TS=("Continuous blood glucose monitoring" OR "Continuous glucose monitoring" OR "Implantable CGM system" OR CGM OR FGM OR "Flash glucose monitoring" OR "Ambulatory glucose monitoring" OR "Continuous glucose sensors" OR "Real-time glucose monitoring" OR rtCGM OR "Subcutaneous glucose monitoring" OR "Continuous glucose measurement" OR "Continuous glycemic monitoring" OR

"Continuous glucose sensing" OR "Continuous glucose meters") AND TS=(Diabetes* OR "Diabetes mellitus*"), while limiting document types to "Article" or "Review Article". Articles and reviews written in English were considered, while meeting abstracts, early access articles, editorial material, letters, collections, proceeding papers, news items, book chapters, hardware reviews, and withdrawn publications were excluded. The initial screening process yielded a total of 3680 original English articles, comprising 3207 articles and 473 reviews, which were deemed to be potential candidates for inclusion in the study.

To ensure the precision and caliber of the acquired data, a dual review process was undertaken by two researchers, Laixi Kong and Maoting Guo, who independently scrutinized the abstracts and keywords of literature to obtain the most pertinent articles. The objective of this study was to investigate the clinical practice of CGM in diabetes; thus, these clinical practice encompass various aspects: improvements in blood glucose control following CGM use, the utilization and interpretation of CGM-related metrics, remote monitoring and telemedicine, artificial pancreas (closed-loop systems), and the integration of CGM with multiple insulin pump systems. Exclusion criteria encompass topics such as technical design in CGM sensors, sensor material research, and unrelated reviews. Following manual screening, a total of 3024 papers were deemed suitable for inclusion in this study. From each publication, the title, publication year, country or region, institution, author, journal, references, author and keywords were methodically extracted. Further details pertaining to the literature extraction process are presented in Figure 1.

2.2 Statistical analysis

Initially, a basic statistical analysis of the dataset was conducted utilizing Rstudio (v.4.2.2). The "bibliometrix" format was employed to store the data, and the "biblishiny" package was utilized to extract a range of features related to the research literature between 2012 to 2022 (13). These features, including Main Information, Most Relevant Authors, Author's Production Over Time, Most Global Cited Documents, served for quantitative analysis. Subsequently, CiteSpace 6.1.R6 was utilized to cluster the keywords of institutions present in the literature, perform dual map overlay analysis of journals, unveil keyword clustering analyses within the text, identify the strongest cited bursts, and construct co-cited references timeline maps of publications. In addition, VOS viewer was employed to identify the collaborative networks of countries and institutions, evaluate the keywords pertaining to the subject, and visualize the post-analysis of the results.

3 Results

3.1 Publications

In this review, a comprehensive analysis of 3024 literature sources was conducted, and the resulting search data was used to plot the trends in studies related to the application of continuous glucose monitoring (CGM) to clinical practice in diabetes using R studio. As illustrated in Figure 2, the analysis revealed a consistent

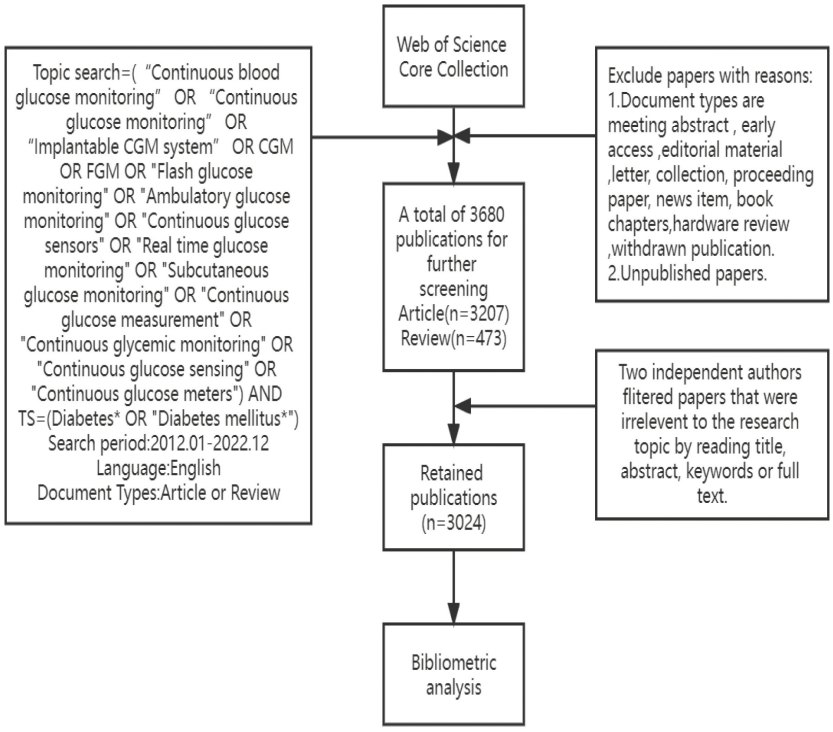

FIGURE 1
The framework diagram illustrates the comprehensive screening methodology employed in the evaluation of research literature pertinent to the clinical practice of Continuous Glucose Monitoring (CGM) in Diabetes Mellitus from 2012-2022.

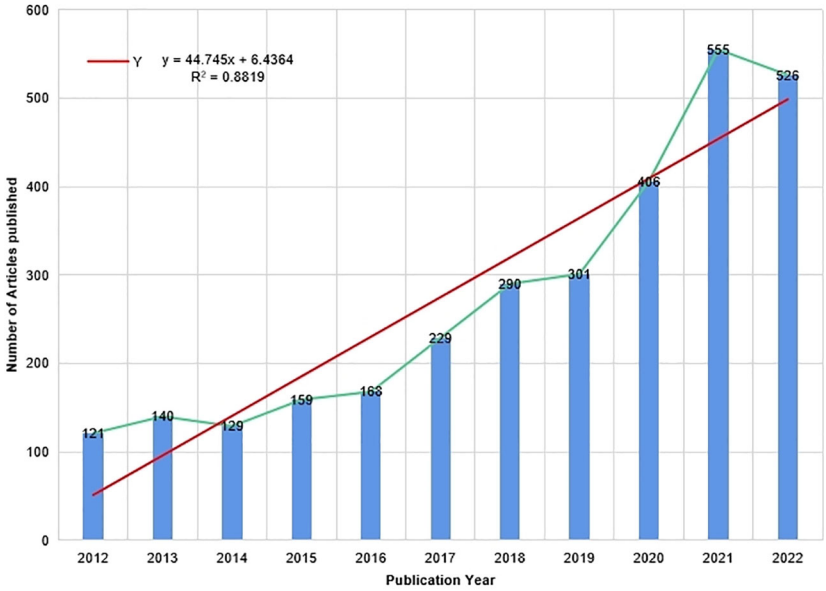

FIGURE 2
Trends in the Number of Publications on the Clinical Practice of CGM in Diabetes Mellitus from 2012 to 2022.

annual increase in the volume of research articles on this subject from 2012 to 2019, followed by a sharp rise in the number of publications from 2019 to 2021, suggesting a heightened interest in research pertaining to clinical practice of CGM in diabetes during this period. Notably, 2021 recorded the highest output of 555 articles. Furthermore, a linear trend line of annual publications was developed to gain further insights into the output trend, resulting in the equation Y=44.745X+6.4364, where Y represents the annual publications and X denotes the year. This model exhibits a coefficient of determination (R^2) of 0.8819. Figure 3 presents an overview of the analyzed articles, encompassing a total of 46243 references and an average publication year of 4.37. Moreover, each article garnered an average of 22.88 citations, while the annual publication growth rate was 15.83%.

3.2 Countries and regions

A total of 91 countries have conducted studies on the topic at hand. The Figure 4A indicated that the United States had the highest number of articles published (1029), followed by the United Kingdom (331) and China (264). The top 10 countries in terms of output were summarized in the Table 1, with the United States exhibiting the highest centrality (0.17), H-index (86), and Citations Per Papers (32.00), surpassing other countries by a significant margin. Although China and Japan ranked high, their H-index and centrality were comparatively lower than those of other countries. The international cooperation relationship of each country was visualized using the CiteSpace, as shown in Figure 4B, where nodes represented countries and node size reflected the amount of national issuance. The purple portion of the circle represented centrality, with the United States positioned at the center, indicating frequent cooperation with other countries. Furthermore, the circle of the United States was the largest, indicative of the most influential issuance in the region.

3.3 Institutions

Table 2 illustrates the top 10 institutions with the highest literature output, where in HARVARD UNIVERSITY,

Description	Results
MAIN INFORMATION ABOUT DATA	
Timespan	2012:2022
Sources (Journals, Books, etc)	489
Documents	3024
Annual Growth Rate %	15.83
Document Average Age	4.37
Average citations per doc	22.88
References	46243
DOCUMENT CONTENTS	
Keywords Plus (ID)	2940
Author's Keywords (DE)	3430
AUTHORS	
Authors	12578
Authors of single-authored docs	59
AUTHORS COLLABORATION	
Single-authored docs	69
Co-Authors per Doc	7.76
International co-authorships %	22.59
DOCUMENT TYPES	
article	2672
review	352

FIGURE 3
Main information about all Related Articles from 2012 to 2022.

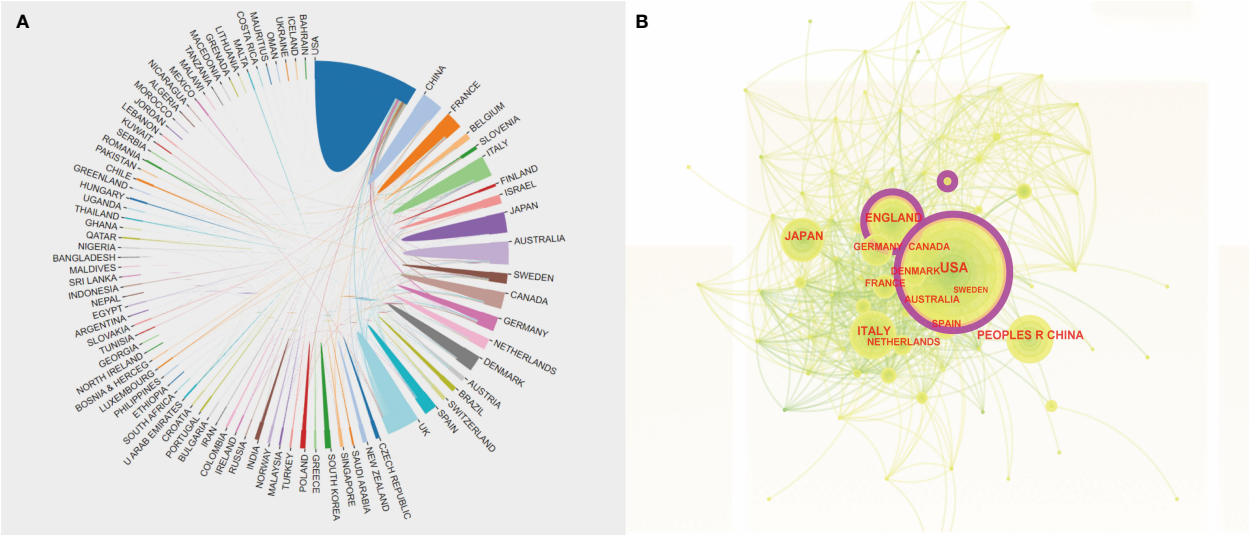

FIGURE 4
(A) An Analysis of International Cooperation Between Diverse Countries. The correlation among distinct color blocks signifies the bilateral collaborative association between the two countries. **(B)** Cooperation of Countries or Regions that Contributed to Publications on the Clinical Practice of CGM in Diabetes Mellitus from 2012 to 2022. The size of the purple ring area serves as an indicator of the scope of influence of the regional articles and is equivalent to their centrality.

UNIVERSITY OF COLORADO SYSTEM, and UNIVERSITY OF COLORADO ANSCHUTZ MEDICALCAMPUS emerged as the top three institutions with the highest number of published articles (151, 144, and 132, respectively). Notably, HARVARD UNIVERSITY exhibited a significantly higher H-Index compared to other two institutions, indicating its dominant influence in publishing articles. Seven out of the top 10 institutions were affiliated with the United States.

The collaborative relationships between institutions were disclosed through the use of CiteSpace, as depicted in Figure 5A. The connecting line between each of the two labels in Figure 5B shows that the institutions in the same country cooperate closely.

3.4 Analysis of authors

Figure 6A presents the roster of the ten most pertinent authors within this research domain, with particular emphasis on the 61 articles affiliated with Roy W. Beck. A nuanced comprehension of the potency of influence and the yearly evolution of publications among these ten authors over the past decade is facilitated by Figure 6B. Evidently, Roy W. Beck sustains a conspicuously high echelon of scientific impact within this research sphere (14). Remarkably, it is salient that seven studies associated with him have ascended to constitute the upper echelon of the ten most frequently cited articles within this field (15–21).

TABLE 1 Top 10 countries or regions with publications on clinical practice of CGM in diabetes mellitus from 2012 to 2022.

Rank	Country/Region	Count	Centrality	H-index	Citations Per Papers
1	USA	1029	0.17	86	32.00
2	England	331	0.15	47	26.42
3	China	264	0.00	28	12.07
4	Japan	261	0.00	27	11.86
5	Italy	253	0.10	42	21.30
6	Germany	183	0.08	40	34.72
7	Australia	173	0.09	35	17.08
8	France	142	0.05	36	18.36
9	Canada	141	0.03	31	27.68
10	Denmark	127	0.07	31	20.26

TABLE 2 The top 10 institutions with publications on clinical practice of CGM in diabetes mellitus from 2012-2022.

Rank	Institutions	Counts	H-Index	Countries or Regions
1	HARVARD UNIVERSITY	151	41	America
2	UNIVERSITY OF COLORADO SYSTEM	144	38	America
3	UNIVERSITY OF COLORADO ANSCHUTZ MEDICALCAMPUS	132	36	America
4	STANFORD UNIVERSITY	111	39	America
5	JAEB CENTER FOR HEALTH RESEARCH	103	45	America
6	N8 RESEARCHPARTNERSHIP	97	33	England
7	UNIVERSITY OF CAMBRIDGE	94	31	England
8	UNIVERSITY OF COPENHAGEN	84	29	Denmark
9	HARVARD MEDICAL SCHOOL	77	31	America
10	JOSLIN DIABETES CENTER INC	77	32	America

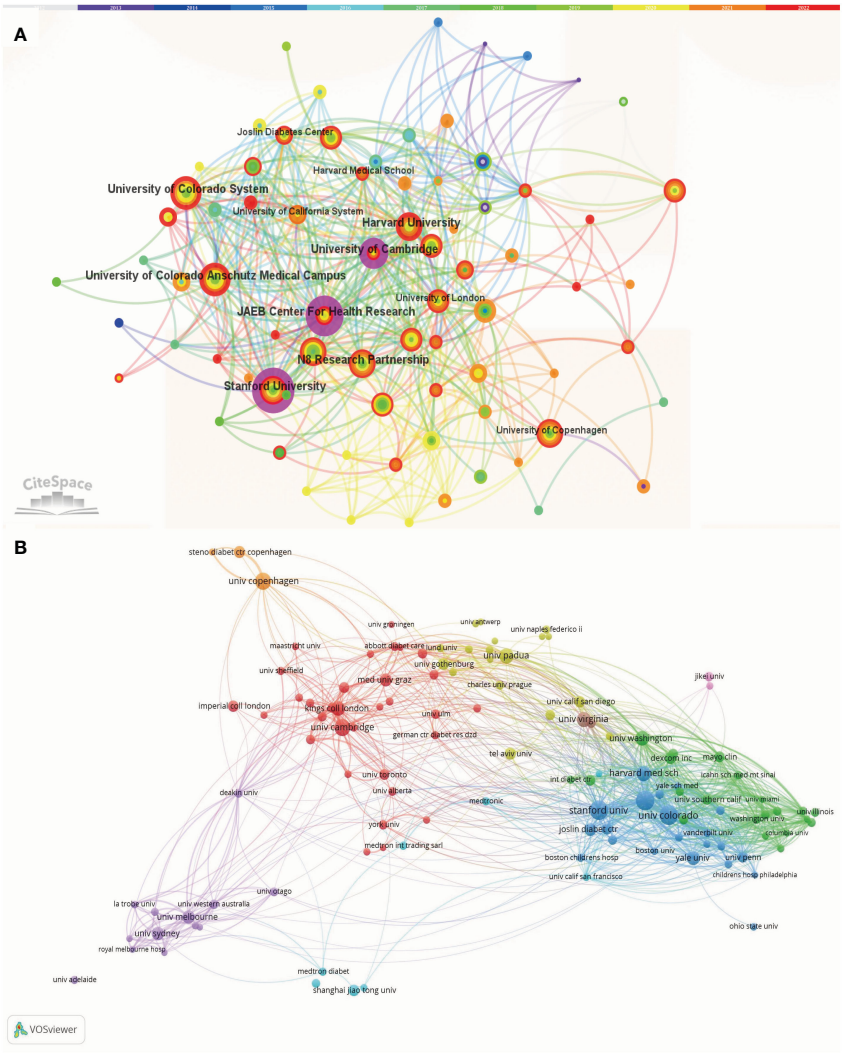

FIGURE 5
(A) Collaborative Network Analysis by CiteSpace Amongst Institutions Pertaining to the Clinical Practice of CGM in Diabetes Mellitus from 2012 to 2022. Each node with colorful annual rings represents an institution, and the size of each node represents its relative quantity of research output. **(B)** The overlay visualization map of Institution co-authorship analysis conducted by VOSviewer.

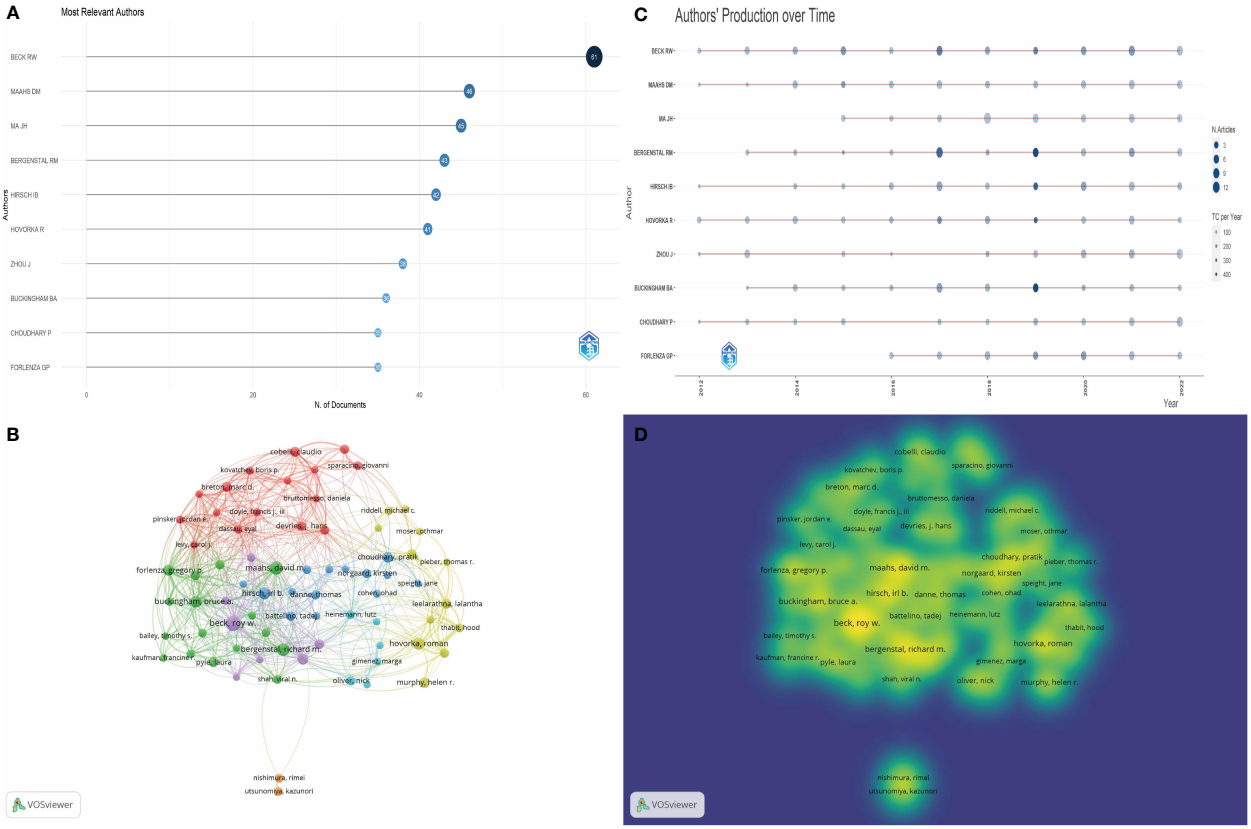

FIGURE 6
(A) Top 10 most relevant authors in this field. **(B)** The visual depiction of author co-citation analysis using VOSviewer showcases a graphical representation where each author is symbolized as a distinct node. The size of these nodes is proportionate to the total number of citations received. Connections between nodes signify instances of co-citation, implying a connection between the authors' works. The proximity between nodes reflects their degree of association, with shorter distances denoting a stronger relationship. Nodes with closer proximity are grouped together using matching colors, indicating their membership in a shared cluster. **(C)** Top 10 authors' production over time. The circle size represents the number of documents (N. Documents), and the shade of the color signifies the total number of citations (TC). **(D)** The visualization of author collaboration patterns produced by VOSviewer depicts clusters denoting groups of authors with significant collaborative ties. Authors closely linked in terms of cooperation are represented within a shared cluster, visually distinguished by a common color.

In light of these dynamics, collaborative networks of research materialize as instrumental conduits for researchers to augment the breadth of their investigative pursuits or to conjoin forces with cohorts engaged in cognate inquiries. Accordingly, a judicious author threshold of 107 was established. Employing VOSviewer, we proceeded to visualize the extant panorama and gradation of author interplay within this domain, with the ensuing outcomes being expounded in Figures 6C, D.

3.5 Journals

Upon analyzing the literature's cited and citing journals, it was possible to determine the influential journals in the field. Table 3 illustrated the top ten cited and citing journals, with DIABETES TECHNOLOGY & THERAPEUTICS holding the highest rank as the first citing journal, followed by DIABETES CARE and DIABETES RESEARCH AND CLINICAL PRACTICE. Among the cited journals, DIABETES CARE held the top spot, followed by DIABETES TECHNOLOGY & THERAPEUTICS and J DIABETES SCI TECHNOL. In 2022, DIABETES CARE held the highest impact factor among the citing journals, with a score of 17.152, followed by DIABETES TECHNOLOGY & THERAPEUTICS with a score of 7.337.

Furthermore, in plotting the Dual map overlay using CiteSpace, the journals that contributed to publications on the clinical practice of CGM in Diabetes Mellitus were analyzed. The resulting map in Figure 7 was divided into two halves, with the left side representing the research area of the cited journals and the right side depicting the research area of the citing journals. The colored curves between the nodes on the left and right halves illustrated the relationship between the highly active research areas of the two journals. The examination of the graph indicated the presence of two discernible green curves, which implied that publications pertaining to medicine, medical and clinical domains have a higher likelihood of being referenced by journals that focus on molecular, biological, and genetic areas, as well as health, nursing, and medical fields.

3.6 Keywords

In this study, we utilized VOSviewer to visualize the 100 high-frequency keywords in the literature pertaining to the topic of

10.3389/fendo.2023.1229494

TABLE 3 The Top 10 citing and cited journals of publications on the clinical practice of CGM in diabetes mellitus from 2012 to 2022.

Rank	Citing Journals	Counts	2022 Journal Impact Factor	Rank	Cited Journals	Counts	2022 Journal Impact Factor
1	DIABETES TECHNOLOGY \& THERAPEUTICS	453	7.337	1	DIABETES CARE	2865	17.152
2	DIABETES CARE	190	17.152	2	DIABETES TECHNOLOGY \& THERAPEUTICS	2208	7.337
3	DIABETES RESEARCH AND CLINICAL PRACTICE	142	8.180	3	J DIABETES SCI TECHNOL	1547	0
4	PEDIATRIC DIABETES	114	3.409	4	DIABETOLOGIA	1538	10.460
5	DIABETES OBESITY \& METABOLISM	108	6.408	5	DIABETIC MED	1533	4.213
6	DIABETIC MEDICINE	98	4.213	6	NEW ENGL J MED	1490	176.079
7	DIABETES THERAPY	88	3.595	7	DIABETES	1380	9.337
8	FRONTIERS IN ENDOCRINOLOGY	70	6.055	8	DIABETES RES CLIN PR	1262	8.180
9	JOURNAL OF CLINICAL ENDOCRINOLOGY \& METABOLISM	55	6.134	9	JAMA-J AM MED ASSOC	1198	157.335
10	JOURNAL OF DIABETES INVESTIGATION	52	3.681	10	LANCET	1135	202.731

interest. A threshold of 41 occurrences was set for the selection of these keywords. The resulting visualization in Figure 8A demonstrated that darker color blocks corresponded to higher frequency of occurrence of the respective keyword in the literature. Furthermore, proximity of a color block to the center of the yellow block indicated higher citation frequency and cited frequency. The top ten hot keywords, as ranked by frequency, were presented in Table 4. Notably, "Type 1 diabetes", "Glycemic control", "Hypoglycemia" were among the top keywords, suggesting their significance as hot topics in this research field over the past decade. And Figure 8B illustrates the chronological depiction of keyword clustering analysis, offering a timeline perspective. The diagram portrays various clusters denoted by distinctively colored horizontal lines on the right side, each

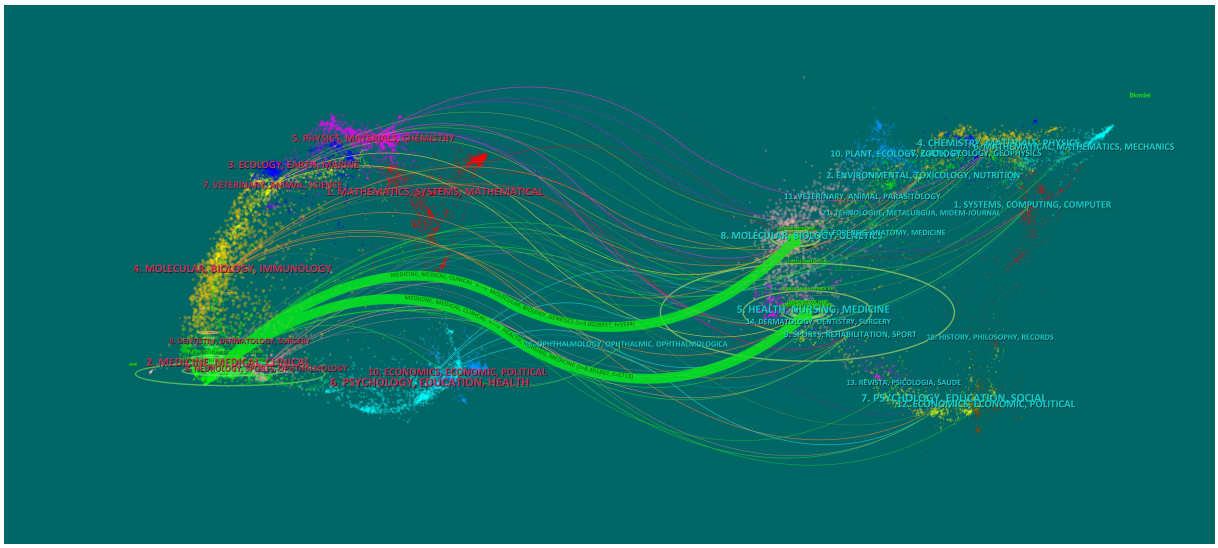

FIGURE 7
The Dual-map Overlay of Journals on the Clinical Practice of CGM in Diabetes Mellitus. The green path at the top suggests that research literature from MEDICINE, MEDICAL, CLINICAL area may be utilized to support the results and findings in the field of MOLECULES, BIOLOGY, GENETICS research. The findings from research literature in the MEDCINE, MEDICAL, CLINICAL area may be utilized to support the results from research conducted in the HEALTH, NURSING, MEDICINE area.

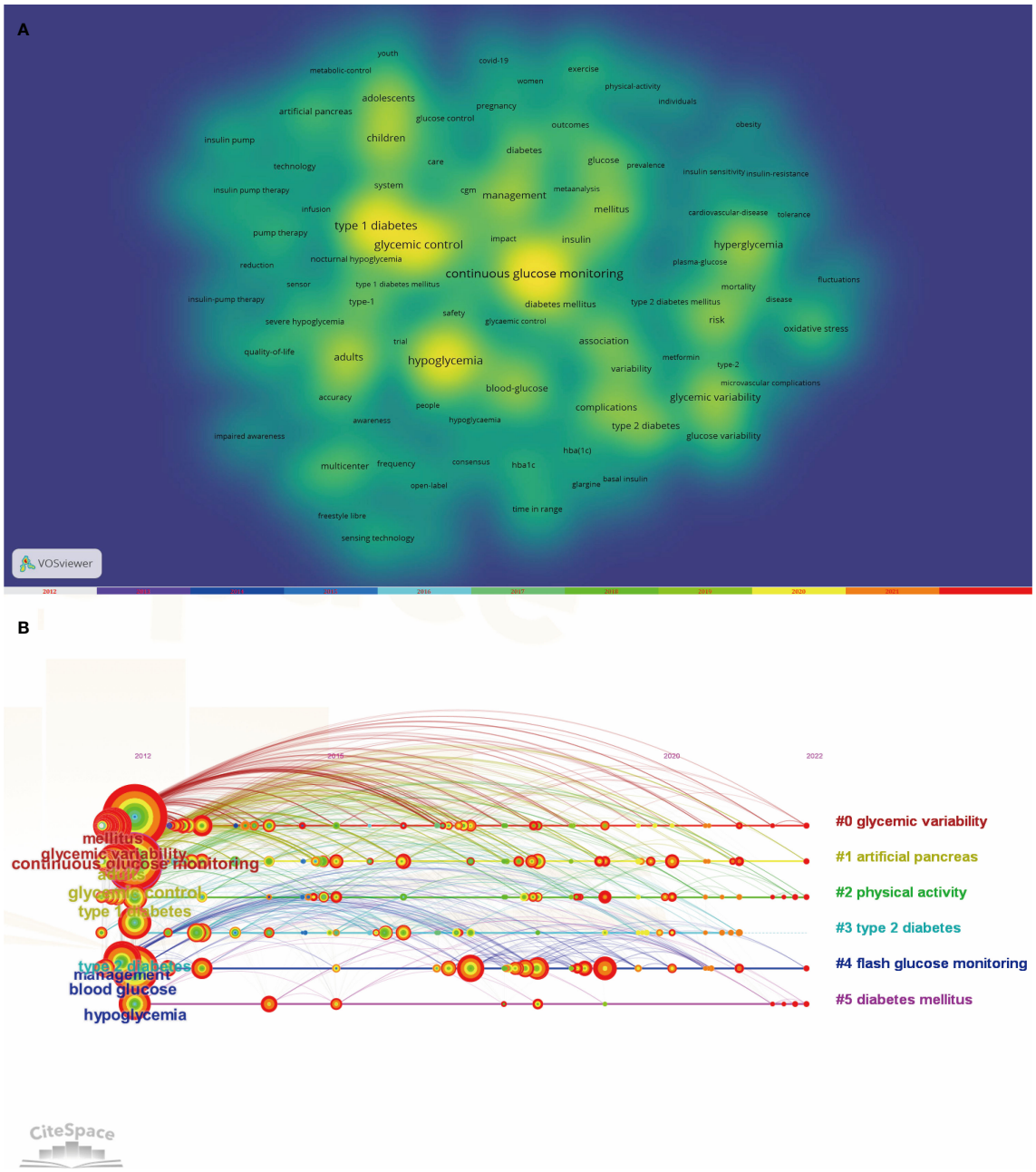

FIGURE 8
(A) Co-occurrence Keywords Network and Density Visualization on the Clinical Practice of CGM in Diabetes Mellitus from 2012-2022. **(B)** CiteSpace visualization timeline view of keywords clustering analysis related to the clinical practice of CGM in diabetes.

corresponding to a collection of keywords. The nodes positioned along these horizontal lines symbolize individual keywords. Notably, the spatial arrangement of these nodes along the horizontal axis signifies the inaugural appearance year within the scholarly literature for the associated keyword, thereby constituting a comprehensive temporal representation of the keyword cluster's evolutionary progression. The cluster "0# glycemic variability" is the largest, Next is "#1 artificial pancreas", "#2 physical activity", "#3 type 2 diabetes", "#4 flash glucose monitoring" and "#diabetes mellitus"

The CiteSpace is capable of identifying keywords that experience significant changes in frequency during a specific time period, commonly known as emergent words. Keywords that exhibit a delayed emergence and extended duration are indicative of the most recent research trends in a given field, enabling a temporal review of research hotspots and the projection of future trends. The default configuration of CiteSpace was substituted with the ensuing modes: "Year Per Slice" set to 1, "Top N%" set to 30.0%, and "Minimum Duration" set to 1. After conducting an analysis on the keywords with citation bursts, we determined that the 8

TABLE 4 Top 10 keywords related to the clinical practice of CGM in diabetes mellitus from 2012-2022.

Rank	Keywords	Counts
1	Type 1 diabetes	683
2	Glycemic control	672
3	Hypoglycemia	523
4	Adults	410
5	Blood-glucose	352
6	Management	343
7	Glycemic variability	343
8	Children	307
9	Risk	301
10	Adolescents	299

strongest burst keywords should be displayed as illustrated in Figure 9. During the period spanning from January 2012 to December 2022, the ensuing keywords surfaced as outcomes: fluctuation (2012-2018), plasma glucose (2012-2016), hyperglycemia (2013-2016), cardiovascular disease (2013-2016), reduction (2014-2017), intensive treatment (2018-2020), time in range (2020-2022), and young adults (2020-2022). In the preceding two years, the keywords "Time in Range" and "Young Adult" have surfaced and persisted throughout 2020 and beyond. Of the two, "Time in Range" has exhibited the most intense outbreak with a value of 20.47, indicating that it currently represents the primary research focus and potentially marks a pivotal juncture with notable implications for future inquiry.

3.7 Co-cited references

A timeline map of co-cited references was constructed using CiteSpace with the aim of comprehending the principal research topics and their progression within the field. The outcomes of the keyword clustering analysis of the references were exhibited on the right-hand side of Figure 10, with "#flash glucose monitoring" comprising the most significant cluster. On the left-hand side, the citation relationship among each reference was presented over time, wherein larger nodes signified more frequent citations, and node color indicated the time when the reference was cited. The top 10 most frequently cited references were enumerated in Table 5.

4 Discussion

4.1 General information

In brief, the annual production of scholarly articles in this field exhibited an upward trend overall, with a significant and substantial surge observed in 2020, likely due to the outbreak of the COVID-19 pandemic. The pandemic-induced public health measures have altered people's lifestyles, potentially impacting the glycemic control of individuals with diabetes by limiting physical activity to some extent (22). Furthermore, the use of glucocorticoid therapy may exacerbate hyperglycemia once severe infections such as COVID-19 pneumonia have developed. Consequently, a study has suggested that a system that integrates telemedicine and continuous glucose monitoring (CGM) can effectively manage blood glucose levels and prevent adverse outcomes (23, 24). As a result, CGM has gained increasing adoption in clinical settings, with a peak in related research output in 2021. In the analysis of countries within a particular research area, the United States emerged as the leading contributor in terms of number of publications, centrality, H-index, and citations. This suggested that the United States possessed a greater level of influence within this research area and engages in frequent collaborations with other countries. Based on the aforementioned analysis, it is recommended that research teams hailing from Asian countries seek to augment their international influence by engaging in heightened cooperation with their counterparts in European and American nations. The dual map overlay depicted in Figure 7 reveals a wide range of subject areas covered by cited and citing journals, indicating untapped potential for further exploration within this research area. By employing a clustering analysis approach and examining the

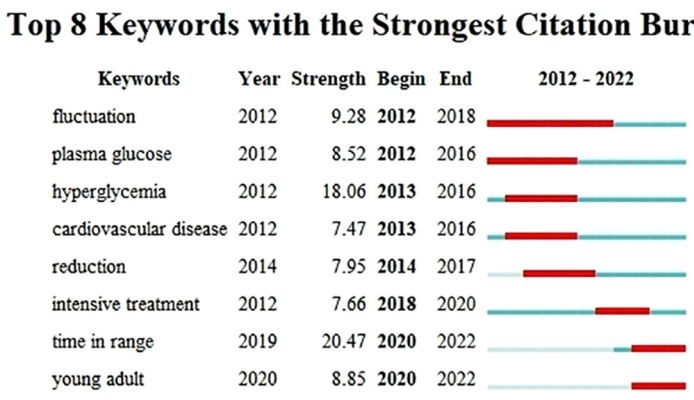

FIGURE 9
Keywords with the Strongest Citation Bursts for Publications on the Clinical Practice of CGM in Diabetes Mellitus Diabetic from 2012- 2022.

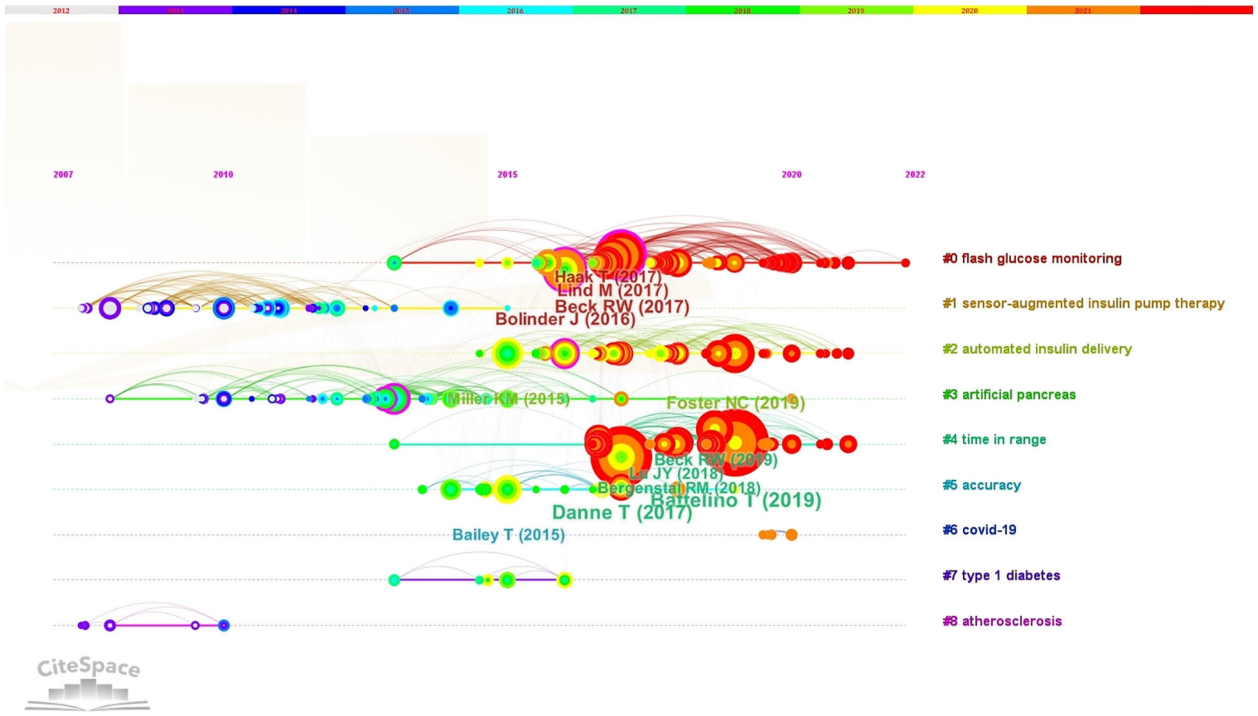

FIGURE 10
The Timeline View of Keyword Clustering Analysis Related to the Clinical Practice of CGM in Diabetes Mellitus was Visualized Using CiteSpace. The clusters formed by the keywords were represented by different colored horizontal lines, with labels on the right. The nodes positioned on these horizontal lines depicted the keywords themselves, while the position of the nodes on the horizontal lines indicated the year of the literature in which the keywords first appeared, thus forming a timeline representing the evolution of the keyword clusters.

emergence of keywords and references, we have been able to identify research hotspots between 2012 and 2022 and forecast future trends in this research area. Notably, the most cited reference is a review authored by Tadej Battelino, Thomas Danne et al. This international consensus validated the feasibility of using the TIR index as a clinical endpoint and outcome measure to supplement HbA1c in various relevant populations, and the target thresholds outlined in the article serve as a valuable framework and point of reference for the clinical application of CGM (15).

4.2 Research hotspots

The fundamental essence of an academic field can be encapsulated by its keywords, and through visual analysis of these keywords, one can discern the prevailing research trends and trajectories (25). Based on the high-frequency keywords extracted and the keyword clustering timeline mapping generated by CiteSpace, the primary research areas in this field during the past decade can be identified. These areas include continuous glucose monitoring (CGM), glycemic variability, type 1 diabetes, and hypoglycemia. Significantly, the other three hot keywords were all generated based on CGM.

In the realm of diabetes management, the advent of continuous glucose monitoring (CGM) technology has bestowed unprecedented prospects for the monitoring and regulation of patient glycemic levels. Traditional intermittent approaches to glucose monitoring have progressively exhibited their inherent limitations, rendering the comprehensive capture of blood glucose fluctuations throughout a patient's diurnal existence a challenging endeavor. In contrast, the real-time and uninterrupted monitoring attribute intrinsic to CGM technology introduces a novel instrument for therapeutic guidance, both for medical practitioners and their patients. The study of glycemic variability has emerged as a pivotal domain of investigation in contemporary times, and concomitant with the evolution of CGM technology, its integration within clinical practice has experienced a notable escalation in recent years (26, 27). Recent findings have indicated a correlation between elevated glycemic variability (GV) and the advancement and escalation of vascular complications in diabetic patients, heightened susceptibility to hypoglycemic episodes, as well as a decline in the quality of life (QOL) for affected individuals (28–30). The metrics encompassing Glycemic Variability are presently acknowledged as a significant gauge of glycemic management (31). This underscores the imperative of delving into the systematic examination of continuous glucose monitoring (CGM) data, and underscores the criticality of adeptly harnessing and interpreting CGM data to effectively serve its role within the realm of clinical practice.

The assessment of transient glycemic fluctuations is frequently derived from continuous glucose monitoring standard deviation (CGM.SD), a readily computable metric commonly employed to quantify short-term glycemic variability. However, it is worth noting that CGM.SD is influenced by the prevailing mean glucose levels, thereby rendering it susceptible to this parameter. Conversely, the coefficient of variation (CV), derived from both

TABLE 5 The Top 10 references of publications on the clinical practice of CGM in diabetes mellitus from 2012 to 2022.

Rank	Title of citing documents	DOI	Times cited	Interpretation of the research
1	Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range	doi: 10.2337/dci19-0028	557	This article summarizes the clinical practice of CGM in different populations, and if retrospective analysis of CGM data enables clinicians to set achievable clinical goals with their patients with diabetes and confirms that TIR is appropriate and useful in complementing clinical goals and outcome measures.
2	International Consensus on Use of Continuous Glucose Monitoring	doi:10.2337/dc17-1600	462	This article presents a synthesis of the consensus recommendations established by the Advanced Technologies and Treatments for Diabetes (ATTD) conference and serves as a comprehensive depiction of the contemporary comprehension regarding the potential impacts of continuous glucose monitoring (CGM) outcomes on clinical outcomes.
3	Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections The DIAMOND Randomized Clinical Trial	doi 10.1001/jama.2016.19975	291	A randomized controlled trial concludes that in patients with type 1 diabetes who receive multiple daily insulin injections, the use of CGM resulted in a significant decrease in HbA1c levels over 24 weeks compared to usual care.
4	Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial	doi 10.1016/s0140-6736(16)31535-5	219	A multicenter, prospective, unmasked, randomized controlled trial concludes that the novel CGM reduces the duration of T1D hypoglycemia in adults.
5	Randomized Controlled Trial Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections: The GOLD Randomized Clinical Trial	doi 10.1001/jama.2016.19976	200	This paper further validates the result that CGM reduces glycated hemoglobin
6	State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016–2018	doi 10.1089/dia.2018.0384	199	This article shows that only a small number of adults and youth with TID in the United States meet ADA goals
7	Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials	doi 10.2337/dc18-1444	177	This study provides validation that Time in Range (TIR) is highly correlated with the likelihood of microvascular complications and thus represents a valid endpoint for clinical trials.
8	Glucose Management Indicator (GMI): A New Term for Estimating A1C From Continuous Glucose Monitoring	doi 10.2337/dc18-1581	133	Introducing eA1C from CGM, a new glucose assessment metric for diabetes education or management
9	Continuous Glucose Monitoring Versus Usual Care in Patients With Type 2 Diabetes Receiving Multiple Daily Insulin Injections A Randomized Trial	doi 10.7326/m16-2855	132	Through a randomized controlled trial, the results of this study raise the possibility that CGM is potentially beneficial for adult patients with T2D who are treated with insulin, although CGM is rarely used.
10	Current State of Type 1 Diabetes Treatment in the U.S.: Updated Data From the T1D Exchange Clinic Registry	doi 10.2337/dc15-0078	131	An analysis of the data collected from 2010-2012 and 2013-2014 on T1D patients in the United States is conducted to provide insight into the current status of T1D patients.

the standard deviation and mean glucose, serves to ameliorate this inherent limitation by compensating for the aforementioned sensitivity to mean glucose levels (15). Furthermore, within clinical settings, diverse indices such as the mean amplitude of glycemic excursion (MAGE), J-index, low blood glucose index/high blood glucose index, average daily risk range, and mean of daily differences (MODD) are employed to evaluate distinct facets of glycemic fluctuations in patients (32–36). Additionally, the Time in Range (TIR) parameter, denoting the proportion of time during which blood glucose levels remain within specified glycemic thresholds, while not strictly categorized as a glycemic variability metric, assumes significance as a supplementary clinical target and an outcome measure for HbA1c assessment across a spectrum of diabetes mellitus presentations, as established by international consensus (15). Consensus opinions have also established a link between TIR and the risk of diabetic complications, such as the close association between TIR and the risk of microvascular complications (19), as well as the good correlation between TIR and HbA1c. Additional research has further substantiated the notion that HbA1c inadequately captures data pertaining to the fluctuation of blood glucose levels or the duration of time spent within the hypoglycemic or hyperglycemic spectrum. Consequently, the Time in Range (TIR) metric is presently being embraced as a favored metric for prognosticating the susceptibility to diabetic complications, delineating outcomes in clinical investigations, and evaluating glycemic management in patient cohorts (37, 38).

As the keyword emergence shown in Figure 9, the emerging keywords for 2020 to 2022 are “Time in Range” and “Young Adult”. Research conducted in the realm of clinical practice concerning

Continuous Glucose Monitoring (CGM) throughout this timeframe has been predominantly centered around acquiring more precise and up-to-the-minute data pertaining to glycemic regulation. Additionally, investigations have been dedicated to the viability of employing Time in Range (TIR) as a quantifiable parameter, alongside examinations concentrated on the demographic of young adults. Envisioning the future, the burgeoning prominence of TIR as a measurable criterion is anticipated to persistently mirror the evolving methodology within the domain of diabetes management. Progressions in technological innovations coupled with an increasingly profound comprehension of the intricacies inherent in diabetes are poised to propel these transformations forward, culminating in a sustained emphasis on ameliorating long-term prognosis and enhancing the quality of life for individuals afflicted with diabetes.

Although Continuous Glucose Monitoring (CGM) can furnish real-time insights into blood glucose levels and trends, alongside retrospective analyses of glycemic regulation patterns and glycemic metrics over specific temporal intervals (4, 39), their assimilation into clinical practice falls short of reaching optimal levels (40). The suboptimal adoption can be attributed, in significant part, to the dearth of software possessing the capacity for relatively straightforward and standardized statistical and graphical depiction, as well as interpretation, of glycemic data, thereby engendering uncertainty and reluctance among clinicians towards integrating CGM into their professional milieu (41, 42). Consequently, to surmount these obstacles and harness the full potential of continuous glucose monitoring (CGM) data within clinical settings, a method christened as the "ambulatory glucose profile" (AGP) was devised. The AGP is a tool utilized for assessing short-term glycemic variability indices in diabetic patients. By analyzing CGM data, it generates charts depicting median, interquartile range (IQR), and other statistical values, thereby providing a comprehensive evaluation of intra-day and inter-day glycemic fluctuations for patients (43, 44). A methodical examination of AGP reports proves to be a valuable and pragmatic approach, enabling real-time and comprehensive assessment of glycemic control and the effectiveness of any therapeutic modifications (45, 46). Through meticulous scrutiny of AGP charts, clinical practitioners can attain enhanced comprehension of patients' glycemic patterns, identify potential issues, and discern opportunities for refining treatment regimens. Thorough AGP analysis aids in pinpointing pivotal factors for achieving optimal glycemic control, thereby furnishing robust support for formulating appropriate therapeutic adjustments and further integrating CGM data into routine clinical practice (47, 48). With the introduction of the AGP approach, clinicians are better equipped to expound upon and communicate glycemic data, collaboratively establish personalized treatment objectives with patients, and monitor their progress throughout the course of treatment. This endeavor fosters closer doctor-patient relationships, heightens patients' awareness of glycemic control, and ultimately augments the efficacy of diabetes management. In addition, there are a number of Software Packages and Tools that support comprehensive analysis of CGM data (49).

Ultimately, through a bibliometric analysis of this research domain, we can discern with clarity that the focal point of clinical practice research transcends the mere analysis of various metrics and has surpassed conventional data analysis. As depicted by the keyword clustering analysis in Figure 8, investigations are progressively expanding into the application of cutting-edge technologies such as artificial pancreas, machine learning, and artificial intelligence. These studies not only furnish diabetic patients with more advanced therapeutic modalities but also usher in novel possibilities for technological innovation and advancement within the realm of medicine. Looking ahead, we can anticipate witnessing further breakthroughs in these domains, heralding a positive impact on the well-being and quality of life for individuals afflicted by diabetes.

5 Conclusion

The current clinical practice of continuous glucose monitoring (CGM) holds great promise. Since its introduction in the United States in 1999 (50), the accuracy of CGM systems has steadily improved, facilitating better daily management of diabetes. The present state of glycemic management in diabetic patients is deemed precarious, as it falls short of the established standards set forth by the World Health Organization. Nevertheless, the burgeoning utilization of continuous glucose monitoring (CGM) has garnered significant interest and is anticipated to be comprehensively explored in the realm of research.

6 Limitations

The present study exhibits certain potential limitations that should be acknowledged. Firstly, the pertinent articles were exclusively obtained from a solitary database, WOSCC, which may have resulted in a biased sample, particularly in comparison to other databases, such as Scopus and PubMed. Secondly, some studies that could have provided valuable insights to the study are ongoing and hence not yet included. Thirdly, researcher bias is a possibility, as the screening process for literature necessitates the artificial exclusion of articles that do not bear relevance to the study. Fourthly, the study solely focused on the clinical practice of CGM in diabetes and did not encompass the technological advancements of CGM sensors, which may have caused the omission of certain potentially beneficial articles.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

LK, BD, and MG contributed to conception and design of the study. LY and ZX organized the database. BD performed the statistical analysis. LK and BD wrote the first draft of the

manuscript. MG, MC, XW, MZ, HT, and QW wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Ogle GD, James S, Dabelea D, Pihoker C, Svennson J, Maniam J, et al. Global estimates of incidence of type 1 diabetes in children and adolescents: Results from the International Diabetes Federation Atlas, 10th edition. *Diabetes Res Clin Pract* (2022) 183:109083. doi: 10.1016/j.diabres.2021.109083

2. Ogurtsova K, Da RFJ, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract* (2017) 128:40–50. doi: 10.1016/j.diabres.2017.03.024

3. Ajjan RA. How can we realize the clinical benefits of continuous glucose monitoring? *Diabetes Technol Ther* (2017) 19:S27–36. doi: 10.1089/dia.2017.0021

4. Peters AL. Integration of diabetes technology in clinical practice. *Endocrinol Metab Clin North Am* (2020) 49:69–77. doi: 10.1016/j.ecl.2019.10.002

5. Garg SK, Akturk HK. Flash glucose monitoring: the future is here. *Diabetes Technol Ther* (2017) 19:1–03. doi: 10.1089/dia.2017.0098

6. Riveline JP, Schaepelynck P, Chaillous L, Renard E, Sola-Gazagnes A, Penfornis A, et al. Assessment of patient-led or physician-driven continuous glucose monitoring in patients with poorly controlled type 1 diabetes using basal-bolus insulin regimens: a 1-year multicenter study. *Diabetes Care* (2012) 35:965–71. doi: 10.2337/dc11-2021

7. Battelino T, Alexander CM, Amiel SA, Arreaza-Rubin G, Beck RW, Bergenstal RM, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. *Lancet Diabetes Endocrinol* (2023) 11:42–57. doi: 10.1016/S2213-8587(22)00319-9

8. Hirsch IB, Miller E. Integrating continuous glucose monitoring into clinical practices and patients' lives. *Diabetes Technol Ther* (2021) 23:S72–80. doi: 10.1089/dia.2021.0233

9. Aleppo G, Webb K. Continuous glucose monitoring integration in clinical practice: A stepped guide to data review and interpretation. *J Diabetes Sci Technol* (2019) 13:664–73. doi: 10.1177/1932296818813581

10. Guler AT, Waaijer CJ, Palmblad M. Scientific workflows for bibliometrics. *Scientometrics* (2016) 107:385–98. doi: 10.1007/s11192-016-1885-6

11. Wu H, Cheng K, Guo Q, Yang W, Tong L, Wang Y, et al. Mapping knowledge structure and themes trends of osteoporosis in rheumatoid arthritis: a bibliometric analysis. *Front Med (Lausanne)* (2021) 8:787228. doi: 10.3389/fmed.2021.787228

12. Cheng K, Guo Q, Yang W, Wang Y, Sun Z, Wu H. Mapping knowledge landscapes and emerging trends of the links between bone metabolism and diabetes mellitus: a bibliometric analysis from 2000 to 2021. *Front Public Health* (2022) 10:918483. doi: 10.3389/fpubh.2022.918483

13. Wu W, Xie Y, Liu X, Gu Y, Zhang Y, Tu X, et al. Analysis of scientific collaboration networks among authors, institutions, and countries studying adolescent myopia prevention and control: a review article. *Iran J Public Health* (2019) 48:621–31. doi: 10.18502/ijph.v48i4.983

14. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* (2019) 42:1593–603. doi: 10.2337/dci19-0028

15. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care* (2017) 40:1631–40. doi: 10.2337/dc17-1600

16. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. *Jama* (2017) 317:371–78. doi: 10.1001/jama.2016.19975

17. 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) 21:66–72. doi: 10.1089/dia.2018.0384

18. Beck RW, Bergenstal RM, Riddlesworth TD, Kollman C, Li Z, Brown AS, et al. Validation of time in range as an outcome measure for diabetes clinical trials. *Diabetes Care* (2019) 42:400–05. doi: 10.2337/dc18-1444

19. Beck RW, Riddlesworth TD, Ruedy K, Ahmann A, Haller S, Kruger D, et al. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. *Ann Intern Med* (2017) 167:365–74. doi: 10.7326/M16-2855

20. Miller KM, Foster NC, Beck RW, Bergenstal RM, DuBose SN, DiMeglio LA, et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. *Diabetes Care* (2015) 38:971–78. doi: 10.2337/dc15-0078

21. Swaich H, Advani A. Sustained improvement in glycemic control in emerging adults with type 1 diabetes 2 years after the start of the COVID-19 pandemic. *Diabetes Ther* (2023) 14:153–65. doi: 10.1007/s13300-022-01346-5

22. Romeo GR, Shaikh YA, Middelbeek R. Post-graduate medical education in the time of COVID-19: Not a remotely simple task. *Front Endocrinol (Lausanne)* (2022) 13:980505. doi: 10.3389/fendo.2022.980505

23. Kodani N, Ohsugi M. The patient-centered diabetes management during the COVID-19 pandemic. *Glob Health Med* (2022) 4:210–15. doi: 10.35772/ghm.2022.01031

24. Zhang W, Zhang S, Dong C, Guo S, Jia W, Jiang Y, et al. A bibliometric analysis of RNA methylation in diabetes mellitus and its complications from 2002 to 2022. *Front Endocrinol (Lausanne)* (2022) 13:997034. doi: 10.3389/fendo.2022.997034

25. Zhou Z, Sun B, Huang S, Zhu C, Bian M. Glycemic variability: adverse clinical outcomes and how to improve it? *Cardiovasc Diabetol* (2020) 19:102. doi: 10.1186/s12933-020-01085-6

26. Psoma O, Makris M, Tselepis A, Tsimihodimos V. Short-term glycemic variability and its association with macrovascular and microvascular complications in patients with diabetes. *J Diabetes Sci Technol* (2022), 550756024. doi: 10.1177/19322968221146808

27. Rodbard D. Interpretation of continuous glucose monitoring data: glycemic variability and quality of glycemic control. *Diabetes Technol Ther* (2009) 11 Suppl 1: S55–67. doi: 10.1089/dia.2008.0132

28. Penckofer S, Quinn L, Byrn M, Ferrans C, Miller M, Strange P. Does glycemic variability impact mood and quality of life? *Diabetes Technol Ther* (2012) 14:303–10. doi: 10.1089/dia.2011.0191

29. Ceriello A. The post-prandial state and cardiovascular disease: relevance to diabetes mellitus. *Diabetes Metab Res Rev* (2000) 16:125–32. doi: 10.1002/(sici)1520-7560(200003/04)16:2<125::aid-dmrr90>3.0.co;2-4

30. Chen Y, Jia T, Yan X, Dai L. Blood glucose fluctuations in patients with coronary heart disease and diabetes mellitus correlates with heart rate variability: A retrospective analysis of 210 cases. *Niger J Clin Pract* (2020) 23:1194–200. doi: 10.4103/njcp.njcp_529_19

31. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes* (1970) 19:644–55. doi: 10.2337/diab.19.9.644

32. Kovatchev B. Glycemic variability: risk factors, assessment, and control. *J Diabetes Sci Technol* (2019) 13:627–35. doi: 10.1177/1932296819826111

33. Wojcicki JM. "J"-index. A new proposition of the assessment of current glucose control in diabetic patients. *Horm Metab Res* (1995) 27:41–2. doi: 10.1055/s-2007-979906

34. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Young-Hyman D, Schlundt D, Clarke W. Assessment of risk for severe hypoglycemia among adults with IDDM: validation of the low blood glucose index. *Diabetes Care* (1998) 21:1870–75. doi: 10.2337/diacare.21.11.1870

35. Kovatchev BP, Otto E, Cox D, Gonder-Frederick L, Clarke W. Evaluation of a new measure of blood glucose variability in diabetes. *Diabetes Care* (2006) 29:2433–38. doi: 10.2337/dc06-1085

36. Vigersky RA, McMahon C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes. *Diabetes Technol Ther* (2019) 21:81–5. doi: 10.1089/dia.2018.0310

37. Yapanis M, James S, Craig ME, O'Neal D, Ekinci EI. Complications of diabetes and metrics of glycemic management derived from continuous glucose monitoring. *J Clin Endocrinol Metab* (2022) 107:e2221–36. doi: 10.1210/clinem/dgac034

38. Bergenstal RM, Ahmann AJ, Bailey T, Beck RW, Bissen J, Buckingham B, et al. Recommendations for standardizing glucose reporting and analysis to optimize clinical decision making in diabetes: the ambulatory glucose profile. *J Diabetes Sci Technol* (2013) 7:562–78. doi: 10.1177/193229681300700234

39. Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, DuBose SN, Hall CA. The T1D Exchange clinic registry. *J Clin Endocrinol Metab* (2012) 97:4383–89. doi: 10.1210/jc.2012-1561

40. Benhalima K, Mathieu C. The role of blood glucose monitoring in non-insulin treated type 2 diabetes: what is the evidence? *Prim Care Diabetes* (2012) 6:179–85. doi: 10.1016/j.pcd.2012.05.001

41. Beck RW, Bergenstal RM. Beyond A1C-standardization of continuous glucose monitoring reporting: why it is needed and how it continues to evolve. *Diabetes Spectr* (2021) 34:102–08. doi: 10.2337/ds20-0090

42. Carlson AL, Mullen DM, Bergenstal RM. Clinical use of continuous glucose monitoring in adults with type 2 diabetes. *Diabetes Technol Ther* (2017) 19:S4–11. doi: 10.1089/dia.2017.0024

43. Peters AL. The evidence base for continuous glucose monitoring. In: *Role of continuous glucose monitoring in diabetes treatment*. Arlington (VA): American Diabetes Association (2018) 3–07. doi: 10.2337/db20181-3

44. Rodbard D. Clinical interpretation of indices of quality of glycemic control and glycemic variability. *Postgrad Med* (2011) 123:107–18. doi: 10.3810/pgm.2011.07.2310

45. Forlenza GP, Pyle LL, Maahs DM, Dunn TC. Ambulatory glucose profile analysis of the juvenile diabetes research foundation continuous glucose monitoring dataset-Applications to the pediatric diabetes population. *Pediatr Diabetes* (2017) 18:622–28. doi: 10.1111/pedi.12474

46. Czupryniak L, Dzida G, Fichna P, Jarosz-Chobot P, Gumprecht J, Klupa T, et al. Ambulatory glucose profile (AGP) report in daily care of patients with diabetes: practical tips and recommendations. *Diabetes Ther* (2022) 13:811–21. doi: 10.1007/s13300-022-01229-9

47. Bergenstal RM, Ahmann AJ, Bailey T, Beck RW, Bissen J, Buckingham B, et al. Recommendations for standardizing glucose reporting and analysis to optimize clinical decision making in diabetes: the Ambulatory Glucose Profile (AGP). *Diabetes Technol Ther* (2013) 15:198–211. doi: 10.1089/dia.2013.0051

48. Piersanti A, Giurato F, Gobl C, Burattini L, Tura A, Morettini M. Software packages and tools for the analysis of continuous glucose monitoring data. *Diabetes Technol Ther* (2023) 25:69–85. doi: 10.1089/dia.2022.0237

49. Clarke SF, Foster JR. A history of blood glucose meters and their role in self-monitoring of diabetes mellitus. *Br J BioMed Sci* (2012) 69:83–93. doi: 10.1080/09674845.2012.12002443

50. Aria M, Cuccurullo C. bibliometrix: An R-tool for comprehensive science mapping analysis. *J Informetr* (2017) 11:959–75. doi: 10.1016/j.joi.2017.08.007

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Are all HCL systems the same? long term outcomes of three HCL systems in children with type 1 diabetes: real-life registry-based study

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Objective: To compare parameters of glycemic control among three types of hybrid closed loop (HCL) systems in children with T1D (CwD) using population-wide data from the national pediatric diabetes registry ČENDA.

Methods: CwD aged <19 years treated with Medtronic MiniMed 780G (780G), Tandem t:slim X2 (Control-IQ) or do-it-yourself AndroidAPS (AAPS) systems for >12 months and monitored by CGM >70% of the time were included. HbA1c, times in glycemic ranges, and Glycemia Risk Index (GRI) were used for cross-sectional comparison between the HCL systems.

Results: Data from 512 CwD were analyzed. 780G, Control-IQ and AAPS were used by 217 (42.4%), 211 (41.2%), and 84 (16.4%) CwD, respectively. The lowest HbA1c value was observed in the AAPS group (44 mmol/mol; IQR 8.0, p<0.0001 vs any other group), followed by Control-IQ and 780G groups (48 (IQR 11) and 52 (IQR 10) mmol/mol, respectively). All of the systems met the recommended criteria for time in range (78% in AAPS, 76% in 780G, and 75% in Control-IQ users). CwD using AAPS spent significantly more time in hypoglycemia (5% vs 2% in 780G and 3% in Control-IQ) and scored the highest GRI (32, IQR 17). The lowest GRI (27, IQR 15) was seen in 780G users.

Conclusion: Although all HCL systems proved effective in maintaining recommended long-term glycemic control, we observed differences that illustrate strengths and weaknesses of particular systems. Our findings could help in individualizing the choice of HCL systems.

KEYWORDS

type 1 diabetes, pediatrics, hybrid closed loop, AndroidAPS, registry

1 Introduction

Recent advances in technology increased the chance of optimizing long-term glycemic control in people with type 1 diabetes (T1D). The latest breakthrough is represented by the hybrid closed-loop (HCL) algorithms that can modify blood glucose level based on automated insulin dose adjustment (1). Growing evidence shows that HCL represent a safe and effective tool for the overall improvement of glycemic outcomes (2–6). Several randomized trials showed superiority of HCL over any other treatment modality in children and adults with T1D (7–11).

To date, there are several HCL systems available. Among them, Tandem t:slim X2 with Control-IQ algorithm (Tandem Diabetes Care, San Diego, CA, USA) and Medtronic MiniMed 780G with SmartGuard algorithm (Medtronic Inc. Minneapolis, MN, USA) are the ones most widely used in Europe. In addition, AndroidAPS (AAPS), an unofficial do-it-yourself (DIY) HCL system, continues to maintain significant popularity (12). Although all HCL systems share the same principle of manual pre-prandial bolus administration and automated insulin dose adjustment in case of predicted hypo- or hyperglycemia, there are also several differences mainly related to glycemic targets, reaction to hyperglycemia and user adjustable settings. Moreover, the systems differ in the used algorithm: whereas Control-IQ and AAPS use manually fully adjustable algorithms, 780G uses a self-adjusting technology that limits the users ability to influence insulin dosage. Although there are proofs of the efficacy to improve glycemic outcomes in each of these systems individually (3, 13, 14), studies directly comparing different HCL systems head-to-head in real-life settings are limited.

The aim of this study is to compare the parameters of glycemic control among the three most common types of HCL algorithms used in Czechia (MiniMed 780G with SmartGuard, Tandem t:slim X2 with Control-IQ and AAPS) in children with T1D (CwD) using the population-wide data from the national pediatric diabetes registry ČENDA.

2 Materials and methods

2.1 Study population and compared parameters

This retrospective multicenter study is based on data from the national pediatric diabetes web-based registry ČENDA, described in detail elsewhere (15). In brief, the registry stores anonymized data about CwD aged <19 years who are followed in one of the participating pediatric diabetes outpatient clinics in the Czech Republic. The data in this study are based exclusively on the annual report from 2022. Forty-seven pediatric diabetes outpatient clinics participated in ČENDA in 2022. As of December 2022, the ČENDA registry included 4427 CwD which is estimated to be more than 95% of all pediatric diabetes cases in the Czech Republic. Participation in the registry is voluntary, all participants and/or their legal representatives signed a written informed consent. ČENDA registry is approved by the Ethical Committee of the Motol University Hospital and registered at the National Bureau for Personal Data Protection.

In ČENDA registry, collected data include basic demographic information, glycemic control status, data on acute or chronic complications and comorbidities and data on the type of treatment modality and continuous glucose monitoring use and their change. CGM usage is further categorized based on the proportion of time the child spent on CGM in the past year: no use,≤19%, 20%-39%, 40%-69%, 70%-89% and ≥90% category (16).

All children with T1D aged <19 years treated with one of the following HCLs - Medtronic MiniMed 780G (780G), Tandem t:slim X2 with Control-IQ algorithm (Control-IQ) or AAPS with Dana Diabecare RS (SOOIL Development, Seoul, Republic of Korea) or Accu-Chek Insight (Roche Diabetes Care, Mannheim, Germany) insulin pump for at least 12 months and monitored by CGM more than 70% of the time were included in the analysis. The study flowchart is shown in the Supplementary Figure 1. Before the initiation of HCL therapy, all children were educated about the proper configuration of the system and its appropriate utilization.

The median HbA1c, CGM-derived parameters and Glycemia Risk Index (GRI) from the last available visit were calculated and compared between the HCL groups. CGM-derived parameters included the following parameters: time in range – TIR (3.9-10.0 mmol/L; 70-180 mg/dL); time in hyperglycemia level 1 – TAR1 (10.1-13.9 mmol/L; 181-250 mg/dL); time in hyperglycemia level 2 – TAR2 (>13.9 mmol/L; >250 mg/dL); time in hypoglycemia level 1 – TBR1 (3.0-3.8 mmol/L; 54-69 mg/dL); time in hypoglycemia level 2 – TBR2 (<3.0 mmol/L; <54 mg/dL) (17). The median of the CGM-derived parameters were calculated from the last 14 days' CGM records before the last outpatient visit. The Glycemia Risk Index was calculated using the standard formula: GRI = (3.0 × TBR <50 mg/dL) + (2.4 × TBR <70 mg/dL) + (1.6 × TAR >250 mg/dL) + (0.8

× TAR >180 mg/dL) (18). The occurrence of severe hypoglycemia (SH) and/or diabetic ketoacidosis (DKA) in 2022 was also collected and compared across the groups. A separate age-category analysis (0–5.99, 6–11.99, and 12-18.99 years) was performed for all of the above-mentioned parameters.

2.2 Statistical analysis

Data were summarized as means with standard deviation (SD) or medians with interquartile range where appropriate. The differences between HCL groups were assessed using ANOVA F-test or Kruskall-Wallis ANOVA. Categorical variables were summarized using absolute and relative frequencies and differences between the groups were tested using χ^2-test. For better insight, cumulative distribution functions for HbA1c, TIR, and GRI were used to examine the relationship between the HCL groups.

To reduce the imbalance of baseline characteristics between the groups, we used the *mnps* function for multiple groups of the TWANG (The Toolkit for Weighting and Analysis of Nonequivalent Groups) library (19) to estimate the propensity score weights based on gender, current age, T1D duration, insulin dose, and BMI. This type of analysis differs from usual propensity score matching, in that it allows for multiple groups to be considered at once and keeps the original sample sizes. Weighted means/medians, 1st and 3rd quartiles were computed to reassess the differences. Comparisons between HCL groups were then carried out using weighted ANOVA regression models and Tukey *post-hoc* analysis for pairwise comparisons.

3 Results

3.1 Baseline characteristics

Data from 512 CwD (276 males and 236 females) who met the inclusion criteria were analyzed. 780G, Control-IQ and AAPS were used by 217 (42.4%), 211 (41.2%) and 84 (16.4%) children, respectively. The mean age of CwD in the study cohort was 12.8 ± 4.2 years, with the age category 12+ years the most represented (n = 323), followed by children aged 6–11.99 (n = 142) and <6 years (n = 46). The mean diabetes duration was 7.0 ± 3.6 years. We observed a statistically significant difference in age, T1D duration, duration of HCL therapy, daily insulin requirement and BMI-SDS between the users of studied HCL systems. The basic characteristics of the study group are summarized in the Supplementary Table 1 in detail.

3.2 HbA1c

The median of HbA1c in the whole study group was 49 mmol/mol (6.6%). The ISPAD target of HbA1c <48 mmol/mol (<6.5%) (20) was reached by 76.2% of AAPS users, 49.8% of Control-IQ users, and 29.5% of 780G users. (Figure 1A). The lowest HbA1c value was seen in the AAPS users (44 mmol/mol; 6.2%; p<0.001 vs any other group), followed by the Control-IQ (48 mmol/mol, 6.5%) and 780G group (52 mmol/mol; 6.9%) (p<0.001 between the latter). (Supplementary Figure 2A). Similar results of HbA1c were observed after propensity score weighting recalculation (Figure 2A) and in all of the evaluated age groups (Supplementary Figure 3A; Supplementary Table 2).

3.3 Times in glycemic ranges

A detailed overview of TIR in the study groups is shown in Table 1, the means of TIR are illustrated in Figure 3. The recommended target of TIR 70% (20) was achieved by 75% of CwD in the AAPS group, 74.2% of CwD in the 780G group, and 65.9% of CwD in the Control-IQ group. (Figure 1B) The highest median of TIR was achieved by AAPS users (78%), followed by 780G (76%), and Control-IQ users (75%). Only the difference between the AAPS and the Control-IQ group was assessed as statistically significant (p=0.035). On the other hand, the AAPS group spent the longest time in hypoglycemia with the mean of TBR1 5.2% (vs 2.9% for Control-IQ and 2.5% for 780G) and TBR2 1.5% (vs 0.8% for Control-IQ and 0.6% for 780G).

After the recalculation using the propensity score weighting, the similar results were observed in all of the groups, with the TIR of 76% scored by 780G users, 75% by AAPS users and 75% by Control-IQ users. While the TIR of the 780G group did not differ significantly from the AAPS group (p=0.99), there was a statistical difference between the 780G and the Control-IQ group

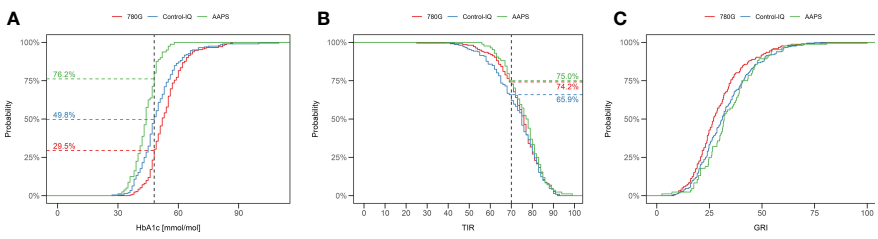

FIGURE 1
Percentage of children using 780G (red), Control-IQ (blue) and AAPS (green) achieving the ISPAD target of HbA1c 48mmol/mol **(A)**, and TIR (70%) **(B)**. The difference in proportions of CwD reaching a particular GRI value are depicted as C. **(C)** TIR, time in range; GRI, glycemia risk index.

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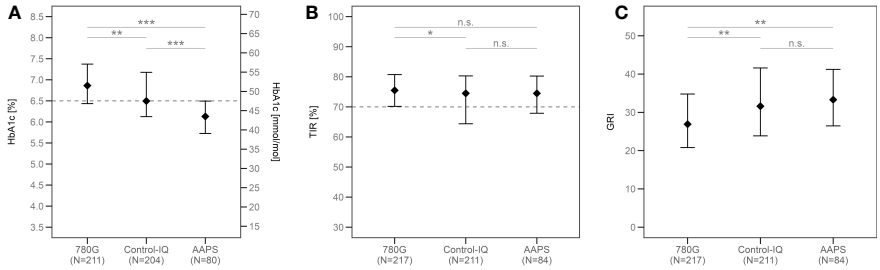

FIGURE 2
The medians of HbA1c **(A)**, TIR **(B)** and GRI **(C)** in all groups according to the type of HCL system used after the propensity score weighting. ***p<0.001, **p<0.01, *p<0.05, ns, not significant. TIR, time in range; GRI, glycemia risk index; AAPS, AndroidAPS.

(p=0.02, Figure 2B). The medians of TIR in all age groups are shown in detail in Supplementary Table 2.

3.4 Glycemia Risk Index

The median GRI of all CwD included in the study was 30. The lowest GRI value was achieved by the users of 780G (27), followed by Control-IQ (31) and AAPS (32) (Table 1). The difference in GRI between 780G users and the other two assessed HCL systems was significant (p<0.05), whereas no significant difference was found between the Control-IQ and AAPS groups (p=0.72). An overview of GRI results is shown in Table 1 and Supplementary Figure 2C. The cumulative distribution of GRI by HCL systems is shown in Figure 1C.

The lowest GRI in the 780G group (p<0.005 vs both other groups) as well as no significant difference between AAPS and Control-IQ users (p=0.53) was consistently observed also in the matched cohort (Figure 2C) and all age categories (Supplementary Figure 3C; Supplementary Table 2).

TABLE 1 Parameters of glycemic control by the type of HCL used. The results are shown as medians (IQR), and for DKA and SH the results are shown as events per 100-patient years.

	All patients					Recalculation after propensity score weighting				
	780G	Control-IQ	AAPS	Total	p-value	780G	Control-IQ	AAPS	Total	p-value
HbA1c [mmol/mol]	52 (48-58)	48 (44-55)	44 (40-48)	49 (44-56)	< 0.001	51 (47-57)	48 (44-55)	44 (39-48)	48 (43-55)	< 0.001
HbA1c (%)	6.9 (6.5-7.5)	6.5 (6.2-7.2)	6.2 (5.8-6.5)	6.6 (6.2-7.3)	< 0.001	6.8 (6.5-7.4)	6.5 (6.2-7.2)	6.2 (5.7-6.5)	6.5 (6.1-7.2)	< 0.001
TIR [%]	76 (69-81)	75 (65-81)	78 (70-82)	76 (68-81)	0.127	76 (70-81)	75 (65-80)	75 (68-80)	75 (68-81)	0.015
TAR >180 mg/dL [%]	17 (13-21)	17 (12-22)	12 (9.0-16)	16 (12-21)	< 0.001	17 (13-20)	17 (12-22)	12 (9.3-17)	16 (1-20)	< 0.001
TAR >250 mg/dL [%]	4.0 (1.0-7.0)	4.0 (2.0-8.0)	3.0 (2.0-6.0)	4.0 (2.0-7.0)	0.035	2.5 (0.7-6.1)	3.5 (1.6 -8.0)	3.5 (1.4 -7.2)	3.5 (1.2 -6.8)	0.009
TBR <70 mg/dL [%]	2.0 (1.0-3.0)	2.0 (1 -4)	4.0 (3.0 -7.0)	3.0 (1.0-4.0)	< 0.001	1.5 (0.6 -3.2)	2.5 (1.0 -3.5)	3.5 (2.2 -6.7)	2.5 (0.9-4.0)	< 0.001
TBR <54 mg/dL [%]	0.0 (0.0-1.0)	1.0 (0.0-1.0)	1.0 (0.0-2.0)	0.0 (0.0-1.0)	< 0.001	0.0 (0 -0.6)	0.5 (0 - 0.8)	0.5 (0 -1.9)	0.0 (0.0 -1.9)	0.009
GRI	27 (21-36)	31 (24-41)	32 (26-41)	30 (22-39)	0.001	27 (21 -35)	32 (24 -42)	34 (26 -41)	31 (23 -40)	< 0.001
GRI hyperglycemia component	13 (8.5-17)	12.5 (8.2-20)	9.2 (6.5-15)	12 (8.0-18)	< 0.001	12 (8.0-16)	13 (8.4 -20)	9.8 (6.5-16)	12 (7.7-17)	< 0.001
GRI hypoglycemia component	1.6 (0.8-3.6)	2.6 (0.9-4.2)	5.2 (2.4-8.1)	2.6 (0.8-4.4)	< 0.001	1.7 (0.5 -3.8)	2.5 (1.1 -4.2)	4.1 (2.2 -8.5)	2.5 (1-4.9)	< 0.001
DKA	3.3	2.0	0.0	2.2	NS	NA	NA	NA	NA	NA
SH	0.9	2.0	1.2	1.4	NS	NA	NA	NA	NA	NA

NS, non-significant; NA, not available.
AAPS, AndroidAPS; TIR, time in range; GRI, glycemia risk index; DKA, diabetic ketoacidosis; SH, severe hypoglycemia; IQR, interquartile range.

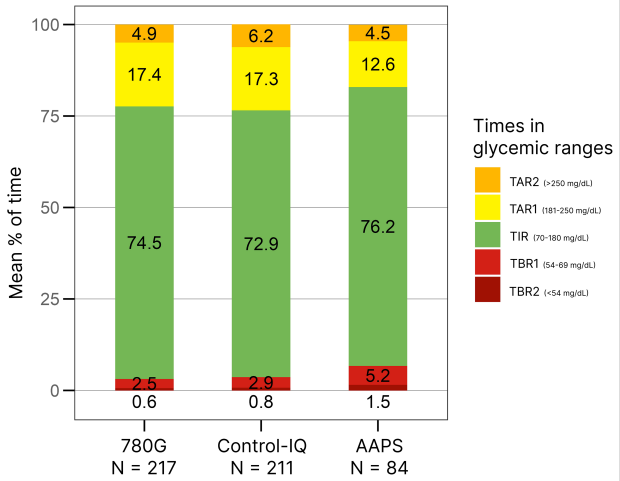

FIGURE 3
The means of times in glycemic ranges. AAPS, AndroidAPS.

3.5 DKA and severe hypoglycemia

There was no statistically significant difference observed in the occurrence of diabetic ketoacidosis nor severe hypoglycemia events between the groups over the observed study period (Table 1).

4 Disscusion

This population-based study compared the parameters of glycemic control in CwD treated by one of the HCL systems (MiniMed 780G, Control-IQ, AAPS) for at least one year. The results revealed that all three systems are effective in achieving the international recommended goals of T1D control. Nevertheless, there are clearly discernible differences that illustrate the strengths and weaknesses of the systems assessed.

The results of well-powered pediatric studies testing the HCL systems individually are in line with our data. Arrieta et al. demonstrated a mean of TIR 73.9% in a cohort of 3211 CwD treated with 780G (21). Similarly Breton et al. described TIR 73.5% in a group of 9451 children using Control-IQ (13). These data are comparable with our findings as in our cohort the mean TIR values of 74.5% and 72.9% were recorded for 780G and Control-IQ, respectively.

To date, similarly focused studies are characterized by small number of participants and limited spectrum of outcomes. The 1-month real-life observational study of 31 CwD did not reveal any significant differences in CGM-derived parameters between Control-IQ and 780G (mean TIR 70.5% vs 70.1%) (22). In contrast, Bassi et al. compared these two systems retrospectively in a 1-year follow-up study comprising 74 children and adults with type 1 diabetes and observed a significant superiority of the 780G system in terms of time in range (71% vs 68%, p=0.001), time above range (p=0.001), average glucose levels (p=0.001) and standard deviation of glycemia (p=0.031) (23). The DIY AAPS system has not been subjected to a comparison in similar studies yet.

Our study revealed some differences in the parameters of glucose control between the HCL systems. Generally, AAPS users achieved the lowest HbA1c, however, they also presented with the highest hypoglycemia rates. In contrast, CwD using 780G were characterized by the lowest time spent in hypoglycemia and consequently scored the lowest GRI. The explanation for these differences might lie in the system settings and the algorithms used by the systems. 780G uses a self-adjusting technology and only allows users to set the insulin-to-carbohydrate ratio, target glycemia, and insulin activity. This setting significantly reduces the potential for insulin overdose when hyperglycemia is corrected by the user. This might explain the lowest hypoglycemia rate in the 780G group and consequently, the highest HbA1c value since hypoglycemia is one of the main factors contributing to the HbA1c value (24). Additionally, the 780G scored the lowest GRI underlining the fact that this index is preferentially driven by hypoglycemia rather than hyperglycemia (18).The position of AAPS is on the opposite side of the spectrum as this system enables the user to individualize and adjust any of the settings. Moreover, AAPS is a DIY system that requires the user to initially download and set it up possibly biasing this group with more motivated and tech-savvy CwD and/or their parents/guardians. Given the flexibility of AAPS input settings and the potentially higher motivation of AAPS users to achieve the lowest possible HbA1c, these users may be prone to overcorrect hyperglycemia with a subsequent risk of hypoglycemia. The Control-IQ algorithm represents a kind of middle ground between these systems. Most settings can be adjusted by the user but some functionalities (i.e. target glycemia) can only be changed to a limited extent. Thus, it scores mostly in the middle between 780G and AAPS in the evaluated parameters.

Based on our results, we propose that 780G might be an advantageous option for CwD with recurrent hypoglycemia episodes or CwD with a fear or impaired awareness of hypoglycemia. On the other hand, higher time in hypoglycemia found in the AAPS group suggests that clinicians should preferentially focus on addressing this in CwD treated with this system, possibly adjusting the settings accordingly and emphasizing the risks of hypoglycemia and its prevention.

Our study has several strengths, which encompass a representativeness of the study population (including children younger than 6 years), unique data on AAPS, and a broad spectrum of parameters (including first data on GRI in HCL systems).

There are several limitations of our study. Firstly, there were pre-existing differences between the groups in diabetes duration, age, insulin dose, and BMI-SD. The number of CwD using a specific HCL also differed. To this end, we used propensity score weighting to minimize the bias and enable a meaningful comparison. The results remained similar even after propensity score weighting which might give our findings more credence. However, despite the use of propensity score weighting, we were unable to eliminate the bias stemming from differences in individual device settings, bolus timing, and the correct use of automatic mode by the participants (25). On the other hand, all of the subjects underwent similar standardized education during the introduction of HCL which should minimize this bias. As this is a

cross-sectional observational study, we cannot exclude selection bias at the level of individual diabetologists preference of one of the HCL systems. A large number of children included and the propensity score weighting analysis nonetheless mitigates this risk. Additionally, we were not able to include some relevant information that were not collected in the ČENDA database in 2022 such as average glycemia and glycemic variability.

Although all of the tested HCL systems proved effective in maintaining recommended long-term glycemic control, we observed differences that might illustrate strengths and weaknesses of particular systems. Our findings could help individualizing the choice of HCL systems.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics committee of the Motol University Hospital, Prague, Czechia. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

AS: Conceptualization, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. LuP: Conceptualization, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. VN: Conceptualization, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. MP: Data curation, Formal Analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. LeP: Conceptualization, Writing – original draft, Writing – review & editing. PK: Investigation, Writing – original draft, Writing – review & editing. PV: Investigation, Writing – original draft, Writing – review & editing. JaS: Investigation, Writing – review & editing. RP: Investigation, Writing – review & editing. DN: Investigation, Writing – review & editing. JV: Investigation, Writing – review & editing. KK: Investigation, Writing – review & editing. BO: Investigation, Writing – review & editing. SP: Conceptualization, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. OC: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. ZS: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. JiS: Investigation, Writing - review & editing.

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Conflict of interest

ZS, LP and SP reported speakers' honoraria from Medtronic, Abbott and A-Import. VN reported speakers' honoraria from Medtronic.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1283181/full#supplementary-material

References

1. Boughton CK, Hovorka R. New closed-loop insulin systems. *Diabetologia* (2021) 64:1007–15. doi: 10.1007/s00125-021-05391-w

2. Carlson AL, Sherr JL, Shulman DI, Garg SK, Pop-Busui R, Bode BW, et al. Safety and glycemic outcomes during the miniMed™ advanced hybrid closed-loop system pivotal trial in adolescents and adults with type 1 diabetes. *Diabetes Technol Ther* (2022) 24:178–89. doi: 10.1089/dia.2021.0319

3. Da Silva J, Lepore G, Battelino T, Arrieta A, Castañeda J, Grossman B, et al. Real-world performance of the miniMed™ 780G system: first report of outcomes from 4120 users. *Diabetes Technol Ther* (2022) 24:113–9. doi: 10.1089/dia.2021.0203

4. Pinsker JE, Müller L, Constantin A, Leas S, Manning M, McElwee Malloy M, et al. Real-world patient-reported outcomes and glycemic results with initiation of control-IQ technology. *Diabetes Technol Ther* (2021) 23:120–7. doi: 10.1089/dia.2020.0388

5. Sumnik Z, Pavlikova M, Neuman V, Petruzelkova L, Konecna P, Venhacova P, et al. Glycemic control by treatment modalities: national registry-based population data in children and adolescents with type 1 diabetes. *Horm Res Paediatr* (2023). doi: 10.1159/000530833

6. Braune K, O'Donnell S, Cleal B, Lewis D, Tappe A, Willaing I, et al. Real-world use of do-it-yourself artificial pancreas systems in children and adolescents with type 1 diabetes: online survey and analysis of self-reported clinical outcomes. *JMIR Mhealth Uhealth* (2019) 7:e14087. doi: 10.2196/14087

7. Collyns OJ, Meier RA, Betts ZL, Chan DSH, Frampton C, Frewen CM, et al. Improved glycemic outcomes with medtronic miniMed advanced hybrid closed-loop delivery: results from a randomized crossover trial comparing automated insulin delivery with predictive low glucose suspend in people with type 1 diabetes. *Diabetes Care* (2021) 44:969–75. doi: 10.2337/dc20-2250

8. Breton MD, Kanapka LG, Beck RW, Ekhlaspour L, Forlenza GP, Cengiz E, et al. A randomized trial of closed-loop control in children with type 1 diabetes. *N Engl J Med* (2020) 383:836–45. doi: 10.1056/NEJMoa2004736

9. Wadwa RP, Reed ZW, Buckingham BA, DeBoer MD, Ekhlaspour L, Forlenza GP, et al. Trial of hybrid closed-loop control in young children with type 1 diabetes. *N Engl J Med* (2023) 388:991–1001. doi: 10.1056/NEJMoa2210834

10. Choudhary P, Kolassa R, Keuthage W, Kroeger J, Thivolet C, Evans M, et al. Advanced hybrid closed loop therapy versus conventional treatment in adults with type 1 diabetes (ADAPT): a randomised controlled study. *Lancet Diabetes Endocrinol* (2022) 10:720–31. doi: 10.1016/S2213-8587(22)00212-1

11. Petruzelkova L, Jiranova P, Soupal J, Kozak M, Plachy L, Neuman V, et al. Pre-school and school-aged children benefit from the switch from a sensor-augmented pump to an AndroidAPS hybrid closed loop: A retrospective analysis. *Pediatr Diabetes* (2021) 22:594–604. doi: 10.1111/pedi.13190

12. Braune K, Lal RA, Petruželková L, Scheiner G, Winterdijk P, Schmidt S, et al. Open-source automated insulin delivery: international consensus statement and practical guidance for health-care professionals. *Lancet Diabetes Endocrinol* (2022) 10:58–74. doi: 10.1016/S2213-8587(21)00267-9

13. Breton MD, Kovatchev BP. One year real-world use of the control-IQ advanced hybrid closed-loop technology. *Diabetes Technol Ther* (2021) 23:601–8. doi: 10.1089/dia.2021.0097

14. Gawrecki A, Zozulinska-Ziolkiewicz D, Michalak MA, Adamska A, Michalak M, Frackowiak U, et al. Safety and glycemic outcomes of do-it-yourself AndroidAPS hybrid closed-loop system in adults with type 1 diabetes. *PLoS One* (2021) 16:e0248965. doi: 10.1371/journal.pone.0248965

15. Šumník Z, Venháčová J, Škvor J, Pomahačová R, Konečná P, Neumann D, et al. Five years of improving diabetes control in Czech children after the establishment of the population-based childhood diabetes register ČENDA. *Pediatr Diabetes* (2020) 21:77–87. doi: 10.1111/pedi.12929

16. Šumník Z, Pavlíková M, Pomahačová R, Venháčová P, Petruželková L, Škvor J, et al. Use of continuous glucose monitoring and its association with type 1 diabetes control in children over the first 3 years of reimbursement approval: Population data from the ČENDA registry. *Pediatr Diabetes* (2021) 22:439–47. doi: 10.1111/pedi.13184

17. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* (2019) 42:1593–603. doi: 10.2337/dci19-0028

18. Klonoff DC, Wang J, Rodbard D, Kohn MA, Li C, Liepmann D, et al. A glycemia risk index (GRI) of hypoglycemia and hyperglycemia for continuous glucose monitoring validated by clinician ratings. *J Diabetes Sci Technol* (2022) 193229682210852. doi: 10.1177/19322968221085273

19. Cefalu M, Ridgeway G, Mccaffrey D, Morral A, Griffin AB, Burgette L. Toolkit for weighting and analysis of nonequivalent groups. *R Package* (2006).

20. Sundberg F, deBeaufort C, Krogvold L, Patton S, Piloya T, Smart C, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Managing diabetes in preschoolers. *Pediatr Diabetes* (2022) 23:1496–511. doi: 10.1111/pedi.13427

21. Arrieta A, Battelino T, Scaramuzza AE, Da Silva J, Castañeda J, Cordero TL, et al. Comparison of MiniMed 780G system performance in users aged younger and older than 15 years: Evidence from 12 870 real-world users. *Diabetes Obes Metab* (2022) 24:1370–9. doi: 10.1111/dom.14714

22. Schiaffini R, Deodati A, Nicoletti MC, Carducci C, Ciampalini P, Lorubbio A, et al. Comparison of two advanced hybrid closed loop in a pediatric population with type 1 diabetes: a real-life observational study. *Acta Diabetol* (2022) 59:959–64. doi: 10.1007/s00592-022-01886-z

23. Bassi M, Patti L, Silvestrini I, Strati MF, Ponzano M, Minuto N, et al. One-year follow-up comparison of two hybrid closed-loop systems in Italian children and adults with type 1 diabetes. *Front Endocrinol (Lausanne)* (2023) 14:1099024. doi: 10.3389/fendo.2023.1099024

24. Tsujino D, Nishimura R, Onda Y, Seo C, Ando K, Morimoto A, et al. The relationship between HbA1c values and the occurrence of hypoglycemia as assessed by continuous glucose monitoring in patients with type 1 diabetes. *Diabetol Metab Syndr* (2016) 8:53. doi: 10.1186/s13098-016-0167-z

25. Lombardo F, Passanisi S, Alibrandi A, Bombaci B, Bonfanti R, Delvecchio M, et al. MiniMed 780G six-month use in children and adolescents with type 1 diabetes: clinical targets and predictors of optimal glucose control. *Diabetes Technol Ther* (2023) 25:404–13. doi: 10.1089/dia.2022.0491

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Evaluating a systematic intensive therapy using continuous glucose monitoring and intermittent scanning glucose monitoring in clinical diabetes care: a protocol for a multi-center randomized clinical trial

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Introduction: As many people with type 1 diabetes find it hard to reach the recommended glycemic goals, even with CGM, this study aims to determine if a closer, digitally supported collaboration on interpreting CGM data together with a diabetes nurse can improve glycemic control.

Methods and analysis: A total of 120 individuals, 18 years and older and with HbA1c ≥ 58 mmol/mol will be included in the study at 8 different sites in Sweden and Norway. To be included, the participants must use a CGM or isCGM and be able to upload the data to the appropriate online service for their clinic and sensor. Both those with insulin pumps and insulin pens will be included in the study. Participants will be randomized into two different groups, that is, the intensive therapy group and the control group. The intensive therapy group will upload their glucose data weekly for the first 4 months and have telephone contact with their diabetes care team to receive support in interpreting CGM data and taking appropriate actions if their mean blood glucose level is above 8.4 mmol/L. After the 4-month-long intensive treatment phase, both randomized groups will have the same number of clinical visits and receive the same type of diabetes support.

Discussion: It is of great importance to find new ways to help people with type 1 diabetes manage their condition as well as they can to help them achieve better glycemic control so that hopefully more people can achieve the recommended glycemic goals, which are associated with fewer diabetes complications. If it is shown that people with type 1 diabetes achieve better glycemic control with intensive therapy, then this can be incorporated into clinical praxis as an option for those not currently reaching the recommended glycemic goals.

Clinical Trial Registration: https://clinicaltrials.gov/study/NCT03474393?locStr=Uddevalla,%20Sweden&country=Sweden&distance=50&cond=Diabetes&aggFilters=ages:adult%20older&state=V%C3%A4stra%20G%C3%B6taland%20County&city=Uddevalla&page=4&rank=34, identifier 03474393.

KEYWORDS

continuous glucose monitor (CGM), intermittent scanning -continuous glucose monitor (isCGM), telemedicine, diabetes nurse, type 1 diabetes, glycemic control

1 Introduction

Good glycemic control is a key element in the reduction of long-term diabetes complications in people with type 1 diabetes (1). Over the last few years, continuous glucose monitors (CGMs) have been shown to be an efficient way of improving glycemic control, both in people treated with insulin pumps and those treated with multiple daily insulin injections (2, 3). In addition, it was shown that CGM led to an improvement of time in hypoglycemia as well as quality of life and their levels of hypoglycemic confidence (4). Intermittent scanning CGMs (isCGMs) have also recently been shown to efficiently reduce time in hypoglycemia (5, 6).

A CGM is a subcutaneous sensor that continuously estimates blood glucose levels, which are then displayed on a small handheld monitor or a mobile phone. A CGM also informs users of glucose trends and alerts them if their blood glucose levels are low or high (7). An isCGM is a subcutaneous sensor that is placed in the upper arm and needs to be scanned with a small handheld monitor or by a mobile phone to measure estimated blood glucose levels and to show the current glucose trends (8).

Although CGMs and isCGMs are used by approximately 90% of patients with type 1 diabetes in Sweden, 70% of patients still do not achieve the good glycemic control associated with a low risk of diabetes complications (9). This is in line with findings in clinical trials, which demonstrate that although the use of CGMs can efficiently lower HbA1c levels, a reduction of only approximately 0.4% has been demonstrated, meaning that the use of CGMs alone is insufficient for solving the problem of poor glycemic control for most patients (3, 10, 11).

However, in earlier studies, patients have in general received education about their systems only at the beginning of the studies and then gone on to use them in their daily life, with regular clinical visits as support. It is possible that the effects of isCGM and CGM on glycemic control could be greatly improved with greater clinical support. A CGM/isCGM could even be used as a motivational tool for patients that increases communication between them and their caregivers. It is possible that diabetes care could be developed into forms of assistance for patients other than the current system of regular clinical visits every 3–6 months.

isCGM and CGM data can be electronically transferred to the caregiver. This opens new opportunities for more intense discussion and support of glucose values and trends that are closer to actual daily living. The question is whether or not such an approach would be more beneficial than the current approach of regular clinical visits and what effects could be obtained. If mean blood glucose levels are elevated, glucose data could be transferred weekly to the diabetes care team for guidance. In addition to enabling patients to obtain assistance, such an approach could possibly improve patient motivation. Specific individual targets could be set for each patient, depending on their individual needs and how far from the recommended guidelines their measurements lie. In this way, they could achieve several sub-goals in the process of achieving their final goal.

Currently, diabetes care teams in many countries are not financially set up to provide support *via* telephone contact or other media. However, if distance contact was shown to be more effective, it is likely that financial resources would be allocated to the provision of this service and that the systems for registering the financial costs associated with such work could be changed.

The aim of the study is to evaluate whether glycemic control in persons with type 1 diabetes can be improved by a close collaboration between persons with diabetes and diabetes-care teams using isCGM and CGM data. In addition, we will evaluate if this approach has a sustained effect on glycemic control after it is discontinued.

The primary objective of this study is to evaluate whether or not systematic intensive therapy in combination with transferring isCGM and CGM data to diabetes care teams will improve glycemic control (measured by HbA1c levels at baseline and after 18 weeks) compared with conventional care in people with type 1 diabetes with impaired glycemic control over an 18-week period.

The secondary objective is the comparison of the following variables between patients with type 1 diabetes who have been randomized into the systematic intensive therapy group and the conventional care group:

- HbA1c levels at 32 weeks;
- HbA1c levels at 52 weeks;
- Mean blood glucose levels at 18, 32, and 52 weeks;
- Change in time in range (3,9-10 mmol/l) and time in target (3,9-7,8mmol/l) at week 18;
- Change in time in range (3,9-10 mmol/l) and time in target (3,9-7,8mmol/l) at week 52;
- Glycemic variability as measured by standard deviation, CV, and MAGE at 18, 32, and 52 weeks;
- Time in hypoglycemia at 18, 32, and 52 weeks;
- Time in hyperglycemia 18, 32, and 52 weeks;

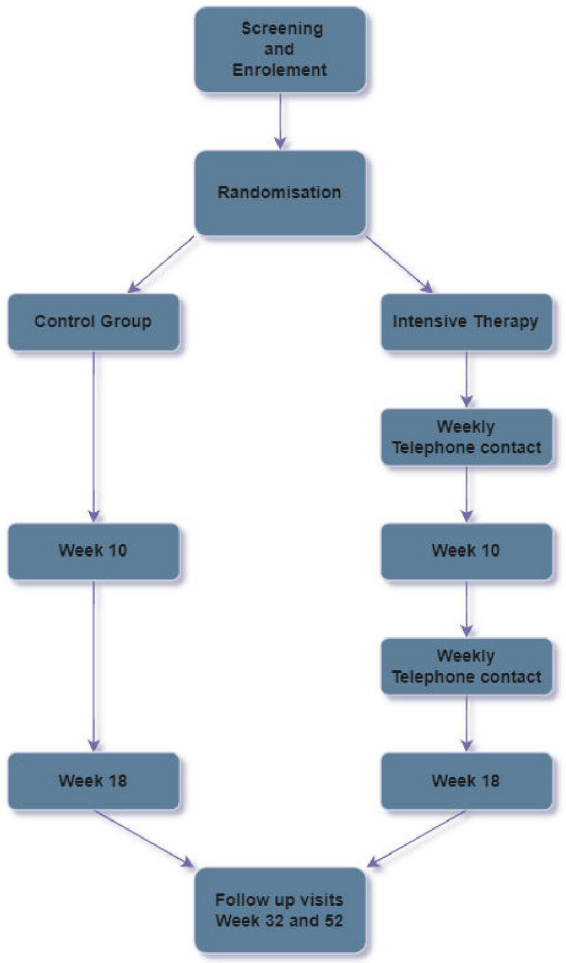

FIGURE 1
Flowchart of study.

- Hypoglycemia confidence (hypoglycemia confidence scale) at 18, 32, and 52 weeks;
- Diabetes distress (DDS) questionnaire results at 18, 32, and 52 weeks; and
- Treatment satisfaction (measured by DTSQs and DTSQc questionnaire results) at 18, 32, and 52 weeks.

2 Method and analysis

2.1 Study design and locations

The study will take place at eight outpatient clinics in Sweden and Norway. It is a non-blinded, multi-center randomized clinical trial with a parallel design that we plan to conduct between November 2019 and March 2023. The study will include 120 individuals who will be randomized into two equal groups, that is, the control group and the intensive therapy group. Intensive therapy will be conducted over 18 weeks, followed by a 34-week follow-up period. The study design is shown in Figure 1.

TABLE 1 Inclusion/exclusion criteria.

Inclusion criteria: • Informed consent obtained before trial-related activities (i.e., any activity that would not have been performed during routine patient management); • Clinical diagnosis of type 1 diabetes; • Adult patients over 18 years of age; • HbA1c level ≥ 58 mmol/mol; • Currently using a CGM or isCGM; • Is able to upload and share isCGM/CGM data. Exclusion criteria: • Type 2 diabetes; • Diabetes duration <1 year; • Long-term systemic glucocorticoid treatment during the last 3 months; • Planning to change or have changed diabetes treatment in the last 3 months, regarding change from MDI to insulin pump or started/stopped CGM or IsCGM • Current or planned pregnancy or breastfeeding during the next 12 months; • Planned move during the next 12 months making it impossible to participate in study activities; • Other reason determined by the investigator to not be appropriate for participation.

2.2 Eligibility criteria

Patients with type 1 diabetes with HbA1c levels of ≥ 58 mmol/mol, who are currently using a CGM or an isCGM and who have the ability to be able to upload data from their devices to the appropriate online service for their clinic and sensor from home, will be included. The full list of inclusion and exclusion criteria is shown in Table 1.

2.3 Randomization

Patients will be allocated 1:1 to systematic intensive therapy or conventional therapy using a minimization algorithm to achieve balance between treatment groups on important prognostic factors, that is, age, sex, HbA1c level, treatment type (injections or pump), and sensor type (CGM/isCGM). A centralized data system will be used. The use of this randomization method will increase the probability that key variables overall are evenly distributed between treatment groups (12–14).

2.4 Treatment

2.4.1 Systematic intensive therapy

Patients randomized to the systematic intensive therapy group will continue to follow their regular planned clinical visits and contacts. As part of the patient-centered care provided, all patients will be taught how to upload CGM/isCGM data to their home computer/laptop. In addition, by drawing on their prior knowledge of how to use the software suitable for their device, they will be taught to interpret the data. They will be taught how to interpret the data by looking at variables such as:

A) High/low overnight and morning profile;

B) Excursions before and after meals;

Timing of insulin in relation to mealtimes and exercise; and

C) Time spent in various glycemic ranges and glycemic variability *via* the standard deviation.

D) For most devices, it will be possible to use Diasend®, a software that is compatible with most CGM systems, but for some CGM systems specific software will be needed, such as CareLink™ for Medtronic products or LibreView for Libres isCGMs.

We will explain the relationship between mean glycemic control and HbA1c levels to the patients, and we will also give them a graph representing this relationship that further explains how these two variables are connected.

An individual HbA1c-level goal will be discussed with patients, and a target for mean blood glucose levels that matches this HbA1c-level goal will be set. The mean glucose goal will be discussed in relation to the mean blood glucose level at randomization. The patients will be taught how to upload data from their device during the first visit and will receive further assistance if necessary. If needed, more support will be given in the beginning by internet or telephone contact as patients upload data from their device at home.

We intend that the first contact *via* telephone will take place up to and no later than 1 week after randomization. The patient will be expected to have uploaded data from their device prior to this contact so that both the caregiver and patient have access to all CGM glucose profiles for the previous week. The visit will take place the same day each week ±1 day.

Together with the participant, the caregiver will conduct an analysis of the prior week's glucose profiles. This analysis will be conducted in relation to mean blood glucose levels and the standard deviation, before-bedtime data, the overnight glucose profile, blood glucose levels before and after meals and exercise, and time spent in hypoglycemia. The patient will also be able to discuss any particular situations that have proven to be more difficult than others.

Using their unique expertise, the caregiver will be expected to make an overall judgement regarding what needs to be done to improve the patient's glucose profiles.

If the patient has achieved their first mean blood glucose goal but not the recommended goal of 8.4mmol/L, a new target will be decided on. The recommended mean blood glucose level of 8.4mmol/L corresponds to an estimated HbA1c level of 52 mmol/mol, which is the national recommendation in Sweden (15). Therefore, if patients achieve a mean blood glucose level of 8.4mmol/L, they are expected to have an HbA1c level that is associated with a lower risk of complications (16).

During the first 4 weeks, weekly contact by telephone will be made. After this time, it might be necessary to reduce this to every second week, depending on the patients' mean blood glucose levels.

If the patient achieves the recommended blood glucose goal of mean glucose < 8.4 mmol/L, no telephone contact will be made that week, but the participant will need to upload their data again the following week, and if their mean blood glucose level is found to be above 8.4 mmol/L, contact *via* telephone will need to be made again.

Clinical visits will be scheduled after 10, 18, 32, and 52 weeks for both groups to evaluate the effects of each care provision model on the patients' HbA1c levels and other glycemic variables (mean blood glucose levels, SD of blood glucose levels, time in hypoglycemia and hyperglycemia, and time in range).

2.4.2 Conventional therapy

Clinical visits will be scheduled 10, 18, 32, and 52 weeks after randomization for HbA1c level measurement and downloading of CGM/isCGM curves. During weeks 18, 32, and 52, the participants will fill in follow-up questionnaires from those registered at baseline. The visits at weeks 10 and 18 will take place exactly 10 and 18 weeks after randomization (± 1 week), and the visits at weeks 32 and 52 will take place exactly 32 and 52 weeks after randomization (± 2 weeks).

2.4.3 Follow-up phase

After 18 weeks, the participants will return to their regular care schedule at their diabetes clinic, but HbA1c levels will be measured at 32 and 52 weeks. No distance intervention will be carried out during this time, but glucose data will be uploaded from their devices at each visit. The participants will be encouraged to, and hopefully will continue to, upload data from their devices at home so that they can analyze their glucose profiles as they have been taught during the intervention. If they actively make contact with their diabetes team due to technical problems regarding uploading data from their devices or with specific questions regarding their analysis, advice and support will be given, but no further contact will be planned.

2.4.4 Data collection

In addition to randomization, the patients will have visits at weeks 10,18, 32, and 52 with a diabetes nurse. At the week 10 visit with the diabetes nurse, data from the CGM/isCGM will be uploaded, and HbA1c levels will be measured. At the week 18, 32, and 52 visits, data from the CGM/isCGM will be uploaded, and the following variables will be measured: HbA1c level, weight, type of insulin and doses of insulin, AEs, SAEs, DTSQs score, DTSQc score, DDS score, and hypoglycemia confidence score. At week 52, a physical examination will be conducted. Detailed trial procedures are shown in Table 2.

2.5 Endpoints

The primary endpoint will be the change in HbA1c level from baseline to week 18. All predefined endpoints are shown in Table 3.

2.6 Monitoring and laboratory analyses

Researchers at Wallenberg Laboratory at the University of Gothenburg will monitor the trial. Capillary tests will be carried out at each visit using a DCA Advance analyzer, which is Equalis calibrated.

2.7 Statistics

All analyses will be specified in the statistical analysis plan (SAP) prior to database lock.

TABLE 2 Trial procedures.

Variables	Visits **					
	Inclusion (visit 1)*	Randomization (visit 2)	10-week follow-up visit 3	18-week follow-up (visit 4)	32-week follow-up (visit 5)	52-week follow-up (visit 6)
Visit window		Scheduled within 28 days after inclusion	± 1 weeks	± 1 weeks	± 2 weeks	± 2 weeks
Informed consent	X					
Inclusion/exclusion criteria	X					
Demographics, medical history	X					
Physical examination	X					X
HbA1c level	X	X	X	X	X	X
Uploading device	X	X	X	X	X	X
Education on uploading device		X				
Weight		X		X	X	X
DTSQs		X		X	X	X
DTSQc				X		
DDS scale		X		X	X	X
Hypoglycemia confidence scale		X		X	X	X
AEs (severe hypoglycemia and diabetes ketoacidosis) and SAEs		X	X	X	X	X

* Before the visits in the schedule above, patient information will be given either via telephone or at a clinical visit.
** If randomized to systematic intensive treatment, the first telephone contact will take place 1 week after randomization and, after that, on a weekly basis or until mean blood glucose levels reach the target level.

2.7.1 Sample size calculation

The study will be designed to detect if there is an improvement of 0.4% in patients' HbA1c levels from baseline to the 18-week follow-up visit. An SD of 0.8% for change in HbA1c level has been assumed for both treatment groups, indicating that 54 individuals per group are needed to obtain a power of 80% at an alpha level of 0.05. Accounting for a dropout rate of 10%, 120 individuals will be needed. Initially, the plan was to include 142 individuals, which would also allow the detection of a 0.4% improvement in HbA1c levels. However, due to the difficulty in recruiting during the COVID-19 pandemic, it was decided to reduce this to 120 individuals. The protocol amendment was made and approved by the ethics committee in June 2022.

TABLE 3 predefined endpoints.

The primary endpoint will be the change in HbA1c level from baseline to week 18.
The secondary endpoints will be:
- Change in HbA1c levels from baseline to week 32;
- Change in HbA1c levels from baseline to week 52;
- Change in time in range (3,9-10mmol/l) and time in target (3,9-7,8mmol/l) from baseline to week 18;
- Change in time in range (3,9-10mmol/l) and time in target (3,9-7,8mmol/l) from baseline to week 52;
- Change in mean blood glucose levels from baseline to 18, 32, and 52 weeks;
- Change in glycemic variability, measured by standard deviation, CV, and MAGE from baseline to 18, 32, and 52 weeks;
- Change in time in hypoglycemia from baseline to 18, 32, and 52 weeks;
- Change in time in hyperglycemia from baseline to 18, 32, and 52 weeks;
- Change in hypoglycemic confidence score from baseline to 18, 32, and 52 weeks;
- Change in DDS score from baseline to 18, 32, and 52 weeks;
- Change in DTSQs score from baseline to 18, 32, and 52 weeks and DTSQc score at 18, 32, and 52 weeks.

2.7.2 Primary and secondary analyses

The primary analysis will be of the change in HbA1c levels from baseline to the 18-week follow-up visit between the two treatment groups using analysis of covariance (ANCOVA), with the HbA1c level at baseline as a covariate on the ITT population using a two-sided test and with a significance level of 0.05.

Secondary analyses will be of:

- Change in HbA1c levels, mean blood glucose levels, glycemic variability and times in hypoglycemia and hyperglycemia, time in range, and time in target, analyzed in a similar way to those described above for the primary variable;

- Change in the DDS score and hypoglycemia confidence score from baseline to weeks 18, 32, and 52 between the two treatment groups using ANCOVA with the score of the evaluated variable at baseline as a covariate;
- The difference in DTSQc scores at week 18 between the two treatment groups using ANCOVA in case the assumption of normal distribution is met or, if it is not, by using a Mann–Whitney U-test.
- The difference in DTSQs scores at weeks 18, 32, and 52 between the two treatment groups using ANCOVA in case the assumption of normal distribution is met or, if it is not, by using a Mann–Whitney U-test.

3 Discussion

This is a description of the protocol for a randomized multicenter study that investigates the effect of intensive telephone contact to support the interpretation of CGM data and the taking of appropriate actions as a complement to traditional diabetes care, both in the short term and over a longer period.

In recent years, new continuous glucose monitoring and more advanced insulin pumps have been introduced to the market, e.g., HCL pumps, which have shown great glycemic improvement (17, 18). The current study will include only patients taking multiple daily insulin injections, using insulin pumps not connected to a CGM, or using sensor-augmented pumps where the basal rate stops if blood glucose levels are expected to fall below a certain level. However, it is essential to note that, currently, advanced insulin pumps are only used by a small minority of people with type 1 diabetes, although this number is expected to increase. From an international perspective, most type 1 diabetes patients do not even have the option of using an CGM/isCGM (19). For example, in Asia, Africa, South America, and Eastern Europe, capillary testing is still the most common glucose monitoring method and injections are still the most common method of insulin delivery. Hence, an understanding of how to best use CGM for patients using MDIs and simpler insulin pumps is knowledge that will remain essential for a long time. Moreover, patients with more advanced insulin pumps may also need more intensive counseling, and the current study will also indicate if such an approach could be of use for these patients. As technology improves, it is important to facilitate more person-centered care, and telemedicine can be one means of doing this (20).

Many patients have the possibility of using both CGM and isCGM, but of those, there are still too few who are achieving the recommended glycemic goals at a level that is sufficient to minimize diabetes complications. It is of great importance to gain knowledge of the potential benefits of systematic intensive therapy administered by a diabetes nurse in type 1 diabetes care. If the treatment improves glycemic control, diabetes distress, or hypoglycemic confidence, it could be a complement to the routine care provided by diabetes teams. If more people can achieve the recommended glycemic goals, their risk of diabetes complications will decrease. Furthermore, if it is shown that people with type 1 diabetes achieve better glycemic control with intensive therapy, this can be incorporated into diabetes guidelines as an option for those not currently achieving the recommended glycemic goals.

Ethics statement

The studies involving humans were approved by Ethics Committee at the University of Gothenburg, Gothenburg, Sweden. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AÓ and ML designed the study. ML is the PI of the study. AÓ drafted the manuscript. Both authors reviewed and approved the final manuscript.

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Conflict of interest

AO has received consultancy fees from Nordic Infucare. ML has received research grants from Eli Lilly and Novo Nordisk and has been a consultant for or received honoraria from Eli Lilly and Novo Nordisk, all for work outside of the current study.

Publisher's note

References

1. Lind M, Svensson AM, Kosiborod M, Gudbjörnsdottir S, Pivodic A, Wedel H, et al. Glycemic control and excess mortality in type 1 diabetes. *N Engl. J. Med.* (2014) 371(21):1972–82. doi: 10.1056/NEJMoa1408214

2. Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time contiuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *MBJ (clinical Res. ed)* (2011) 343:d3805. doi: 10.1136/bmj.d3805

3. Lind M, Polonsky W, hirsch IB, Heise T, Bolinder J, Dahlqvist S, et al. Continuous glucose monitoring vs conventional Therapy for Glycemec Control in Adults With Type 1 Diabetes Treated with Multiple Daily Insulin Injections: The GOLD Randomized clinical trial. *Jama* (2017) 317(4):379–87. doi: 10.1001/jama.2016.19976

4. Ólafsdóttir AF, Polonsky W, Bolinder J, Hirsch IB, Dahlqvist S, Wedel H, et al. A randomized clinical trial of the effect of continuous glucose monitoring on nocturnal hypoglycemia, daytime hypoglycemia, glycemic variability, and hypoglycemia confidence in persons with type 1 diabetes treated with multiple daily insulin injections (GOLD-3). *Diabetes Technol. Ther.* (2018) 20(4):274–84. doi: 10.1089/dia.2017.0363

5. Bolinder J, Antuna R, Geelhoed-Duijvetijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *Lancet* (2016) 388(10057):2254–63. doi: 10.1016/S0140-6736(16)31535-5

6. Leelarathna L, Evans ML, Neupane S, Rayman G, Lumley S, Cranston I, et al. Intermittently scanned continuous glucose monitoring for type 1 diabetes. *N Engl. J. Med.* (2022) 387(16):1477–87. doi: 10.1056/NEJMoa2205650

7. Hanås R. *Type 1 diabetes in children, adolescents and young adults. 6th ed.* Uddevalla: BetaMed (2015).

8. Abbott. *FreeStyle libre* (2017). Available at: https://www.freestylelibre.se.

9. Eeg-Olofsson K, Åkesson K, Nåtman J, Almskog I, Hermansson Carter V, Linder E, et al. *Årsrapport NDR 2022 Resultat*. Available at: https://www.ndr.nu/pdfs/Arsrapport_NDR_2022.pdf.

10. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. *JAMA* (2017) 317(4):371–8. doi: 10.1001/jama.2016.19975

11. Battelino T, Conget I, Olsen B, Schütz-Fuhrmann I, Hommel E, Hoogma R, et al. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia* (2012) 55(12):3155–62. doi: 10.1007/s00125-012-2708-9

12. Socialstyrlesen. Nationella riktlinjer för diabetes vård . Available at: https://www.socialstyrelsen.se/kunskapsstod-och-regler/regler-och-riktlinjer/nationella-riktlinjer/riktlinjer-och-utvarderingar/diabetes/.

13. Taves DR. Minimization: a new method of assigning patients to treatment and control groups. *Clin. Pharmacol. Ther.* (1974) 15(5):443–53. doi: 10.1002/cpt1974155443

14. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* (1975) 31(1):103–15. doi: 10.2307/2529712

15. Lind M, Hirsch IB, Tuomilehto J, Dahlqvist S, Ahrén B, Torffvit O, et al. Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial). *BMJ* (2015) 351:h5364. doi: 10.1136/bmj.h5364

16. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ, et al. Translating the A1C assay into estimated average glucose values. *Diabetes Care* (2008) 31(8):1473–8. doi: 10.2337/dc08-0545. Erratum in: Diabetes Care. 2009 Jan;32(1):207.

17. Carlson AL, Sherr JL, Shulman DI, Garg SK, Pop-Busui R, Bode BW, et al. Safety and glycemic outcomes during the miniMed™ Advanced hybrid closed-loop system pivotal trial in adolescents and adults with type 1 diabetes. *Diabetes Technol. Ther.* (2022) 24(3):178–89. doi: 10.1089/dia.2021.0319

18. Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC, et al. iDCL trial research group. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. *N Engl. J. Med.* (2019) 381(18):1707–17. doi: 10.1056/NEJMoa1907863

19. Conway RB, Gerard Gonzalez A, Shah VN, Geno Rasmussen C, Akturk JK, Pyle L, et al. Racial disparities in diabetes technology adoption and their association with hbA1c and diabetic ketoacidosis. *Diabetes Metab. Syndr. Obes.* (2023) 16:2295–310. doi: 10.2147/DMSO.S416192

20. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 1. Improving care and promoting health in populations: standards of care in diabetes-2023. *Diabetes Care* (2023) 46(Supple 1):S10–8. doi: 10.2337/dc23-S001

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Effects of mulberry twig alkaloids(Sangzhi alkaloids) and metformin on blood glucose fluctuations in combination with premixed insulin-treated patients with type 2 diabetes

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Introduction: We aimed to evaluated the effect of premixed insulin (Ins), premixed insulin combined with metformin (Ins+Met) or mulberry twig alkaloids(Ins+SZ-A) on blood glucose fluctuations in patients with type 2 diabetes (T2DM) using continuous glucose monitors (CGM).

Methods: Thirty patients with T2DM and poor blood glucose control using drugs were evaluated for eligibility during the screening period. Subsequently, their original hypoglycemic drugs were discontinued during the lead-in period, and after receiving Ins intensive treatment for 2 weeks, they were randomly assigned to receive either Ins, Ins+Met, or Ins+SZ-A treatment for the following 12 weeks. The main efficacy endpoint comprised changes in their CGM indicators changes (mean blood glucose level [MBG], standard deviation of blood glucose [SDBG], mean amplitude of glycemic excursions [MAGE], postprandial glucose excursions [PPGE], the largest amplitude of glycemic excursions [LAGE], mean of daily difference [MODD], time in range between 3.9–10.0 mmol/L [TIR] and area under the curve for each meal [AUCpp]) during the screening, lead-in, and after 12-week treatment period. Changes in glycosylated hemoglobin (HbA1c), fasting blood glucose (FBG), 1-h postprandial blood glucose (1h-PBG), 2-h postprandial blood glucose (2h-PBG), fasting blood lipids and postprandial blood lipids were also measured at baseline and after 12 weeks of treatment

Results: The CGM indicators of the three groups during the lead-in period all showed significant improvements compared to the screening period ($P<0.05$). Compared with those in the lead-in period, all of the CGM indicators improved in the the Ins+Met and Ins+SZ-A groups after 12 weeks of treatment ($P<0.05$), except for MODD. After 12-week treatment, compared with the Ins group, Ins+Met and Ins+SZ-A groups showed improved MBG, SDBG, TIR, breakfast AUCpp,lunch AUCpp, HbA1c, FBG, 1h-PBG, fasting blood lipid and postprandial blood lipid indicators ($P<0.05$). Further, the LAGE, PPGE, MAGE, dinner AUCpp and 2h-PBG

levels of the Ins+SZ-A group were significantly lower than those of the Ins+Met and Ins groups (P<0.05).

Conclusion: Our findings highlight the efficacy of combination therapy (Ins+SZ-A or Ins+Met) in improving blood glucose fluctuations, as well as blood glucose and lipid levels. Ins+SZ-A reduces postprandial blood glucose fluctuations more than Ins+Met and Ins groups.

Trial registration number: ISRCTN20835488.

KEYWORDS

mulberry twig alkaloids, metformin, blood glucose fluctuations, premixed insulin, continuous glucose monitors

1 Introduction

Mulberry twig alkaloids (SZ-A) represent the first original natural hypoglycemic drug to be discovered in China. They are capable of effectively inhibiting α-glycosidase and thus exerting beneficial hypoglycemic effects. One multi-center, randomized, double-blinded, and parallel controlled trial showed that after 24 weeks of treatment with SZ-A, patient levels of glycosylated hemoglobin (HbA1c) decreased by 0.93% from baseline, and their rate of achieving the HbA1c target (HbA1c<7%) was 47.7%—which was equivalent to that of treatment with acarbose for reducing postprandial blood glucose (1). SZ-A is mainly composed of five compounds: 1-deoxynojirimycin, 1,4-dideoxy-1,4-imino-D-arabinitol, fagomine, arginine and polysaccharide. SZ-A can reduce inflammation, regulate gut microbiota, promote glucose-stimulated insulin secretion, promote glucagon-like peptide 1 secretion, and lower weight in obese animals (2, 3). Whether administered by gavage or intraperitoneal injection, SZ-A can both improve non-alcoholic fatty liver disease in obese mice, indicating that the mechanism of its action is independent of its pathway connected to intestinal α- glycosidase. This may be due to the diversity of compounds contained in SZ-A mixtures (4).

When oral hypoglycemic drugs fail to control blood glucose in patients with type 2 diabetes (T2DM), these patients typically begin using insulin (5). T2DM is characterized by insulin resistance, and deficiency. Insulin resistance occurs in the early stages of abnormal glucose metabolism. In the later stages, insulin deficiency is the main factor. Most of these patients eventually require exogenous insulin, and the use of premixed insulin is currently the predominant treatment for this condition in China. One multi-center cross-sectional survey of outpatients in Chinese hospitals showed that approximately 65.6% of patients with diabetes used premixed insulin (6). However, premixed insulin is prone to causing hypoglycemia, which leads to weight gain and poor control of postprandial blood glucose levels (7, 8). A combination of insulin and oral medication can have more comprehensive benefits, such as increasing the effect of peripheral insulin, reducing insulin dosage, reducing the risk of hypoglycemia, improving blood glucose control, and reducing weight gain (9, 10).

Metformin(Met) is the first-line drug for the treatment of T2DM and plays an anti-hyperglycemic role mainly by inhibiting liver glucose through AMPK-dependent or -independent pathways (11–14). The Chinese MERIT study showed that premixed insulin combined with Met resulted in a greater reduction in HbA1c, less insulin consumption, less weight gain, a lower incidence of hypoglycemia, and lower cardiovascular risk than premixed insulin alone (15–17).

Continuous glucose monitors (CGM) can measure glucose concentrations in the subcutaneous interstitial fluid 288 times per day using multiple glucose sensors, allowing them to provide continuous, complete,and reliable glucose measurements with good compliance. To our knowledge, no studies have investigated the effects of SZ-A on blood glucose fluctuations.

Therefore, in this study, CGMs were used to comprehensively evaluate blood glucose changes in patients with T2DM who were treated with premixed insulin combined with SZ-A or Met, compared to other treated with premixed insulin alone. We also considered blood lipid parameters, to provide a basis for exploring the hypoglycemic characteristics of SZ-A and determining the most suitable patients population for this treatment.

2 Materials and methods

2.1 Study design and participants

This was a 12-week open-label, randomized, parallel-controlled, clinical trial. We enrolled patients with T2DM who had poorly controlled blood glucose levels when using oral hypoglycemic agents, and had been hospitalized in the Department of Endocrinology and Metabolism of the First Affiliated Hospital of Harbin Medical University between June 2022 and March 2023.

The inclusion criteria were patients who: 1) were aged 18–70 years old, regardless of sex; 2) had body mass index(BMI) between 19 kg/m^2 and 30 kg/m^2; 3) had been diagnosed with T2DM

according to the diagnostic criteria for T2DM formulated by 1999 World Health Organization; 4) were taking oral hypoglycemic agents, who had poor blood glucose control, and had 7% ≤ HbA1c ≤ 10%; 5) were able to understand the procedures and methods of this clinical study, participate voluntarily and sign the informed consent form.

The exclusion criteria were patients who: 1) were allergic or intolerant to α-glucosidase inhibitors, or for whom these drugs had been proven to be ineffective; 2) had severe diabetic complications; 3) had secondary diabetes mellitus, specific types of diabetes, and type 1 diabetes mellitus; 4) had chronic gastrointestinal dysfunction, obvious digestive and absorption disorders, as well as other endocrine diseases, such as hyperthyroidism, Cushing's syndrome, or acromegaly, etc; 5) had diseases that could be worsened by flatulence (such as Roeheld's syndrome, severe hernia, intestinal obstruction, following gastrointestinal surgery and intestinal ulcers); 6) had unstable angina pectoris within 6 months prior to the study, had serious heart diseases, or were likely to die during the treatment and follow-up period; 7) had mental and neurological disorders who could not clearly express themselves; 8) were suffering from alcoholism or other substance addictions; 9) were women of childbearing age who were pregnant, lactating, had a positive pregnancy test (urine or blood HCG), intended to become pregnant over the study and follow-up period, or could not take effective contraceptive measures during the study and follow-up period (including measures such as sterilization, intrauterine devices, and oral contraceptives); 10) had participated in clinical trials of other drugs or medical devices in the three months preceding the study's start date.

This study was approved by the Ethics Review Committee of the First Affiliated Hospital of Harbin Medical University (Harbin, China). All participants provided written informed consent prior to registration. All experiments were conducted in accordance with the principles of the Declaration of Helsinki.

2.2 Randomization and treatment

During the screening period patients used their regular hypoglycemic drugs and evaluations for eligibility to select study subjects were conducted based on the inclusion and exclusion criteria. During the lead-in period, the patients' regular hypoglycemic drugs were discontinued and a premixed insulin-intensive treatment was administered for 2 weeks to quickly correct hyperglycemia. After 2 weeks of this intensive treatment, the patients were randomly divided into premixed insulin (Ins), premixed insulin plus SZ-A (Ins+SZ-A) and premixed insulin plus Met (Ins+MET) groups for the following 12 weeks (Figure 1). Premixed insulin was defined as a mixed protamine-zinc recombinant human insulin lispro injection(50 R; Lilly France, IN, USA).

The goal in terms of fasting blood glucose control for this study was 4.4–7.0 mmol/L. The initial premixed insulin dose was 0.4–0.5 IU/kg, after which, it was adjusted as needed, according to plasma glucose values obtained through self-monitoring. The initial dose of SZ-A (Beijing Guokaihua Intellectual Property Agency Co., LTD, Beijing, China) was 50mg, administered three times per day, at mealtimes. After four weeks, this dose was increased to 100mg three times per day at mealtimes. The Met dose (Sino-American Shanghai Squibb Pharmaceuticals Co., Ltd, Shanghai, China) was 500mg three times per day at mealtimes, throughout the entire observation period. The first 6 weeks of the treatment phase comprised the insulin dose titration period. Patients were required to self-monitor their blood glucose levels, and a trained doctor adjust their insulin doses based on the results obtained. The following 6 weeks comprised the steady dose period. The patients received diabetes education during this phase, in order to promote reasonable dietary control and proper exercise over the rest of the study period.

2.3 Anthropometric indicators

The general patients information collected included sex, age, diabetes history, height, weight, BMI, waist circumference, hip circumference, and insulin dose. Fasting blood glucose (FBG), HbA1C, C-peptide, cholesterol (CHOL), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were measured during the screening period and after 12 weeks of treatment. An automatic biochemical analyzer assessed

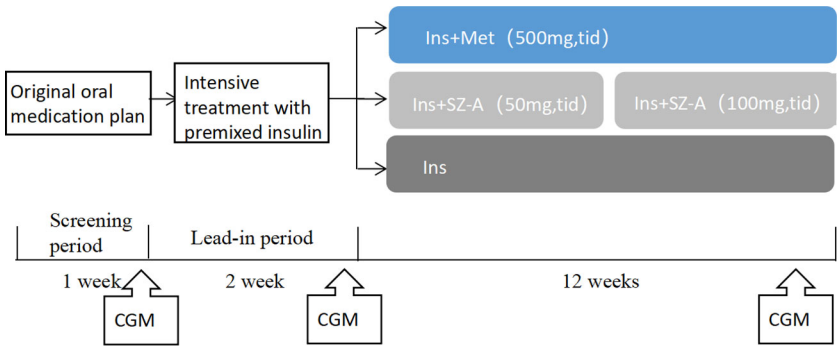

FIGURE 1
Flowchart of the study.

hypoglycemia, adverse events, alanine aminotransferase (ALT), aspartate transaminase (AST), creatinine (Cr), and uric acid (UA).

The insulin resistance index was assessed for each patients using modified homeostasis model, and expressed as [HOMA-IR(CP)] = 1.5 + FPG (mmol/L) × fasting C-peptide (pmol/L)/2,800 (18).

The oral glucose tolerance tests (OGTT) experiment was conducted during the lead-in period, where participants received 75 g of orally-administered glucose in the morning after fasting for 10 to 12h. Blood samples were collected at 0, 60, and 120 min afterward, to measure plasma glucose concentrations.

After 12 weeks of treatment, the participants fasted overnight, were treated with their corresponding hypoglycemic drugs (Ins, Ins+Met, or Ins+SZ-A), and consumed 70 g of instant noodles (500 kcal, 70 g of carbohydrates) within 15 min (19). Blood samples were collected before the test meal, and at 60 and 120 min afterward, to measure FBG, 1-hour postprandial blood glucose (1h-PBG), 2-hour postprandial blood glucose (2h-PBG), fasting blood lipids, 1-hour postprandial blood lipids, and 2-hour postprandial blood lipids. The area under the PBG curve (BG AUC) and the area under the curves for the other blood lipid indicators were then calculated.

2.4 CGM parameters

Subcutaneous interstitial glucose monitoring was conducted using a CGM system (Medtronic, Inc,Minnesota,USA) during the screening, lead-in, and after 12-week treatment period, for three consecutive days. The study parameters included mean blood glucose level (MBG), standard deviation of blood glucose (SDBG), mean amplitude of glycemic excursions (MAGE), postprandial glucose excursions (PPGE), largest amplitude of glycemic excursions (LAGE), mean of daily difference (MODD), and time-in-range between 3.9 and 10.0 mmol/L (TIR). The area under the curve (AUCpp) was calculated within 4 h of the start of each meal.

2.5 End point

The primary endpoints included changes in MBG, SDBG, MAGE, PPGE, LAGE, MODD, TIR, breakfast AUCpp, lunch AUCpp, and dinner AUCpp readings during the screening period, lead-in period, and after 12 weeks of treatment.

The secondary endpoints were changes in HbA1c, FBG, 1h-PBG, 2h-PBG, fasting blood lipids, postprandial blood lipids at baseline and after 12 weeks of treatment.

2.6 Statistical method

All statistical analyses were performed using SPSS 25.0. For normally-distributed numerical variables, one-way analysis of variance (ANOVA) was used to compare differences between groups, and paired Student's t-tests were used before and after treatment to assess differences in intra-group outcome measures. For non-normally distributed variables, the Kruskal–Wallis test was used to compare intergroup differences, and the Wilcoxon signed-rank test was used to assess differences in intra-group outcome measures before and after the interventions. The Bonferroni method was used for *post-hoc* multiple comparisons. For categorical variables, Fisher's exact test was used for comparisons between groups. The α-level was set at 5%, and the significance level at 95%. Statistical significance was set at $P < 0.05$.

3 Results

3.1 Baseline patient characteristics

We included 30 patients with T2DM for whom blood glucose levels could not be successfully controlled. Of them, 10 were assigned to each of the INS, INS+Met, and INS+SZ-A groups. No significant differences were observed in the general characteristics (such as age, sex ratio, weight, BMI, waist circumference, waist-to-hip ratio, and duration of diabetes) and efficacy and safety indicators (including CHOL, TG, HDL,LDL, FBG, HbA1c, HOMA-IR (CP), ALT, AST, Cr, UA, OGTT AUC (h·mmol/L), and insulin dose)between the three groups (P >0.05; Table 1).

3.2 General conditions at baseline and after the 12-week treatment

Compared those during screening period, HbA1c and FBG in the three groups were significantly improved after 12 weeks of treatment (P<0.05), but weight changes were not statistically significant (P>0.05). Compared with those during the lead-in period, the insulin doses in the Ins+Met and Ins+SZ-A groups decreased after 12 weeks of treatment (P<0.05). After 12-week treatment, the HbA1c, FBG and insulin dosages of Ins+Met and Ins+SZ-A groups were lower than those of the Ins group (P<0.05), and there was no statistically significant difference in weight between the three groups (P>0.05; Table 2).

Compared with those in the screening period, the TG and HDL indicators of the Ins+Met group (P<0.05), the TG, HDL and LDL levels of the Ins+SZ-A group (P<0.05), and the LDL levels of the Ins group (P<0.05) all improved after the 12 weeks of treatment, there were no significant differences in the other indicators (P<0.05). After 12 weeks treatment, the improvement in TG and HDL levels seen in the Ins+Met and Ins+SZ-A groups was greater than those in the Ins group (P<0.05). There were no significant differences in the other indicators (P>0.05; Table 2).

3.3 Fasting and postprandial blood glucose and lipid levels after 12 weeks of treatment

After 12 weeks of treatment, FBG and 1h-PBG levels were lower in the Ins+Met and Ins+SZ-A groups than in the Ins group (P<0.05; Figure 2A). The 2h-PBG and BG AUC were also lower in the Ins+SZ-A group than in the Ins+Met and Ins groups (P<0.05; Figure 2F).

After 12 weeks of treatment, the fasting TG, 1-hour postprandial TG, 2-hour postprandial TG, and TG AUC indicators were lower in the Ins+Met and Ins+SZ-A groups than

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TABLE 1 Baseline data of three groups.

	Ins+Met	Ins+SZ-A	Ins	P
Age (year)	49.00 ± 12.86	48.40 ± 13.76	51.40 ± 9.06	0.842
Sex (Female/Male)				0.500
Female	7 (70.00%)	8 (80.00%)	5 (50.00%)	
Male	3 (30.00%)	2 (20.00%)	5 (50.00%)	
Body weight (kg)	73.85 ± 8.79	64.55 ± 8.78	67.95 ± 8.48	0.070
BMI (kg/m^2)	25.18 ± 2.61	22.95 ± 3.03	24.56 ± 2.00	0.154
Waist circumference (cm)	89.75 ± 3.39	86.40 ± 7.62	89.40 ± 6.33	0.407
waist-to-hip ratio	0.93 ± 0.05	0.94 ± 0.07	0.96 ± 0.06	0.554
diabetic duration (year)	8.10 ± 5.45	8.60 ± 4.99	7.80 ± 5.12	0.941
HbA1c (%)	9.65 (7.38,9.80)	9.65 (8.68,9.80)	9.70 (9.38,9.80)	0.531
FPG (mmol/L)	9.31 ± 1.73	9.79 ± 3.32	10.85 ± 2.79	0.438
Insulin dose (U)	29.00 (24.00.34.50)	32.00 (20.50,33.25)	36.00 (28.00,36.50)	0.093
HOMA-IR (CP)	3.35 ± 0.79	3.15 ± 0.78	3.62 ± 0.86	0.436
OGTT AUC (h·mmol/L)	29.00 ± 5.92	28.48 ± 2.72	28.65 ± 3.25	0.961
CHOL (mmol/L)	4.65 ± 0.86	4.99 ± 1.52	4.68 ± 0.98	0.764
TG (mmol/L)	2.33 (0.98.4.10)	1.97 (1.34,2.74)	2.18 (1.40,3.78)	0.882
HDL (mmol/L)	0.89 (0.69,1.02)	1.07 (1.00,1.32)	0.90 (0.73,1.07)	0.070
LDL (mmol/L)	2.67 ± 0.72	3.12 ± 1.28	2.81 ± 0.72	0.564
AST (U/L)	15.93 ± 3.23	16.64 ± 4.25	15.82 ± 4.47	0.885
ALT (U/L)	21.72 ± 7.36	20.10 ± 7.62	20.96 ± 10.66	0.917
Cr (umol/L)	52.92 ± 7.34	51.84 ± 8.85	47.70 ± 11.48	0.433
UA (umol/L)	306.83 ± 68.55	306.94 ± 77.27	303.81 ± 59.41	0.933

All P>0.05, Fisher's precision probability test, one-way ANOVA, Kruskal-Wallis H test or Fisher's precision probability test were performed among the three groups.

TABLE 2 General conditions at baseline and after 12-week treatment.

	Ins+Met		Ins+SZ-A		Ins	
	Baseline	After 12 weeks	Baseline	After 12 weeks	Baseline	After 12 weeks
HbA1c (%)	9.65 (7.38,9.80)	6.70 (6.48,7.35)*#	9.65 (8.68,9.80)	6.65 (6.25,7.60)*&	9.70 (9.38,9.80)	8.30 (7.40,8.75)*
FPG (mmol/L)	9.31 ± 1.73	6.90 ± 0.97*#	9.79 ± 3.32	6.83 ± 1.20*&	10.85 ± 2.79	7.93 ± 0.94*
Body weight (kg)	73.85 ± 8.79	73.05 ± 8.02	64.55 ± 8.78	64.15 ± 8.58	67.95 ± 8.48	68.45 ± 8.28
Insulin dose (U)	29.00 (24.00.34.50)	19.00 (15.5,28.50)*#	32.00 (20.50,33.25)	21.00 (18.50,30.50)*&	36.00 (28.00,36.50)	35.00 (31.00,38.00)
CHOL (mmol/L)	4.65 ± 0.86	4.69 ± 0.94	4.99 ± 1.52	4.31 ± 1.02	4.68 ± 0.98	4.38 ± 0.98
TG (mmol/L)	2.33 (0.98.4.10)	1.38 (0.88,1.64)*#	1.97 (1.34,2.74)	0.83 (0.64,1.01)*&	2.18 (1.40,3.78)	2.07 (1.66,3.53)
HDL (mmol/L)	0.89 (0.69,1.02)	1.35 (1.10,1.59)*#	1.07 (1.00,1.32)	1.23 (1.11,1.33)*&	0.90 (0.73,1.07)	0.89 (0.76,0.95)
LDL (mmol/L)	2.67 ± 0.72	2.64 ± 0.68	3.12 ± 1.28	2.37 ± 0.76*	2.81 ± 0.72	2.52 ± 0.82*

*represents P < 0.05 (comparison between baseline and after 12-week treatment in each group).
#represents P < 0.05 (comparison between Ins+Met and Ins groups after 12-week treatment).
&represents P < 0.05 (comparison between Ins+SZ-A and Ins groups after 12-week treatment).

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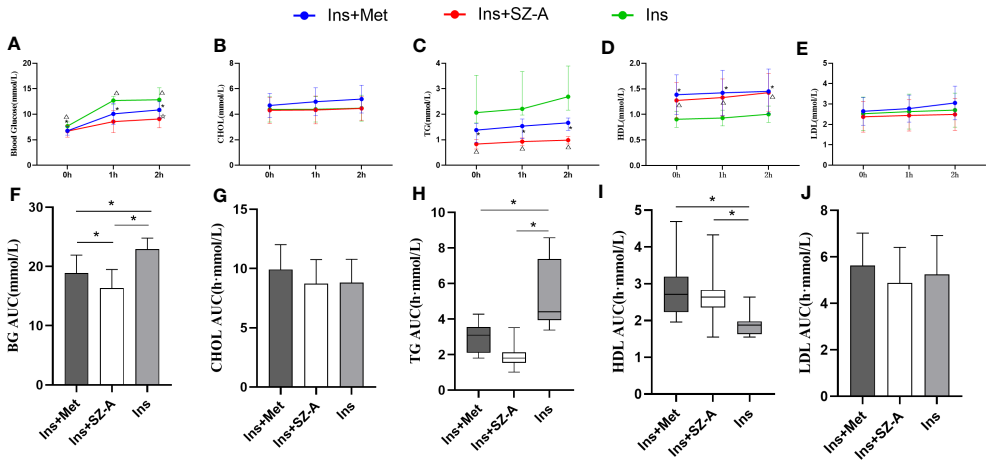

FIGURE 2
Fasting and Postprandial Blood Glucose and Lipid Levels After 12 Weeks of Treatment **(A)** changes in fasting and postprandial blood glucose levels in three groups. **(B)** changes in fasting and postprandial CHOL levels in three groups. **(C)** changes in fasting and postprandial TG levels in three groups. **(D)** changes in fasting and postprandial HDL levels in three groups. **(E)** changes in fasting and postprandial LDL levels in three groups. *P<0.05 Ins vs Ins+Met, △P<0.05 Ins vs Ins+SZ-A, ☆P<0.05 Ins+Met vs Ins+SZ-A, BG AUC **(F)**,CHOL AUC **(G)**, TG AUC **(H)**,HDL AUC **(I)**,LDL AUC **(J)** levels among the groups. *P<0.05.

in the Ins group (P<0.05; Figures 2C, H). The fasting HDL, 1-hour postprandial HDL, 2-hour postprandial HDL,and HDL AUC were also higher in the Ins+Met and Ins+SZ-A groups than in the Ins group (P<0.05; Figures 2D, I). There were no statistically significant differences observed in terms of the other indicators (P>0.05; Figures 2B, E, G, J).

3.4 Continuous glucose monitoring results

No statistically significant differences were noted in terms of CGM indicators such as MBG, SDBG, LAGE, PPGE, MAGE, MODD, TIR, breakfast AUCpp, lunch AUCpp, and dinner AUCpp among the three groups during the screening and lead-in period (P>0.05). Compared to the screening period, the MBG, SDBG, LAGE, PPGE, MAGE, MODD, TIR, breakfast AUCpp, lunch AUCpp, and dinner AUCpp indicators of all three groups showed significant improvements during the lead-in period (P<0.05; Table 3; Figure 3).

Compared with those during the lead-in period, the Ins+Met and Ins+SZ-A groups showed significant improvements in terms of MBG, SDBG, LAGE, PPGE, MAGE, TIR, breakfast AUCpp, lunch AUCpp, and dinner AUCpp after the 12-week treatments (P<0.05); there was no statistically significant difference observed in MODD (P>0.05). None of

TABLE 3 CGM results.

	Ins+Met			Ins+SZ-A			Ins		
	Screeing period	Lead-in period	After 12 weeks	Screeing period	Lead-in period	After 12 weeks	Screeing period	Lead-in period	After 12 weeks
MBG(mmol/L)	10.59±0.30	7.64 ±0.57*	6.91±0.32#	10.49±0.29	7.91 ±0.35*	6.78±0.25#	10.65±0.36	8.03 ±0.62*	7.71±0.31
SDBG(mmol/L)	2.20±0.07	1.65 ±0.15*	1.54±0.11#	2.28±0.15	1.75 ±0.25*	1.44±0.17#	2.26±0.15	1.80 ±0.32*	1.77±0.12
LAGE(mmol/L)	9.03±0.40	6.98 ±0.55*	6.11±0.44#	9.17±0.65	6.95 ±0.71*	5.59±0.41#	9.04±0.83	7.28 ±1.13*	7.10±0.34
PPGE(mmol/L)	5.84±0.50	4.03 ±0.40*	3.52±0.37#	5.69±0.46	3.83 ±0.54*	2.83±0.60#	5.64±0.43	3.80 ±0.34*	4.02±0.35
MAGE(mmol/L)	6.00±0.39	4.29 ±0.71*	3.66±0.31#	5.90±0.50	4.58 ±0.72*	3.19±0.54#	6.08±0.50	4.71 ±0.87*	4.46±0.35
MODD(mmol/L)	2.33±0.19	1.31 ±0.22*	1.24±0.30	2.28±0.13	1.42 ±0.42*	1.30±0.17	2.33±0.20	1.70 ±0.44*	1.48±0.33

(Continued)

TABLE 3 Continued

	Ins+Met			Ins+SZ-A			Ins		
	Screeing period	Lead-in period	After 12 weeks	Screeing period	Lead-in period	After 12 weeks	Screeing period	Lead-in period	After 12 weeks
TIR(%)	39.78±4.80	88.44 ±5.93*	93.65±3.75#	40.24±5.51	86.96 ±3.67*	94.98±2.99#	40.19±3.84	85.45 ±6.58*	88.62±3.37
Breakfast AUCpp (h·mmol/L)	47.34±3.14	35.18 ±2.39*	30.71±3.06#	46.54±3.20	35.87 ±2.29*	29.25±3.52#	47.06±1.88	35.48 ±3.76*	34.69±2.39
Lunch AUCpp (h·mmol/L)	46.57±1.82	33.59 ±3.11*	31.45±2.22#	46.66±2.14	34.04 ±2.78*	31.23±1.68#	47.55±3.37	35.73 ±4.49*	34.28±2.85
Dinner AUCpp(h·mmol/L)	48.05±2.38	33.89 ±3.07*	30.91±1.94#	48.22±2.86	34.85 ±3.08*	28.47±1.90#	48.04±3.22	34.16 ±3.29*	34.21±3.27

*represents P < 0.05(comparison between screening and lead-in period for each group,matched-samples Student's t- test).
#represents P < 0.05(comparison between lead-in and after 12-week treatment period for each group,matched-samples Student's t- test).

these indicators improved significantly in the Ins group (P>0.05). After 12 weeks of treatment,the MBG, SDBG, TIR,breakfast AUCpp, and lunch AUCpp indicators of the Ins+Met and Ins+SZ-A groups showed significantly greater than those of the Ins group (P<0.05).In addition, the LAGE, PPGE, MAGE, and dinner AUCpp levels of the Ins+SZ-A group were lower than those of the Ins+Met nd Ins groups (P<0.05). However,there were no statistically significant differences in MODD among the three groups (P>0.05; Table 3; Figure 3).

3.5 Adverse reactions

After 12 weeks of treatment, there were no statistically significant changes in ALT, AST, Cr, and UA in any of the groups (P>0.05). The three treatment regimens did not show any severe hypoglycemic reactions during any of the study phases. There were no significant differences in the hypoglycemic responses of the three groups during the screening, lead-in, and after 12-week treatments periods (P>0.05). One case of abdominal distension and one case of diarrhea occurred in the Ins+Met group, and the Ins+SZ-A group experienced one case of abdominal distension and no cases of diarrhea. The patients who experienced these events received appropriate medications administered during mealtimes, starting with low doses that were then gradually increased until the adverse reactions were ameliorated, without altering their main treatment regimens.

4 Discussion

It is important to reach the target levels for blood glucose and HbA1c when treating patients with T2DM. Good control over blood glucose fluctuations is also important. Patients with diabetes who have similar HbA1c levels may have different blood glucose stabilities, and large blood glucose fluctuations may be associated with a greater risk of diabetic complications (20). A higher TIR has been linked to reduced risks of albuminuria, retinopathy, cardiovascular disease mortality, all-cause mortality, and abnormal carotid intima-media thickness. Peripheral neuropathy is associated with SDBG and MAGE; therefore, strengthening the management of blood glucose fluctuations plays a key role in preventing macrovascular and microvascular complications related to diabetes (21, 22). Hyperlipidemia also increases the risk of atherosclerotic cardiovascular disease in patients with diabetes (23). Postprandial

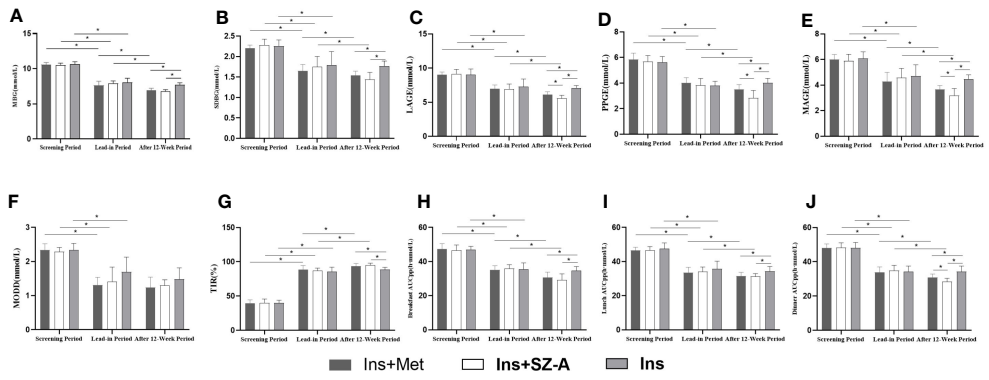

FIGURE 3
CGM results Changes in MBG **(A)**, SDBG **(B)**, LAGE **(C)**, PPGE **(D)**, MAGE **(E)**, MODD **(F)**, TIR **(G)**, breakfast AUCpp **(H)**, lunch AUCpp **(I)**, and dinner AUCpp **(J)** at different stages among the three groups. * P<0.05.

hyperlipidemia is an important risk factor, particularly in patients who have both metabolic syndrome and diabetes (24). Studies have shown that SZ-A can improve fasting blood glucose and lipids levels, but there are currently no data on blood glucose fluctuations and postprandial blood lipids in patients taking SZ-A (1, 4).

In this study, the three treatment regimens all improved the patients' blood glucose levels, and the results in the Ins+SZ-A group were superior to those in the Ins+Met and Ins groups in terms of improving postprandial blood glucose fluctuations. All three treatment regimens reduced fasting blood lipids, but the Ins+Met and Ins+SZ-A treatments also improved the patients' postprandial blood lipid indicators.

HbA1c, which reflects long-term blood glucose control, has become the gold standard for evaluating blood glucose control and guiding clinical decisions regarding the management of diabetes. Compared to during the screening period, the HbA1c and FBG levels in all three groups decreased following the 12-week treatment period. After 12 weeks treatment, the HbA1c, FBG, and administered insulin doses in the Ins+Met and Ins+SZ-A groups were lower than those in the Ins group. The insulin doses in the Ins+Met and Ins+SZ-A groups during the lead-in period were 29.00 (24.00, 34.5) and 32.00 (20.50, 33.25), respectively. Following the 12-week treatment period, these doses decreased to 19.00 (15.50, 28.50) and 21.00 (18.50, 30.50), respectively. Although the absolute values of insulin doses in the Ins +SZ-A group were greater than those in the Ins+Met group, both during the lead-in period and after 12 weeks of treatment, this difference was not statistically significant. Therefore, we believe that drugs, rather than insulin, decrease hypoglycemia and hyperlipidemia.

TIR is a key CGM indicator that describes short-term blood glucose control and quantifies the time within the target range (25). Research has shown a correlation between HbA1c and TIR levels, with a 10% change in TIR being equated to a 0.8% change in HbA1C (26). In this study, the TIR levels were higher during the lead-in period for all three groups, compared to during the screening period. However, when compared to the lead-in period, the TIR of the Ins +Met and Ins+SZ-A groups were found to be significantly improved after the 12-week treatment period. There was no significant difference found in terms of this indicator in the Ins group. The TIR of the Ins+Met and Ins+SZ-A groups were both higher than those of the Ins group after 12 weeks of treatment. This indicates that insulin combined with oral medication can improve short-term blood glucose control more effectively than insulin alone.

MBG reflects the average blood glucose level, whereas SDBG reflects the magnitude of overall deviations in glucose levels from the average (27, 28). In our study, MBG and SDBG levels of all of the groups were lower during the lead-in period than during the screening one. However, when compared to the lead-in period, the Ins+Met and Ins+SZ-A groups showed significant decreases in MBG and SDBG levels after 12 weeks treatment. And after 12 weeks treatment,the MBG and SDBG levels in the Ins+Met and Ins +SZ-A groups were lower than those in the Ins group, indicating that the blood glucose levels in the Ins+Met and Ins+SZ-A groups were closer to normal than those in the Ins group.

LAGE is the difference between the maximum and minimum daily glucose levels, and may be an independent predictor of nocturnal asymptomatic hypoglycemia in patients with T2DM. LAGE measurements of >3.48 mmol/L can be used as an early warning sign of nocturnal asymptomatic hypoglycemia (29). MAGE is the average value obtained by removing all blood glucose fluctuations with an amplitude of <1SD, and is the gold standard for evaluating blood glucose fluctuations within a single day. A MAGE measurements of <3.9 mmol/L is recommended as the normal reference range for blood glucose fluctuations in Chinese adults (28). In our study, the LAGE and MAGE levels of all of the groups were lower during the lead-in period than during the screening period. Compared to the lead-in period, the LAGE and MAGE measurements of the Ins+Met and Ins+SZ-A groups were significantly reduced after 12-week treatment. After the 12-week treatment, the LAGE and MAGE indicators of the Ins+SZ-A group were lower than those of the Ins+Met and Ins groups, indicating that, compared to the Ins+SZ-A and Ins groups, Ins+SZ-A is able to better stabilize within-day blood glucose fluctuations.

MODD reflects day-to-day blood glucose excursions, which are the differences between blood glucose values measured at the same time point on two consecutive days. The MODDs of all three groups in our study cohort were lower during the lead-in period than during the screening period. There were no statistically significant differences observed in terms of MODDs among the three groups during the lead-in period or after 12-week treatment period.

Postprandial blood glucose control is crucial for achieving overall blood glucose control, with postprandial hyperglycemia being the main factor that leads to general hyperglycemia (30). Postprandial hyperglycemia is generally believed to be a predictor of cardiovascular diseases and microvascular complications (31, 32). Therefore, it is necessary to consider postprandial glucose control as an important strategy in the comprehensive treatment plan for patients with diabetes. The PPGEs of all three groups in our study were lower during in the lead-in period than in the screening one. Compared with those during the lead-in period, the Ins+Met and Ins+SZ-A groups showed significant improvements in PPGE measurements after the 12-week treatment period, whereas the Ins group showed no significant changes in PPGE. The PPGE and 2h-PBG levels of the Ins +SZ-A group were lower than those of the Ins+Met and Ins groups after 12 weeks of treatment. This indicates that Ins+SZ-A may improve postprandial blood glucose fluctuations more effectively compared with the Ins+Met and Ins groups.

After the 12 weeks of treatment, the dinner AUCpp of the Ins+SZ-A group was lower than that of the Ins+Met and Ins groups, indicating that the Ins+SZ-A group experienced a more significant improvement in post-dinner blood glucose levels, which may be partially due to the cumulative effect of α-glucosidase inhibitors (33). Although no human data available, it has been reported that the turnover time of disaccharidase in rats is 11.5 h. Thus, when SZ-A is taken at every meal, its cumulative effects are most observable at dinnertime (34). This may also be due to differences in the nutritional composition of each meal, and the higher carbohydrate content generally found in Chinese dinners. Thus, SZ-A may be more effective at controlling postprandial hyperglycemia in the Chinese population.

Animal experiments have shown that SZ-A significantly reduces liver weight, liver triglycerides, and total cholesterol levels. However, there is still no data regarding the effects of SZ-A on postprandial blood lipids (4). In our experiment, we verified that

SZ-A was able to effectively improve blood lipid levels. After 12 weeks of treatment, HDL increased and both TG and LDL decreased in the Ins+SZ-A group, whereas HDL increased and TG decreased in the Ins+Met group. Furthermore, the Ins+SZ-A and Ins+SZ-A groups showed improved postprandial blood lipid levels. Compared with the Ins group, the Ins+SZ-A and Ins+SZ-A groups showed better-corrected postprandial TG and HDL levels.

Gastrointestinal side effects are one of the limitations to the clinical application of α-glycosidase inhibitors and Met. These may include flatulence, abdominal distension, diarrhea, abdominal pain, and other symptoms. In our experiment, the incidence of GDs in the Ins+SZ-A group was very low. *In vitro* experiments have shown that SZ-A exerts a strongly inhibitory effect on maltase (IC50 = 0.06 μG/mL) and sucrase (IC50 = 0.03 μG/mL).With regard to α-amylase, however, SZ-A had no inhibitory activity at 100 μg/mL (35). Therefore, SZ-A selectively inhibits disaccharidases in order to reduce postprandial hyperglycemia. These findings may partially explain the mechanism underlying the low incidence of GDs observed in the Ins+SZ-A group in our research.

To the best of our knowledge, this is the first research to evaluate the effects of SZ-A or Met combined with premixed insulin on blood glucose fluctuations in patients with T2DM. The combination of SZ-A or Met with premixed insulin not only improved blood glucose control, but also reduced blood glucose fluctuations and blood lipid indicators in our cohort of patients with T2DM whose blood glucose levels could not be controlled through the use of oral medications. SZ-A combined with premixed insulin proved to be better for reducing postprandial blood glucose fluctuations than Met combined with premixed insulin and premixed insulin alone. However, this study also had some limitations worth noting. This was a single-center study with a relatively small number of patients and a study period of only 3 months. Thus, it would be best to extend the treatment period to 6 months or 1 year. Further multi-center studies with larger sample sizes are also warranted to evaluate the safety and efficacy of long-term treatment with SZ-A.

The results of this study suggest that the combination of SZ-A and Met with premixed insulin is a potential treatment option for patients with T2DM whose blood glucose levels cannot be adequately controlled by oral medications, and SZ-A combined with premixed insulin may be more suitable for Chinese patients who consume higher levels of carbohydrates. Further prospective studies with more patients over longer periods are required to verify this hypothesis.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Review Committee of the First Affiliated Hospital of Harbin Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZM: Writing – original draft. CX: Writing – original draft. HL: Writing – original draft. XG: Writing – original draft. XL: Writing – original draft. WL: Writing – original draft. XM: Writing – original draft. CY: Writing – original draft. MH: Writing – original draft. KZ: Writing – original draft. YH: Writing – original draft. YW: Writing – original draft. HK: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Qu L, Liang X, Tian G, Zhang G, Wu Q, Huang X, et al. Efficacy and safety of mulberry twig alkaloids tablet for the treatment of type 2 diabetes: A multicenter, randomized, double-blind, double-dummy, and parallel controlled clinical trial. *Diabetes Care* (2021) 44(6):1324–33. doi: 10.2337/dc20-2109

2. Liu Q, Liu S, Cao H, Ji W, Li C, Huan Y, et al. Ramulus mori (Sangzhi) alkaloids (SZ-A) ameliorate glucose metabolism accompanied by the modulation of gut microbiota and ileal inflammatory damage in type 2 diabetic KKAy mice. *Front Pharmacol* (2021) 12:642400. doi: 10.3389/fphar.2021.642400

3. Cao H, Ji W, Liu Q, Li C, Huan Y, Lei L, et al. Morus alba L. (Sangzhi) alkaloids (SZ-A) exert anti-inflammatory effects *via* regulation of MAPK signaling in macrophages. *J Ethnopharmacol* (2021) 280:114483. doi: 10.1016/j.jep.2021.114483

4. Chen YM, Lian CF, Sun QW, Wang TT, Liu YY, Ye J, et al. and Y.L. Liu.Ramulus mori (Sangzhi) alkaloids alleviate high-fat diet-induced obesity and nonalcoholic fatty liver disease in mice. *Antioxidants (Basel)* (2022) 11(5):905. doi: 10.3390/antiox11050905

5. Blonde L, Umpierrez GE, Reddy SS, McGill JB, Berga SL, Bush M, et al. American association of clinical endocrinology clinical practice guideline: developing a diabetes mellitus comprehensive care plan-2022 update. *Endocrine Pract* (2022) 28(10):923–1049. doi: 10.1016/j.eprac.2022.08.002

6. Ji LN, Lu JM, Guo XH, Yang WY, Weng JP, Jia WP, et al. Glycemic control among patients in China with type 2 diabetes mellitus receiving oral drugs or injectables. *BMC Public Health* (2013) 13:602. doi: 10.1186/1471-2458-13-602

7. Li FF, Xu XH, Fu LY, Su XF, Wu JD, Lu CF, et al. Influence of acarbose on plasma glucose fluctuations in insulin-treated patients with type 2 diabetes: A pilot study. *Int J Endocrinol* (2015), 903524. doi: 10.1155/2015/903524

8. McCall AL. Insulin therapy and hypoglycemia. *Endocrinol Metab Clin North Am* (2012) 41(1):57–87:doi: 10.1016/j.ecl.2012.03.001

9. Massi-Benedetti M, Orsini-Federici M. Treatment of type 2 diabetes with combined therapy: what are the pros and cons? *Diabetes Care* (2008) 31 Suppl 2: S131–5. doi: 10.2337/dc08-s233

10. Yki-Järvinen H. Combination therapies with insulin in type 2 diabetes. *Diabetes Care* (2001) 24(4):758–67. doi: 10.2337/diacare.24.4.758

11. Shaw RJ, Lamia KA, Vasquez D, Koo S-H, Bardeesy N, Depinho RA, et al. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. *Science* (2005), 1642–6, 310(5754). doi: 10.1126/science.1120781

12. Fullerton MD, Galic S, Marcinko K, Sikkema S, Pulinilkunnil T, Chen ZP, et al. Single phosphorylation sites in Acc1 and Acc2 regulate lipid homeostasis and the insulin-sensitizing effects of metformin. *Nat Med* (2013) 19(12):1649–54. doi: 10.1038/nm.3372

13. Miller RA, Chu Q, Xie J, Foretz M, Viollet B, Birnbaum MJ. Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. *Nature* (2013) 494 (7436):256–60. doi: 10.1038/nature11808

14. Madiraju AK, Erion DM, Rahimi Y, Zhang XM, Braddock DT, Albright RA, et al. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. *Nature* (2014) 510(7506):542–6. doi: 10.1038/nature13270

15. Walicka M, Jozwiak J, Rzeszotarski J, Zarzycka-Lindner G, Zonenberg A, Bijos P, et al. PROGENS-HbA(1c) study: safety and effectiveness of premixed recombinant human insulin (Gensulin M30). *Arch Med Sci* (2016) 12(5):985–91. doi: 10.5114/aoms.2016.61910

16. Guo L, Chang B, Chen L, Yang L, Liu Y, Feng B, et al. Composite cardiovascular risk and BMI affected comparative profiles of BIAsp 30 + metformin vs BIAsp 30 monotherapy: a MERIT *post-hoc* analysis. *Sci Rep* (2021) 11(1):4131. doi: 10.1038/s41598-021-83410-x

17. Guo L, Chen L, Chang B, Yang L, Liu Y, Feng B. A randomized, open-label, multicentre, parallel-controlled study comparing the efficacy and safety of biphasic insulin aspart 30 plus metformin with biphasic insulin aspart 30 monotherapy for type 2 diabetes patients inadequately controlled with oral anti. *Diabetes Obes Metab* (2018) 20(12):2740–7. doi: 10.1111/dom.13454

18. Zhou W, Li J, Yuan X, Wang W, Zhou H, Zhang H, et al. Application of urine C-peptide creatinine ratio in type 2 diabetic patients with different levels of renal function. *Front Endocrinol* (2022) 13:1052794. doi: 10.3389/fendo.2022.1052794

19. Li J, Li J, Shan Z, Yang W, Liu J, Tian H, et al. Gender-differential effects on blood glucose levels between acarbose and metformin in Chinese patients with newly diagnosed type 2 diabetes: a sub-analysis of the MARCH trial. *Endocrine J* (2021) 68 (1):69–79. doi: 10.1507/endocrj.EJ20-0006.

20. Del Prato S. In search of normoglycaemia in diabetes: controlling postprandial glucose. *Int J Obes Relat Metab Disord* (2002) 26 Suppl 3:S9–17. doi: 10.1038/sj.ijo.0802172

21. Yapanis M, James S, Craig ME, O'Neal D, Ekinci EI. Complications of diabetes and metrics of glycemic management derived from continuous glucose monitoring. *J Clin Endocrinol Metab* (2022) 107(6):e2221–36. doi: 10.1210/clinem/dgac034

22. Suh S, Kim JH. Glycemic variability: how do we measure it and why is it important? *Diabetes Metab J* (2015) 39(4):273–82. doi: 10.4093/dmj.2015.39.4.273

23. Wang CCL, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus - mechanisms, management, and clinical considerations. *Circulation* (2016) 133(24):2459–502. doi: 10.1161/CIRCULATIONAHA.116.022194

24. Nakamura K, Miyoshi T, Yunoki K, Ito H. Postprandial hyperlipidemia as a potential residual risk factor. *J Cardiol* (2016) 67(4):335–9. doi: 10.1016/j.jjcc.2015.12.001

25. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care* (2017) 40(12):1631–40. doi: 10.2337/dc17-1600

26. Vigersky RA, McMahon C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes. *Diabetes Technol Ther* (2019) 21(2):81–5. doi: 10.1089/dia.2018.0310

27. Monnier L, Wojtusciszyn A, Colette C, Owens D. The contribution of glucose variability to asymptomatic hypoglycemia in persons with type 2 diabetes. *Diabetes Technol Ther* (2011) 13(8):813–8. doi: 10.1089/dia.2011.0049

28. Zhou J, Li H, Ran X, Yang W, Li Q, Peng Y, et al. Establishment of normal reference ranges for glycemic variability in Chinese subjects using continuous glucose monitoring. *Med Sci monitor* (2011) 17(1):CR9–13. doi: 10.12659/msm.881318

29. Wang S, Tan Z, Wu T, Shen Q, Huang P, Wang L, et al. Largest amplitude of glycemic excursion calculating from self-monitoring blood glucose predicted the episodes of nocturnal asymptomatic hypoglycemia detecting by continuous glucose monitoring in outpatients with type 2 diabetes. *Front Endocrinol* (2022) 13:858912. doi: 10.3389/fendo.2022.858912

30. Moon J, Kim JY, Yoo S, Koh G. Fasting and postprandial hyperglycemia: their predictors and contributions to overall hyperglycemia in korean patients with type 2 diabetes. *Endocrinol Metab (Seoul)* (2020) 35(2):290–7. doi: 10.3803/EnM.2020.35.2.290

31. The DECODE Study Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Internal Med* (2001) 161 (3):397–405. doi: 10.1001/archinte.161.3.397

32. Shiraiwa T, Kaneto H, Miyatsuka T, Kato K, Yamamoto K, Kawashima A, et al. Postprandial hyperglycemia is a better predictor of the progression of diabetic retinopathy than HbA1c in Japanese type 2 diabetic patients. *Diabetes Care* (2005) 28(11):2806–7. doi: 10.2337/diacare.28.11.2806

33. Yuhong H, Wenxu F, Yanfen L, Yu L, Ziqiang L, Liu Y, et al. Comparison of the effects of acarbose and TZQ-F, a new kind of traditional chinese medicine to treat diabetes, chinese healthy volunteers. *Evid Based Complement Alternat Med* (2014), 308126. doi: 10.1155/2014/308126

34. James WP, Alpers DH, Gerber JE, Isselbacher KJ. The turnover of disaccharidases and brush border proteins in rat intestine. *Biochim Biophys Acta* (1971) 230(2):194–203. doi: 10.1016/0304-4165(71)90204-2

35. Liu Z, Yang Y, Dong W, Liu Q, Wang R, Pang J, et al. Investigation on the enzymatic profile of mulberry alkaloids by enzymatic study and molecular docking. *Molecules* (2019) 24(9):1776. doi: 10.3390/molecules24091776

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Evaluation of HbA1c from CGM traces in an Indian population

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Introduction: The development of continuous glucose monitoring (CGM) over the last decade has provided access to many consecutive glucose concentration measurements from patients. A standard method for estimating glycated hemoglobin (HbA1c), already established in the literature, is based on its relationship with the average blood glucose concentration (aBG). We showed that the estimates obtained using the standard method were not sufficiently reliable for an Indian population and suggested two new methods for estimating HbA1c.

Methods: Two datasets providing a total of 128 CGM and their corresponding HbA1c levels were received from two centers: Health Centre, Savitribai Phule Pune University, Pune and Joshi Hospital, Pune, from patients already diagnosed with diabetes, non-diabetes, and pre-diabetes. We filtered 112 data-sufficient CGM traces, of which 80 traces were used to construct two models using linear regression. The first model estimates HbA1c directly from the average interstitial fluid glucose concentration (aISF) of the CGM trace and the second model proceeds in two steps: first, aISF is scaled to aBG, and then aBG is converted to HbA1c via the Nathan model. Our models were tested on the remaining 32 data-sufficient traces. We also provided 95% confidence and prediction intervals for HbA1c estimates.

Results: The direct model (first model) for estimating HbA1c was $HbA1c_{mmol/mol} = 0.319 \times aISF_{mg/dL} + 16.73$ and the adapted Nathan model (second model) for estimating HbA1c is $HbA1c_{mmol/dL} = 0.38 \times (1.17 \times ISF_{mg/dL}) - 5.60$.

Discussion: Our results show that the new equations are likely to provide better estimates of HbA1c levels than the standard model at the population level, which is especially suited for clinical epidemiology in Indian populations.

KEYWORDS

continuous glucose monitoring (CGM), glycated hemoglobin (HbA1c), type 2 diabetes (T2D), average blood glucose concentration (aBG), average interstitial fluid glucose concentration (aISF)

1 Introduction

Type 2 diabetes mellitus (T2D) is one of the most common metabolic disorders in India. Understanding the metabolic pathways and mechanisms involved in the development of T2D in patients play an important role in its diagnosis and treatment. Traditionally, it involves measuring the fasting blood glucose concentration (FBG) and postprandial blood glucose concentration (PPBG). Since the late 1970s, there have been reports of a correlation between HbA1c and blood glucose concentration (BG), and that HbA1c could be a useful tool for long-term BG control. Gabbay et al. (1) studied the correlation between HbA1a, HbA1b, and HbA1c with 24-hour urinary glucose concentration collected over periods of 1, 2, and 3 months for 220 diabetic patients and suggested that glycosylated hemoglobin could act as a good index for long-term BG levels in people with T2D. Santiago et al. (2) further studied the correlation between HbA1c and PPBG. Clarke et al. (3) showed that HbA1c is correlated with aBG over 2 months, and therefore, is a good index for aBG and is a useful tool for understanding the quality of BG control in a patient. Lecomte et al. (4) also confirmed in a group of 138 patients that HbA1c is a good index for BG control. Distiller (5) compared the efficacy of PPBG and HbA1c as indices for BG control and showed that HbA1c is a significantly better index.

There is a plethora of other new metrics being developed to understand the glycemic state of the patient, such as time in range (TIR). HbA1c is one of the most reliable metrics for understanding long-term BG changes in a patient. Therefore, accurate experimental methods (6) have been developed to measure HbA1c levels. However, with the development of flash glucose monitoring (FGM) and eventually CGM technologies, clinicians now have access to many consecutive interstitial fluid glucose concentration (ISF) measurements (CGM traces). This encouraged the development of methods for estimating metrics such as FGM, PPBG, TIR, and HbA1c from the CGM traces.

Sikaris (7) showed that although for a single measurement HbA1c and BG had been shown to be correlated, including multiple measurements like CGM traces improved the correlation further. They concluded that not only was estimating HbA1c from the HbA1c–BG relationship viable, but also that it would become the standard method of estimating HbA1c. Mazze (8) also showed that BG from self-monitoring blood glucose (SMBG) and CGM traces were highly correlated, and that the HbA1c estimates obtained using them were not significantly different, although different patterns of SMBG and CGM traces could produce the same HbA1c. This suggests that HbA1c is a metric that can be reliably estimated. Nathan et al. (9) used linear regression to estimate aBG from HbA1c levels at the population level. This relationship has been used to develop a method for estimating HbA1c levels from aBG. This method was adopted as the standard for obtaining HbA1c estimates (10). This method was also used to estimate HbA1c values using the Abbot Libre FreeStyle Pro device for the CGM report generated by the device.

In recent years, after Nathan et al. (9) published their method, many similar methods have been developed for estimating HbA1c. Kovatchev et al. (11) provided a dynamic method for accurately estimating average HbA1c using regular SMBG readings for T2D patients. The method was later validated in patients with type 1 diabetes (T1D) and showed similar performance (12). Beck et al. (13) showed that experimentally measured HbA1c alone cannot be reliably used as a metric for glycemic control in an individual. They suggested that the glucose profile from the CGM trace and aBG calculated from the CGM trace were also considered. They also provided a method for estimating HbA1c from a given CGM trace and suggested that estimated HbA1c should also be considered as a metric for an individual's glycemic control. Fan et al. (14) had established a relationship between HbA1c and FBG and PPBG which are both categorized as SMBG. They also provided a method for estimating HbA1c but also showed that FBG and HbA1c levels are strongly correlated.

Bergenstal et al. (15) renamed the estimated HbA1c as the glucose management indicator (GMI), a metric for glycemic control and management. They also provided a new method for estimating GMI from a given CGM trace. The model was then validated by Leelarathna et al. (16) using guardian 3 and navigator 2 sensor data. Perlman et al. (17) however showed that there can be a substantial difference between experimentally measured HbA1c and GMI values for T1D patients especially, with patients having advanced chronic kidney disease. Shah et al. (18) also showed that it does not correlate well with HbA1c for non-diabetic patients. Estimated HbA1c is increasingly being replaced by GMI, which is used as a metric for glycemic control. Therefore, attempts to improve GMI to closely reflect HbA1c levels and be a reliable metric for glycemic control are an active field of research.

Recently, Oriot and Hermans (19) showed that HbA1c values were overestimated using Nathan's equation from CGM traces obtained using the Free Style Libre device for T1D patients. This contrasts with Hu et al. (20), who showed that HbA1c estimated using Nathan's equation on CGM traces obtained by FreeStyle Libre underestimated the experimental HbA1c values. Hu et al. (20) also produced a total of seven models, based on linear and nonlinear regression analysis for estimating HbA1c values from a given CGM trace. These reliability issues of GMI or estimated HbA1c indicate that there is still a need for a new method for estimating HbA1c from a given CGM trace for an individual that works for all pre-diabetic, diabetic, and non-diabetic groups. Xu et al. (21) suggested a kinetic model for estimating HbA1c and showed that it provides a highly accurate estimate of HbA1c. He also improved the kinetic model to include the life-cycle of the red blood cells (RBC) containing the HbA1c molecules (22).

We show that the HbA1c estimates obtained using Nathan's equation are not statistically reliable for the Indian population, and we provide two new methods for estimating HbA1c.

2 Materials and methods

2.1 Subject recruitment and measurement of blood biochemical parameters

A CGM dataset containing traces of 50 participants was collected at the Primary Care Health Centre, Savitribai Phule Pune University, Pune. For each participant, a FreeStyle Libre Pro

CGM sensor (Abbott, UK) was inserted subcutaneously on the back of the upper arm by Dr. Shashikant Dudhgaonkar at the Health Centre, Savitribai Phule Pune University, Pune, India, between July 2021 and September 2021. This factory-calibrated glucose sensor recorded subcutaneous ISF every 15 min for 14 days. All participants were advised to continue their normal diet and exercise routine. On the 14th day, the CGM device was removed, and the data were downloaded and analyzed using FreeStyle Libre Pro software. The CGM devices were provided to the participants through the Rastriya Ucchattar Shiksha Abhiyan (RUSA) grant from Savitribai Phule Pune University. We refer to this dataset as the Pune-2021 dataset.

The CGM data collected in the Pune-2021 dataset were then filtered into two sets: a *data-sufficient* Pune-2021 dataset and a *data-insufficient* Pune-2021 dataset in the following way. Data sufficiency was checked according to (i) the number of days the sensor was active, and (ii) the percentage of measurements recorded, as suggested by Danne et al. (10): From the measurement ID provided in the CGM trace data file, the number of ISF measurements, N, recorded by the device was calculated. The timestamps provided in the CGM trace were used to calculate the effective number of days, n_d for which the CGM device was active. However, this number was rounded off to the nearest integer using the `round` function provided by the `NumPy` package (23). The percentage of measurements recorded by the device was calculated using Δt_m, which is the time difference in seconds between the first and last readings. Δt_m was used to calculate the total number of readings recorded by the device as $N_{total} = \lfloor \frac{\triangle t_m}{60\times 15} \rfloor + 1$. The percentage of measurements was calculated as $N_p = 100 \times N/N_{\text{total}}$. If $n_d \geq 14$ and $N_p \geq 70\%$ for a given CGM trace, we categorized the CGM trace as data-sufficient; otherwise, it was categorized as data-insufficient.

After the data-insufficient CGM traces were filtered out, 12 pre-diabetic, 13 diabetic, and 14 non-diabetic CGM traces remained and were categorized as data-sufficient.

A second dataset of 78 CGM traces along with their HbA1c levels (by HPLC) was collected by Dr. K. M. Shelgikar at the Tertiary Care Center, Joshi Hospital, Shivaji Nagar, Pune from 2018 to 2020. Data were collected as part of routine patient care and anonymized for analysis. This dataset is referred to as the Joshi-2018 dataset. Similar to the Pune-2021 dataset, the Joshi-2018 dataset was filtered as data-sufficient and data-insufficient subsets. After filtering out the data-insufficient CGM traces from the Joshi-2018 dataset, only 73 CGM traces were considered as data sufficient.

The complete CGM-dataset, including both the Pune-2021 dataset and the Joshi-2018 dataset, contained the CGM traces and the corresponding HbA1c levels of 128 participants, 15 of whom were pre-diabetic, 94 were diabetic, and 19 were non-diabetic. The data-sufficient subset of the CGM-dataset contained 112 CGM traces, of which 12 were pre-diabetic, 86 were diabetic, and 14 were non-diabetic. A sample of 32 data-sufficient CGM traces and their corresponding HbA1c measurements was separated as a test set for validation purposes; the remaining 80 data-sufficient CGM traces were grouped as the training CGM-dataset. The complete CGM-dataset including the data-insufficient CGM traces was used to validate the HbA1c estimates obtained using the Nathan model (9) but only the data-sufficient CGM traces of the training CGM-dataset were used to construct our models, which were then validated using the data-sufficient CGM traces of the test CGM-dataset.

2.2 Comparing Nathan HbA1c estimates with experimentally measured HbA1c

Nathan et al. (9) collected a dataset of 2,700 glucose measurements from 268 T1D patients, 159 T2D patients, and 80 non-diabetic participants. Their dataset contained CGM traces and finger-stick measurements that were collected as different measures of glycemia.

The ISF measurements were scaled by a factor of 1.05 to estimate the corresponding BG. aBG was calculated by taking the weighted average of all the blood glucose concentration measurements collected. All measurements in a day were given equal weights, which were inversely proportional to the number of measurements taken on that day. The aBG was calculated by taking the mean of all measurements, giving the measurements on each day an equal weight. The expression to obtain the aBG is

$$\text{aBG} = \frac{1}{(m_1 + m_2)} \left\{ \sum_{i=1}^{i=m_1} \left(\frac{1}{n_{1,i}} \right) \text{BG}_i + \sum_{i=1}^{i=m_2} \left(\frac{1}{n_{2,i}} \right) (1.05 \times \text{ISF}_i) \right\}, \tag{1}$$

where aBG represents the average blood glucose concentration, BG_i is the ith SMBG measurements, ISF_i is the ith CGM measurement, m_1 and m_2 are the number of SMBG and CGM measurements respectively, $n_{1,i}$ is the number of SMBG measurements taken on the day BG_i was taken, and $n_{2,i}$ is the number of CGM measurements taken on the day ISF_i was taken.

A linear regression analysis was performed by Nathan et al. (9) taking the calculated aBG as the dependent variable and the HbA1c as the independent variable and obtained this relation:

$$aBG_{mg/dL} = 28.7 \times HbA1c_{\%} - 46.7, \tag{2}$$

(2) can also be written as:

$$\text{HbA1c}_{\%} = \frac{1}{28.7} \left\{ 46.7 + (1.05 \times \text{aISF}_{mg/dL}) \right\}, \tag{3}$$

$$= 1.627 + 0.035 \times (1.05 \times \text{aISF}_{mg/dL}), \tag{4}$$

$$\text{HbA1c}_{mmol/mol} = 0.38 \times (1.05 \times \text{aISF}_{mg/dL}) - 5.60, \tag{5}$$

to relate HbA1c and aISF directly.

We used a paired t-test to verify whether the two groups, that is, the experimentally measured HbA1c from the CGM-dataset and the corresponding HbA1c calculated using the Nathan model Eq. (5), and Eq. (1), are statistically indistinguishable. Calculations were performed using the `ttest_rel` function of the `stats` module of the `SciPy` package (24). Similarly, a paired t-test was performed with only the data sufficient (including both the training and test datasets) CGM traces from the CGM dataset.

2.3 Direct model

To directly construct a model between aISF and HbA1c, we assumed a linear relationship and performed a regression analysis. Note that the aISF here is an equally weighted average of all the ISF measurements in a given CGM trace,

$$\text{aISF}_{mg/dL} = \frac{1}{N}\sum_{i=1}^{i=N}\text{ISF}_{i,mg/dL}, \tag{6}$$

where $\text{aISF}_{\text{mg/dL}}$ represents the calculated aISF in mg/dL, $\text{ISF}_{i,\text{mg/dL}}$ represents the ith ISF measurement from the given CGM trace in mg/dL and N represents the total number of measurements in the given CGM trace. The linear regression equation for the direct model is

$$HbA1c_{mmol/mol} = \beta_1 \times aISF_{mg/dL} + \beta_0, \tag{7}$$

where $\text{aISF}_{\text{mg/dL}}$ represents the aISF in mg/dL, $\text{HbA1c}_{\text{mmol/mol}}$ represents the HbA1c in mmol/mol, β_1 the slope in mmoldL/(molmg) and β_0 the intercept in mmol/mol.

We obtained the ordinary least square (OLS) estimates $\hat{\beta}_0$ and, $\hat{\beta}_1$ of the parameters β_0 and, β_1. We also calculated the 95% confidence interval for $\hat{\beta}_0$ and $\hat{\beta}_1$ along with 95% confidence interval and the 95% prediction interval of HbA1c for any given aISF. This analysis was performed using the `LinearRegression` function from the `linear_model` module of the `scikit-learn` package (25). However, the confidence and prediction intervals were calculated using the standard OLS solution formulae.

A paired t-test was then performed on the HbA1c estimated using the direct model and the experimental values for the data-sufficient CGM traces from the test CGM-dataset to verify whether the HbA1c estimates obtained using $\hat{\beta}_0$ and $\hat{\beta}_1$ were statistically indistinguishable from the experimental HbA1c value at the population level. The t-test was performed using the `ttest_rel` function of the `stats` module of the `SciPy` package.

We also used the training dataset of CGM traces and calculated the 5-fold cross validation root mean squared error (RMSE) to validate the 95% confidence interval for the direct model.

2.4 Adapted Nathan model

In *Section 2.3*, we constructed a linear model for estimating HbA1c from the aISF calculated from a given CGM trace. Although such a relationship, if reliable, can be valuable, it requires us to base our HbA1c estimates on the ISF values. Traditionally, however, for the diagnosis of T2D and analysis of the glycemic state of an individual, various metrics such as FBG, PPBG, and HbA1c have always been based on BG. The current CGM devices, however, report ISF readings, and therefore, to use these CGM traces with our current diagnostic methods, it is important to develop a reliable method for converting the ISF readings to their corresponding BG readings. The ISF measurements in the CGM traces of the dataset used by Nathan et al. (9) were scaled to their BG values using a scaling factor of 1.05. We suspected that obtaining a better estimate of this scaling factor would improve HbA1c estimates.

Therefore, we constructed a linear model for estimating HbA1c from the calculated aISF [aISF was constructed using Eq. (6)] via the aBG. We considered a model in which we estimated aBG by scaling aISF by a factor of ω and used Eq. (2) to obtain the estimate of HbA1c. This model represented by Eq (8). is

$$HbA1c_{mmol/mol} = 0.38 \times (\omega \times aISF_{mg/dL}) - 5.60, \tag{8}$$

where $\text{aISF}_{\text{mg/dL}}$ represents the aISF in mg/dL, $\text{HbA1c}_{\text{mmol/mol}}$ represents the HbA1c in mmol/mol and, ω the scaling factor. Now, Eq. (8) can also be written as:

$$\frac{HbA1c_{mmol/mol} + 5.60}{0.38} = (\omega \times aISF_{mg/dL}), \tag{9}$$

The OLS solutions for the estimate $\hat{\omega}$, of the coefficient ω are the same for both Eqs. (8) and (9).

We obtain the OLS estimate $\hat{\omega}$ using Eq. (9), where we took the calculated $\text{aISF}_{\text{mg/dL}}$ as the independent variable and the transformed experimental HbA1c values, $\frac{HbA1c_{mmol/mol}+5.60}{0.38}$, as the dependent variable. The analysis was performed using the `LinearRegression` function from the `linear_model` module of the `scikit-learn` package. Data-sufficient CGM traces and their corresponding HbA1c values from the training CGM dataset were used for this analysis. We calculated the 95% confidence interval for $\hat{\omega}$, the 95% confidence interval and 95% prediction interval for estimated HbA1c corresponding to an aISF calculated from any CGM trace. These intervals were calculated using standard OLS solution formulae for constrained linear regression.

A paired t-test was performed with the HbA1c estimates made using the adapted Nathan model and the experimentally measured HbA1c values for the data-sufficient traces of the test CGM-dataset, using the `ttest_rel` function from the `stats` module of the `SciPy` package to confirm that the HbA1c estimates from the adapted Nathan model were not significantly different from the experimental HbA1c values at the population level.

Finally, using the training CGM-datset a 5-fold cross validation RMSE was calculated for the adapted Nathan model to validate the reliability of the 95% confidence intervals of the adapted Nathan model.

3 Results

We show that the mean of the estimates provided by the standard Nathan et al. (9) method for HbA1c at the population level is not statistically reliable with respect to the experimental HbA1c values for an Indian population. Next, we provide the results for the direct model and the adapted Nathan model based on OLS linear regression for estimating HbA1c from a given CGM trace. We provide the 95% confidence interval for the two models and the 95% prediction intervals for the HbA1c estimates of these two models, which are visualized in Figures 1, 2, showing the three models for estimating HbA1c along with the 95% confidence interval (Figure 1) and the 95% prediction interval (Figure 2). We also provide a user-friendly web app for academic use, CGM Analyzer [version 0.1] (https://digimed.acads.iiserpune.ac.in/fgm-

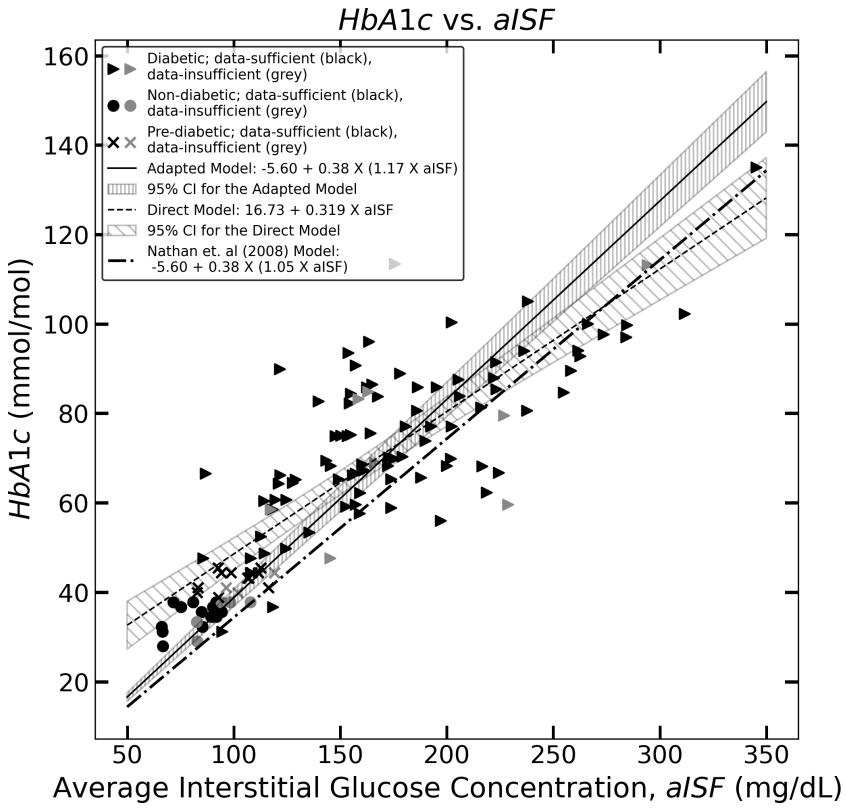

FIGURE 1
The figure represents the experimentally measured HbA1c and aISF values (calculated as described in *Section 2.3*) of the CGM dataset. The pre-diabetic participants are represented by crosses, diabetic participants are represented by solid triangles and non-diabetic participants are represented by solid circles. The scatter points representing participants with a data-sufficient CGM trace [according to Danne et al. (10)] are colored black, whereas the participants with a data-insufficient CGM trace are colored gray. The solid black line and the corresponding hatched region represent Eq. (11), which the 95% confidence interval, and the dashed line along with its corresponding hatched region, represents Eq. (10) and its corresponding 95% confidence interval. The dotted dash line represents Eq. (5).

tools), created using MATLAB R2022a. The HbA1c estimates along with their 95% prediction intervals can be calculated for a given CGM trace.

3.1 Coefficient estimates for the direct model

The paired t-test was performed using the CGM traces of the complete CGM-dataset between the experimental HbA1c values and the corresponding Nathan HbA1c estimates calculated using Eqs (1). and (5) generated a p-value<0.001. Similarly, a paired t-test with data-sufficient CGM traces from the CGM-dataset also generated a p-value of<0.001. Considering $\alpha = 0.05$, the Nathan model-estimated HbA1c values, both for data-sufficient and data-insufficient CGM traces, were significantly different from the corresponding experimentally measured HbA1c values for the Indian population.

This led us to construct a direct model for estimating HbA1c levels from aISF. We performed a linear regression analysis to establish a relationship between aISF and HbA1c using the data-sufficient CGM traces of the training CGM dataset. We obtained an estimate of the coefficient β_0 of the model, Eq. (7), $\hat{\beta}_0 = 16.73\ \ mmol/mol$, with a 95% confidence interval of [9.39 mmol/mol, 24.07 mmol/mol] and an estimate for β_1, $\hat{\beta}_1 = 0.319\ \ mmol\ \ dL/(molmg)$ with a 95% confidence interval of [0.274 mmol dL/(molmg), 0.363 mmol dL/(molmg)]. The analysis yielded Eq. (10), with an $R^2 = 0.726$ and a *p-value* <0.01. Therefore, the direct model, Eq. (7) with the estimates $\hat{\beta}_0$ and $\hat{\beta}_1$is given by

$$HbA1c_{mmol/mol} = 0.319 \times aISF_{mg/dL} + 16.73, \qquad (10)$$

where $aISF_{mg/dL}$ represents the aISF in mg/dL, and $HbA1c_{mmol/mol}$ represents HbA1c in mmol/mol. Figure 1, shows Eq. (10) as the black dashed line along with the 95% confidence interval for $HbA1c_{mmol/mol}$, corresponding to any $aISF_{mg/dL}$ calculated from a given CGM trace. The formulae for obtaining the 95% confidence and prediction interval for any HbA1c estimate are provided in the Supplementary Material. The 95% prediction interval width calculated for the HbA1c estimates was on the order of 48.50 mmol/mol.

3.2 Coefficient estimates of the adapted Nathan model

We constructed a direct model, given by Eq. (10) to estimate HbA1c from the aISF for any given CGM trace. However, we suspect that the model described in Eq. (8), where HbA1c was estimated from a

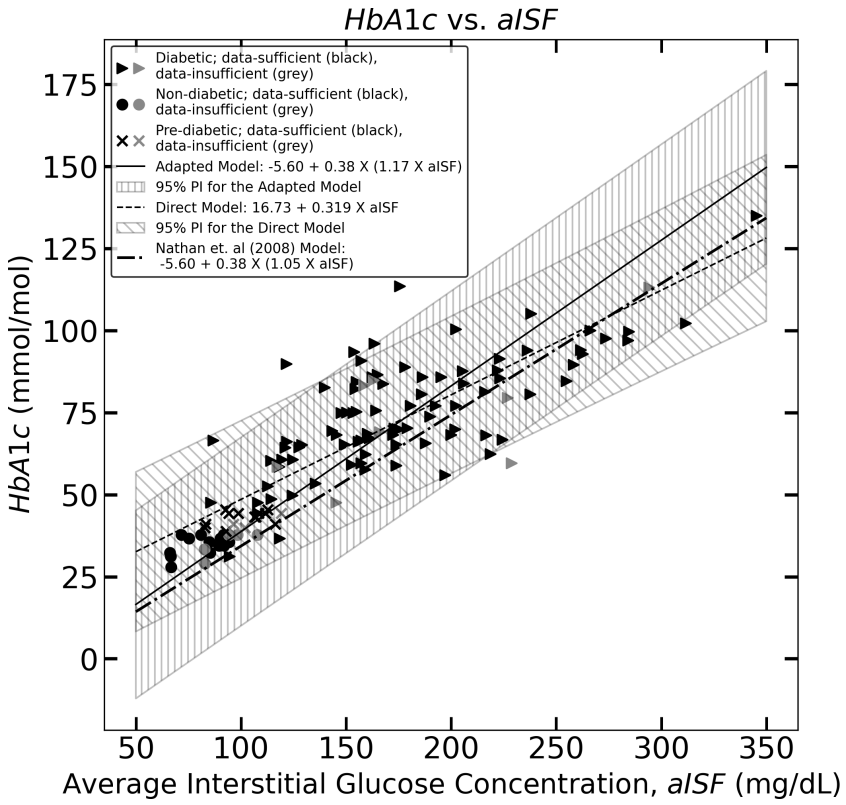

FIGURE 2
The figure represents the experimentally measured HbA1c and aISF values (calculated as described in *Section 2.3*) of the CGM dataset. The pre-diabetic participants are represented by crosses, diabetic participants are represented by solid triangles and, non-diabetic participants are represented by solid circles. The scatter points representing participants with a data-sufficient CGM trace [according to Danne et al. (10)] are colored black, whereas the participants with a data-insufficient CGM trace are colored gray. The solid black line and the corresponding hatched region represent Eq. (11), which the 95% prediction interval, and the dashed line, along with its corresponding hatched region, represents Eq. (10) and its corresponding 95% prediction interval. The dotted dash line represents Eq. (5).

scaled aISF value using Eq. (2) would provide better estimates of HbA1c levels. The OLS solution for linear regression analysis using Eq. (9), while keeping the intercept zero, would provide us with an estimate of the scaling factor for obtaining aBG from aISF.

The estimation of the scaling factor in Eq. (9), $\hat{\omega}$, obtained using the `LinearRegression` function of the `scykit-learn` package with the intercept set to zero, on the data-sufficient training CGM-dataset, is $\hat{\omega} = 1.17$, with a 95% confidence interval (1.12, 1.22). The analysis yielded an $R^2 = 0.595$ and, a *p-value*<0.01. The estimate, $\hat{\omega}$, obtained using the analytical solution for obtaining the OLS estimate of ω from Eq. (8) yields an identical result. The equation for obtaining HbA1c estimates using the adapted Nathan model is represented by Eq. (11) below

$$HbA1c_{mmol/dL} = 0.38 \times (1.17 \times aISF_{mg/dL}) - 5.60, \qquad (11)$$

where $aISF_{mg/dL}$ represents the aISF in mg/dL, and $HbA1c_{mmol/mol}$ represents HbA1c in mmol/mol. Figure 1 shows Eq. (11) as a solid black line, along with the 95% confidence interval for $HbA1c_{mmol/mol}$ corresponding to any $aISF_{mg/dL}$. The formulae for obtaining the confidence and prediction intervals for any HbA1c value estimated using Eq. (11) are provided in the Supplementary Material. The 95% prediction interval width calculated for the HbA1c estimates are in the order of 57.87 mmol/mol.

3.3 Validation of the direct and adapted models

In *Sections 3.1 and 3.2*, we constructed two models for estimating HbA1c from the aISF calculated from any given CGM trace. We then constructed 95% prediction intervals for HbA1c estimates calculated using the models. The formulae for constructing the prediction interval corresponding to any estimated HbA1c level for both models are provided in the Supplementary Material.

A paired t-test performed between the experimentally measured HbA1c from the test CGM-dataset and the HbA1c estimates obtained from their corresponding CGM trace using the direct model generates a p-value of 0.643 and using the adapted Nathan model it generates a p-value of 0.715. This indicates that at the population level, the HbA1c estimates for an independent sample of CGM traces were statistically ($\alpha = 0.05$) indistinguishable from the experimental HbA1c. The 5-fold cross validation root mean squared error (RMSE) for the HbA1c estimates obtained using the direct model on the training CGM-datasets is 11.9 mmol/mol and for the estimates obtained using the adapted Nathan model it is 14.3 mmol/mol. The 95% confidence interval for the direct model was on the order of 9.48 mmol/mol and for the adapted Nathan model the 95% confidence interval was on the order of 7.70 mmol/mol.

A t-test performed using the Nathan model HbA1c estimates for the test CGM-dataset generated a p-value<0.01, indicating that at the population level, the Nathan model HbA1c estimates were statistically different from the experimental value (taking $\alpha = 0.05$).

4 Discussion

The development of CGM technology provides a large number of glucose concentration measurements. This provides a great opportunity to study the glucose dynamics and glycemic state of an individual. The current CGM devices, however, only provide ISF measurements, while traditionally it has been the norm to study glucose dynamics with BG measurements. Therefore, a large bulk of our understanding of glucose dynamics, glycemic states, and metabolic diseases, such as diabetes, is based on BG values. To use the CGM traces provided by these devices, it is important to reliably estimate the corresponding BG, especially HbA1c, from any given CGM trace. Typically, regression estimates are used to relate the average glucose level from the CGM to HbA1c. Bailey et al. (26) showed that a 7-day CGM trace provides a satisfactory estimate of GMI or estimated HbA1c comparable to estimates obtained from 14-day CGM.

The analyses conducted by Nathan et al. (9), Hu et al. (20), Bergenstal et al. (15), and Xu et al. (21) used large CGM trace datasets and their corresponding HbA1c values. While these are important estimates, it is equally important to ask if these models continue to be applicable to different populations. Indeed, it has been shown that regression equations vary with ethnicity; for instance, Hu et al. (20) and Oriot and Hermans (19) cite over- or underestimation relative to the Nathan model. To the best of our knowledge, no major study has validated these estimates in an Indian population.

We used a dataset of 128 CGM traces collected from an Indian population, sorted to use only data-sufficient CGM traces to construct models suitable for this population. We showed that the standard method of estimating HbA1c using Nathan's equation does not provide a statistically reliable estimate. Therefore, we suggest two new methods for estimating HbA1c that are better suited to the Indian population. The direct method for estimating HbA1c from ISF values, as described in *Section 2.3*, provides an estimate along with a 95% confidence and prediction interval for the estimate given an aISF value. The mean HbA1c estimates provided by the direct model were statistically indistinguishable from the mean experimental HbA1c measurement for the data-sufficient test CGM-dataset. Furthermore, we suspected that the inclusion of an improved method of estimating BG from ISF could improve the estimates provided by Eq. (5). Therefore, in *Section 3.2*, we constructed a new linear model for estimating BG from ISF using linear regression. The mean HbA1c estimates provided by this method were indistinguishable from the mean experimentally measured HbA1c values of the data-sufficient test CGM-dataset. However, the 95% prediction interval was large. We showed that the mean HbA1c estimates obtained using these two models, the direct model, and the adapted Nathan model, were not significantly different from the mean experimental HbA1c. However, the mean experimental HbA1c level was significantly different from the mean estimates provided by the Nathan model at the population level.

From the analysis of the model performance on the test CGM-dataset, we can conclude that although our models for estimating HbA1c provide a wide 95% prediction interval, which includes the HbA1c estimates obtained using the Nathan model, the mean HbA1c estimates provided by our models at the population level are statistically indistinguishable from the mean experimental HbA1c values, unlike the HbA1c estimates obtained using the Nathan model. This shows that the direct and adapted Nathan models can provide a more reliable HbA1c estimate than the Nathan model can. Such estimates are valuable at the population level, as in clinical epidemiological studies.

The strength of thsi study is that it is the first investigation of its kind in an Indian population. Furthermore, we outline that there are subtleties in the estimation procedure; depending on the question of interest, these lead to alternate formulations of the problem. We applied both approaches to the same dataset, which made it easier to compare the two methods. The weakness of our study is that the dataset was limited, and the results should be seen as prospective. We hope that future studies will test these hypotheses with greater statistical power.

Because the computed prediction intervals are rather wide, we claim that none of the models described above are suitable for estimating HbA1c in individuals with (clinical) reliability. This raises a deeper question: Can individual HbA1c estimates be obtained using only aISF values calculated from a CGM trace? Or does it require knowledge of some additional information regarding the individual not contained in their CGM? That is, it remains an open question although ISF and BG are highly correlated with HbA1c, why are the models unable to provide tighter estimates of HbA1c from aISF or aBG values alone?

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study protocol for the Pune-2021 dataset was approved by the Institutional Ethical Committee (IEC) of Savitribai Phule Pune University, Pune, India (SPPU/IEC/2020/102). The study protocol for the Joshi-2018 dataset was approved by the IEC of Maharashtra Medical Research Society (ECR/311/Inst/MH/2013/RR-19; Dated 14 March 2023). Informed consent from all participants was collected prior to their participation in the studies. The data analysis was reviewed and approved by the Institutional Human Ethics Committee (IHEC) of IISER Pune (IHEC/Admin/2021/015).

Author contributions

SM: Software, Visualization, Writing – original draft, Methodology. SK: Data curation, Writing – review & editing, Investigation. SD: Data curation, Writing – review & editing, Investigation. KS: Data curation, Writing – review & editing, Investigation. SG: Data curation, Funding

acquisition, Project administration, Writing – review & editing, Conceptualization, Investigation, Supervision. PG: Supervision, Writing – original draft, Writing – review & editing, Methodology, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1264072/full#supplementary-material

References

1. Gabbay KH, Hasty K, Breslow JL, Ellison RC, Bunn HF, Gallop PM. Glycosylated hemoglobins and long-term blood glucose control in diabetes mellitus. *J Clin Endocrinol Metab* (1977) 44:859–64. doi: 10.1210/jcem-44-5-859

2. Santiago JV, Davis J, Fisher F. Hemoglobin a1c levels in a diabetes detection program. *J Clin Endocrinol Metab* (1978) 47:578–80. doi: 10.1210/jcem-47-3-578

3. Clarke J, Passa P, Canivet J. Hba1c: need of its dosage in diabetics (author's transl). *La Nouvelle Presse Medicale* (1979) 8:513–7.

4. Lecomte M, Schoos R, Schoos-Barbette S, Luyckx A, Lambotte C, Lefebvre P. Hemoglobin a1c and diabetes control (author's transl). *Diabete Metabolisme* (1979) 5:57–61.

5. Distiller LA, Zail SS. The use of glycosylated haemoglobin measurements in the control of the diabetic patient. *South Afr Med J* (1979) 55:335–7.

6. Davis J, Mcdonald JM. Jarett L. A high-performance liquid chromatography method for hemoglobin a1c. *Diabetes* (1978) 27:102–7. doi: 10.2337/diab.27.2.102

7. Sikaris K. The correlation of hemoglobin a1c to blood glucose. *J Diabetes Sci Technol* (2009) 3:429–38. doi: 10.1177/193229680900300305

8. Mazze R. The future of self-monitored blood glucose: mean blood glucose versus glycosylated hemoglobin. *Diabetes Technol Ther* (2008) 10:S–93. doi: 10.1089/dia.2008.0006

9. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ, et al. Translating the a1c assay into estimated average glucose values. *Diabetes Care* (2008) 31:1473–8. doi: 10.2337/dc08-0545

10. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care* (2017) 40:1631–40. doi: 10.2337/dc17-1600

11. Kovatchev BP, Flacke F, Sieber J, Breton MD. Accuracy and robustness of dynamical tracking of average glycemia (a1c) to provide real-time estimation of hemoglobin a1c using routine self-monitored blood glucose data. *Diabetes Technol Ther* (2014) 16:303–9. doi: 10.1089/dia.2013.0224

12. Kovatchev BP, Breton MD. Hemoglobin a1c and self-monitored average glucose: validation of the dynamical tracking ea1c algorithm in type 1 diabetes. *J Diabetes Sci Technol* (2016) 10:330–5. doi: 10.1177/1932296815608870

13. Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM. The fallacy of average: how using hba1c alone to assess glycemic control can be misleading. *Diabetes Care* (2017) 40:994–9. doi: 10.2337/dc17-0636

14. Fan W, Zheng H, Wei N, Nathan DM. Estimating hba1c from timed self-monitored blood glucose values. *Diabetes Res Clin Pract* (2018) 141:56–61. doi: 10.1016/j.diabres.2018.04.023

15. Bergenstal RM, Beck RW, Close KL, Grunberger G, Sacks DB, Kowalski A, et al. Glucose management indicator (gmi): a new term for estimating a1c from continuous glucose monitoring. *Diabetes Care* (2018) 41:2275–80. doi: 10.2337/dc18-1581

16. Leelarathna L, Beck RW, Bergenstal RM, Thabit H, Hovorka R. Glucose management indicator (gmi): insights and validation using guardian 3 and navigator 2 sensor data. *Diabetes Care* (2019) 42:e60–1. doi: 10.2337/dc18-2479

17. Perlman JE, Gooley TA, McNulty B, Meyers J, Hirsch IB. Hba1c and glucose management indicator discordance: a real-world analysis. *Diabetes Technol Ther* (2021) 23:253–8. doi: 10.1089/dia.2020.0501

18. Shah VN, Vigers T, Pyle L, Calhoun P, Bergenstal RM. Discordance between glucose management indicator and glycated hemoglobin in people without diabetes. *Diabetes Technol Ther* (2023) 25:324–8. doi: 10.1089/dia.2022.0544

19. Oriot P, Hermans MP. "mind the gap please": estimated vs. measured a1c from continuous measurement of interstitial glucose over a 3-month period in patients with type 1 diabetes. *Acta Clinica Belgica* (2020) 75:109–15. doi: 10.1080/17843286.2018.1561780

20. Hu Y, Shen Y, Yan R, Li F, Ding B, Wang H, et al. Relationship between estimated glycosylated hemoglobin using flash glucose monitoring and actual measured glycosylated hemoglobin in a chinese population. *Diabetes Ther* (2020) 11:2019–27. doi: 10.1007/s13300-020-00879-x

21. Xu Y, Dunn TC, Ajjan RA. A kinetic model for glucose levels and hemoglobin a1c provides a novel tool for individualized diabetes management. *J Diabetes Sci Technol* (2021) 15:294–302. doi: 10.1177/1932296819897613

22. Xu Y, Bergenstal RM, Dunn TC, Ajjan RA. Addressing shortfalls of laboratory hba1c using a model that incorporates red cell lifespan. *Elife* (2021) 10:e69456. doi: 10.7554/eLife.69456

23. Harris CR, Millman KJ, van der Walt SJ, Gommers R, Virtanen P, Cournapeau D, et al. Array programming with numPy. *Nature* (2020) 585:357–62. doi: 10.1038/s41586-020-2649-2

24. Virtanen P, Gommers R, Oliphant TE, Haberland M, Reddy T, Cournapeau D, et al. SciPy 1.0: fundamental algorithms for scientific computing in python. *Nat Methods* (2020) 17:261–72. doi: 10.1038/s41592-019-0686-2

25. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O, et al. Scikit-learn: machine learning in python. *J Mach Learn Res* (2011) 12:2825–30. doi: 10.48550/arXiv.1201.0490

26. Bailey R, Calhoun P, Bergenstal RM, Beck RW. Assessment of the glucose management indicator using different sampling durations. *Diabetes Technol Ther* (2023) 25:148–50. doi: 10.1089/dia.2022.0284

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Comprehensive management of children and adolescents with type 1 diabetes mellitus through personalized physical exercise and education using an mHealth system: The Diactive-1 study protocol

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Introduction: The use of new technologies presents an opportunity to promote physical activity, especially among young people with type 1 diabetes (T1DM), who tend to be less active compared to their healthy counterparts. The aim of this study is to investigate the impact of a personalized resistance exercise program, facilitated by the Diactive-1 App, on insulin requirements among children and adolescents diagnosed with T1DM.

Methods and analysis: A minimum of 52 children and adolescents aged 8-18 years, who were diagnosed with T1DM at least 6 months ago, will be randomly assigned to either a group engaging in an individualized resistance exercise program at least 3 times per week over a 24-week period or a waiting-list control group. The primary outcome will be the daily insulin dose requirement. The secondary outcomes will include glycemic control, cardiometabolic profile, body composition, vascular function, physical fitness, 24-hour movement behaviors, diet, and psychological parameters. The usability of the app will also be assessed.

Ethics and dissemination: Ethical approval to conduct this study has been granted by the University Hospital of Navarra Research Board (PI_2020/140). Parents or legal guardians of minors participating in the study will provide written consent, while children and adolescents will sign an assent form to indicate their

voluntary agreement. The trial's main findings will be shared through conference presentations, peer-reviewed publications, and communication directly with participating families. This study aims to offer valuable insights into the holistic management of children and adolescents with T1DM by utilizing personalized exercise interventions through an mHealth system.

Trial registration: NCT06048757

KEYWORDS

insulin-dependent diabetes mellitus, physical exercise, resistance training, mobile-health, pediatrics

1 Introduction

Type 1 diabetes mellitus (T1DM) imposes a substantial burden on children and adolescents worldwide. According to estimates from the International Diabetes Federation (IDF), 1.2 million individuals under age 20 have T1DM globally (1). Not maintaining optimal glycemic control is associated with chronic health issues later in life. However, achieving and sustaining appropriate glycemic control poses a significant challenge for young individuals with T1DM, particularly during the transition from childhood to adulthood. Inadequate glycemic control in T1DM patients can lead to long-term complications including cognitive dysfunction (2), cardiovascular disease (3), diabetic neuropathy (4), diabetic retinopathy (5), chronic kidney disease (6), diabetic foot ulcers (7), and dry skin (8). While technology has enhanced self-management capacity (9), novel strategies that are accessible and cost-effective are urgently needed to improve glycemic control in young T1DM patients.

The American Diabetes Association (ADA) recommends that individuals under 20 years old with diabetes engage in 60 minutes of moderate to vigorous aerobic physical activity daily. This should be paired with vigorous muscle-strengthening and bone-strengthening activities at least three days per week (10). However, children and adolescents with T1DM are less active, more sedentary, and less fit than their healthy counterparts (11). A recent meta-analysis showed that exercise training has a moderate effect on reducing glycated hemoglobin (HbA1c) and insulin dose per day in youths with T1DM (12). Specifically, resistance training seems to be one of the most effective strategies for improving glycemic control among children and adolescents with T1DM (13). In adults, resistance exercise has proven efficacy in minimizing exercise-induced hypoglycemia risk in T1DM (14, 15). However, lack of awareness and fear of hypoglycemia can discourage young people from participating in physical activities, especially resistance exercise (16). This highlights the need for new technologies to support the T1DM population in managing hypoglycemia situations and promoting exercise.

In 2023, 6.92 billion people worldwide own a smartphone, representing 86.29% of the global population (17). Fitness apps have gained popularity among smartphone users, with some proving highly effective for increasing physical fitness (18) and physical activity levels (19). While some apps are designed for the general population and may present challenges for those with health conditions, there are also apps that are specifically helpful for managing certain conditions like T1DM. For instance, diabetes apps have shown benefits for glycemic control (20), reducing HbA1c (21), and improving health-related quality of life (HRQL) (22).

Evidence suggests that mHealth interventions can moderately reduce physical inactivity in children and adolescents (23). Specifically, a recent narrative review by Kordonouri et al. (24), explored smartphone apps for exercise management in T1DM, primarily in adults. Although emerging apps offer exercise support, none exclusively address resistance training for children and adolescents with T1DM. This gap presents a significant opportunity to improve disease management in this population. Specialized apps tailored to the unique needs of young T1DM patients could empower them to take control of their health. Such apps should consider appropriate exercise types and intensities based on fitness level. Integration with continuous glucose monitoring (CGM) systems could enable real-time feedback to prevent hypo/hyperglycemia. By promoting physical activity, enhancing fitness, and supporting effective diabetes management, these customized apps have the potential to provide significant benefits to children and adolescents with T1DM (25).

Based on prior research, our primary hypothesis posits that implementing the Diactive-1 App intervention over 24 weeks will result in a reduced daily insulin dose requirement, specifically in terms of insulin dose per kilogram of body weight, among children and adolescents with T1DM compared to standard care.

Our main aim is to compare the effects of a 24-week Diactive-1 App intervention versus standard care on insulin dose requirements in children and adolescents with T1DM. Our secondary aims are to evaluate the impact of the Diactive-1 App intervention on glycemic control, cardiometabolic profile, body composition, vascular function, physical fitness, 24-hour movement behaviors, dietary habits, and psychological well-being in comparison to the control group receiving standard care, over a 24-week intervention period.

2 Methods and analysis

2.1 Trial design

The study will be a randomized controlled single-blind parallel group study, conducted at a single center, and registered in the Clinical Trials Registry (NCT06048757). The protocol includes all elements from the Clinicaltrials.gov registry platform. This protocol is developed in accordance with the SPIRIT guidelines for randomized controlled trials (RCTs) (26).

2.2 Study setting

The Pediatric Endocrinology Unit at the University Hospital of Navarra, in collaboration with Navarrabiomed, located in Pamplona, Spain, is currently conducting this pragmatic trial. For additional information, please refer to the Clinical Trials Registry: NCT06048757.

2.3 Eligibility criteria

Children and adolescents of both sexes, aged 8-18 years diagnosed with T1DM, will be recruited as participants from the Pediatric Endocrinology Unit at University Hospital of Navarra (Pamplona, Spain). Participants will be eligible to be part of the study if they meet the following inclusion criteria: a willingness to participate in the intervention, proficiency in the Spanish language, and a minimum of six months having passed since the diagnosis. The exclusion criteria include any comorbidity that limits the capacity to participate in physical activity or an inadequate understanding of the Spanish language. Additionally, participants will be excluded if they lack an internet connection, do not own a smartphone or tablet, or do not have the ability to use the application.

2.4 The intervention – the Diactive-1 App

The Diactive-1 Study is a 24 weeks smartphone intervention with the aim of improving daily insulin dose requirements, glucose control management, adherence to resistance training, and compliance with PA guidelines recommendations (10, 27, 28) for children and adolescents with T1DM. The Diactive-1 App has been developed to be compatible with both IOS and Android smartphones. A screenshot of the Diactive-1 App is displayed in Figure 1.

2.5 Development of the intervention

The Diactive-1 App was developed by a team of researchers with expertise in PA and T1DM. Intervention includes evidence-based recommendations at management of glucose control and physical exercise for children and adolescent with T1DM (10, 27, 28).

2.6 Content and use of the intervention

The Diactive-1 App consists of an automated program designed to offer evidence-based guidance for creating exercise training sessions (10, 27, 28). The sessions are tailored based on the individual's physical fitness level (assessed beforehand), glucose levels, and glucose trend arrow at the moment. Furthermore, the Diactive-1 App can be integrated with CGM Freestyle 2 devices to display glucose levels and trend arrows prior to the commencement

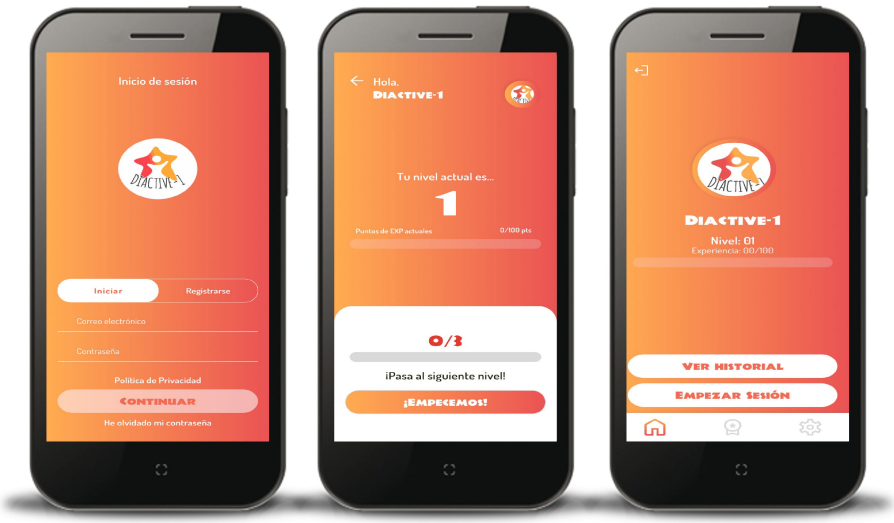

FIGURE 1
Screenshots of the Diactive-1 App for children and adolescents with type 1 diabetes.

10.3389/fendo.2024.1354734

and at the end of the session. If patients use a different device for CGM (e.g., MiniMedTM 780G, Medtronic), the application will ask them to manually enter their glucose levels and trends before and after the exercise session.

Educational glucose monitoring is a feature included in the Diactive-1 App. This feature presents messages after users input their glucose levels and trend arrow. Depending on these two parameters and, in special cases, patients may also be prompted to input their ketone levels. In accordance with the position statement from the European Association for the Study of Diabetes (EASD) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) (27), the Diactive-1 app sends advisory messages to the patient based on their present condition. For instance, if their blood glucose exceeds 330 mg/dL regardless of ketone levels, the app recommends refraining from exercise, suggests correcting glucose levels with insulin, and proposes attempting exercise again after a 30-minute interval.

The Diactive-1 App incorporates a gamification concept. Each patient starts at player level 1, which increases based on the number of training sessions completed. As previously mentioned, each patient must complete three sessions per week (mandatory) with a maximum of seven sessions (including the three mandatory ones). Completing each of the mandatory sessions' rewards participants with 20 experience points. Additional sessions beyond the mandatory three yield 30 experience points each. Upon accumulating 100 experience points, they advance to the next level. To continue leveling up, they must accumulate another 100 experience points. Furthermore, the Diactive-1 App includes a ranking system that positions patients based on their player levels. This feature aims to encourage healthy competition and promote patient adherence to using the Diactive-1 App.

The interventions offered by the Diactive-1 App can take place at locations chosen by the participants, such as their homes, parks, or schools. A face-to-face session will be conducted before commencing the intervention to ensure that participants are familiar with the fundamental movements, thus reducing the risk of potential muscle injuries. Each training session is designed to last between 13 and 33 minutes. The level of fitness—low, medium, or high—determines the number of exercises within the sessions: four exercises for those with low fitness and five for those with medium and high fitness levels. Reference values for handgrip strength in European children and adolescents aged 6 to 18 will be employed (29). Using the median percentile of the handgrip strength, individuals falling below the 20th percentile will be classified as having low fitness levels, those between the 21st and 79th percentiles will be considered to have moderate fitness levels, and those at or above the 80th percentile will be categorized as having high fitness levels, with consideration for their sex and age. The training sessions consist of three types: equipment-based training (utilizing resistance bands and an aqua ball, which will be provided to the participants before the intervention), equipment-free training (bodyweight exercises), and partner-assisted training. Participants will be guided through their workouts by a 3D Avatar displayed on their smartphone screen. This Avatar will show the exercises for the training session, offering visual cues for correct movements (Figure 2). Additionally, a background voice (narrator) will provide verbal instructions, including the start and end of each set, transitions to the other side (in the case of unilateral exercises), and designated rest periods.

The Diactive-1 App's training program will include performing 3 to 4 sets, each comprising 6 to 12 repetitions. When training with equipment, the weight level of the aquaball and the resistance color band will vary based on the participant's fitness level and age group: 8-12 for children and ≥13 for adolescents. However, training without equipment will follow the same prescribed regimen for both children and adolescents. Progression in weight level (aquaball) is calculated based on the average body weight of the longitudinal Diactive-1 project participants (approximately 60 kg). This progression is tailored to specific body segments (upper limb, lower limb, and core) and fitness levels. The exercises are

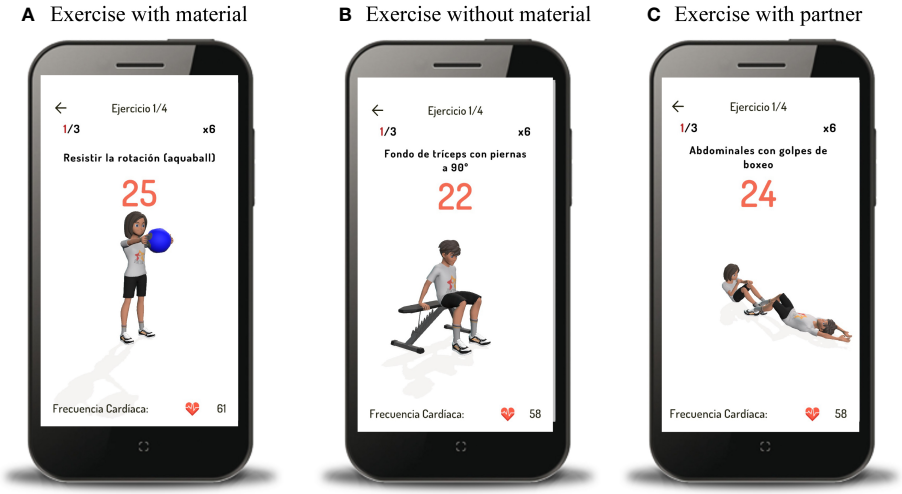

FIGURE 2
Example of guided exercises with material **(A)**, without material **(B)**, and with partner **(C)**.

categorized into three main muscle groups: upper body, lower body, and core. Examples of exercises include bench press, triceps press, squat, leg extensions, plank, and sit-ups. In exceptional cases, if the Diactive-1 App determines that performing resistance training would be counterproductive (for instance, when glucose levels range from 271 to 330 mg/dL with a trend arrow indicating an increase, diagonal increase, or to the right, and ketone levels are ≤ 1.5 mM before the exercise session), the session will exclusively consist of aerobic exercise. In such situations, the patient can return to the app and proceed with their strength training session later, provided their blood glucose levels allow it. Recovery periods between sets will range from 30 to 60 seconds, while recovery between exercises will last from 60 to 75 seconds. After completing five training sessions, the training load will increase. This can involve adding more repetitions, sets, kilograms of weight (if using an aquaball), or using a different color band (if using an elastic band). Users can access these options within the Diactive-1 App. Various progression examples are included in Supplementary Tables 1-10. After participating in the intervention for four and a half months, participants will transition from their current fitness level to the next tier (e.g., from low to medium or medium to high fitness), receiving new intensities and exercises accordingly. The overall program will span 24-weeks, equivalent to a minimum of 72 sessions.

The waiting-list control group will receive standard hospital care, and after 24 weeks of the Diactive-1 App intervention, they will be given access to the App and training material.

An overview of the general procedure is provided in Figure 3.

2.7 Intervention adherence measurement

An electronic monitoring system will be used to oversee participants' adherence to the training sessions. This will involve checking our database to verify the sessions completed by the participants. Additionally, we will employ the Polar Varity Sense device (Polar Electro, Kempele, Finland), which displays heart rate (HR) during training sessions, to facilitate verification. Throughout the intervention, the research team will maintain regular communication with participants through phone calls and messages to provide encouragement and support, with the aim of promoting participant retention. Moreover, participants will receive a monthly report detailing goal achievement summaries and their progress relative to other participants.

2.8 Outcomes

A summary of the variables analyzed in the Diactive-1 Study is presented in Table 1.

2.9 Primary outcome

The primary outcome measure is the daily insulin dosage requirement. Participants will maintain a diary for nine days, recording their carbohydrate intake and insulin doses. This diary will record information about insulin injections. Children and

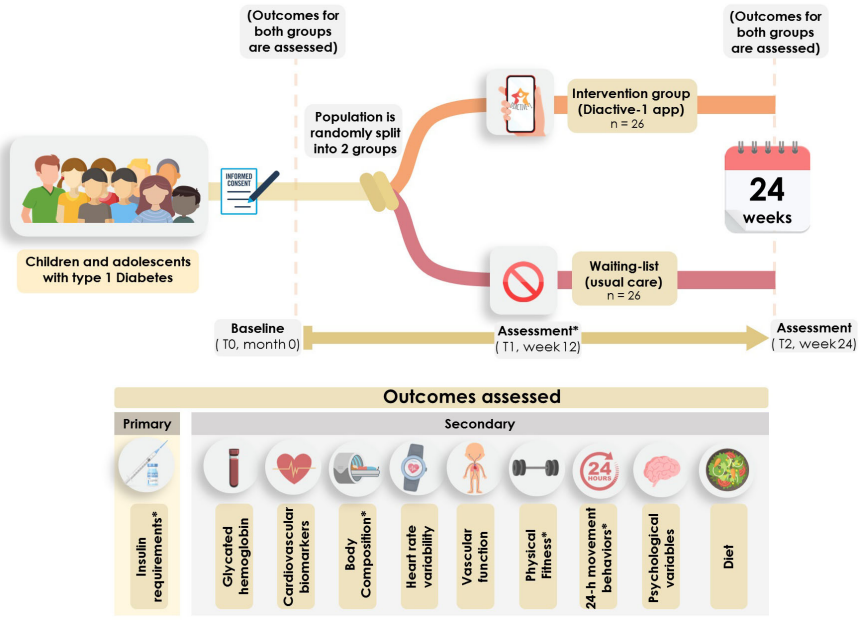

FIGURE 3
General procedure and timeline of the Diactive-1 study. * Insulin dosage assessments, body composition measurements, handgrip strength evaluations, and accelerometer-based physical activity assessments will be conducted at baseline, 12 weeks, and 24 weeks.

10.3389/fendo.2024.1354734

TABLE 1 Summary of the variables examined in the Diactive-1 App study.

Outcome	Measurement	Tool
Insulin dose requirements	Self-reported/Objective	*Ad hoc* diary/Insulin pump
Glycemic control	Objective	FreeStyle 2® or MiniMed™ 780G
Cardiovascular biomarkers	Objective	Central laboratory of the University Hospital of Navarra in Pamplona, Spain
Anthropometric	Objective	SECA 213 stadiometer and SECA electronic scale (Scale 869)
Sexual maturation	Objective	Tanner criteria
Peak height velocity	Objective	Moore's equations
Body composition	Objective	DXA Lunar iDXA, GE Healthcare
Heart rate variability	Objective	Polar V800
Vascular function	Objective	Vasera VS-2000 Vascular Screening System
Cardiorespiratory fitness	Objective	Cosmed K5 b2
Muscular fitness	Objective	Takei III Smedley Type Digital Dynamometer and EGYM Smart Strength machines
Physical activity, sedentary time, and sleep duration (accelerometers)	Objective	GENEActive triaxial accelerometer (ActivInsights)
Sleep quality and duration	Self-reported	PSQI
Sedentary behaviors (screen time)	Self-reported	YLSBQ
Self-reported physical activity	Self-reported	*Ad hoc* questionnaire
Self-reported physical fitness	Self-reported	IFIS
Inadvertent hypoglycemia	Self-reported	Clarke test
Sociodemographic information	Parent-reported	*Ad hoc* questionnaire.
Health-related Quality of life related to chronic diseases (T1DM)	Self-reported	Disabkids
Health-related Quality of life	Self-reported	KIDSCREEN-10
Subjective well-being	Self-reported	CUBE
Adherence to the Mediterranean diet	Self-reported	KIDMED
Food consumption	Self-reported	FFQ
Disordered eating	Self-reported	mSCOFF
Usability of the app	Self-reported	uMARS
Adherence with intervention (engagement)	Objective	Diactive-1 App

CUBE, Cuestionario Único de Bienestar Escolar; Disabkids, Questionnaire for Young people with diabetes; IFIS, The International Fitness Scale; KIDSCREEN, Screening for and Promotion of Health Related Quality of Life in Children and Adolescents; KIDMED, Mediterranean Diet Quality Index for Children and Teenagers; mSCOFF, Modified SCOFF questionnaire; uMARS, User Version of the Mobile Application Rating Scale; PSQI, The Pittsburgh Sleep Quality Index; YLSBQ, Youth Leisure-Time Sedentary Behavior Questionnaire.

adolescents who use an insulin pump will be assessed by obtaining objective information through downloading their data. The collected information will be used to calculate the insulin units per day per kilogram of body weight. A comparison will be made by providing participants with the same diary again, both at 12 weeks into the intervention and 9 days before the intervention concludes at week 24.

2.10 Secondary outcomes

2.10.1 Glycemic control

A significant portion of the sample will use either the CGM FreeStyle 2® Libre device (Abbott Diabetes Care) or the MiniMedTM 780G (Medtronic) during the intervention period. These devices measure interstitial glucose levels every 60 seconds and generate glucose values every 15 minutes, along with corresponding glucose curves. The collected data will be summarized in the ambulatory glucose profile report, including the following percentages of time-in-range (TR) (30): very high (glucose >250 mg/dL), high (181–250 mg/dL), target (70–180 mg/dL), low (54–69 mg/dL), and very low (<54 mg/dL). Additionally, the glucose coefficient of variation (CV) will be calculated (30) and the number of hypoglycemic events per day, mean glucose level during this period, and percentage of time the CGM sensor was active will be recorded. In accordance with ADA guidelines (10), we will consider the following metrics as meeting glycemic targets: HbA1c <7%; CV ≤36%; TR very high <5%; TR high <25%; TR target >70%; TR low <4%; and TR very low <1%.

2.11 Cardiovascular biomarkers

Venous blood samples will be collected from the antecubital vein between 7:00 and 9:00 AM after a 10–12 hour overnight fast. These samples will encompass measurements of fasting glucose, glycated hemoglobin, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, apolipoproteins, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). All assessments will be conducted both before and after the intervention at the central laboratory of the University Hospital of Navarra in Pamplona, Spain.

2.12 Anthropometric parameters

Standing height will be measured in bare feet using a SECA 213 stadiometer (Hamburg, Germany). Participants will be instructed to stand with their heels together and touching the base of the vertical measuring column, with their back straight and their head positioned in the Frankfurt horizontal plane (31). The standing height will be recorded to the nearest 0.1 cm.

Sitting height will be measured using the SECA 213 stadiometer and a wooden box.

Body weight will also be measured in bare feet and light clothing, using a SECA electronic scale (Scale 869), and recorded to the nearest 0.1 kg. Body mass index (BMI) will be calculated by dividing the weight in kilograms by the square of height in meters.

2.13 Sexual maturation and peak height velocity

Sexual maturation will be assessed by the Pediatric Endocrinology Unit at the University Hospital of Navarra (Pamplona, Spain), reporting the pubertal status on a scale of 1 to 5 in relation to secondary sexual characteristics. The assessment will be conducted using the Tanner and Whitehouse criteria (32). For girls, assessment will be based on the stage of breast development (Tanner A) and the distribution of pubic hair (Tanner B), while for boys, assessment will be based on the stage of genital development (penis size and testicular volume - Tanner A) and pubic hair distribution (Tanner B).

To obtain the peak height velocity (PHV), a common indicator of growth and development in children and adolescents (33), we will use anthropometric measures (weight, height, and seated height) as per Moore's equations (34). To calculate the years after PHV, we will subtract the age at PHV from the actual age. The difference in years between these values will be referred to as the maturity offset.

2.14 Body composition parameters

Total body fat, lean mass, subcutaneous and visceral adiposity, bone mineral content and density will be measured using dual-energy x-ray absorptiometry (DXA Lunar iDXA, GE Healthcare). Participants will be positioned in a supine position, with their arms slightly separated from the body and their feet and legs hip-width apart. This assessment will take place in weeks 12 and 24.

2.15 Heart rate variability

Heart rate variability (HRV), sympathetic and parasympathetic nervous system indices, as well as low and high frequencies, will be measured using the Polar V800, among other variability data. These measurements are related to autonomic function at the cardiac level and serve as indicators of autonomic dysfunction at this level. The HRV data will be analyzed using Kubios software (Kubios HRV Premium, ver. 3.5, Kubios Oy, Kuopio, Finland) (35).

2.16 Vascular function

Vascular function will be measured in the four extremities, the cardio-ankle vascular index, the brachial-ankle pulse wave velocity and the ankle-brachial index at rest using the Vasera VS-2000 Vascular Screening System (Fukuda Denshi, Japan).

2.17 Physical fitness components

Cardiorespiratory fitness will be assessed through a graded stress test using ergospirometry (Cosmed, K5 b2, Italy) on a cycle ergometer (Excalibur Sport 925909, Lode, The Netherlands). A standardized protocol for children and adolescents will be followed, including a warm-up phase, a systematic increase in resistance (10 or 20W per minute) until reaching maximum exertion, and then transitioning into the recovery phase. Peak oxygen consumption (VO_{2peak}) and metabolic equivalents (METs) will be determined.

Muscular fitness will be measured by handgrip strength using the Takei III Smedley Type Digital Dynamometer, which provides an estimate of an individual's overall strength. Then, EGYM Smart Strength machines (developed by eGym® GmbH in Munich, Germany) will be used to measure both maximal strength and muscular power in upper (chest and arms) and lower (legs and hip) extremity muscles. Handgrip strength assessment will take place in weeks 12 and 24.

2.18 Physical activity, sedentary time, and sleep duration by accelerometers

The volume and intensity of physical activity will be measured using a GENEActive triaxial accelerometer (ActivInsights) worn on the wrist of the nondominant hand. The accelerometers will be programmed to measure at a frequency of 87.5 Hz over a period of nine consecutive days (36). The research team will determine that sampling 86 times per second is sufficient to capture the majority of movements performed by patients. The accelerometer data will be extracted using GENEActiv PC Software (version 3.3) and processed and analyzed using the R package GGIR (37). Waking wear time for valid cases represented children and adolescents with at least seven days and at least 10 hours of waking wear time in a 24-hour period, including one weekend day, will be considered for analysis. Validated cut points will be used to determine different physical activity variables (38, 39): sedentary activity (for children: 0–56.3 mg; for adolescents: 0–50 mg), light physical activity (for children: 56.3–191.6 mg; for adolescents: 50–150 mg), moderate physical activity (for children: 191.6–695.8 mg; for adolescents: 150–500 mg), and vigorous physical activity (for children: >695.8 mg; for adolescents: >500 mg). Moderate-to-vigorous physical activity will be defined as activities for which at least 80% of 1 minute of time satisfies the moderate physical activity

threshold criteria (i.e., 191.6 mg for children and 150 mg for adolescents), in order to remove signals related to random wrist movement (40). The duration of sleep will also be determined. According to van Hees et al. (41) a sleep algorithm will be used to detect sleep and wake between bedtime and get uptime.

2.19 Sleep quality and duration

The Pittsburgh Sleep Quality Index (PSQI) will be used. It evaluates seven established aspects of sleep quality: subjective sleep quality, time taken to fall asleep, duration of sleep, sleep efficiency, sleep disturbances (such as nightmares, pain, or feeling too hot or cold), use of sleep medication, and daytime dysfunction (42).

2.20 Sedentary behaviors (screen time)

Sedentary behaviors will be assessed using the Youth Leisure-Time Sedentary Behavior Questionnaire (YLSBQ). Participants will report the time spent on TV, video games, computers, and mobile phones on both weekdays and weekends. To calculate the weighted average daily sedentary screen time for each behavior, we will use a 5:2 ratio. For instance, this calculation involves multiplying the daily TV viewing time on weekdays by five, the daily TV viewing time on weekend days by two, and then dividing the sum by seven (43). The total daily sedentary screen time will be determined by summing the durations of various daily screen time activities. Additionally, total screen time for both weekdays and weekends will be calculated.

2.21 Self-reported physical activity

The measurement of physical activity will be based on the following question: "Typically, how many days will you engage in physical activity for a total of at least 60 minutes?". Response options will range from 0 to 7 days per week, in 1-day increments. Physical activity will be defined as less than 60 minutes of physical activity per day on at least 7 days per week (44). The measurement of muscle-strengthening activities will be based on the following questions: "In the past 7 days, how many days did you perform exercises to enhance or tone your muscles, such as pushups, sit-ups, or weightlifting?" The response choices ranged from 0 to 7 days.

2.22 24-h hour movement guidelines

Participants who engaged in at least 60 minutes of moderate to vigorous physical activity per day and at least three days of muscle-strengthening activities, had less than two hours of recreational screen time per day, and achieved uninterrupted sleep for 9 to 11 hours per day (for children) or 8 to 10 hours per day (for adolescents) will be categorized as meeting the comprehensive 24-hour movement guidelines (45).

2.23 Self-reported physical fitness

The International Fitness Scale (IFIS) is designed for assessing self-reported physical fitness. This scale consists of five elements that employ a 5-point Likert scale to inquire about the children's general perception of their physical fitness, as well as their perception of their cardiorespiratory fitness, muscular fitness, speed-agility, and flexibility relative to their peers. The Likert scale provides choices ranging from very poor to poor, average, good, and very good physical fitness (46, 47).

2.24 Inadvertent hypoglycemia

The perception of hypoglycemia will be measured using the Clarke test, which consists of eight questions with different possible answers, A score greater than three reflects impaired awareness of hypoglycemia (48).

2.25 Sociodemographic information

Self-reported variables will be collected via a questionnaire administered to the participants' parent(s) or guardian(s). The questionnaire will cover participant details such as school, sex, age, birthplace, race/ethnicity, and language spoken at home. Additionally, it will include information about the parent(s) or guardian(s), including birthplace, age, education level, professional qualifications, employment status, job role, monthly income, household location, neighborhood, and birth weight.

2.26 Psychological assessments

To evaluate the HRQL in context of a chronic illness, the Spanish version of the "Questionnaire for Young people with Diabetes" (DISABKIDS) will be used (49). This questionnaire comprises 12 questions about how a patient has felt in the last four weeks that require answers on a 5-point Likert scale from 1 (never) to 5 (always).

We will also assess the HRQL using the Screening for and Promotion of HRQL in Children and Adolescents (KIDSCREEN-10) (50). This is a generic 10-item unidimensional instrument that focuses on the functional, mental, and social aspects of well-being in children and adolescents aged 8-18 years. The instrument will consist of the following items, starting with "thinking of last week, have you: 1) felt physically fit and well, 2) felt full of energy, 3) felt sad, 4) felt lonely, 5) had enough time for yourself, 6) been able to do the things you want in your free time, 7) felt treated fairly by your parent(s), 8) had fun with your friends, 9) got along well at school, 10) been able to pay attention at school?". For each item, participants will provide their responses on a five-point scale, ranging from "never" to "always" or from "not at all" to "extremely".

We will also assess subjective well-being using the "*Cuestionario Unico de Bienestar Escolar*" (CUBE) (51). The CUBE questionnaire consists of 5 items that assess various aspects of life satisfaction. All

these variables will be measured using a 10-point Likert scale ranging from 0 to 10 (0 = totally disagree, 10 = totally agree).

In terms of positive affect, the scale includes five items assessing emotions such as happiness, joy, cheerfulness, contentment, and fun. Additionally, there are five items evaluating negative affect, which encompasses feelings of humiliation, annoyance, irritation, bitterness, and sadness. The scale follows a bifactorial structure with five items per factor.

2.27 Adherence to the Mediterranean diet

We will use the Mediterranean Diet Quality Index for Children and Teenagers (KIDMED) index to assess adherence to the Mediterranean diet (52). The KIDMED index ranges from 0 to 12 and is based on a 16-question test. Unhealthy characteristics associated with the Mediterranean diet are assigned a score of -1 point, while healthy characteristics receive a score of +1 point.

The sum of all scores obtained from the KIDMED test will be utilized to classify individuals into three different levels: (a) optimal Mediterranean diet (>8 points), (b) improvement needed to align with Mediterranean dietary patterns (scores ranging from 4 to 7), and (c) very low diet quality (≤3 points).

2.28 Food consumption

Food frequency consumption will be assessed some food frequency questionnaires (FFQs) for the Spanish young population (53, 54). These FFQs includes several items groped into 17 food groups and were previously validated for its use among children (54) and adolescents (53) in a self-reported way. Subsequently, macronutrients, micronutrients, total energy consumption and other diet-related variables will be estimated. On the other hand, adherence to the healthy and sustainable dietary recommendations (e.g., fruits, vegetables, nuts, etc.) of the Ministry of Consumer Affairs of the Government of Spain will be determined (55).

2.29 Screening for eating disorders

To evaluate disordered eating, the modified SCOFF (mSCOFF) questionnaire will be used. This screening tool consists of five straightforward questions and can be conveniently incorporated into a routine check-up. It has proven to be reliable and valid in its assessment of eating disorders among children and adolescents with T1DM (56).

2.30 App usability

We will use the Spanish Version of the User Version of the Mobile Application Rating Scale (uMARS) (57), that will serve as a comprehensive and objective measure of app usability, consisting of 20 items. Each item is assessed using a 5-point scale, ranging from 1 (inadequate) to 5 (excellent). The uMARS will be structured into four subscales: engagement, functionality, aesthetics, and information quality. Subscale scores will be calculated as the average of their respective items, and the mean of these subscale scores will provide an overall app quality score.

2.31 Participant timeline

Eligible and consenting participants will complete a baseline assessment. The intervention group will then be allocated to a 24-weeks exercise training program using the Diactive-1 App. The control group will continue standard care. Outcomes will be assessed at baseline (T0), 12-week (T1) and after the 24-week intervention period (T2) (Table 2).

2.32 Sample size and recruitment

At least 52 children and adolescents of both sexes, aged between 8 and 18 years old, will be recruited from the Pediatric Endocrinology Unit at University Hospital of Navarra (Pamplona, Spain). This sample size was determined based on the results of a previous meta-analysis (12), which suggested an expected effect size on daily insulin dose requirements of 0.81. Using the G*Power software (58) and considering a power of 0.80, a significance level of 0.05 and accounting for a dropout of 15% (59, 60), a minimum of 26 children and adolescents per group is required.

2.33 Randomization, allocation concealment, and blinding

Participants meeting eligibility criteria will be randomly assigned to one of two groups in a 1:1 ratio using block randomization with a computer-generated schedule (Research Randomizer V.4). This will ensure equal group sizes. Randomization will continue until a predetermined number of participants are assigned. The allocation code will be kept confidential at Navarrabiomed until final analysis. To ensure blinding, each study group will be assigned an alpha-numeric code. Researchers will receive the code for their assigned group. Data analysts will not have access to the code until completing the coded intervention analysis. Due to the nature of the study, patients in the Diactive-1 App group will not be blinded.

2.34 Procedure for unblinding if needed.

This study is an unblinded, practice-level intervention.

2.35 Data collection methods and management

Researchers will be responsible for finalizing the study protocol and maintaining regular communication through

10.3389/fendo.2024.1354734

TABLE 2 Schedule depicting the enrollment and interventions for the Diactive-1 Study in accordance with the SPIRIT 2013 guidelines [26].

	STUDY PERIOD				
	Enrolment	Allocation		Post-allocation	
TIMEPOINT	$-t_1$	0	*Baseline (T0)*	T_1 *(12 weeks)*	T_2 *(24 weeks)*
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Diactive-1		X	◆———	———	———◆
Waiting-list control group		X	◆———	———	———◆
ASSESSMENTS:					
Daily insulin dosage requirement			X	X	X
Glycemic control (time in range, glucose coefficient of variation, number of hypoglycemic and hyperglycemic events)			X		X
Cardiovascular biomarkers (of fasting glucose, glycated hemoglobin, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, apolipoproteins, alanine aminotransferase, and aspartate aminotransferase)			X		X
Anthropometric parameters (body weight, standing and sitting height)			X		X
Sexual maturation and peak height velocity			X		X
Body composition parameters (total body fat, lean mass, subcutaneous and visceral adiposity, bone mineral content and density)			X	X	X
Heart rate variability			X		X
Vascular function			X		X
*Physical fitness components (cardiorespiratory and muscular fitness)**			X	X	X
*Physical activity, sedentary time, and sleep duration by accelerometers and questionnaires **			X	X	X
Sleep quality			X		X
Inadvertent hypoglycemia			X		X
Psychological assessments (Health-Related Quality of Life and subjective well-being)			X		X
Diet (adherence to the Mediterranean diet and food consumption)			X		X
Eating disorders			X		X
App usability					X

* It will only evaluate handgrip strength and accelerometer-based physical activity at 12-week mark.
T, represents a time-point.

phone calls, emails, and meetings. Weekly meetings will also be held for investigators and pediatric staff to discuss progress and updates.

The provided information will be documented in the database using individualized study codes assigned to each participant. This data will be securely stored on a computer that requires a password for access. Only the data manager, who operates independently and without conflicting interests, will have permission to access and retrieve the data. Due to the low level of risk associated with the study, there is no requirement for a Data Monitoring Committee. However, any significant modifications to the study protocol will be promptly communicated and updated on both the Clinical Trial Registry and the publication journal. Within a maximum timeframe of

three years from the collection of the end-line assessment at the 24-week mark, a fully anonymized dataset will be submitted to an appropriate data archive for sharing purposes.

2.36 Statistical methods

The quantitative variables will have their mean (M) and standard deviation (SD) provided, whereas the qualitative variables will include frequencies (n) and percentages (%). To assess data normality visual inspection of Q-Q plots and Shapiro-Wilk test will be used. For the homogeneity of variances, Levene's test will be used. Subsequently, for two-group comparisons, either Student's t-test or Mann–Whitney U test will be used based on adherence to the normality assumption.

Associations among qualitative variables will be examined using Pearson's chi-square (χ^2) test. For quantitative variables, the association will be tested using Spearman's rank correlation coefficient (ρ) or Pearson's correlation coefficient (r), depending on the assumption of normality. Initial analyses will establish frequency, range, variability, and distribution patterns of each variable, guiding the choice of the most appropriate statistical test for comparisons.

Given the experimental design of this RCT involving two data collections—baseline (t0 = 0 weeks) and post-intervention (t1, t2 = 12 and 24 weeks)—in both intervention and control groups, a comparative analysis will be conducted to identify intergroup differences. Multilevel mixed-effects regression models with repeated measures will be used to evaluate the intervention effect for each dependent variable. Multivariate analyses will account for autocorrelation between repeated measures.

For data analysis, both intention-to-treat (ITT) and per-protocol (PP) approaches will be employed. ITT measures the impact of intervention assignment, while PP analysis gauges the effect of intervention receipt. Statistical analyses will be performed using Stata software (version 17.0) (StataCorp, College Station, TX, USA), the statistical software R (Version 4.1.1) (R Core Team, Vienna, Austria), and RStudio (Version 2021.09.2) (Posit, Boston, MA, USA). Statistical significance will be determined by a p-value ≤ 0.05.

In situations where exercise sessions are missing, the analysis of outcomes will incorporate a dose-response approach. This approach will consider potential variations in outcome measurements based on the degree of exposure to the intervention. Additionally, depending on the nature of the missing data for both primary and secondary outcome measures, a range of techniques like multiple imputation, listwise deletion, or specific analytical methods will be employed. These measures aim to mitigate the impact of missing data, thereby minimizing any potential reduction in the generalizability of the collected data (61).

Subgroup analyses will be carried out to ascertain whether exercise is more or less effective in reducing secondary outcomes compared to the waiting-list control group. These subgroup analyses will adhere to the same methodology as the primary analysis, including both the primary analysis variables and their interaction with the experimental condition.

2.37 Data monitoring

The team will oversee and document any unfavorable incidents, ensuring that severe adverse events are promptly reported to the designated committee, following their recommendations. There won't be a requirement for a formal data monitoring committee in this particular RCT. The need for a data monitoring committee was not deemed necessary given the low-risk nature of this intervention.

2.38 Adverse event reporting and harms

Serious adverse events associated with the intervention will be reported to the Pediatric Endocrinology Unit at the ethics committees from the University Hospital of Navarra (Pamplona, Navarra).

2.39 Frequency and plans for auditing trial conduct

As detailed in this protocol, the team will conduct weekly monitoring of all RCT aspects. This encompasses ensuring adherence to the protocol, maintaining ethical and governance standards, overseeing database management, assessing outcomes, conducting research staff training, and regularly reporting on informed consent.

3 Discussion

This 24-week study aims to explore reductions in daily insulin dosage per kilogram of weight through the use of the Diactive-1 App in children and adolescents with T1DM. Including the assessment of daily insulin dosage in an intervention for this population is vital for various reasons. Firstly, it enables the monitoring of glycemic control, facilitating adjustments in insulin dosage to prevent hypo- and hyperglycemia (10). Secondly, the regular review and adjustment of the daily insulin dose are necessary, considering factors such as age, sex, BMI, pubertal status, and mode of therapy, to ensure optimal glucose control (62). Therefore, regular assessment and adjustment of the daily insulin dose are essential for personalized treatment (63).

Additionally, the study will assess glucose control, physical activity levels, body composition, app usability, and other health outcomes. Previous investigations have demonstrated that exercise training exerts a positive impact on metabolic and psychological health in children and adolescents with T1DM (12, 64). The

evidence also indicates that smartphone-based intervention may be a promising strategy to increase physical activity in children and adolescents (65). Therefore, while exercise interventions offer positive effects on physiological and biochemical outcomes, including glycemic control and body composition, personalized approaches to exercise promotion and meticulous management of insulin doses are crucial for this demographic (66). Since it has previously demonstrated promising results with just two weekly exercise sessions, the use of strength training in this population is also innovative (13).

The integration of technology is central to this study, demonstrating the potential of apps and digital platforms to transform diabetes care. This shift from traditional methods enables clinicians to explore integrating mobile apps into care. A recent meta-analysis in young patients with T1DM revealed a non-significant trend of reduced HbA1c levels from the beginning to the end of the study when using smartphone apps, and this reduction did not lead to an increase in hypoglycemia (67). While not statistically significant, this suggests apps could provide consistent monitoring and education to manage T1DM with minimal intrusion. The goals of the studies included in this meta-analysis are to improve glycemic control through diverse strategies, such as promoting glucose monitoring, facilitating data collection, coaching individuals with diabetes, providing guidance on healthy nutrition and medication dosing, and supporting lifestyle modifications. Building on this previous research and leveraging emerging tech for T1DM, the Diactive-1 Study is expected to provide a personalized, user-friendly non-pharmacological intervention for managing T1DM through the prescription of physical exercise. Additionally, the study incorporates education on insulin and carbohydrate management in the context of this exercise, enhancing the comprehensive approach to T1DM care.

The study's recognition of resistance exercise as a therapeutic strategy reflects a paradigm shift in managing T1DM (10). It underscores the potential for exercise to become an integral component of the overall treatment plan, extending beyond purely physical benefits. By encouraging clinicians to tailor exercise prescriptions to each patient's unique needs, age, capabilities, and glucose requirements, this approach elevates exercise to a personalized therapeutic strategy that can significantly enhance holistic T1DM management. The study also underscores the significance of tailored education for patients regarding glycemic control and exercise. This emphasis on empowering young patients can help cultivate self-confidence, enhance monitoring capabilities, and develop decision-making skills, enabling them to proactively manage their condition and daily activities. Educational strategies that prioritize self-management empower clinicians to effectively instill a sense of ownership and agency in children and adolescents.

In conclusion, smartphone apps for diabetes management have shown encouraging trends in improving glycemic control, indicating the potential of mobile apps as valuable tools for effective management. Aligning with this evolving landscape, the Diactive-1 study capitalizes on this trend through a groundbreaking mHealth App exploring potential benefits for various aspects of T1DM management, including personalized physical exercise. The insights from this study could play a pivotal role in shaping health promotion and prevention initiatives that leverage technology innovations to significantly benefit individuals navigating T1DM challenges.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by University Hospital of Navarra Research Board (PI_2020/140). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

IH: Formal analysis, Visualization, Writing – original draft. JM: Resources, Writing – review & editing. JL: Conceptualization, Formal analysis, Funding acquisition, Investigation, Writing – review & editing. NH: Project administration, Writing – review & editing. MC: Funding acquisition, Methodology, Resources, Writing – review & editing. SB: Funding acquisition, Resources, Writing – review & editing. ES: Supervision, Writing – review & editing. MI: Conceptualization, Investigation, Writing – review & editing. YE: Funding acquisition, Visualization, Writing – review & editing. AG-H Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1354734/full#supplementary-material

References

1. Magliano D, Boyko EJ. *IDF diabetes atlas. 10th edition*. Brussels: International Diabetes Federation (2021).

2. He J, Ryder AG, Li S, Liu W, Zhu X. Glycemic extremes are related to cognitive dysfunction in children with type 1 diabetes: A meta-analysis. *J Diabetes Investig* (2018) 9(6):1342–53. doi: 10.1111/jdi.12840

3. Nathan DM, Cleary PA, Backlund JC, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* (2005) 353(25):2643–53. doi: 10.1056/NEJMoa052187

4. Dyck PJ, Albers JW, Andersen H, Arezzo JC, Biessels GJ, Bril V, et al. Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity: Diabetic Polyneuropathies. *Diabetes Metab Res Rev* (2011) 27(7):620–8. doi: 10.1002/dmrr.1226

5. Klein BEK, Moss SE, Klein R. Effect of pregnancy on progression of diabetic retinopathy. *Diabetes Care* (1990) 13(1):34–40. doi: 10.2337/diacare.13.1.34

6. De Boer IH. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. *Arch Intern Med* (2011) 171(5):412. doi: 10.1001/archinternmed.2011.16

7. Boulton AJM, Armstrong DG, Albert SF, Frykberg RG, Hellman R, Kirkman MS, et al. Comprehensive foot examination and risk assessment. *Diabetes Care* (2008) 31 (8):1679–85. doi: 10.2337/dc08-9021

8. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJG, Armstrong DG, et al. 2012 Infectious diseases society of america clinical practice guideline for the diagnosis and treatment of diabetic foot infectionsa. *Clin Infect Dis* (2012) 54(12):e132–73. doi: 10.1093/cid/cis346

9. Miller KM, Foster NC, Beck RW, Bergenstal RM, DuBose SN, DiMeglio LA, et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D exchange clinic registry. *Diabetes Care* (2015) 38(6):971–8. doi: 10.2337/dc15-0078

10. American Diabetes Association Professional Practice Committee. 14. Children and adolescents: standards of care in diabetes—2024. *Diabetes Care* (2024) 47 (Supplement1):S258–81. doi: 10.2337/dc24-S014

11. Huerta-Uribe N, Hormazábal-Aguayo IA, Izquierdo M, García-Hermoso A. Youth with type 1 diabetes mellitus are more inactive and sedentary than apparently healthy peers: A systematic review and meta-analysis. *Diabetes Res Clin Pract* (2023) 200. doi: 10.1016/j.diabres.2023.110697

12. García-Hermoso A, Ezzatvar Y, Huerta-Uribe N, Alonso-Martínez AM, Chueca-Guindulain MJ, Berrade-Zubiri S, et al. Effects of exercise training on glycaemic control in youths with type 1 diabetes: A systematic review and meta-analysis of randomised controlled trials. *Eur J Sport Sci* (2022) 24:1–12. doi: 10.1080/17461391.2022.2086489

13. Petschnig R, Wagner T, Robubi A, Baron R. Effect of strength training on glycemic control and adiponectin in diabetic children. *Med Sci Sports Exerc.* (2020) 52 (10):2172–8. doi: 10.1249/MSS.0000000000002356

14. Yardley JE, Kenny GP, Perkins BA, Riddell MC, Balaa N, Malcolm J, et al. Resistance versus aerobic exercise: acute effects on glycemia in type 1 diabetes. *Diabetes Care* (2013) 36(3):537–42. doi: 10.2337/dc12-0963

15. Yardley JE, Kenny GP, Perkins BA, Riddell MC, Malcolm J, Boulay P, et al. Effects of performing resistance exercise before versus after aerobic exercise on glycemia in type 1 diabetes. *Diabetes Care* (2012) 35(4):669–75. doi: 10.2337/dc11-1844

16. Yardley JE, Sigal RJ. Exercise strategies for hypoglycemia prevention in individuals with type 1 diabetes. *Diabetes Spectr.* (2015) 28(1):32–8. doi: 10.2337/diaspect.28.1.32

17. bankmycell. *HOW MANY SMARTPHONES ARE IN THE WORLD?* Available at: https://www.bankmycell.com/blog/how-many-phones-are-in-the-world#157970https://www.bankmycell.com/blog/how-many-phones-are-in-the-world.

18. Stork MJ, Bell EG, Jung ME. Examining the impact of a mobile health app on functional movement and physical fitness: pilot pragmatic randomized controlled trial. *JMIR MHealth UHealth.* (2021) 9(5):e24076. doi: 10.2196/24076

19. Yoshimura E, Tajiri E, Michiwaki R, Matsumoto N, Hatamoto Y, Tanaka S. Long-term effects of the use of a step count–specific smartphone app on physical activity and weight loss: randomized controlled clinical trial. *JMIR MHealth UHealth.* (2022) 10(10):e35628. doi: 10.2196/35628

20. Chatzakis C, Floros D, Papagianni M, Tsiroukidou K, Kosta K, Vamvakis A, et al. The beneficial effect of the mobile application *euglyca* in children and adolescents with type 1 diabetes mellitus: A randomized controlled trial. *Diabetes Technol Ther* (2019) 21(11):627–34. doi: 10.1089/dia.2019.0170

21. Oliveira FMD, Calliari LEP, Feder CKR, Almeida MFOD, Pereira MV, Alves MTTDAF, et al. Efficacy of a glucose meter connected to a mobile app on glycemic control and adherence to self-care tasks in patients with T1DM and LADA: a parallel-group, open-label, clinical treatment trial. *Arch Endocrinol Metab* (2021). doi: 10.20945/2359-3997000000334

22. Holtz B, Mitchell KM, Holmstrom AJ, Cotten SR, Dunneback JK, Jimenez-Vega J, et al. An mHealth-based intervention for adolescents with type 1 diabetes and their parents: pilot feasibility and efficacy single-arm study. *JMIR MHealth UHealth.* (2021) 9 (9):e23916. doi: 10.2196/23916

23. Baumann H, Fiedler J, Wunsch K, Woll A, Wollesen B. mHealth interventions to reduce physical inactivity and sedentary behavior in children and adolescents: systematic review and meta-analysis of randomized controlled trials. *JMIR MHealth UHealth.* (2022) 10(5):e35920. doi: 10.2196/35920

24. Kordonouri O, Riddell MC. Use of apps for physical activity in type 1 diabetes: current status and requirements for future development. *Ther Adv Endocrinol Metab* (2019) 10:204201881983929. doi: 10.1177/2042018819839298

25. Huerta-Uribe N, Ramírez-Vélez R, Izquierdo M, García-Hermoso A. Association between physical activity, sedentary behavior and physical fitness and glycated hemoglobin in youth with type 1 diabetes: A systematic review and meta-analysis. *Sports Med* (2022). doi: 10.1007/s40279-022-01741-9

26. Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* (2013) 346:e7586–6. doi: 10.1136/bmj.e7586

27. Moser O, Riddell MC, Eckstein ML, Adolfsson P, Rabasa-Lhoret R, van den Boom L, et al. Glucose management for exercise using continuous glucose monitoring (CGM) and intermittently scanned CGM (isCGM) systems in type 1 diabetes: position statement of the European Association for the Study of Diabetes (EASD) and of the International Society for Pediatric and Adolescent Diabetes (ISPAD) endorsed by JDRF and supported by the American Diabetes Association (ADA). *Pediatr Diabetes.* (2020) 21(8):1375–93. doi: 10.1111/pedi.13105

28. Adolfsson P, Taplin CE, Zaharieva DP, Pemberton J, Davis EA, Riddell MC, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Exercise in children and adolescents with diabetes. *Pediatr Diabetes.* (2022) 23(8):1341–72. doi: 10.1111/pedi.13452

29. Ortega FB, Leskošek B, Gil-Cosano JJ, Mäestu J, Tomkinson GR, Ruiz JR, et al. European fitness landscape for children and adolescents: updated reference values, fitness maps and country rankings based on nearly 8 million test results from 34 countries gathered by the FitBack network. *Br J Sports Med* (2023) 57(5):299–310. doi: 10.1136/bjsports-2022-106176

30. Battelino T, Alexander CM, Amiel SA, Arreaza-Rubin G, Beck RW, Bergenstal RM, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. *Lancet Diabetes Endocrinol* (2023) 11(1):42–57. doi: 10.1016/S2213-8587(22)00319-9

31. NHANES. *National Health and Nutrition Examination Survey (NHANES) Anthropometry Procedures Manual.* Atlanta, Ga, USA: CDC, (2016). Available at:

https://wwwn.cdc.gov/nchs/data/nhanes/2015-2016/manuals/2016_Anthropometry_Procedures_Manual.pdf.

32. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. *Arch Dis Child.* (1976) 51 (3):170–9. doi: 10.1136/adc.51.3.170

33. Malina RM, Rogol AD, Cumming SP, Coelho E Silva MJ, Figueiredo AJ. Biological maturation of youth athletes: assessment and implications. *Br J Sports Med* (2015) 49(13):852–9. doi: 10.1136/bjsports-2015-094623

34. Moore SA, Mckay HA, Macdonald H, Nettlefold L, Baxter-Jones ADG, Cameron N, et al. Enhancing a somatic maturity prediction model. *Med Sci Sports Exerc.* (2015) 47(8):1755–64. doi: 10.1249/MSS.0000000000000588

35. Tarvainen MP, Niskanen JP, Lipponen JA, Ranta-aho PO, Karjalainen PA. Kubios HRV – Heart rate variability analysis software. *Comput Methods Programs Biomed* (2014) 113(1):210–20. doi: 10.1016/j.cmpb.2013.07.024

36. Esliger DW, Rowlands AV, Hurst TL, Catt M, Murray P, Eston RG. Validation of the GENEA accelerometer. *Med Sci Sports Exerc.* (2011) 43(6):1085–93. doi: 10.1249/MSS.0b013e31820513be

37. Migueles JH, Rowlands AV, Huber F, Sabia S, Van Hees VT. GGIR: A research community–driven open source R package for generating physical activity and sleep outcomes from multi-day raw accelerometer data. *J Meas Phys Behav* (2019) 2(3):188–96. doi: 10.1123/jmpb.2018-0063

38. Hildebrand M, Van Hees VT, Hansen BH, Ekelund U. Age group comparability of raw accelerometer output from wrist- and hip-worn monitors. *Med Sci Sports Exerc.* (2014) 46(9):1816–24. doi: 10.1249/MSS.0000000000000289

39. Sanders SG, Jimenez EY, Cole NH, Kuhlemeier A, McCauley GL, Lee Van Horn M, et al. Estimated physical activity in adolescents by wrist-worn geneactiv accelerometers. *J Phys Act Health* (2019) 16(9):792–8. doi: 10.1123/jpah.2018-0344

40. Menai M, Van Hees VT, Elbaz A, Kivimaki M, Singh-Manoux A, Sabia S. Accelerometer assessed moderate-to-vigorous physical activity and successful ageing: results from the Whitehall II study. *Sci Rep* (2017) 7(1):45772. doi: 10.1038/srep45772

41. Van Hees VT, Sabia S, Anderson KN, Denton SJ, Oliver J, Catt M, et al. A novel, open access method to assess sleep duration using a wrist-worn accelerometer. *PloS One* (2015) 10(11). doi: 10.1371/journal.pone.0142533

42. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Res* (1989) 28(2):193–213. doi: 10.1016/0165-1781(89)90047-4

43. Cabanas-Sánchez V, Martínez-Gómez D, Esteban-Cornejo I, Castro-Piñero J, Conde-Caveda J, Veiga ÓL. Reliability and validity of the youth leisure-time sedentary behavior questionnaire (YLSBQ). *J Sci Med Sport* (2018) 21(1):69–74. doi: 10.1016/j.jsams.2017.10.031

44. Prochaska JJ, Sallis JF, Long B. A physical activity screening measure for use with adolescents in primary care. *Arch Pediatr Adolesc Med* (2001) 155(5):554. doi: 10.1001/archpedi.155.5.554

45. Tremblay MS, Carson V, Chaput JP, Connor Gorber S, Dinh T, Duggan M, et al. Canadian 24-hour movement guidelines for children and youth: an integration of physical activity, sedentary behaviour, and sleep. *Appl Physiol Nutr Metab* (2016) 41(6 (6 Suppl. 3):S311–27. doi: 10.1139/apnm-2016-0151

46. Ortega FB, Ruiz JR, España-Romero V, Vicente-Rodriguez G, Martínez-Gómez D, Manios Y, et al. The International Fitness Scale (IFIS): usefulness of self-reported fitness in youth. *Int J Epidemiol.* (2011) 40(3):701–11. doi: 10.1093/ije/dyr039

47. Sánchez-López M, Martínez-Vizcaíno V, García-Hermoso A, Jiménez-Pavón D, Ortega FB. Construct validity and test-retest reliability of the International Fitness Scale (IFIS) in Spanish children aged 9-12 years. *Scand J Med Sci Sports.* (2015) 25(4):543–51. doi: 10.1111/sms.12267

48. Jansa M, Quirós C, Giménez M, Vidal M, Galindo M, Conget I. Análisis psicométrico de las versiones en lengua castellana y catalana de un cuestionario de percepción de la hipoglucemia. *Med Clínica.* (2015) 144(10):440–4. doi: 10.1016/j.medcli.2013.11.036

49. Alonso Rubio P, Bahíllo Curieses MP, Prieto Matos P, Bertholt Zuber ML, Martín Alonso MM, Murillo Vallés M, et al. Adaptación, fiabilidad y validez de los cuestionarios de calidad de vida relacionada con la salud: DISABKIDS, enfermedad crónica y específico de diabetes, en niños y adolescentes con diabetes mellitus tipo 1. *Endocrinol Diabetes Nutr* (2022) 70:S2530016422001549. doi: 10.1016/j.endien.2023.07.004

50. The European KIDSCREEN Group, Ravens-Sieberer U, Erhart M, Rajmil L, Herdman M, Auquier P, et al. Reliability, construct and criterion validity of the KIDSCREEN-10 score: a short measure for children and adolescents' well-being and health-related quality of life. *Qual Life Res* (2010) 19(10):1487–500. doi: 10.1007/s11136-010-9706-5

51. Miranda R, Oriol X, Amutio A, Ortúzar H. Adolescent bullying victimization and life satisfaction: can family and school adult support figures mitigate this effect? *Rev Psicodidáct Engl Ed* (2019) 24(1):39–45. doi: 10.1016/j.psicoe.2018.07.001

52. Serra-Majem L, Ribas L, Ngo J, Ortega RM, García A, Pérez-Rodrigo C, et al. Food, youth and the Mediterranean diet in Spain. Development of KIDMED, Mediterranean Diet Quality Index in children and adolescents. *Public Health Nutr* (2004) 7(7):931–5. doi: 10.1079/phn2004556

53. Notario-Barandiaran L, Freire C, García-de-la-Hera M, Compañ-Gabucio LM, Torres-Collado L, González-Palacios S, et al. Reproducibility and validity of a food frequency questionnaire for dietary assessment in adolescents in a self-reported way. *Nutrients* (2020) 12(7). doi: 10.3390/nu12072081

54. Vioque J, Garcia-de-la-Hera M, Gonzalez-Palacios S, Torres-Collado L, Notario-Barandiaran L, Oncina-Canovas A, et al. Reproducibility and validity of a short food frequency questionnaire for dietary assessment in children aged 7¯ 9 years in Spain. *Nutrients* (2019) 11(4). doi: 10.3390/nu11040933

55. García EL, Lesmes IB, Perales AD, Moreno V, Baquedano MPP, Velasco AMR, et al. Informe del Comité Científico de la Agencia Española de Seguridad Alimentaria y Nutrición (AESAN) sobre recomendaciones dietéticas sostenibles y recomendaciones de actividad física para la población española. *Rev Com Científico AESAN.* (2022) 36):11–70.

56. Zuijdwijk CS, Pardy SA, Dowden JJ, Dominic AM, Bridger T, Newhook LA. The mSCOFF for screening disordered eating in pediatric type 1 diabetes. *Diabetes Care* (2014) 37(2):e26–7. doi: 10.2337/dc13-1637

57. Martin-Payo R, Carrasco-Santos S, Cuesta M, Stoyan S, Gonzalez-Mendez X, Fernandez-Alvarez M del M. Spanish adaptation and validation of the User Version of the Mobile Application Rating Scale (uMARS). *J Am Med Inform Assoc* (2021) 28 (12):2681–6. doi: 10.1093/jamia/ocab216

58. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* (2007) 39(2):175–91. doi: 10.3758/BF03193146

59. Bullard T, Ji M, An R, Trinh L, Mackenzie M, Mullen SP. A systematic review and meta-analysis of adherence to physical activity interventions among three chronic conditions: cancer, cardiovascular disease, and diabetes. *BMC Public Health* (2019) 19 (1):636. doi: 10.1186/s12889-019-6877-z

60. Schafer JL, Graham JW. Missing data: our view of the state of the art. *Psychol Methods* (2002) 7(2):147. doi: 10.1037/1082-989X.7.2.147

61. Pigott TD. A review of methods for missing data. *Educ Res Eval.* (2001) 7 (4):353–83. doi: 10.1076/edre.7.4.353.8937

62. Wiegand S, Raile K, Reinehr T, Hofer S, Näke A, Rabl W, et al. Daily insulin requirement of children and adolescents with type 1 diabetes: effect of age, gender, body mass index and mode of therapy. *Eur J Endocrinol* (2008) 158(4):543–9. doi: 10.1530/EJE-07-0904

63. Malik FS, Taplin CE. Insulin therapy in children and adolescents with type 1 diabetes. *Pediatr Drugs* (2014) 16(2):141–50. doi: 10.1007/s40272-014-0064-6

64. Absil H, Baudet L, Robert A, Lysy PA. Benefits of physical activity in children and adolescents with type 1 diabetes: A systematic review. *Diabetes Res Clin Pract* (2019) 156:107810. doi: 10.1016/j.diabres.2019.107810

65. He Z, Wu H, Yu F, Fu J, Sun S, Huang T, et al. Effects of smartphone-based interventions on physical activity in children and adolescents: systematic review and meta-analysis. *JMIR MHealth UHealth.* (2021) 9(2):e22601. doi: 10.2196/22601

66. Aljawarneh YM, Wardell DW, Wood GL, Rozmus CL. A systematic review of physical activity and exercise on physiological and biochemical outcomes in children and adolescents with type 1 diabetes. *J Nurs Scholarsh.* (2019) 51(3):337–45. doi: 10.1111/jnu.12472

67. Pi L, Shi X, Wang Z, Zhou Z. Effect of smartphone apps on glycemic control in young patients with type 1 diabetes: A meta-analysis. *Front Public Health* (2023) 11:1074946. doi: 10.3389/fpubh.2023.1074946

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Adolescents with type 1 diabetes' perspectives on digital health interventions to enhance health literacy: a qualitative study

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Introduction: Digital health intervention offers the potential to enhance health literacy, which is crucial for effective diabetes management, especially among adolescents. Diabetes is a major global public health issue, leading to devastating complications and increasing mortality rates. The incidence of type 1 diabetes mellitus (T1DM) is also on the rise, particularly among adolescents, necessitating multisectoral strategies to combat this disease. This study explores the perceptions of adolescents with T1DM in Germany regarding digital health interventions, with the aim of improving healthcare by addressing specific needs and guiding future research.

Methodology: This study employed a qualitative approach using semi-structured individual interviews with adolescents with T1DM ($n = 20$) aged 14 to 18 years old in Germany to explore their perspectives on digital interventions for health literacy promotion. The study adopted content analysis according to Kuckartz et al. and the research followed the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist. Ethical considerations were paramount and data were rigorously analyzed using coding and iterative processes to ensure data quality and reliability.

Results: The findings indicate that within three prominent domains, namely the utilization of digital health intervention for accessing and comprehending information, facilitating peer-to-peer interactions, and enhancing physician-patient communication and interaction, digital health interventions are either underutilized or insufficiently deployed. In addition, a notable observation is the apparent lack of patient-centered approaches for adolescents with T1DM in relation to digital health interventions and health literacy.

Conclusion: In order to enhance the utilization of digital health interventions and enhance health literacy it is essential to focus on capacity building through a patient-centered approach, to promote digital health literacy, and foster the cultivation of a participatory culture. The outcomes of this study offer valuable insights that can inform practical applications, further research endeavors, and influence policymaking.

KEYWORDS

digital health, digital interventions, health literacy, adolescents, type 1 diabetes, patient-centered, patient-participation

1 Introduction

Adolescence is a vulnerable period of life characterized by significant physiological and psychosocial changes and a need to gain autonomy from parents (1). When it coincides with the presence of a chronic disease such as type 1 diabetes, the transition into adulthood is made even more challenging (2, 3). Today's generations of adolescents are known for their massive use of digital tools (4, 5); thus offering an opportunity to integrate digital interventions into the healthcare system to improve the management of their conditions. Diabetes is considered one of the most significant global public health challenges, having evolved into a major worldwide public health concern (6). It not only represents a leading cause of blindness but also contributes to kidney failure, heart attacks, strokes, and lower limb amputations (7). Between 2000 and 2019, diabetes-related mortality rates increased by 3% per age group (7). The incidence rates of Type 1 Diabetes (T1DM) are also on the rise, contributing to the overall increase in diabetes prevalence (8). In Germany, the incidence of T1DM among children and adolescents has shown a consistent increase over the past 30 years (9). Projections predict a rise in case numbers in the coming decades, underscoring the urgency of developing and implementing multisectoral strategies to combat this disease (8). Effective management of this chronic condition demands a comprehensive understanding of both medical and behavioral aspects, highlighting the crucial importance of health literacy within this population, not only for reducing mortality (10), but also for mitigating health inequalities (11). Young individuals afflicted with this condition must be capable of navigating a complex landscape of medical information and making informed healthcare decisions, all while traversing the vulnerable period of adolescence.

Digital health interventions (DHI), such as telehealth, mobile health, messaging systems, mobile applications, gamified support, social platforms, and patient portals (12) have rapidly expanded in recent decades, offering improved disease management (13–17). They hold the potential to enhance health literacy and the management of T1DM among adolescents (18). Digital health and the use of digital technologies have become a global health priority for improving healthcare delivery and chronic disease management. The recent report from the World Health Organization Regional Office for Europe clearly addresses the need for action and emphasizes the role of national government agencies in overseeing the adoption and application of digital health, ensuring funding availability, and promoting health literacy and digital inclusion (19). Germany has also embarked on this path by developing national initiatives aimed at integrating digital tools into the healthcare domain (20). The objective of the present study was to explore the specific perceptions related to DHI among adolescents with T1DM residing in Germany. This study aimed to enhance the comprehension of DHI accessibility, their utilization, their roles, as well as their associations with health literacy. The results of this qualitative analysis are anticipated to provide further insights into DHI research, facilitating the promotion of health literacy and allowing for a targeted approach to address the specific requirements and actions required to align with national and international strategies in this domain.

2 Methodology

2.1 Research design

A qualitative approach was chosen to account for the exploratory nature of the study. Semi-structured individual interviews involving adolescents aged 14 to 18 years old with type 1 diabetes mellitus (T1DM) were considered as an appropriate method, especially for recruiting a hard-to-reach target group discussing potentially sensitive topics. Additionally, this method allowed for an in-depth understanding of participants' experiences, including their perceptions and interpretations (21). The content analysis approach by Kuckartz et al. (22) was adopted to explore their perspectives on digital health interventions aimed at promoting health literacy. The study followed the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist developed by Tong et al. (23) to transparently report the study. The completed COREQ checklist, consisting of 32 items, is available and can be requested directly from the corresponding author of this study (AN.N).

2.2 Inclusion criteria and recruitment

The target population consisted of adolescents aged 14 to 18 years old with T1DM. An additional inclusion criterion was a command of the German language sufficient to allow for full participation in interviews. Moreover, participants under the age of 18 required informed consent from their parents in addition to their own informed consent. The recruitment process occurred in two phases. In the first phase, various recruitment methods were employed, such as distributing flyers in hospitals and specialized diabetes centers in different German cities, sending flyers via email to diabetes centers, disseminating information in support groups dedicated to young people with T1DM, as well as via online forums, official Instagram accounts of the T1DM community, Facebook groups, private requests on social media to influencers with T1DM and finally, through word-of-mouth. In total, 87 networks and institutions were approached. The second phase of recruitment took place during a six-week observation period at a pediatric diabetes center. The number of participants was two in the first phase and 18 in the second phase.

2.3 Data collection and processing

Semi-structured individual interviews were conducted. The first interview was conducted by phone, while the second took place via video conference. Subsequently, a total of 18 interviews were conducted within the pediatric diabetes department of a hospital in Germany. The first two interviews occurred between November and December 2022, and the remaining 18 were conducted between May and June 2023. All interviews were conducted by a single researcher, AN.N, a doctoral candidate experienced in qualitative interviews. It should be noted that one of the interviewees had a familial connection to an acquaintance of the researcher; the other 19 participants were unknown individuals prior to data collection. Before starting the interview with the recording, the researcher created a relaxed atmosphere, considered crucial as a "warm-up" by Reinders (24), to make the participants feel comfortable during the interview. Once situated in the room where the interview was to take place, the

researcher reiterated the study's purpose and the interviewee's rights during and after the interviews. The introduction phase also allowed participants to ask questions. The interview was conducted using a semi-structured interview guide with open-ended questions to ensure that all themes were addressed while maintaining flexibility and adaptability for each interview. The interview guide was created following Reinders' (24) structure and was divided into seven parts:

1 The "Warm-Up-Phase," individualized for each interview, following Reinders (24)
2 Peer relationship
3 Communication between physicians and adolescents with T1DM
4 Training
5 Access to information more generally
6 Open-ended questions
7 Conclusion, socio-demographic data

The interview guide is available in the Supplementary material.

The interviews were recorded as digital audio recordings and transcribed in full by AN.N. Furthermore, field notes were taken after each interview, including observations and impressions. Age and the number of years since adolescents were diagnosed with T1DM were requested during the interview. Education, nationality, and gender were not requested. Gender was classified based on the researcher's perception.

2.4 Data analysis

The interview guide was initially deductively coded inspired by the definitions of health literacy of Bröder et al. (25) and Naef et al. (18). Before commencing the study, a pilot test was conducted with two adolescents with T1DM. For this current study, a total of 20 adolescents (8 girls and 12 boys) with T1DM living in Germany were interviewed. Participants' ages ranged from 14 to 18 years with an average age of 16 years. The authors did not provide the interview guide containing the questions to the interviewees. Interviews lasted between 17 and 33 min, with an average duration of 23 min. The adolescents had been living with T1DM for an average of 7 years, with a range of 6 months and 16 years. Individual interviews were conducted in person (by AN.N), by phone, via video conference, and in face-to-face settings. The authors discussed and determined that saturation of sampling (26) had been achieved. The coding system was conducted iteratively using MAXQDA software (2022; VERBI Software GmbH, Berlin, Germany). The analysis was subsequently refined through an iterative process involving structural content analysis (22). Two authors (AN.N and N.F) consolidated 100% of the entire coding material to ensure data quality, consistency, validity, and reliability of results (22).

2.5 Ethics statement

The study design was approved by the ethics committee of the Hannover Medical School on October 18, 2022. Information about the study was communicated orally and in writing to adolescents, and their parents in the case of minors, before the interview. Adolescents were informed that their participation was entirely voluntary, independent of the institutions where they received treatment, and the researcher emphasized multiple times during the interview that adolescents had the right not to answer questions or to terminate the interview without providing a reason. Adolescents were also informed that they could contact the researcher in the week following the interview if they wished for their interview not to be considered for the study. Interviews were audio-recorded and transcribed, after which the recordings were deleted. To ensure anonymity, any information that could identify participants was removed from the transcripts. All participants provided written consent for their participation and digital voice recording with additional written consent from parents or legal guardians obtained for minors. Participants did not receive vouchers or money for participating in the study. Personal data was processed in accordance with the General Data Protection Regulation and the Declaration of Helsinki.

3 Results

The coding system comprises 11 main categories and 26 subcategories (see Supplementary material). To address the research question, three main themes were analyzed in detail. The first theme focuses on access to information between digital and non-digital sources. The second theme examines digital interventions for peer relationships. Finally, the third theme explores the use of digital interventions for communication and interaction during medical consultations, outside of consultations, and in a hospital setting (see Table 1: Summary of the main results). The cited sources have been translated from German to English (AN.N & NF).

TABLE 1 Summary of the main results.

Information	• Source of information: training programs, rehabilitation programs, consultations (non-digital) • Parents as a source of information (non-digital) Manufacturers as a source of information (digital)
Peer-to-peer	• Online forums and social media do not play a major role in peer relations ➔ lack of information about existing platforms and little interest • Parents for parents • Friends, family or other contact person / confidants play an • important role, not only to get information, but for emotional support
Communication and interaction between patient and physician	• Little use of digital interventions • Different perspective about the use of digital interventions • E-mails not used by adolescents ➔ perceived as a not efficient and non-secure • Communication and interaction happen between parents and physicians, excluding patients

3.1 Access to information

Three primary sources of information regarding disease management were highlighted by the interviewees. The first encompasses all official information sources directly from institutions where adolescents with T1DM are being cared for. This includes those receiving inpatient care with an intensive training program, those participating in occasional training programs conducted in group or individual settings, as well as those attending REHA facilities (rehabilitation institutions) either on an inpatient or outpatient basis. Additionally, it encompasses information obtained during outpatient appointments during regular consultations with experts, including physicians and/or diabetologists. Information from these sources is primarily conveyed in person, with digital tools used only in rare cases. The second primary source of information highlighted was parents or close family members. While T1DM primarily manifests in minors, or family member may also be affected by the disease as T1DM is a genetic condition. The third primary source of information identified was the manufacturers of digital tools, such as pumps or sensors. Manufacturers play a significant informative role, mainly through digital channels like online chat features.

Initially, the primary sources of information for adolescents with T1DM in Germany are accessible during training sessions/programs that take place during the initial diagnosis. Adolescents spend an average of 2 weeks in inpatient care and receive information about disease management during an intensive training, often with the involvement of parents. These training sessions are conducted on-site and organized by the hospital. Specific, tailored training can occur either individually or in groups, with the majority being conducted in person, with a few exceptions, such as during the COVID-19 pandemic. Furthermore, the German healthcare system allows patients to undergo inpatient or outpatient rehabilitation (REHA) for several weeks, accompanied by one or both parents. Finally, regular outpatient hospital appointments, typically four times a year, also serve as a source of information for adolescents with T1DM, and are mainly conducted in person. As regards this type of official information dissemination (via hospital or institutions), some adolescents mentioned being overloaded with information:

> "*It was too much. And getting everything explained in general, because it was all, everything intertwined, so many topics were covered simultaneously here.*" (P15:77)

This mass of information received all at once led at least one interviewee to seek information on the internet. Another interviewee received a book to read the information herself, which had already been mentioned during the training sessions. This participant admitted that she had not read the book, mainly because there was too much information.

> "*Okay, I'll be honest, I didn't really look at the book, it was way too much. I only did the exercise for calculation, just so I have some basic knowledge. But I didn't go through the book again.*" (P16:24)

This information overload also leads to forgetting some information. For some, printed materials serve as a useful resource to check information.

> "*I had already learned it. It was somewhere in my head. So, partly, when it was explained to me again, it did come back to me, but I'm a very, very forgetful person. That's why I'm a bit afraid that if, for example, if I want to change something again, I'll have to ask again or get another booklet that tells me what I can change. I think I'd look into that again.*" (P16:106)

For some individuals, language difficulty, for example limited German language skills and/or lack of knowledge of specific medical jargon, adds a barrier to understanding the information. Others may not always feel comfortable asking questions, depending on the context. For example, in a situation where eight medical students were present during the consultation, it made the patient nervous and prevented her from asking a question because she did not understand what the doctor was saying.

> "*Yes, sometimes I do dare to ask questions if it's something very complicated. But, for example, before, I was a bit unsure. I didn't dare to ask.*" (P16:102)

To seek more information or better understand information provided by healthcare experts, some adolescents use digital interventions such as YouTube or social media platforms like TikTok or Instagram. These sources are not directly recommended by healthcare experts. Videos are considered a more easily understandable digital tool by adolescents than text or online searches, where information filtering is considered complicated. Some adolescents do not verify the information found on the internet or social media (*"I do not discuss that with my doctor."* (P17:48)), while others have mixed opinions about the quality of the information but still take it into account:

> "*So, I wouldn't consider it a reliable source, but (…) So, if, for example, if I had very high values (.) Yeah, I don't know, if something strange were to happen and there was information on YouTube like, 'You should eat nuts or something.' I don't know. Then I would try that.*" (P18:51)

For others, in-person consultations provide an opportunity to ask questions and obtain information from healthcare experts. In some cases, young patients may come across information on the internet, like Instagram posts about someone using a closed-loop system, and take the opportunity to discuss it with their physicians during their next appointment.

> "*Yeah, so, I did (.) bring it up during the next appointment, that I would like to try it, and so on. (.) And that's how I tried the Loop System last month.*" (P19:28)

Official training sessions organized by healthcare institutions are generally considered to be an overload of information, too complex, or difficult to understand due to the language used. Interviewees mention seeking information outside of official sources, primarily on the internet and social media platforms like

YouTube, Instagram, or TikTok. Sometimes, this information is not subject to expert scrutiny; in other cases, adolescents may express criticisms regarding this information but still use it, and in yet other instances, the information is discussed during subsequent consultations with healthcare experts.

The second major source of information often used by interviewees is the knowledge of parents, who play a significant role in accessing information. This is mainly because T1DM largely affects children and adolescents, and most of the interviewed adolescents were diagnosed in childhood. In such cases, parents have played a major role in managing the disease and have become experts through training and experience. The situation remains similar for adolescents who were diagnosed later because young people are still minors, and parents continue to be heavily involved in training.

> "*If I have a question, I'll quickly discuss it with my mother because she knows a lot, of course. I got this when I was five, so I probably didn't understand it all that well. And so, she explained it to me bit by bit, as I got older, a little more each time […] And yes, we still do quite a bit together.*" (P9: 52)

This is not always the case, especially for patients whose parents do not speak neither German nor English. In such cases, other family members can play an important role, as is the case with a brother in this example:

> "*My brother speaks perfect German. My parents only know a few words, and he can understand better.*" (P10:130)

Furthermore, the third significant source of information is the manufacturers of technologies such as sensors and pumps, which many adolescents use. This source of information is often compared to efficient customer service.

> "*They answer immediately. So, there is, how should I say it, like a customer service. So, let's say, first-level customer service, okay? There is also higher customer service that can answer many difficult questions. If the first-level has problems, the first one, then they forward it to better customer service.*" (P5:98)

Some adolescents clearly differentiate where to seek information between technical problems, directly from the manufacturers, and clinical questions, at the hospital. Others are more hesitant about navigating between information sources, for example, when asked if they would talk to a doctor if a technical problem occurred:

> "*I don't think so. Because the app is from [Company] and not from the [Institution]. So, I believe you can only contact the company.*" (P7:51)

In this theme, "Access to Information," the results shows that adolescents with T1DM often find the initial dissemination of information from official sources overwhelming, leading them to seek additional information online or through alternative means. Language barriers, hesitation to ask questions, and the influence of social media also shape their information-seeking behaviors. These adolescents frequently turn to their parents, who play a crucial role in managing T1DM, and also rely on manufacturers' customer support for technical assistance.

3.2 Peer-to-peer relations

The relationship between peers (adolescents with T1DM) is relatively limited, whether through digital interventions or in-person interactions. One reason for this is that most adolescents are unaware of the opportunities for exchanging or communicating with peers, whether through digital interventions or otherwise. Some study participants argue that such contact is unnecessary and that they lack interest in engaging with peers, emphasizing that everyone's experience with the disease is unique:

> "*I'm mainly interested in my own affairs, like how my blood sugar is regulated, and ultimately, everyone has a different perception of the disease, and everyone sees it a bit differently […] So, I'm more focused on my diabetes.*" (P9:16)

In rare cases, a classmate or schoolmate may also have T1DM. However, these interactions are often brief and superficial, focusing on topics like whether they use specific technologies such as insulin pumps, the manufacturer's brand, or their HbA1c values:

> "*We talked about our measuring and pumping systems. She doesn't like the sensor system. I'm not a hundred percent sure, but I think she had a pump with a tube. […] And that's basically all we said about diabetes.*" (P9:10)

Some adolescents express an unmet desire to exchange experiences with peers:

> "*But (…) Now (…) looking back (…) […] I would like to talk to others about how they experienced it.*" (P1:48)

For some, the idea of exchanging experiences with peers becomes more appealing when combined with another activity. For example, one interviewee expressed interest in a sailing camp for adolescents with diabetes, which they can join from the age of 16. The flyer for the camp was seen in the hospital corridor. The combination of learning to sail and interacting with peers seemed to attract their attention:

> "*At first (…) to learn how to sail. But it would also be cool to spend time with people who also have diabetes, to see how they do it. And, you know, how they manage it in school, for example.*" (P18: 32)

Some prefer to talk to their close friends rather than unfamiliar peers. These close friends are knowledgeable about the disease and are considered a significant source of support:

> "*My classmates also knew about it. And my closest friends, the ones I'm always with, I explained to them what they should look out for or symptoms, for example, if I get pale, they should ask if I want to check my blood sugar. I told them some things about symptoms of both hypoglycemia and hyperglycemia, and they really help me.*" (P16:131)

A reference person who can provide support in more challenging times can also be someone who does not have the disease. In this case, they are seen as offering emotional support:

> "*I already know everything, and I don't necessarily need other people there. But simply having that emotional support could mean that people can throw in ideas or something like that. And just the fact that even if neither I nor the others have diabetes and stuff, you still don't feel so alone at the moment. […] But maybe that came up later in the conversation. Always having someone there who listens to me. Maybe also brings in their own thoughts so that it happens. Maybe we can discuss this here again. So, somehow, a reference person.*" (P19:88)

For others, communicating with peers of the same age who have the same disease is of value, allowing them to ask questions they might not ask an adult, such as their parents, perhaps due to tension within the family. They feel better understood by peers of their own age, without indicating a preference for in-person or digital contact:

> "*I think it's important because they can understand. And you feel like you can relate to everything, and you get suggestions or something. So, if you ask someone who doesn't have diabetes, they can't make suggestions.*" (P2:90)

For others, the age of their peers does not seem to play a crucial role, either in information exchange or in more personal or emotional exchanges. However, the fact that others have the same disease, regardless of age, plays a significant role. These individuals with T1DM can be, for example, an older distant cousin, a teacher, an aunt, or an individual from a support group. In one instance, the interviewee received individual support from an adult at school:

> "*I had assistance from the first grade to the sixth grade, and she was only with me at school, helping me. I built a very strong relationship with her, and it really (…) She was like an aunt to me, who just stood by me and understood me […] She also helped me deal with giving insulin injections outside. I always had a problem with that (.) Okay, so why do I want to pull this pump out now? Everyone will look at me strangely. I was always afraid of that. But she helped me normalize it.*" (P7:91-97)

Finally, individuals followed on social media without personal contact are considered peers and examples, whether for learning or community-building purposes, the latter of which reducing feelings of loneliness:

> "*It's still different to see people who have it themselves, how they deal with it, rather than just being told by a doctor, who may know a lot about it but doesn't have it themselves. It's still different to have those experiential values. To have it and because, usually, the people are a bit older and have more experience, so that you can integrate it well or just not feel so alone.*" (P19:34)

In general, adolescents report that peer groups are more active for parents who exchange information with other parents, whether online or in face-to-face meetings, sharing insights into new technologies and more.

3.3 Communication and interaction between individuals and physicians

Digital tools are relatively underutilized in Germany, both for video conferences during regular outpatient consultations and for other tools related to scheduling appointments or asking questions outside of appointments. Some young individuals prefer in-person consultations, believing that personal contact is important, especially for receiving advice, and find it more pleasant:

> "*So. That was different. Definitely. So, personal conversation is better. And you ask more questions, maybe get some better advice, and it's just more pleasant. But it worked over the phone.*" (P4:60)

Others would prefer online consultations because they live far from hospitals and believe it does not affect the quality of communication:

> "*That would be better. I wouldn't have to spend 1.5 hours coming here. I could save a lot of time.*" (P6:134)

Some would opt for a combination of both:

> "*Well, definitely come here once every six months. Just to discuss, check the values, and make sure everything is okay. But maybe, for example, suggest that we meet the other time and alternate between in-person and phone consultations. That way, people who are a bit busier or always there don't lose so much time, but can do it from home and save some stress or something.*" (P4:64)

Others, taking a pragmatic view of the situation, propose a combination of face-to-face and online contact points. This is because some tests or checks must be done in person, and they are also aware of the healthcare system's billing requirements for health insurance:

> "*Actually, quite good, especially when you drive for an hour that day. And if it's just about talking about the values, where I have them and she also has them in front of her, then it's actually unnecessary to drive extra. It's necessary for measurements. So, giving blood values, body weight […] So, I have to come once a quarter. So, I'm not exactly sure why, but I think it's because of the health insurance billing, that's necessary.*" (P17:90-92)

Outside of appointments, communication primarily occurs between parents and physicians or other experts via phone or email, regardless of the adolescent's age. Most adolescents do not use these two means of communication, and some even consider them unreliable:

> "*I find email a bit unreliable.*" (P4:82),

> "*Well, I think it would work. But the experience I've had is that you overlook it very quickly. So, that you misunderstand it. Either a problem arises where it doesn't get through, and stuff like that.*" (P16:96)

Some adolescents would prefer other digital tools to facilitate communication, especially in time-sensitive situations where there is a risk of not getting answers to their questions:

> *"I don't know of an example, but for instance, we had a situation where my values were really high one evening. All through the night, too. And then we called the next day. And if that could be solved more quickly with some kind of app, I don't know, I'm not familiar with it, but if it could be resolved more quickly, so you don't have to call, and then the doctor has something to do, but instead, I don't know, write something where you can see it right away or something like this. It would help me."* (P4:76)

Some have drawn parallels with applications implemented by schools during the COVID-19 pandemic for course management. Consequently, they expressed a desire to have the option to use a similar type of application in the medical field. For instance, they wished to engage in direct chats with physicians for inquiries, rescheduling appointments, interacting with other individuals with T1DM, or swiftly perform calculations to determine whether certain foods are suitable for consumption or not, all in real-time.

In this section, the results show that adolescents, regardless of their age, are relatively less engaged in communication with physicians or experts outside of appointments. Preferences for in-person or digital consultations are highly heterogeneous, and technological ideas have been clearly expressed by the interviewees.

4 Discussion

This study and its results identify an urgent need for development within the space of digital intervention aimed at improving health literacy for adolescents with type 1 diabetes. Such digital interventions as those widely used by the target group have the potential to support adolescents as they navigate the management of this chronic disease during a vulnerable period of life. Based on literature reviews (18, 25), this study and its results allow a deeper understanding of the specific needs of those directly affected, i.e., adolescents with type 1 diabetes. This is a valuable perspective for healthcare systems to take into account.

The analysis and findings of this study have identified three dominant themes. The first theme pertains to information access and adolescent perspectives' revealing diverse opinions on various sources of information, both digital and non-digital. The second theme, focusing on peer relationships, exhibits heterogeneous statements regarding the significance of peer relationships, but relatively uniform opinions concerning the lack of knowledge about existing digital structures and platforms. The third theme, concerning perceptions, opinions and wishes regarding communication and interaction between adolescents and physicians, highlighted the desire for new digital forms of communication.

Based on these results, the authors emphasize three key points for future reflection, research, and policy formulation. Firstly, it is essential to provide adolescents with T1DM better access to available digital health interventions from institutions and experts (such as physicians) to enhance their disease management alongside the information received in institutional settings. This accessibility should be paralleled by the promotion of digital health literacy to ensure adolescents are well-equipped to use digital tools optimally. Secondly, it is crucial for this digital offering to be tailored and personalized to individual patients, catering to their unique needs. Finally, strategies for integrating digital tools should be developed with the active participation of adolescents with T1DM to better address the needs of this population.

This study reveals that across the three analyzed themes (information access, peer exchange, and communication), that there is a lack of communication from experts and institutions regarding the availability and accessibility of digital interventions. Officially, access to information occurs either within institutions (such as in hospital settings during regular outpatient consultations or in inpatient or outpatient rehabilitation facilities), or through intensive training programs following guidelines such as the ISPAD, for example (27). The positive effects of these in-person official information sessions on patient engagement and motivation have been demonstrated (28, 29). However, despite the positive impact of this information, the study results show that an excess of information, overly complicated information, or the fact that adolescents hesitate to ask questions when they do not understand the information for various reasons can lead some adolescents to seek information through digital interventions (such as YouTube or other social media platforms or the internet); information that is not recommended by physicians and whose quality is not verified. To address this issue, action should be taken on two fronts: First, regarding information overload and poor comprehension, it is crucial to ensure patient understanding, particularly to enhance their health literacy. This could be achieved through techniques such as "Plain Language," which avoids complicated language and medical jargon, "Teach-Back" to confirm understanding of provided information, "Shared Decision Making" to collaborate with patients in reaching a common decision, or "Chunk and Check," a strategy that breaks down large amounts of information into smaller sections, facilitating comprehension and retention of essential information (30, 31). Secondly, as the study shows that due to poor understanding, adolescents seek information elsewhere without expert verification, access to digital interventions should be guided. It is important to emphasize that the effectiveness of digital health interventions for patients with T1DM, whether for clinical improvements (13, 32) or their impact on health literacy (18), is supported by scientific literature. In light of this situation, it is necessary to ensure that the use of digital tools for information seeking occurs in conjunction with institutional training. Additionally, digital offerings should be endorsed and recommended by experts and institutions to ensure the quality of available information. In addition to access to this offering, it is important to support the use of digital tools through the promotion of digital health literacy. Improving the accessibility and visibility of digital offerings and their guidance by experts applies not only to information access and comprehension but also to peer interactions and communication between physicians and patients. The peer relationship and the communication between the physicians and the patient are also seen as an important source of information.

Moreover, recommendations made by experts and institutions to patients for specific types of digital health interventions must be personalized and individualized, considering the diverse needs of adolescents with T1DM. Indeed, the study results demonstrate heterogeneous opinions regarding the needs and desires for digital tool use and their perspectives on usefulness, whether for information access and comprehension, peer interaction, or communication with physicians. The literature also emphasizes the need to be more

patient-oriented and provide personalized approaches to better target patient needs (33–36).

Finally, the study highlights the need to develop tools that allow for the active participation of those concerned, in this case T1DM patients, in institutional strategic planning. It is crucial to involve patients in decisions made at the organizational level (37, 38).

The three points mentioned above, which can serve as the basis for future deliberations, research, and policy development, align with the guidelines outlined in the recent report from the World Health Organization Regional Office for Europe, which explicitly underscores the need for action and highlights the role of national government agencies in monitoring the adoption and implementation of digital health solutions, making funding available, and promoting digital health and literacy (World Health Organization, Regional Office for Europe) (19). Similarly, in Germany, as mentioned by the Federal Ministry of Health (20), digitalization offers immense potential but is currently underutilized. It not only needs to be leveraged more effectively but also in conjunction with the promotion of digital health literacy (39, 40). Improved utilization of digital health interventions must also comply with the General Data Protection Regulation (GDPR) (41), which often restricts possibilities.

One of the major strengths of this study is the inclusion of the hard-to-reach group represented by adolescents with T1DM. The majority of interviews ($n = 18$) in a hospital setting ensured a diversified sample and avoided snowball or convenience sampling effects, allowing for a wide range of perspectives and thus resulting in heterogeneous groups. The interviews provided rich information on the need and manner of integrating digital interventions to promote health literacy among adolescents with T1DM. Data saturation was achieved and approved by the co-authors of this study. The conducted interviews no longer revealed significant new information compared to previous ones, indicating content saturation (26). However, several limitations must be acknowledged. Firstly, the second part of recruitment ($n = 18$) was limited to one hospital, in Germany, to ensure in-person participation. Additionally, self-reflection on one's own position is crucial in qualitative research, especially as an adult who may be perceived as an authoritative figure by adolescents. The author's subjectivity is not denied and is utilized as productive resource in the research (42).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by The study design and the interview guide have been summitted to the ethics committee of Medical School Hannover and have been accepted the 18th of October 2022. Approval number: 10559_BO_K_2022. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

AN: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. NF: Conceptualization, Data curation, Formal analysis, Investigation, Supervision, Validation, Writing – review & editing. HT-G: Methodology, Supervision, Validation, Writing – review & editing. VA: Conceptualization, Supervision, Validation, Writing – review & editing.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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References

1. Jaworska N, MacQueen G. Adolescence as a unique developmental period. *J Psychiatry Neurosci*. (2015) 40:291–3. doi: 10.1503/jpn.150268

2. Pinquart M. *Wenn Kinder und Jugendliche körperlich chronisch krank sind: Psychische und soziale Entwicklung, Prävention, Intervention*. Berlin, Heidelberg: Springer Berlin Heidelberg (2013).

3. Sawyer SM, Drew S, Yeo MS, Britto MT. Adolescents with a chronic condition: challenges living, challenges treating. *Lancet*. (2007) 369:1481–9. doi: 10.1016/S0140-6736(07)60370-5

4. Die 18. Shell Jugendstudie. Shell Energy. (2019). Available at: https://www.shell.de/ueber-uns/initiativen/shell-jugendstudie.html [Accessed December 23, 2023].

5. JIM-Studie. Medienpädagogische Forschungsverbund Südwest (mpfs). (2023). Available at: https://www.mpfs.de/studien/jim-studie/2023/ [Accessed December 23, 2023].

6. Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Sci Rep*. (2020) 10:14790. doi: 10.1038/s41598-020-71908-9

7. World Health Organisation. Diabetes key facts (2023). Available at: https://www.who.int/news-room/fact-sheets/detail/diabetes [Accessed September 8, 2023].

8. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes federation diabetes atlas, 9th edition. *Diabetes Res Clin Pract*. (2019) 157:107843. doi: 10.1016/j.diabres.2019.107843

9. Kordonouri O, Kerner W. Type 1 diabetes: an update. *Internist (Berl)*. (2021) 62:627–37. doi: 10.1007/s00108-021-01009-w

10. Fan Z, Yang Y, Zhang F. Association between health literacy and mortality: a systematic review and meta-analysis. *Arch Public Heal*. (2021) 79:119. doi: 10.1186/s13690-021-00648-7

11. Gibney S, Bruton L, Ryan C, Doyle G, Rowlands G. Increasing health literacy may reduce health inequalities: evidence from a National Population Survey in Ireland. *Int J Environ Res Public Health*. (2020) 17:5891. doi: 10.3390/ijerph17165891

12. Duke DC, Barry S, Wagner DV, Speight J, Choudhary P, Harris MA. Distal technologies and type 1 diabetes management. *Lancet Diabetes Endocrinol*. (2018) 6:143–56. doi: 10.1016/S2213-8587(17)30260-7

13. Eberle C, Löhnert M, Stichling S. Effectiveness of disease-specific mHealth apps in patients with diabetes mellitus: scoping review. *JMIR Mhealth Uhealth*. (2021) 9:e23477. doi: 10.2196/23477

14. Ho Y-X, O'Connor BH, Mulvaney SA. Features of online health communities for adolescents with type 1 diabetes. *West J Nurs Res*. (2014) 36:1183–98. doi: 10.1177/0193945913520414

15. Shan R, Sarkar S, Martin SS. Digital health technology and mobile devices for the management of diabetes mellitus: state of the art. *Diabetologia*. (2019) 62:877–87. doi: 10.1007/s00125-019-4864-7

16. Caburnay CA, Graff K, Harris JK, McQueen A, Smith M, Fairchild M, et al. Evaluating diabetes mobile applications for health literate designs and functionality, 2014. *Prev Chronic Dis*. (2015) 12:E61. doi: 10.5888/pcd12.140433

17. Bakhach M, Reid MW, Pyatak EA, Berget C, Cain C, Thomas JF, et al. Home telemedicine (CoYoT1 clinic): a novel approach to improve psychosocial outcomes in young adults with diabetes. *Diabetes Educ*. (2019) 45:420–30. doi: 10.1177/0145721719858080

18. Naef A. Impact of digital health for adolescents with type 1 diabetes mellitus on health literacy. *Eur J Public Health*. (2023) 33:ckad160.1404. doi: 10.1093/eurpub/ckad160.1404

19. Digital Health in the WHO European Region. The ongoing journey to commitment and transformation. (2023). Available at: https://www.who.int/europe/publications/m/item/digital-health-in-the-who-european-region-the-ongoing-journey-to-commitment-and-transformation [Accessed September 10, 2023].

20. Federal Ministry of Health. Digitalisation Strategy for Health and Care. (2023). Available at: https://www.bundesgesundheitsministerium.de/en/topics/digitalisation/digitalisation-strategy [Accessed September 14, 2023].

21. Willig C. Perspectives on the epistemological bases for qualitative research In: H Cooper, PM Camic, DL Long, AT Panter, D Rindskopf and KJ Sher, editors. *APA handbook of research methods in psychology, Vol. 1. Foundations, planning, measures, and psychometrics*. US: American Psychological Association (2012). 5–21.

22. Kuckartz U, Rädiker S. *Qualitative Inhaltsanalyse. Methoden, Praxis, Computerunterstützung: Grundlagentexte Methoden. 5. Auflage* ed. Weinheim, Basel: Beltz Juventa (2022).

23. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International J Qual Health Care*. (2007) 19:349–57. doi: 10.1093/intqhc/mzm042

24. Reinders H. *Qualitative Interviews mit Jugendlichen führen. Ein Leitfaden*. München und Wien: R. Oldenbourg (2005).

25. Bröder J, Okan O, Bauer U, Bruland D, Schlupp S, Bollweg TM, et al. Health literacy in childhood and youth: a systematic review of definitions and models. *BMC Public Health*. (2017) 17:361. doi: 10.1186/s12889-017-4267-y

26. Saunders B, Sim J, Kingstone T, Baker S, Waterfield J, Bartlam B, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. *Qual Quant*. (2018) 52:1893–907. doi: 10.1007/s11135-017-0574-8

27. Gregory JW, Cameron FJ, Joshi K, Eiswirth M, Garrett C, Garvey K, et al. ISPAD clinical practice consensus guidelines 2022: diabetes in adolescence. *Pediatr Diabetes*. (2022) 23:857–71. doi: 10.1111/pedi.13408

28. Lange K, Klotmann S, Saßmann H, Aschemeier B, Wintergerst E, Gerhardsson P, et al. A pediatric diabetes toolbox for creating centres of reference. *Pediatr Diabetes*. (2012) 13:49–61. doi: 10.1111/j.1399-5448.2012.00913.x

29. Christie D, Thompson R, Sawtell M, Allen E, Cairns J, Smith F, et al. Structured, intensive education maximising engagement, motivation and long-term change for children and young people with diabetes: a cluster randomised controlled trial with integral process and economic evaluation - the CASCADE study. *Health Technol Assess*. (2014) 18:1–202. doi: 10.3310/hta18200

30. Brach C. The Journey to Become a Health Literate Organization: A Snapshot of Health System Improvement. *Stud Health Technol Inform*. (2017) 240:203–372.

31. Cifuentes M, Brega AG, Barnard J, Mabachi NM, Albright K, Weiss BD, et al. *Guide to implementing the health literacy universal precautions toolkit.: Practical ideas for primary care practices*. Rockville, MD: Agency for Healthcare Research and Quality (2015).

32. Stevens S, Gallagher S, Andrews T, Ashall-Payne L, Humphreys L, Leigh S. The effectiveness of digital health technologies for patients with diabetes mellitus: a systematic review. *Front Clin Diabetes Healthc*. (2022) 3:936752. doi: 10.3389/fcdhc.2022.936752

33. Scholl I, Zill JM, Härter M, Dirmaier J. An integrative model of patient-centeredness - a systematic review and concept analysis. *PloS One*. (2014) 9:e107828. doi: 10.1371/journal.pone.0107828

34. Zeh S, Christalle E, Zill JM, Härter M, Block A, Scholl I. What do patients expect? Assessing patient-centredness from the patients' perspective: an interview study. *BMJ Open*. (2021) 11:e047810. doi: 10.1136/bmjopen-2020-047810

35. Hower KI, Vennedey V, Hillen HA, Kuntz L, Stock S, Pfaff H, et al. Implementation of patient-centred care: which organisational determinants matter from decision maker's perspective? Results from a qualitative interview study across various health and social care organisations. *BMJ Open*. (2019) 9:e027591. doi: 10.1136/bmjopen-2018-027591

36. Leidner C, Vennedey V, Hillen H, Ansmann L, Stock S, Kuntz L, et al. Implementation of patient-centred care: which system-level determinants matter from a decision maker's perspective? Results from a qualitative interview study across various health and social care organisations. *BMJ Open*. (2021) 11:e050054. doi: 10.1136/bmjopen-2021-050054

37. The Mental Health Network Switzerland. Ein Leitfaden zur Partizipation von Jugendlichen in Projekten der Gesundheitsförderung. (2023). Available at: https://www.npg-rsp.ch/news/detail/article/ein-leitfaden-zur-partizipation-von-jugendlichen-in-projekten-der-gesundheitsfoerderung.html [Accessed September 14, 2023].

38. World Health Organisation. Youth-centred digital health interventions: A framework for planning, developing and implementing solutions with and for young people. (2020). Available at: https://www.who.int/publications-detail-redirect/9789240011717 [Accessed September 18, 2023].

39. Federal Ministry for Family Affairs, Senior Citizens, Women and Youth. Agenda für smarte Gesellschaftspolitik-Gemeinsam im Wandel. (2023). Available at: https://www.bmfsfj.de/bmfsfj/service/publikationen/agenda-fuer-smarte-gesellschaftspolitik-gemeinsam-im-wandel-179104 [Accessed September 18, 2023].

40. van Kessel R, Wong BLH, Clemens T, Brand H. Digital health literacy as a super determinant of health: more than simply the sum of its parts. *Internet Interv*. (2022) 27:100500. doi: 10.1016/j.invent.2022.100500

41. EU General Data Protection Regulation. Regulation (EU) 2016/679 of the European Parliament and of the council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing directive 95/46/EC (general data protection regulation, GDPR). *Off J Eur Union*. (2016) L119. Art. 28:44–50.

42. Green J, Thorogood N. *Qualitative methods for Health Research*. London: Sage Publications (2004).

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Blood glucose monitoring devices for type 1 diabetes: a journey from the food and drug administration approval to market availability

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Blood glucose monitoring constitutes a pivotal element in the clinical management of Type 1 diabetes (T1D), a globally escalating metabolic disorder. Continuous glucose monitoring (CGM) devices have demonstrated efficacy in optimizing glycemic control, mitigating adverse health outcomes, and augmenting the overall quality of life for individuals afflicted with T1D. Recent progress in the field encompasses the refinement of electrochemical sensors, which enhances the effectiveness of blood glucose monitoring. This progress empowers patients to assume greater control over their health, alleviating the burdens associated with their condition, and contributing to the overall alleviation of the healthcare system. The introduction of novel medical devices, whether derived from existing prototypes or originating as innovative creations, necessitates adherence to a rigorous approval process regulated by the Food and Drug Administration (FDA). Diverse device classifications, stratified by their associated risks, dictate distinct approval pathways, each characterized by varying timelines. This review underscores recent advancements in blood glucose monitoring devices primarily based on electrochemical sensors and elucidates their regulatory journey towards FDA approval. The advent of innovative, non-invasive blood glucose monitoring devices holds promise for maintaining stringent glycemic control, thereby preventing T1D-associated comorbidities, and extending the life expectancy of affected individuals.

KEYWORDS

type 1 diabetes, glycemic control, food and drug administration, electrochemical sensors, continuous glucose monitoring devices, regulatory approval

Introduction

Type 1 diabetes mellitus (T1D) impacts 9.5% of people globally and has an increasing incidence worldwide (1–3). T1D is associated with extensive complications, which fall into three main categories: macrovascular, microvascular, or metabolic (4). In children with T1D, the most common cause of death is related to metabolic issues in children with T1D, including diabetic ketoacidosis (DKA) and hypoglycemia (5, 6). In adults, however, death is more commonly due to macrovascular and microvascular problems (5). Microvascular complications include diabetic neuropathy, nephropathy, and retinopathy whereas macrovascular complications include peripheral vascular disease, stroke, and cardiovascular disease (1, 7).

Due to these complications, patients with T1D have shorter life expectancies than those without T1D. The standardized mortality rate (SMR) for all-cause mortality is 4.5 in individuals with T1D when compared with those who do not have T1D (8). Cardiovascular disease is the largest contributor to the increased mortality in T1D patients and accounts for 37.5% of all deaths due to T1D and almost 50% of the years of life lost (9). T1D patients have an SMR of 6.6 due to cardiovascular disease alone when compared to the general population (8). Endocrine and metabolic diseases are the second largest contributor to T1D mortality and comprise 20.7% of all deaths due to T1D and almost 30% of all years of life lost (9).

Along with increased mortality, T1D has been associated with co-morbidities. Diabetic retinopathy is one of the most common complications of T1D, with a prevalence rate of 20-25% and is the leading cause of acquired blindness (10–12). After 15 to 20 years of living with T1D most adults will have some form of diabetic retinopathy. Approximately 20% to 30% of those cases will lead to blindness (13). Diabetic neuropathy is another common complication of T1D with conditions including gastroparesis, carpal tunnel syndrome, and nerve palsies (14). When diabetic neuropathy is in conjunction with peripheral vascular disease it can cause diabetic foot ulcers, which may require amputation (15, 16). Increased attention to glycemic control is necessary for individuals diagnosed with diabetic retinopathy or diabetic neuropathy to better control their symptoms and prevent further complications.

Unfortunately, it has been shown that 80% of adults with T1D have suboptimal glycemic control, with a mean HbA1c of 8.8% while the American Diabetes Association (ADA) recommends an HbA1c of <7.0% in nonpregnant adults (17). Even the less stringent HbA1c goals recommended by the ADA for those with limited life expectancy or those for whom the benefit of glycemic control does not outweigh the harms is <8.0% (18, 19). Children have also been shown to have suboptimal glycemic control demonstrating HbA1c measurements of 7.63% while the ADA and the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommend an HbA1c goal of <7.0% for children (20, 21). Less stringent goals for children have been set at <7.5% and <8.0% for certain populations (20, 22).

Along with having a large disease burden for the patient, T1D poses a substantial economic constraint to the healthcare system in the United States (23). According to recent data from the American Diabetes Association (ADA), the economic burden of diabetes in the U.S. was estimated at $327 billion in 2017, with approximately $15 billion allocated specifically to T1D-related expenses (24). Pharmacy costs make up over half of the monthly diabetes-related cost and are approximately $440 per person per month (PPPM) (25). Although hospitalizations are relatively rare, they have a large financial burden and comprise 11.5% to 13.9% of the total monthly cost of T1D.

The use of continuous glucose monitoring (CGM) devices among people with T1D is on the rise. These devices are associated with lower levels of HbA1c in this population, indicating better glycemic control (26). CGM device measurements of the amount of time spent within the target blood glucose range correlate negatively with HbA1c (27). CGM measurements of time above range (TAR) > 180mg/dL have been shown to correlate positively with a high blood glucose index whereas time in range (TIR) has a negative correlation with high blood glucose index (22). For every 10% change of TIR there was shown to be a 0.7% change in HbA1c.It has been shown that participants with HbA1c ≤7.0% had a median TIR of 72.1% while those with an HbA1c ≥8.5% had a median TIR of 35.5% (27).

The growing adoption of CGM devices has spurred significant progress in the technology of blood glucose monitoring devices, with a specific emphasis on the development of non-invasive and minimally-invasive methods (28–32). These approaches offer several advantages over more traditional and invasive procedures, such as finger sticks. They provide patients with reduced pain and discomfort, along with lowering the risk of infection and tissue damage (33). Non-invasive devices predominantly utilize sensors placed on the skin's surface to measure blood glucose concentrations, obviating the necessity for needle penetration into the body (34). Minimally-invasive devices either sample interstitial fluid using a less invasive needle or explore alternative bodily fluids such as tears for blood glucose measurement, presenting a less intrusive option compared to traditional needlestick methods (35).

The objective of this narrative review article is to summarize the recent advancements in blood glucose monitoring devices primarily based on electrochemical sensors (Table 1). We provide an overview regarding how these blood glucose monitoring devices are approved and regulated by the U.S. Food and Drug Administration (FDA) before they are available in the market (Figure 1). Ensuring rigorous glycemic control through the use of these blood glucose monitoring devices is essential for the effective management of T1D and the prevention of potentially life-threatening co-morbidities.

The United States food and drug administration regulatory process

Since 1976, the FDA has been responsible for ensuring the safety of medical devices sold to consumers. This responsibility was established when the Federal Food, Drug, and Cosmetic Act was amended to include medical devices (36). According to this act, a device is any "instrument, apparatus, implement, machine,

10.3389/fendo.2024.1352302

TABLE 1 Overview of blood glucose monitoring techniques based on electrochemical sensors.

Device Name	Year of FDA Approval	Key Features	PMN/ PMA Number
Modified Clark Enzyme Electrode	N/A	• Provides a larger surface area for the working electrode	N/A
Senseonics Eversense	2018	• Convenience for users via mobile app • Overcomes miniaturization challenges	P160048
MiniMed 780G™ and Guardian™ 4 Sensor	2018	• Minimally invasive • Demonstrated safety • Improvements in user's glycemic control • Reduction in T1D burden • FDA approved	P160007
Dexcom G6	2018	• Minimally invasive • Improvements in user's glycemic control • Increased capturing of hypoglycemic events • FDA cleared	K182041
Dexcom G7	2022	• Reduced warm-up time • Enhanced accuracy • Smaller and more discreet design • Integrated smartphone app connectivity • Extended wear duration • Advanced alert system • Share feature for remote monitoring • Calibration-free operation	K213919
FreeStyle Libre 3	2022	• Higher accuracy • Real-time glucose monitoring • Minute-by-minute updates • Smaller and more discreet • Enhanced connectivity • Longer sensor wear time • Alarm functionality • No fingerstick calibration • Water-resistant • Improved adhesive	K212132
Raman Spectroscopy	N/A	• Non-invasive • Demonstrated safety • Calibration stability for 15 days • Accurate for a variety of skin tones	N/A
Zinc Oxide Micropipette Tip	N/A	• Uses an affordable plastic to reduce cost • Faster electron transfer	N/A

contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory" which meets the conditions of being: 1) recognized in the official National Formulary, the United States Pharmacopeia, or any supplement to them; 2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in humans or other animals; or 3) intended to affect the structure or any function of the body of humans or other animals, and does not achieve its primary intended purposes through chemical action within or on the body of humans or other animals nor is dependent on being metabolized to achieve its primary intended purposes (37). Medical devices are regulated by the Center for Devices and Radiological Health (38).

Most medical devices on the market are consecutive iterations of previous devices that have already been approved. However, if a device is completely new, it usually goes through the process of being built as a prototype and patented followed by evaluation on preclinical animal models (36). This process is cyclical with many different changes being required as the testing procedure continues and can take 2-3 years as well as $10-20 million in cost. This process is only the preclinical stage for a completely novel device and is required before it can be used in clinical trials (36).

The FDA classifies medical devices into one of three categories (Table 2). Class I devices are associated with low risk of injury or illness (such as toothbrushes), Class II have a moderate risk of injury or illness (such as sutures), and Class III have a high risk of injury or illness (such as pacemakers) (36, 39). Class III devices have the strictest requirements, whereas Class I and II devices do not require extensive preclinical or clinical trial data. All new devices which do not have a predecessor that has been FDA approved are classified as a Class III device unless the company applies for an exemption due to the device being low risk; if granted then the device is classified as a "*de novo*" device (36).

The FDA has three main pathways for approval of medical devices: pre-market approval (PMA), pre-market notification (PMN), and humanitarian device exemption (HDE) (Figure 1). Blood glucose monitoring (BGM) devices are primarily approved through either the PMA or PMN pathways (36).

The PMA pathway is used when there is not an FDA-approved pre-existing device that is equivalent to the new device. This is the pathway that must be used for approval of Class III devices unless they have been reclassified as *de novo* devices. There must be sufficient evidence to show that the device is safe for use and effective. In order to conduct this research, investigators need to obtain an investigational device exemption and institutional review board (IRB) clearance, which can lead to the approval process for research taking upwards of a year. This length of time has led to much of the testing being conducted outside of the United States (36). The level of evidence required is usually Level I or Level II evidence. Once the application has been submitted and approved, the device is considered to be "FDA approved" (39).

The PMN pathway, also known as the 510(K) application, is used when there is already an existing device on the market that is similar to the new device. This is a fast-tracked process that requires demonstration that the new device is substantially equivalent to the device that is currently approved and is available in the market (36).

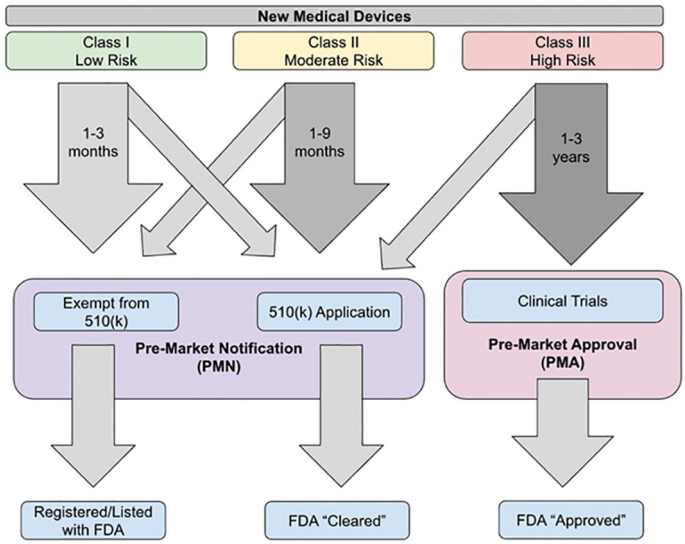

FIGURE 1
A schematic representation of FDA approval procedure.

This is the primary approval pathway for Class I, Class II, and *de novo* devices. For this pathway, preclinical data is usually sufficient and clinical trial data is not generally required (39). There are some critiques of this pathway, including concerns over "serial predicates" in which a device is approved using an existing device as its predicate, even though that existing device was approved using another device as its predicate; such serial predicates may be traced back through several generations of devices. This can leave a substantial gap between the newest device approved and the last device to go through rigorous testing, with many predicate devices in between (36). Once a device is approved through the PMN pathway, it is considered to be "FDA cleared" (39).

TABLE 2 Summary of medical device classification.

Classification	Risk	Pathway	Examples
Class I	Minimal	No FDA approval needed Device registered with FDA website 30-90 days	Toothbrushes
			Adhesive Bandages
			Sanitary Pads
			Tongue Depressors
Class II	Moderate	FDA clearance required "Pre-Market Notification" (PMN) 510(k) Application 1-9 months	Continuous Blood Glucose Monitors
			Ultrasound
			Sutures
			Blood Pressure Cuffs
Class III	High	FDA approval required Requires clinical trials "Pre-Market Approval" (PMA) 1-3 years	Pacemakers
			Defibrillators
			Implanted prosthetics
			Cochlear implants

Prior to 2018, the FDA required CGM devices to be classified as Class III devices, meaning that they were required to go through the more stringent PMA pathway. In 2018, however, the Dexcom G6 was classified as a Class II device and has criteria known as special controls. This has allowed subsequent CGM devices to go through the less strict 510(K) pathway (40–42).

The FDA also has requirements for self-monitoring over-the-counter blood glucose devices that are intended to protect the lay person using these devices (42, 43). The lay person must be able to prick their own finger and perform the blood glucose measurement using only the directions on the packaging of the device. As well as being accessible, the device must also demonstrate accuracy when it comes to these measurements. The FDA requires 95% of the readings to be within ± 15% of the comparator results, and 99% of the measurements to be within ± 20% of the comparator results. These requirements differ from the requirements set forth by the International Standards Organization document ISO15197, which is used in most countries in the European Union and Canada as the standard for blood glucose monitoring devices (42).

Comparison of regulatory processes between the U.S. FDA and European Union

In comparison to the FDA in the United States, the European Union has several key differences in the regulatory and approval process for medical devices and pharmaceuticals. A key difference between the EU and the U.S. in terms of medical device regulation is the absence of a centralized competent authority in the EU (44). This contrasts with the role of the U.S. FDA, which acts as a centralized body overseeing market approvals. In the U.S., once a device receives FDA approval, there is no specific time limit on how long it can remain in the market, provided it is not subject to a recall due to safety

concerns or other issues. In contrast, the EU has a different approach. Medical devices in the EU are subject to a limited validity period, typically around five years. After this period, these devices must undergo a reassessment procedure to renew their market approval (44). A comparison between the regulatory process of U.S. FDA and EMA is summarized in Supplementary Table 1.

Approximately a decade ago, the perception prevailed that European regulatory bodies were more expedient in approving medical devices, particularly in the realm of CGM devices integrated with insulin pumps, compared to the U.S. FDA. This perceived swiftness in Europe could be attributed to a variety of factors, including differing regulatory frameworks and approaches to medical device approval (44). The European system, governed by the Conformité Européenne (CE) mark, often allowed for a quicker path to the market for medical devices. This process was seen as less cumbersome compared to the U.S. FDA's stringent Premarket Approval (PMA) or 510(k) clearance procedures, especially for novel medical technologies. The European Medicines Agency (EMA) and various national regulatory agencies in Europe had an approach that many believed to be more facilitative for rapid introduction of new medical devices (44).

However, in recent years, there appears to be a shift in this dynamic. More often, medical devices, including CGM systems and insulin pumps, are receiving approval in the U.S. before being approved in Europe. Several factors might contribute to this change. A significant number of medical device manufacturers are based in the U.S. These companies may prioritize the U.S. FDA approval to first enter their domestic market, which is one of the largest for medical devices globally (44). In addition, the U.S. FDA has made efforts to streamline its approval process, especially for successor devices or those that represent incremental innovations over existing technologies. This change is partly in response to criticisms of the U.S. FDA's previously lengthy and complex approval processes and is intended to foster innovation while maintaining stringent safety standards. Furthermore, the introduction of the Medical Device Regulation (MDR) in the EU, fully applied from 2021, has brought more stringent requirements for medical devices, including more rigorous clinical evidence and post-market surveillance (44). This shift could potentially slow down the approval process in Europe compared to the past. It is also possible that manufacturers may also be adapting their global strategy, considering various factors such as market size, healthcare reimbursement policies, and the competitive landscape, which could influence where and how they seek regulatory approvals. The shift in the process of regulatory approval reflects the ongoing efforts of global healthcare industry to balance innovation with patient safety and device effectiveness.

Biosensor devices

In the past few years, glucometers, the standard tool for determining blood glucose level, have become less successful and more costly. This has led to the increased popularity of biosensors, analytical instruments with a biological sensing aspect to them, that continuously monitor blood glucose rather than only at a single point in time like a glucometer (45). Biosensors come in various forms, each of which have been optimized for continuous glucose monitoring: electrochemical, optical, enzymatic, non-enzymatic, noninvasive, and real-time biosensors (46, 47) (Table 1).

Minimally invasive and non-invasive blood glucose monitoring devices have been the focus of research in recent years (33, 48–50). These devices are able to monitor blood glucose levels with minimal to no pain or discomfort, or the invasiveness that is associated with traditional methods of measuring blood glucose (33). Minimally-invasive devices, such as CGMs, sample the interstitial fluid to determine the blood glucose concentration (51, 52), while non-invasive devices use technology such as spectroscopy to measure blood glucose from the surface of the body without the need for a needlestick (35). Traditional methods of blood glucose monitoring, by comparison, are more invasive and require whole blood, plasma, or serum for the measurement (33).

Novel modification to the Clark enzyme electrode

An implantable enzyme-electrode sensor remains the most popular interstitial fluid analysis technique for CGM and was one of the first developed for consumers (53). This electrochemical biosensor is widely used but has limited sensitivity, due to a narrow working electrode (WE) area, thus dampening the accurate detection of hypoglycemia. To address this limitation, a new cylindrical, flexible enzyme-electrode with a larger WE surface area has been proposed (47). By utilizing a cylindrical substrate, the sensor overcomes the diameter constraints imposed by conventional pin-like sensors and allows for formation of a WE over not only the radius, but also along the axis of the cylindrical substrate, thus bypassing the diameter restriction. Glucose microsensors were developed by attaching an oxidase enzyme to the tip of this Clark-type oxygen microelectrode, which ranges in size from 15-40 micrometers. These sensors have proven to be rapid and highly sensitive in detecting analyte concentrations, including glucose. However, further research and development is warranted to implement the Clark enzyme electrode in a device.

One main limitation of the modified Clark enzyme electrode is its dependence on oxygen. The blood plasma concentration of dissolved metabolites, for example glucose, is measured by the oxygen electrode with a platinum cathode covered by an oxygen-permeable membrane. To measure glucose specifically, glucose oxidase is immobilized in a gel layer, allowing for the catalysis of glucose, oxygen, and water to yield gluconic acid and hydrogen peroxide. The resulting electrical current is proportional to the glucose concentration.

Senseonics eversense

Various other techniques are being investigated for glucose sensor development, such as infrared spectroscopy, which faces many limitations and challenges when it comes to frequent calibrations, poor selectivity, limited sensitivity, and

miniaturization difficulties (54, 55). One proposed approach, the fluorescence-based device Eversence, designed by Senseonics was developed and FDA approved on June 21, 2018 through the PMA pathway (56). Fluorescence glucose testing assesses signal intensity and duration of decay, and the lifetime of fluorescence differs for each analyte evaluated, thus distinguishing substances (57). This 90-day implanted sensor, after measuring glucose levels, sends information to a mobile app to alert users when there are dangerous fluctuations in blood glucose.

The FDA approved the Eversence device after a clinical study of 71 individuals aged 18 and over with T1D and T2D that reviewed the device's effectiveness by comparing readings obtained by the device to a laboratory glucose analyzer (58). The mean absolute relative difference (MARD) was found to be 11.1% and 81% of hypoglycemia events were detected within 30 minutes. No serious adverse events were reported during the study (58). While adverse effects related to inserting and wearing the device were observed, such as allergic reactions, bleeding, and bruising, the FDA ultimately granted approval of the device due to the benefits of detecting aberrant blood glucose levels outweighing the risks of not doing so (59, 60).

However, several limitations have been identified with the Senseonics Eversense device. A primary constraint is associated with the device removal process, which necessitates a skin incision for dissection to access the sensor beneath the tissue and fibrous capsule. This procedure can pose significant challenges for certain patients, potentially requiring a minor surgical intervention to facilitate the incision and sensor replacement.

Additionally, the Eversense CGM system does not display glucose readings for up to 24 hours after the device is implanted, due to damage to the surrounding tissue from the sensor. This subsequently causes less sensitivity and accuracy for several days. Errors in calibration also affect the sensor's accuracy, and there is likely to be a period of time where the device does not sense glucose at its full capacity, until its next recalibration (61).

The company that designed the Eversence device, Glysens, has been developing a new long-term CGM device called the "Eclipse" with multiple electrochemical glucose and oxygen electrodes that measure glucose at five-minute intervals, providing a more accurate reading and remaining significantly more stable between recalibration periods. This device has been functioning well, maintaining accuracy for more than one year during both animal and human clinical trials. Moreover, when a new sensor is implanted in the same site as a fibrous capsule from the previous sensor, it has no effect on the functioning of this device (61).

MiniMed™ 780G and guardian 4™ sensor

CGM devices are often used in conjunction with automated insulin delivery (AID) devices that use the CGM data to maximize percentage TIR and reduce the amount of time patients spend in a hypoglycemic or hyperglycemic state (62). AID systems using CGM technology have previously demonstrated improvements in HbA1c and percentage TIR in randomized control trials when compared with fingerstick blood glucose monitoring (63–65). Improvements in percentage TIR have been shown to increase TIR by 3.6 hours per day when using AID and CGM technology compared to traditional fingerstick measurements (63). Participants using AID and CGM devices were also shown to have a reduction in HbA1c of 1.42% compared to traditional methods (65).

The MiniMed™ 670G with the Guardian™ sensor 3 was shown to be safe and effective in a 90-day multicenter single-arm study composed of adolescents and adults (66). Safety was demonstrated by having zero adverse or unexpected device effects and zero episodes of DKA during the study period. The study found statistically significant reductions in HbA1c in the adolescent group, the adult group, and overall; the overall reduction in HbA1c was 0.5% during the 90 days (66). There were also statistically significant improvements in %TIR for adolescents, adults, and overall, with the overall %TIR rising from 68% to 72.1% over the study period. The overall MARD was 10.6% (62). The MiniMed™ 670G with the Guardian™ Sensor 3 is the predecessor to the newer MiniMed™ 780G advanced hybrid closed-loop system with the Guardian™ 4 Sensor (66).

In a 3-month multi-center, single-arm, non-randomized study, the MiniMed™ 780G advanced hybrid closed-loop system with the Guardian™ 4 sensor was shown to be safe and reduced the management burden of T1D in both adults and children (62). Safety was shown by having zero serious adverse effects including diabetic ketoacidosis and severe hypoglycemia. Reduction in T1D management burden was shown by having minimal advanced hybrid closed loop system exits, with an average of 0.1 exit per day in both the pediatric and adult groups (62). Percent time below range (%TBR) <54 mg/dL (level 2 hypoglycemia) was 7.8 minutes per day for participants ≤15 years old and 4.8 minutes per day for participants >15 years old. This demonstrates a very low amount of time spent in level 2 hypoglycemia and is a 0.4% reduction (6 minutes/day) compared to using the Guardian™ sensor 3. There have been further improvements from the Guardian™ Sensor 3 with regard to the number of daily blood glucose measurements (BGMs). The number of BGMs in adults decreased from 4.0 ± 1.0 per day to 0.8 ± 0.9 per day when going from the Guardian™ sensor 3 to the Guardian™ 4 sensor. In children this number went from 4.2 ± 1.2 per day to 0.8 ± 0.9 per day (62). The MiniMed 780G and Guardian™ sensor 3 was FDA approved through the PMA pathway on March 8, 2018 (67).

This device has many advantages as demonstrated by its safety, improvements in user's glycemic control, reduction in T1D burden, and FDA approval (63, 67). Disadvantages include the invasive nature of this device and lag time. Although it is minimally invasive, it still requires a needle to sample the interstitial fluid, which can be uncomfortable for users. There is also a lag in time between changes in blood glucose and the device's recognition of this change. This is due to the fact that the device is minimally invasive and therefore samples the interstitial fluid instead of the blood (33).

Dexcom G6

Dexcom G6 is a minimally-invasive CGM that has previously been shown to be efficacious in individuals with T1D by increasing

TIR by 3.5 hours per day, with the greatest improvements in %TIR in those who use more of the device's additional features (68, 69). Additional features include more specific blood glucose alarms, Dexcom CLARITY™ software for analysis, remote monitoring, and a notification system that announces the user's blood glucose and trends. Dexcom G6 always notifies users when blood glucose levels are low, however it also has a smartphone app which allows users to receive more specific notifications about their blood glucose. These additional alarms include warnings about high blood glucose and soon to be low blood glucose (blood glucose ≤55 mg/dL predicted in the next 20 minutes). Users can adjust the thresholds for these alarms with high blood glucose ranging from 120-400 mg/dL and low blood glucose ranging from 60-100 mg/dL (69). Dexcom G6 was FDA cleared through the PMN (510K) pathway on October 26, 2018 (70).

In recent years CGM devices have gained popularity in clinical trials evaluating the efficacy of diabetes medications. Out of all diabetes medication clinical trials from 2013-2019, 9% used CGM devices compared to 2.7% from 2000-2006 and 5.6% from 2007-2012 (71). This is, in part, due to the significant increase in hypoglycemic events that the devices are able to capture compared to using finger stick measurements, especially at night (72).

In a 12-week, phase 4 multicenter, randomized, active-controlled, parallel group, open-label study, Dexcom G6 was used to measure TIR when comparing two basal insulin (BI) analogues, insulin glargine 300 U/ml (Gla-300) and insulin degludec 100 U/ml (IDeg-100) in adults with T1D (73). The CGM data was used to measure hypoglycemic events, %TIR, %TAR, and %TBR in this study to compare the two BIs. In addition, self-measured plasma glucose (SMPG) was also measured and compared against the CGM data to compare rates of hypoglycemic events (<70 mg/dL). Dexcom G6 was shown to capture 2-6 times more hypoglycemic events in patients with T1D compared to SMPG during the same time period. The most prominent difference was with nocturnal hypoglycemic events (73). This is the first large RCT to use CGM data to assess the efficacy and safety of these two BIs in people with T1D (73). However, the use of CGM data in BI research has been increasing in recent years, which is in line with the overall increase in CGM usage in clinical trials. From 2013-2019, 10.7% of BI clinical trials used CGM data, which is an increase from 4.8% from 200-2006 and 8.8% from 2007-2012 (74). No major adverse events were reported, and the safety profile was in line with prior models (73).

Dexcom G6 has shown many advantages including improvements in user's %TIR, its variety of additional features, the ability to capture more hypoglycemic events, and its FDA clearance (68, 69, 71, 73). The disadvantages of this device are similar to the MiniMed™ 780G and Guardian 4™ Sensor as they are both minimally-invasive devices that sample the interstitial fluid. This includes user discomfort due to the use of a needle and the lag-time between changes in blood glucose and device recognition of these changes in the interstitial fluid (33). Another drawback of the device is its required 2-hour warm-up period. This can be inconvenient for those who require immediate glucose readings, as they will be unable to obtain such information instantly during this time (75, 76).

Dexcom G7

Dexcom G7 is a CGM that was cleared by the FDA on December 7, 2022 via the PMN pathway (77). In a 10.5-day non-randomized, multicenter, single-arm study of 316 adults with T1D or T2D, the overall MARD was 8.2% for arm-placed sensors and 9.1% for abdomen-placed sensors (78). The proportion of CGM values within 15% of the control values >100 mg/dL or within 15 mg/dL of control values ≤ 100 mg/dL (%15/15) as well as the %20/20 and %30/30 were reported. The control values were measured using the YSI 2300 STAT PLUS Glucose Analyzer (78). For arm-placed sensors, overall %15/15 rates were 89.6%, overall %20/20 rates were 93.2%, and %30/30 rates were 98.8%. For abdomen-placed sensors, overall %15/15 rates were 85.5%, overall %20/20 rates were 93.2%, and overall %30/30 rates were 98.1%. No major adverse events were reported during the study (78).

The Dexcom G7 offers enhancements over its predecessor, the Dexcom G6. The warmup time was shortened from 2 hours to 27 minutes, the wear length was extended from 10 days to 10.5 days, and the thickness and size of the transmitter was significantly reduced (75, 76). Dexcom G7 carries over many similar features from the Dexcom G6 such as a smartphone app, measuring glucose every 5 minutes, and sending the user smartphone alerts for aberrant glucose levels 75. Although the warm-up time has seen improvement, it is still quite long when compared to other devices that warm up in just seconds. This presents a disadvantage for users who need quick glucose measurements (79).

FreeStyle Libre 3

FreeStyle Libre 3 is a CGM that was cleared by the FDA on May 26, 2022 via the PMN pathway (80). In a 14-day non-randomized, multicenter, single-arm study of 108 participants ≥ 6 years old with T1D or T2D, the overall MARD was 7.8% and a %20/20 rate of 93.4% compared to the control values. The control in this study was plasma venous blood glucose levels measured using the YSI 2300 STAT PLUS Glucose and Lactate Analyzer. No major adverse events were reported (81).

The advantages of FreeStyle Libre 3 are evident in its advancements over the FreeStyle Libre 2. It takes measurements every minute and transmits this data to a smartphone app. This is in contrast to the FreeStyle Libre 2, which required the user to scan the device with a smartphone to obtain glucose measurements (79, 82). This allows for the device to continuously upload data to the app and alert the user when their blood glucose is too high or too low in real-time, as opposed to the prior version which required the user to scan the device to obtain measurements (79). FreeStyle Libre 3 also has one of the lowest MARDs of available CGM devices (79). This device also has advantages in line with other CGMs, such as being minimally invasive and reducing the need for needle-sticks (79).

The disadvantages of the device encompass its 1-hour warm-up time, which may be inconvenient for individuals requiring a glucose reading shortly after inserting the device (79).

Raman spectroscopy

Raman spectroscopy is a non-invasive method of blood glucose measurement that uses light on the skin to vibrate glucose molecules with the resultant vibrations being used to measure blood glucose concentrations (83). The fundamental setup of a Raman spectrometer includes a lens that captures a portion of the scattered radiation and guides it to a filter, allowing only the Raman scattered light to be detected by the sensor (Figure 2). Research in preclinical animal models and human subjects has demonstrated that blood glucose concentrations are able to be measured from the skin using Raman spectroscopy (84, 85). Despite these findings, there have been few clinically significant devices using this technology. The C8 MediSensor was a CE-approved (Conformité Européene) device that used Raman technology, but it no longer exists due to lack of funding and was never FDA approved (83, 86). This lack of CE or FDA approved devices is due in part to challenges with accuracy and calibration stability with non-invasive devices in general (83).

Difficulties with accuracy stem from the non-invasive nature of these devices. Since they measure blood glucose concentrations indirectly, they are more susceptible to measuring physiologic variables other than glucose or having the measurement of blood glucose be disrupted by signals from external sources (87). Device calibration is another challenge faced by these devices as it typically requires frequent and lengthy processes to retain their peak accuracy (88, 89). A device that needs a high level of calibration may not have practical implications for the daily user.

However, there have been recent advances in Raman spectroscopy devices. The Raman non-invasive glucose monitor is a portable, battery-operated device with built-in safety features, WiFi capabilities, and a graphical user interface. This device uses light to measure the levels of blood glucose which is a non-invasive method of detection. The device is confocal, ensuring that the signal measured originates from the upper layers of living skin while the signal from outer layers of dead skin is suppressed. Confocality also increases the consistency of the Raman spectrum by reducing the dependency of the device-skin interface on the collected Raman signal (89).

In a clinical study, the Raman non-invasive glucose monitor was shown to be safe and maintaining calibration stability (90). However, the device was shown to have a slightly less pronounced Raman peak for darker skin colors. As the Raman peaks do not markedly differ in the thenar spectra, where the information regarding physiological glucose concentrations is found, this issue should not be of high concern (90). The device was also shown to have calibration stability by remaining stable over 15 days after the final calibration without professional stabilization. For patients with T1D, the MARD for the device is 19.9%, which is comparable to early CGM on enzyme electrodes which had a MARD between 8.8 and 19.9% (90). The advantages of this device include its safety, calibration stability, accuracy regardless of skin tone, and non-invasive nature. The disadvantages include its lack of FDA approval, the need to recalibrate after 15 days of use, and the bulky non-wearable design of the device (90).

ZnO micropipette tips

For all glucose monitoring biosensors, electrochemical measurement is a central component that provides a highly sensitive and selective measurement of blood glucose, allowing for a wide range of detection. Additionally, it allows for the miniaturization of components, so that analysis can be performed in small volumes or even in the absence of an electrolyte. Many component materials have been tested, such as gold, silver, and platinum but such manufacturing of microelectrodes is costly (91). A cheaper alternative such as plastic is one possible substitute for the miniaturized component, most notably for micropipettes due to their cost and commercial availability.

On the other hand, other materials with more innate electrochemical detection properties, such as semiconducting metal oxides, have proven to be useful in biosensing. Zinc oxide

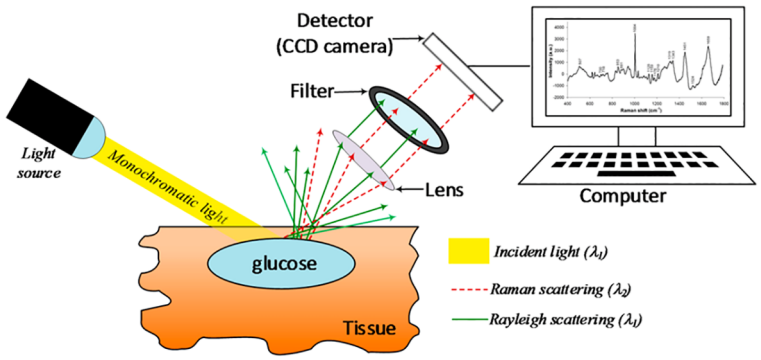

FIGURE 2
Schematic representation of a basic Raman spectroscopy instrument. Taken from Villena Gonzales (33) under the terms and conditions of the Creative Commons Attribution.

(ZnO) has shown to have a faster electron transfer and larger reaction surface coverage. Because of these enhanced properties, a modified working electrode has been developed by growing ZnO directly on the plastic micropipettes themselves, making it a novel technique for blood glucose monitoring (91). This technique has not yet been translated to any specific CGM device; therefore, it has not been FDA approved.

Table 3 provides a detailed summary of the clinical trials that were pivotal in securing FDA approval for various CGM systems.

Conclusion and future directions

Devices designed to continuously monitor blood glucose play a pivotal role in alleviating the burden of disease associated with T1D and represent a significant advancement in diabetes management. By providing real-time insights into glucose levels, CGM devices have transformed the way individuals with diabetes monitor and manage their condition. They offer a higher degree of freedom and control compared to traditional blood glucose testing methods, leading to improved glycemic control and quality of life for many users. Recent advancements in CGM technology, including increased accuracy, user-friendliness, and integration with insulin pumps as well as mobile devices, have further enhanced their appeal.

With the implementation of these glucose monitoring devices, individuals with T1D become empowered to learn about their condition, lifestyle modifications, treatment options, and long-term complications (22, 26, 27). Poor glycemic control can lead to retinopathy, neuropathy, and diabetic nephropathy, all of which can be avoided through meticulous monitoring of glucose levels and symptoms (7, 9–14). The real-time advantage of CGM leads to better health outcomes, both for the individuals with T1D and their providers. However, challenges remain, including the need for broader accessibility, affordability, and education to ensure that more people can benefit from this technology.

CGM devices hold a significant potential not only for managing T1D but also for T2D and gestational diabetes mellitus (GDM) (92–102). This adaptability is crucial, not only for the individual patient but also for the broader diabetes community. The expansion of CGM use into the T2D population and GDM could have several beneficial outcomes, enhancing diabetes care on multiple fronts. Firstly, the wider application of CGM devices across both T1D and

TABLE 3 Key clinical trials and FDA approval milestones for continuous glucose monitoring (CGM) systems.

Device/ Technology	Description of Trial	Key Findings	FDA Approval Date	Reference
Novel Modification to the Clark Enzyme Electrode	• *In vitro* experiments showing the sensor's ability to detect physiologic glucose ranges. • *In vivo* experiments in rats showing comparable results to commercial CGMs.	N/A	N/A	Pu et al. (47)
Senseonics Eversense	• 180-day multinational, multicenter pivotal trial with 71 participants aged 18 years or older with type 1 and type 2 diabetes. • Accuracy was assessed based on comparison with venous glucose values.	• No major adverse events reported • The device has a MARD of 11.1% • The benefit of detecting aberrant glucose levels outweighs the minor adverse effects related to wearing and inserting the device	June 21, 2018	Kropff et al. (57)
MiniMed™ 780G and Guardian 4™ Sensor	• 90-day multicenter, single-arm non-randomized study of adolescents and adults. Glycemic outcomes were assessed by measuring %TIR, %TBR, %TAR, and HbA1c.	• No major adverse events reported • Minimal system exits • Improvements in %TBR • Decreased numbers of daily blood glucose measurements	March 8, 2018	Cordero et al. (61)
Dexcom G6	• 24-week multicenter, open-labeled, randomized, controlled trial of 97 adult and pediatric patients with T1D. • Dexcom G6 was compared to a sensor-augmented insulin pump. • Outcomes were measured using TIR.	• No major adverse events reported • Increased TIR by 3 hours and 21 minutes	October 26, 2018	Burnside et al. (67)
Dexcom G7	• 10.5-day non-randomized, multicenter, single-arm study of 316 adults with T1D or T2D. • Dexcom G7 was compared to venous blood glucose sampling. • Outcomes were measured using %15/15, %20/20, and %30/30, and MARD.	• No major adverse events reported • Overall MARD of 8.2% for arm-based sensors and 9.1% for abdomen-placed sensors • %15/15 of 85.5% • %20/20 of 93.2% • %30/30 of 98.1%	December 7, 2022	Garg et al. (77)
FreeStyle Libre 3	• 14-day non-randomized, multicenter, single-arm study of 108 participants aged 6 years and older with T1D and T2D. • FreeStyle Libre 3 was compared to venous blood glucose sampling. • Outcomes were measured using %20/20 and MARD.	• No major adverse events reported • Overall MARD of 7.8% • %20/20 of 93.4%	May 26, 2022	Alva et al. (80)

T2D populations as well as for GDM can accelerate technological advancements. As demand increases, there is greater motivation for manufacturers to invest in research and development. This could lead to innovations in accuracy, user-friendliness, and integration with other health management tools. Secondly, an increase in the scale of production and adoption of CGM devices could potentially lead to a decrease in cost. Reduced prices would be particularly beneficial for individuals and healthcare systems that currently find cost a barrier to accessing advanced diabetes management tools. Furthermore, the widespread use of CGM devices in T2D and GDM care could significantly improve the availability of modern blood glucose monitoring solutions. Increased demand would likely encourage manufacturers to enhance production capabilities and distribution networks, making these devices more readily available to patients globally. CGM devices may become a standard component of diabetes care for all individuals with the condition, particularly in regions with well-developed healthcare systems. The integration of CGM devices into routine diabetes management can revolutionize care, offering real-time glucose monitoring, reducing the need for invasive finger-prick tests, and providing valuable data for more personalized treatment plans. In summary, the expansion of CGM use from T1D to T2D patients as well as for GDM represents an opportunity to advance diabetes care on a global scale. It could catalyze technological innovation, make diabetes management more cost-effective, and enhance the availability of cutting-edge monitoring tools, ultimately improving the quality of life for all patients with diabetes mellitus.

Blood glucose monitoring technologies have been expanding in recent years, especially in the area of minimally invasive and non-invasive devices (33). While there are FDA approved and cleared minimally-invasive devices, such as the Dexcom G6 and MiniMed™ 780G with Guardian™ 4 Sensor, there is still a paucity of non-invasive devices (66, 69, 73). This deficiency is not attributed to a lack of viable non-invasive technologies but rather stems from various challenges encountered in translating such technologies into functional devices for consumers and ensuring their market availability (86–88). The ongoing research and development hold the potential for the evolution of more sophisticated CGM systems in the future. These advancements may include the integration of predictive analytics and artificial intelligence, offering more personalized strategies for diabetes management. The accessibility of these advanced CGM devices is set to more effectively meet the needs of individuals having T1D, with the ultimate goal of enhancing their overall quality of life.

Author contributions

RM: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. NK: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. JM: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. JL: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. KH: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1352302/full#supplementary-material

References

1. Quattrin T, Mastrandrea LD, Walker LSK. Type 1 diabetes. *Lancet Lond Engl.* (2023) 401:2149–62. doi: 10.1016/S0140-6736(23)00223-4

2. Ong KL, Stafford LK, McLaughlin SA, Boyko EJ, Vollset SE, Smith AE, et al. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*. (2023) 402:203–34. doi: 10.1016/S0140-6736(23)01301-6

3. Tönnies T, Brinks R, Isom S, Dabelea D, Divers J, Mayer-Davis EJ, et al. Projections of type 1 and type 2 diabetes burden in the U.S. Population aged <20 years through 2060: the SEARCH for diabetes in youth study. *Diabetes Care*. (2023) 46:313–20. doi: 10.2337/dc22-0945

4. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. *Lancet.*(2014) 383:69–82. doi: 10.1016/S0140-6736(13)60591-7

5. Vanderniet JA, Jenkins AJ, Donaghue KC. Epidemiology of type 1 diabetes. *Curr Cardiol Rep*. (2022) 24:1455–65. doi: 10.1007/s11886-022-01762-w

6. Ehrmann D, Kulzer B, Roos T, Haak T, Al-Khatib M, Hermanns N. Risk factors and prevention strategies for diabetic ketoacidosis in people with established type 1 diabetes. *Lancet Diabetes Endocrinol*. (2020) 8:436–46. doi: 10.1016/S2213-8587(20)30042-5

7. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet Lond Engl.* (2018) 391:2449–62. doi: 10.1016/S0140-6736(18)31320-5

8. Saner C. Long-term cardiovascular and non-cardiovascular mortality in women and men with type 1 and type 2 diabetes mellitus: A 30-year follow-up in Switzerland. *Swiss Med Wkly*. (2009) 139:576–83. doi: 10.4414/smw.2009.12785

9. Huo L, Harding JL, Peeters A, Shaw JE, Magliano DJ. Life expectancy of type 1 diabetic patients during 1997–2010: a national Australian registry-based cohort study. *Diabetologia*(2016) 59:1177–85. doi: 10.1007/s00125-015-3857-4

10. Daneman D. Type 1 diabetes. *Lancet*. (2006) 367:847–58. doi: 10.1016/S0140-6736(06)68341-4

11. Malone JI, Gao X, Lorenzi GM, Raskin P, White NH, Hainsworth DP, et al. Retinopathy during the first 5 years of type 1 diabetes and subsequent risk of advanced retinopathy. *Diabetes Care*. (2022) 46:680–6. doi: 10.2337/dc22-1711

12. Mangelis A, Wijewickrama P, Nirmalakumaran A, Fountoulakis N, Vas P, Webster L, et al. People with type 1 diabetes of african caribbean ethnicity are at increased risk of developing sight-threatening diabetic retinopathy. *Diabetes Care*. (2023) 46:1091–7. doi: 10.2337/dc22-2118

13. Vujosevic S, Aldington SJ, Silva P, Hernandez C, Scanlon P, Peto T, et al. Screening for diabetic retinopathy: new perspectives and challenges. *Lancet Diabetes Endocrinol*. (2020) 8:337–47. doi: 10.1016/S2213-8587(19)30411-5

14. Galiero R, Caturano A, Vetrano E, Beccia D, Brin C, Alfano M, et al. Peripheral neuropathy in diabetes mellitus: pathogenetic mechanisms and diagnostic options. *Int J Mol Sci*. (2023) 24:3554. doi: 10.3390/ijms24043554

15. Packer CF, Ali SA, Manna B. *Diabetic ulcer* (2024). StatPearls. StatPearls Publishing. Available online at: http://www.ncbi.nlm.nih.gov/books/NBK499887/ (Accessed February 4, 2024).

16. Harjutsalo V, Kallio M, Forsblom C, Groop PH. The impact of diabetic nephropathy and severe diabetic retinopathy on chronic limb threatening ischemia risk in individuals with type 1 diabetes: a nationwide, population study. *Lancet Reg Health - Eur*. (2023) 28:100594. doi: 10.1016/j.lanepe.2023.100594

17. *Understanding A1C | ADA* . Available online at: https://diabetes.org/diabetes/a1c (Accessed September 19, 2023).

18. Pettus JH, Zhou FL, Shepherd L, Mercaldi K, Preblick R, Hunt PR, et al. Differences between patients with type 1 diabetes with optimal and suboptimal glycaemic control: A real-world study of more than 30 000 patients in a US electronic health record database. *Diabetes Obes Metab*. (2020) 22:622–30. doi: 10.1111/dom.13937

19. American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes—2021. *Diabetes Care*. (2021) 44:S73–84. doi: 10.2337/dc21-S006

20. American Diabetes Association. 13. Children and adolescents: standards of medical care in diabetes 2021. *Diabetes Care*. (2021) 44:S180–99. doi: 10.2337/dc21-S013

21. Sundberg F, deBeaufort C, Krogvold L, Patton S, Piloya T, Smart C, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Managing diabetes in preschoolers. *Pediatr Diabetes.*(2022) 23:1496–511. doi: 10.1111/pedi.13427

22. Piona C, Marigliano M, Mozzillo E, Rosanio F, Zanfardino A, Iafusco D, et al. Relationships between HbA1c and continuous glucose monitoring metrics of glycaemic control and glucose variability in a large cohort of children and adolescents with type 1 diabetes. *Diabetes Res Clin Pract*. (2021) 177:108933. doi: 10.1016/j.diabres.2021.108933

23. Patel MR, Anthony Tolentino D, Smith A, Heisler M. Economic burden, financial stress, and cost-related coping among people with uncontrolled diabetes in the U. *S. Prev Med Rep*. (2023) 34:102246. doi: 10.1016/j.pmedr.2023.102246

24. Parker ED, Lin J, Mahoney T, Ume N, Yang G, Gabbay RA, et al. Economic costs of diabetes in the U.S. @ in 2022. *Diabetes Care*. (2023) 47:26–43. doi: 10.2337/dci23-0085

25. Simeone JC, Shah S, Ganz ML, Sullivan S, Koralova A, LeGrand J, et al. Healthcare resource utilization and cost among patients with type 1 diabetes in the United States. *J Manag Care Spec Pharm*. (2020) 26:1399–410. doi: 10.18553/jmcp.2020.26.11.1399

26. 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) 21:66–72. doi: 10.1089/dia.2018.0384

27. Hirsch IB, Welsh JB, Calhoun P, Puhr S, Walker TC, Price DA. Associations between HbA1c and continuous glucose monitoring-derived glycaemic variables. *Diabetes Med*. (2019) 36:1637–42. doi: 10.1111/dme.14065

28. Tang L, Chang SJ, Chen CJ, Liu JT. Non-invasive blood glucose monitoring technology: A review*Sensors.*(2020) 20:6925. doi: 10.3390/s20236925

29. López Albalat A, Sanz Alaman MB, Dejoz Diez MC, Martinez-Millana A, Traver Salcedo V. (2019). Non-invasive blood glucose sensor: A feasibility study, in: *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. (IEEE), pp. 1179–82. IEEE. doi: 10.1109/EMBC.2019.8857261

30. Bent B, Cho PJ, Wittmann A, Thacker C, Muppidi S, Snyder M, et al. Non-invasive wearables for remote monitoring of HbA1c and glucose variability: proof of concept. *BMJ Open Diabetes Res Care*. (2021) 9:e002027. doi: 10.1136/bmjdrc-2020-002027

31. Nazha HM, Darwich MA, Ismaiel E, Shahen A, Nasser T, Assaad M, et al. Portable infrared-based glucometer reinforced with fuzzy logic. *Biosensors.*(2023) 13:991. doi: 10.3390/bios13110991

32. Anand PK, Shin DR, Memon ML. Adaptive boosting based personalized glucose monitoring system (PGMS) for non-invasive blood glucose prediction with improved accuracy*Diagnostics.*(2020) 10:285. doi: 10.3390/diagnostics10050285

33. Villena Gonzales W, Mobashsher A, Abbosh A. The progress of glucose monitoring—A review of invasive to minimally and non-invasive techniques, devices and sensors. *Sensors.*(2019) 19:800. doi: 10.3390/s19040800

34. Caduff A, Hirt E, Feldman Y, Ali Z, Heinemann L. First human experiments with a novel non-invasive, non-optical continuous glucose monitoring system. *Biosens Bioelectron.*(2003) 19:209–17. doi: 10.1016/S0956-5663(03)00196-9

35. Vashist SK. Continuous glucose monitoring systems: A review. *Diagnostics.*(2013) 3:385–412. doi: 10.3390/diagnostics3040385

36. Van Norman GA. Drugs, devices, and the FDA: part 2. *JACC Basic Transl Sci*. (2016) 1:277–87. doi: 10.1016/j.jacbts.2016.03.009

37. U.S. Congress. *Federal food drug and cosmetics act 21 U.S.C.* (1938). Available at: https://www.law.cornell.edu/rio/citation/52_Stat._1040.

38. Naghshineh N, Brown S, Cederna PS, Levi B, Lisiecki J, D'Amico RA, et al. Demystifying the U.S. Food and drug administration: understanding regulatory pathways. *Plast Reconstr Surg*. (2014) 134:559–69. doi: 10.1097/PRS.0000000000000477

39. Kirsh D. Exploring FDA approval pathways for medical devices, in: *MassDevice* (2019). Available online at: https://www.massdevice.com/exploring-fda-approval-pathways-for-medical-devices/ (Accessed July 10, 2023).

40. U.S. Food & Drug Administration. FDA authorizes first fully interoperable continuous glucose monitoring system, streamlines review pathway for similar devices. *Case Med Res* (2018) FDA Press release. doi: 10.31525/fda2-ucm602870.htm.

41. U.S. Food and Drug Administration. Self-monitoring blood glucose test systems for over-the-counter use - guidance for industry and food and drug administration staff.

42. Katz LB, Stewart L, King D, Cameron H. Meeting the new FDA standard for accuracy of self-monitoring blood glucose test systems intended for home use by lay users. *J Diabetes Sci Technol*. (2020) 14:912–6. doi: 10.1177/1932296820906184

43. Darrow JJ, Van de Wiele V, Beran D, Kesselheim AS. An empirical review of key glucose monitoring devices: product iterations and patent protection. *J Diabetes Sci Technol*. (2023) 193229682311780. doi: 10.1177/19322968231178016

44. Fink M, Akra B. Comparison of the international regulations for medical devices–USA versus Europe. *Injury.*(2023) 54:110908. doi: 10.1016/j.injury.2023.110908

45. Jin X, Li G, Xu T, Su L, Yan D, Zhang X. Fully integrated flexible biosensor for wearable continuous glucose monitoring. *Biosens Bioelectron.*(2022) 196:113760. doi: 10.1016/j.bios.2021.113760

46. Shoaib A, Darraj A, Khan ME, Azmi L, Alalwan A, Alamri O, et al. A nanotechnology-based approach to biosensor application in current diabetes management practices. *Nanomaterials.*(2023) 13:867. doi: 10.3390/nano13050867

47. Pu Z, Tu J, Han R, Zhang X, Wu J, Fang C, et al. A flexible enzyme-electrode sensor with cylindrical working electrode modified with a 3D nanostructure for implantable continuous glucose monitoring. *Lab Chip*. (2018) 18:3570–7. doi: 10.1039/C8LC00908B

48. Lubinski T, Plotka B, Janik S, Canini L, Mäntele W. Evaluation of a novel noninvasive blood glucose monitor based on mid-infrared quantum cascade laser technology and photothermal detection. *J Diabetes Sci Technol*. (2020) 15:6–10. doi: 10.1177/1932296820936634

49. Handy C, Chaudhry MS, Qureshi MRA, Love B, Shillingford J, Plum-Mörschel L, et al. Noninvasive continuous glucose monitoring with a novel wearable dial resonating sensor: A clinical proof-of-concept study. *J Diabetes Sci Technol*. (2023) 19322968231170242. doi: 10.1177/19322968231170242

50. Tehrani F, Teymourian H, Wuerstle B, Kavner J, Patel R, Furmidge A, et al. An integrated wearable microneedle array for the continuous monitoring of multiple biomarkers in interstitial fluid. *Nat BioMed Eng.*(2022) 6:1214–24. doi: 10.1038/s41551-022-00887-1

51. Xu N, Zhang M, Xu W, Ling G, Yu J, Zhang P. Swellable PVA/PVP hydrogel microneedle patches for the extraction of interstitial skin fluid toward minimally invasive monitoring of blood glucose level. *Analyst*. (2022) 147:1478–91. doi: 10.1039/D1AN02288A

52. Cobelli C, Schiavon M, Dalla Man C, Basu A, Basu R. Interstitial fluid glucose is not just a shifted-in-time but a distorted mirror of blood glucose: insight from an in silico study. *Diabetes Technol Ther*. (2016) 18:505–11. doi: 10.1089/dia.2016.0112

53. Peteu SF, Emerson D, Mark Worden R. A Clark-type oxidase enzyme-based amperometric microbiosensor for sensing glucose, galactose, or choline. *Biosens Bioelectron.*(1996) 11:1059–71. doi: 10.1016/0956-5663(96)87665-2

54. Delbeck S, Heise HM. Evaluation of opportunities and limitations of mid-infrared skin spectroscopy for noninvasive blood glucose monitoring. *J Diabetes Sci Technol*. (2020) 15:19–27. doi: 10.1177/1932296820936224

55. Olivieri AC, Faber NM, Ferré J, Boqué R, Kalivas JH, Mark H. Uncertainty estimation and figures of merit for multivariate calibration (IUPAC Technical Report). *Pure Appl Chem*. (2006) 78:633–61. doi: 10.1351/pac200678030633

56. *Devices at FDA*. Available online at: https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pma&id=394265 (Accessed February 11, 2024).

57. Irace C, Cutruzzolà A, Tweden K, Kaufman FR. Device profile of the eversense continuous glucose monitoring system for glycemic control in type-1 diabetes: overview of its safety and efficacy. *Expert Rev Med Devices.*(2021) 18:909–14. doi: 10.1080/17434440.2021.1982380

58. Kropff J, Choudhary P, Neupane S. Accuracy and longevity of an implantable continuous glucose sensor in the PRECISE study: A 180-day, prospective, multicenter, pivotal trial. *Diabetes Care*. (2017) 40:63–8. doi: 10.2337/dc16-1525

59. Devices at FDA. Available online at: https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pma&id=394265 (Accessed June 23, 2023).

60. *Commissioner O of the. FDA approves first continuous glucose monitoring system with a fully implantable glucose sensor and compatible mobile app for adults with diabetes* (2020). FDA. Available online at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-continuous-glucose-monitoring-system-fully-implantable-glucose-sensor-and (Accessed June 22, 2023).

61. Joseph JI. Review of the long-term implantable senseonics continuous glucose monitoring system and other continuous glucose monitoring systems. *J Diabetes Sci Technol*. (2020) 15:167–73. doi: 10.1177/1932296820911919

62. Cordero DTL, Dai DZ, Arrieta A, Niu F, Vella M, Shin J, et al. Glycemic outcomes during early use of the MiniMed™ 780G advanced hybrid closed-loop system with Guardian™ 4 sensor. *Diabetes Technol Ther*. (2023), 652–658. doi: 10.1089/dia.2023.0123

63. McAuley SA, Lee MH, Paldus B, Vogrin S, de Bock MI, Abraham MB, et al. Six months of hybrid closed-loop versus manual insulin delivery with fingerprick blood glucose monitoring in adults with type 1 diabetes: A randomized, controlled trial. *Diabetes Care*. (2020) 43:3024–33. doi: 10.2337/dc20-1447

64. Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC, et al. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. *N Engl J Med*. (2019) 381:1707–17. doi: 10.1056/NEJMoa1907863

65. Choudhary P, Kolassa R, Keuthage W, Kroeger J, Thivolet C, Evans M, et al. Advanced hybrid closed loop therapy versus conventional treatment in adults with type 1 diabetes (ADAPT): a randomised controlled study. *Lancet Diabetes Endocrinol*. (2022) 10:720–31. doi: 10.1016/S2213-8587(22)00212-1

66. Carlson AL, Sherr JL, Shulman DI, Garg SK, Pop-Busui R, Bode BW, et al. Safety and glycemic outcomes during the miniMed™ Advanced hybrid closed-loop system pivotal trial in adolescents and adults with type 1 diabetes. *Diabetes Technol Ther*. (2022) 24:178–89. doi: 10.1089/dia.2021.0319

67. *Premarket approval (PMA)*. Available online at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160007 (Accessed June 23, 2023).

68. Burnside MJ, Lewis DM, Crocket HR, Meier RA, Williman JA, Sanders OJ, et al. Open-source automated insulin delivery in type 1 diabetes. *N Engl J Med*. (2022) 387:869–81. doi: 10.1056/NEJMoa2203913

69. Akturk HK, Dowd R, Shankar K, Derdzinski M. Real-world evidence and glycemic improvement using dexcom G6 features. *Diabetes Technol Ther*. (2021) 23: S–21-S-26. doi: 10.1089/dia.2020.0654

70. *Devices at FDA*. Available online at: https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pmn&id=K182041 (Accessed February 4, 2024).

71. *Devices at FDA*. Available online at: https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pmn&id=K223931 (Accessed June 17, 2023).

72. Levy JC, Davies MJ, Holman RR. Continuous glucose monitoring detected hypoglycaemia in the Treating to Target in Type 2 Diabetes Trial (4-T). *Diabetes Res Clin Pract*. (2017) 131:161–8. doi: 10.1016/j.diabres.2017.01.022

73. Battelino T, Danne T, Edelman SV, Choudhary P, Renard E, Westerbacka J, et al. Continuous glucose monitoring-based time-in-range using insulin glargine 300 units/ml versus insulin degludec 100 units/ml in type 1 diabetes: The head-to-head randomized controlled InRange trial. *Diabetes Obes Metab*. (2023) 25:545–55. doi: 10.1111/dom.14898

74. Fox BQ, Benjamin PF, Aqeel A, Fitts E, Flynn S, Levine B, et al. Continuous glucose monitoring use in clinical trials for on-market diabetes drugs. *Clin Diabetes Publ Am Diabetes Assoc*. (2021) 39:160–6. doi: 10.2337/cd20-0049

75. Welsh JB, Psavko S, Zhang X, Gao P, Balo AK. Comparisons of fifth-, sixth-, and seventh-generation continuous glucose monitoring systems. *J Diabetes Sci Technol*. (2024) 18:143–7. doi: 10.1177/19322968221099879

76. Almurashi AM, Rodriguez E, Garg SK. Emerging diabetes technologies: continuous glucose monitors/artificial pancreases. *J Indian Inst Sci*. (2023). doi: 10.1007/s41745-022-00348-3

77. *Devices at FDA*. Available online at: https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pmn&id=K213919 (Accessed February 4, 2024).

78. Garg SK, Kipnes M, Castorino K, Bailey TS, Akturk HK, Welsh JB, et al. Accuracy and safety of dexcom G7 continuous glucose monitoring in adults with diabetes. *Diabetes Technol Ther*. (2022) 24:373–80. doi: 10.1089/dia.2022.0011

79. Nguyen A, White JR. FreeStyle libre 3. *Clin Diabetes.*(2022) 41:127–8. doi: 10.2337/cd22-0102

80. *Devices at FDA* . Available online at: https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pmn&id=K212132 (Accessed February 4, 2024).

81. Alva S, Brazg R, Castorino K, Kipnes M, Liljenquist DR, Liu H. Accuracy of the third generation of a 14-day continuous glucose monitoring system. *Diabetes Ther*. (2023) 14:767–76. doi: 10.1007/s13300-023-01385-6

82. *Abbott's freeStyle libre® 3 receives U.S. FDA clearance - features worlds smallest, thinnest and most accurate 14-day glucose sensor*. Abbott MediaRoom. Available online at: https://abbott.mediaroom.com/2022-05-31-Abbotts-FreeStyle-Libre-R-3-Receives-U-S-FDA-Clearance-Features-Worlds-Smallest,-Thinnest-and-Most-Accurate-14-Day-Glucose-Sensor (Accessed February 4, 2024).

83. Lin T. Non-invasive glucose monitoring: A review of challenges and recent advances. *Curr Trends BioMed Eng Biosci*. (2017) 6. doi: 10.19080/CTBEB.2017.06.555696

84. Kang JW, Park YS, Chang H, Lee W, Singh SP, Choi W, et al. Direct observation of glucose fingerprint using. *Vivo Raman spectroscopy. Sci Adv*. (2020) 6:eaay5206. doi: 10.1126/sciadv.aay5206

85. Dingari NC, Barman I, Singh GP, Kang JW, Dasari RR, Feld MS. Investigation of the specificity of Raman spectroscopy in non-invasive blood glucose measurements. *Anal Bioanal Chem*. (2011) 400:2871–80. doi: 10.1007/s00216-011-5004-5

86. Blood sugar crash, in: *MIT technology review*. Available online at: https://www.technologyreview.com/2014/07/21/172008/blood-sugar-crash/ (Accessed July 15, 2023).

87. Ferrante do Amaral CE, Wolf B. Current development in non-invasive glucose monitoring. *Med Eng Phys*. (2008) 30:541–9. doi: 10.1016/j.medengphy.2007.06.003

88. Amir O, Weinstein D, Zilberman S, Less M, Perl-Treves D, Primack H, et al. Continuous noninvasive glucose monitoring technology based on Occlusion spectroscopy. *J Diabetes Sci Technol*. (2007) 1:463–9. doi: 10.1177/193229680700100403

89. Wentholt IME, Hoekstra JBL, Zwart A, DeVries JH. Pendra goes Dutch: lessons for the CE mark in Europe. *Diabetologia.*(2005) 48:1055–8. doi: 10.1007/s00125-005-1754-y

90. Pors A, Rasmussen KG, Inglev R, Jendrike N, Philipps A, Ranjan AG, et al. Accurate post-calibration predictions for noninvasive glucose measurements in people using confocal raman spectroscopy. *ACS Sens.*(2023) 8:1272–9. doi: 10.1021/acssensors.2c02756

91. Ramasami Sundhar Baabu P, Mani GK, Rayappan JBB, Tsuyuki Y, Inazu T, Tsuchiya K. Sensor-on-microtips: design and development of hydrothermally grown znO on micropipette tips as a modified working electrode for detection of glucose. *Micromachines.*(2023) 14:498. doi: 10.3390/mi14030498

92. Seidu S, Kunutsor SK, Ajjan RA, Choudhary P. Efficacy and safety of continuous glucose monitoring and intermittently scanned continuous glucose monitoring in patients with type 2 diabetes: A systematic review and meta-analysis of interventional evidence. *Diabetes Care*. (2023) 47:169–79. doi: 10.2337/dc23-1520

93. Lu J, Ying Z, Wang P, Fu M, Han C, Zhang M. Effects of continuous glucose monitoring on glycaemic control in type 2 diabetes: A systematic review and network meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. (2024) 26:362–72. doi: 10.1111/dom.15328

94. Conti M, Massari G, Meneghini E, Pasquino B, Agosti B, Chinotti F, et al. Effectiveness and safety of the intermittently scanned continuous glucose monitoring system freeStyle libre 2 in patients with type 2 diabetes treated with basal insulin or oral antidiabetic drugs: an observational, retrospective real-world study. *J Clin Med*. (2024) 13:642. doi: 10.3390/jcm13030642

95. Hanson K, Kipnes M, Tran H. Comparison of point accuracy between two widely used continuous glucose monitoring systems. *J Diabetes Sci Technol*. (2024). doi: 10.1177/19322968231225676

96. Kawaguchi Y, Hajika Y, Rinka M, Masumoto K, Sawa J, Hamazaki K, et al. Comparison of efficacy and safety of insulin degludec/liraglutide and insulin glargine U-100/lixisenatide in individuals with type 2 diabetes mellitus using professional continuous glucose monitoring. *J Diabetes Investig*. (2024). doi: 10.1111/jdi.14151

97. Nemlekar PM, Hannah KL, Green CR, Norman GJ. Association between adherence, A1C improvement, and type of continuous glucose monitoring system in people with type 1 diabetes or type 2 diabetes treated with intensive insulin therapy. *Diabetes Ther*. (2024). doi: 10.1007/s13300-023-01529-8

98. Jiang J, Xia Z, Zheng D, Li Y, Wang W, Ding S, et al. Factors associated with nocturnal and diurnal glycemic variability in patients with type 2 diabetes: a cross-sectional study. *J Endocrinol Invest.*(2024) 47:245–53. doi: 10.1007/s40618-023-02142-z

99. Sanusi AA, Xue Y, McIlwraith C, Howard H, Brocato BE, Casey B, et al. Association of continuous glucose monitoring metrics with pregnancy outcomes in patients with preexisting diabetes. *Diabetes Care*. (2023) 47:89–96. doi: 10.2337/dc23-0636

100. Fishel Bartal M, Ashby Cornthwaite J, Ghafir D, Ward C, Nazeer SA, Blackwell SC, et al. Continuous glucose monitoring in individuals undergoing gestational diabetes screening. *Am J Obstet Gynecol.*(2023) 229:441.e1–441.e14. doi: 10.1016/j.ajog.2023.04.021

101. Kusinski LC, Brown J, Hughes DJ, Meek CL. Feasibility and acceptability of continuous glucose monitoring in pregnancy for the diagnosis of gestational diabetes: A single-centre prospective mixed methods study. *PloS One*. (2023) 18:e0292094. doi: 10.1371/journal.pone.0292094

102. Quah PL, Tan LK, Lek N, Tagore S, Chern BSM, Ang SB, et al. Continuous glucose monitoring feedback in the subsequent development of gestational diabetes: A pilot, randomized, controlled trial in pregnant women. *Am J Perinatol.* (2024). doi: 10.1055/s-0043-1778664

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Turning the tides: achieving rapid and safe glucose control in adolescents with suboptimally controlled type 1 diabetes using advanced hybrid closed loop systems

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Aim: Many adolescents with T1D experience a decline in metabolic control due to erratic eating habits and subpar adherence to treatment regimens. The objective of our retrospective observational study was to assess the effect of the Tandem Control IQ (CIQ) advanced hybrid closed-loop (AHCL) system on a cohort of adolescents with suboptimal glucose control.

Methods: We retrospectively evaluated 20 non-adherent patients with T1D, who were inconsistently using Multiple Daily Injections (MDIs) and flash glucose monitoring and were subsequently started and on CIQ. Glucometrics and the Glucose Risk Index were assessed at baseline and after 2 weeks, 1 month, and 6 months of CIQ use.

Results: The study included 20 adolescents with T1D (HbA1c: 10.0% ± 1.7). Time in range (TIR) increased from 27.1% ± 13.7 at baseline to 68.6% ± 14.2 at 2 weeks, 66.6% ± 10.7 at 1 month, and 60.4% ± 13.3 at 6 months of CIQ use. Time above range (TAR) >250 mg/dL decreased from 46.1% ± 23.8 to 9.9% ± 9.5 at 2 weeks, 10.8% ± 6.1 at 1 month, and 15.5% ± 10.5 at 6 months of AHCL use. Mean glucose levels improved from 251 mg/dL ± 68.9 to 175mg/dL ± 25.5 after 6 months of CIQ use. The Glucose Risk Index (GRI) also significantly reduced from 102 to 48 at 6 months of CIQ. HbA1c also improved from 10.0% ± 1.7 at baseline to 7.0% ± 0.7 after 6 months. Two patients experienced a single episode of mild diabetic ketoacidosis (DKA).

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Conclusions: AHCL systems provide a significant, rapid, and safe improvement in glucose control. This marks a pivotal advancement in technology that primarily benefited those who were already compliant.

KEYWORDS

Type 1 diabetes (or diabetes), HbA1c (A1C), glucose risk index, adolescence, time in range (TIR), Automated insulin delivery (AID)

Research in context

Evidence before this study

Advanced hybrid closed-loop (AHCL) systems are known to improve glycemic control in individuals with type 1 diabetes (T1D). However, the efficacy of these systems has not been extensively studied in the specific population of non-compliant adolescents who struggle with suboptimal glucose control and were previously using multiple daily injections.

Added value of this study

Our study examined the impact of the Tandem Control IQ (CIQ) AHCL system in a cohort of 20 non-compliant adolescents with T1D over 6 months. We found that there was a swift and substantial improvement in time in range (TIR), decrease in time above range (TAR), and a reduction in mean glucose levels with the use of the AHCL system. Interestingly, these positive changes were seen as early as 2 weeks into use of the CIQ system, demonstrating a rapid response to this form of treatment.

Implications of all the available evidence

The results of this study suggest that AHCL systems can be highly beneficial for non-compliant adolescents with T1D, significantly improving their glucose profiles and reducing the risk of future complications. Despite the limitations of the study such as a small sample size and absence of a control group, our findings indicate that AHCL systems could be considered a first-line approach for this challenging group of patients. It is a testament to the potential of AHCL technology as a game changer, offering an improved quality of life and a future with fewer complications for this particular population. Further research with larger cohorts and longer follow-up periods will be useful to confirm and expand upon these findings.

Introduction

Advanced hybrid closed-loop (AHCL) systems represent the next automation step, aiming to maximize normoglycemia by integrating continuous glucose monitoring with automated insulin delivery. Specifically, AHCL technology employs an algorithm that automatically modifies the basal insulin rate based on expected glucose levels, with automated bolus insulin correction for high glucose levels. Patients are only required to estimate carbohydrate consumption for meal boluses. These systems ensure that a significant percent of time is spent within the target glucose range, minimizing both hypo- and hyperglycemia events and significantly improving the quality of life for children with type 1 diabetes (T1D).

These systems represent the most recent available automatism in the treatment of T1D and, in a semi-automatic way, can independently regulate insulin delivery based on dynamic data from a glucose sensor; they are the Medtronic 780G system (Minimed Medtronic, Northridge, CA) and the Tandem Control IQ system (Tandem Inc., San Diego, CA).

Both Medtronic 780G and Tandem Control IQ, with their different algorithms, are equally effective in making possible a personalization of insulin therapy and an adaptation to the different needs of the subjects and their families (REF Schiaffini et al.).

While patients' T1D management skills, such as carbohydrate counting, insulin dose calculations, and insulin-to-carbohydrate ratios, remain crucial components, the introduction of AHCL systems marks a shift towards optimal diabetes control and a significant reduction in patients' self-management (1, 2).

Many adolescents with T1D may experience a deterioration in metabolic control due to erratic meal and exercise patterns, poor adherence to treatment regimens, hazardous and risk-taking behaviors, disordered eating behaviors, other mental health issues, and endocrine changes associated with puberty. These factors can lead to greater insulin resistance, resulting in suboptimal glycated hemoglobin (HbA1c) levels. As HbA1c levels during youth are highly predictive of long-term HbA1c trajectory, timely interventions are necessary to alter a life course predictive of premature development of diabetes complications (3).

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Our retrospective observational study aims to evaluate the impact of the Tandem t:slim X2 Control IQ (CIQ) system (Tandem Diabetes Care, Inc.) in a cohort of diabetic adolescents with suboptimal glucose control.

Methods

This retrospective, real-world, observational study using medical records included 20 patients with T1D and high-risk glycemia, using multiple day injections (MDIs) and flash glucose monitoring. All children met the American Diabetes Association (ADA) criteria for T1D diagnosis (4) with a current HbA1c of ≥8.5%. Exclusion criteria were medication indicating diabetes complications, systemic glucocorticoids, or any concomitant diseases that could interfere with glucometric parameters; patients with genetic disorders were also excluded. Appropriate informed consent/assent was obtained.

We included patients that were started on CIQ between June and December 2022. Carbohydrate counting was not included, as patients had previously expressed non-compliance.

Glucometrics, including time in range (TIR), time above range (TAR), time below range (TBR), glucose management indicator (GMI)%, mean sensor glucose with standard deviation (SD), coefficient of variation (CV), and Glycemia Risk Index (GRI), were evaluated at baseline and after 2 weeks, 1 month, and 6 months of CIQ use. HbA1c was also documented at baseline and after 6 months of CIQ technology.

Serious adverse events, including severe hypoglycemia and diabetic ketoacidosis (DKA), were registered during follow-up.

CGM and insulin data were collected from Tidepool platform. Statistical analyses was performed using SPSS version 23.0 software for Windows (SPSS Inc., Chicago, IL, USA). Values were expressed as mean ± standard deviations (SDs). A p-value <0.05 was considered statistically significant. Comparisons between groups were analyzed with independent samples *t*-test and Mann–Whitney test.

Results

A total of 20 adolescents with T1D were included (mean age: 15.7 ± 1.9 years, 55% female). Table 1 shows the baseline clinical and auxological characteristics of the study population.

During follow-up, TIR increased from 27.1% ± 13.7 at baseline to 68.6% ± 14.2 at 2 weeks (p<0.001), to 66.6% ± 10.7 at 1 month (p<0.001), and to 60.4% ± 13.3 at 6 months (p<0.001) of AHCL use. TAR >250 mg/dL decreased from 46.1% ± 23.8 to 9.9% ± 9.5 at 2 weeks (p<0.001), to 10.8% ± 6.1 at 1 month (p<0.001), and to 15.5% ± 10.5 at 6 months (p<0.001) using the CIQ system. No differences in TAR 180–250 mg/dL, TBR 54–70 mg/dL, or <54 mg/dL were found during follow-up (see Figure 1A). Mean glucose also improved from 251 mg/dL ± 68.9 to 162 mg/dL ± 25.0 after 2 weeks (p<0.001), to 164 mg/dL ± 17.5 after 1 month (p<0.001), and to 175 mg/dL ± 25.5 after 6 months (p<0.001) of follow-up. Accordingly, SD decreased from baseline (88.0 ± 28.8) to 2 weeks (60.6 ± 18.8) (p<0.005), 1 month (61.6 ± 13.1) (p=0.001), and 6 months (69.2 ± 15.8) (p=0.02) of follow-up. However, we did not find and statistically significant improvement in CV during follow-up. GMI% significantly reduced from baseline (9.5 ± 1.6%) (p<0.001) to 2 weeks (7.0 ± 0.5%) (p<0.001), 1 month (7.2 ± 1.6%) (p<0.001), and 6 months (7.5 ± 0.5%) (p<0.001) of CIQ use (see Figure 1B).

TABLE 1 Clinical and auxological characteristics of study population at baseline.

Variables	Mean ± SD
Sample size	20
Gender (Male/Female)	9(45%)/11(55%)
Age (years)	15.7 ± 1.9
Weight (kg) at baseline	57.7 ± 12.7
Height (cm) at baseline	161.5 ± 10.0
BMI (kg/m2) at baseline	21.9 ± 3.3
HbA1c (%)	10.0 ± 1.7
Disease duration at baseline (years)	6.2 ± 4.0

GRI, which closely corresponds to the clinician's ranking of overall glycemia quality, reduced significantly from baseline to 6 months of CIQ technology (see Figure 1C). HbA1c also improve from 10 ± 1.7% at baseline to 7.0 ± 0.7% after 6 months of CIQ use (p<0.001).

No cases of severe hypoglycemia occurred during the study period. Two patients suffered from a single event of moderate DKA, likely due to infusion set occlusion. The events were resolved without complications.

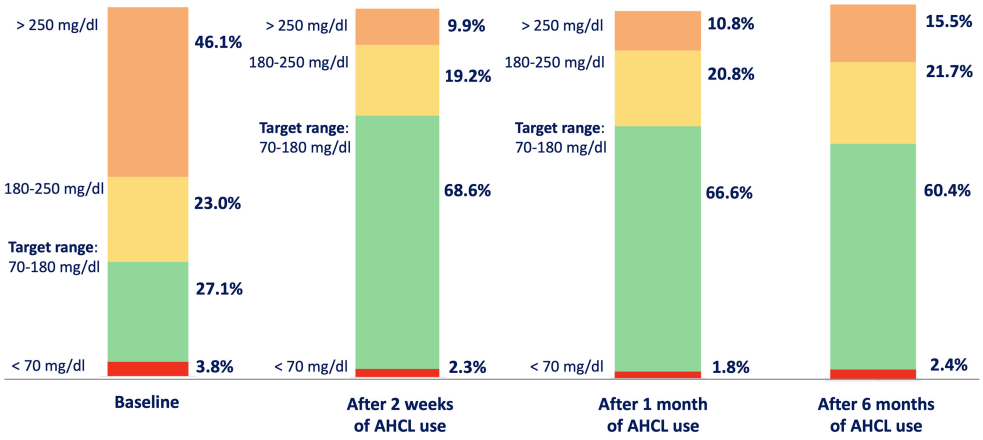
Discussion

Our study shows that non-compliant adolescents with T1D, previously using MDI therapy, may achieve a swift and sustained improvement in glucose profiles using AHCL systems. In particular, mean TIR improved by almost 40% within just 2 weeks of use, primarily accounted for by a significant reduction in time spent above 250 mg/dL. GRI drastically reduced, representing improved exposure to glucose excursions with CIQ technology. HbA1c, which remains one of the main predictors for chronic complications in people with diabetes, also significantly improved after 6 months.

During the 6-month follow-up, we documented only a slight but not statistically significant worsening of glucose control, likely due to patients' poor adherence to treatment regimens over time, particularly with missed meal boluses.

The findings of the present case series align with previous studies using other advanced automated insulin delivery systems (5–8). This consistency of findings underscores the robustness of the AHCL algorithm and supports the application of closed-loop systems across a broad range of individuals with T1D. For the first time, the ADAPT study evaluated the clinical benefits of algorithm AHCL system in adults with T1D and suboptimal glucose control. In particular, the

A



B

Variables	Baseline (T0)	After 2 weeks (T1)	After 1 month (T2)	After 6 months (T3)	*P-value* (T0vsT1)	*P-value* (T1vsT2)	*P-value* (T0vsT2)	*P-value* (T0vsT3)	*P-value* (T2vsT3)
Sample size	20	20	20	20					
Glucose (mg/dl)	251±68.9	162±25.0	164±17.5	175±25.5	**0.000**	0.3	**0.000**	**0.000**	0.29
SD	88.0±28.8	60.6±18.8	61.6±13.1	69.2±15.8	**0.003**	0.6	**0.001**	**0.02**	0.14
CV%	35.8±11.4	36.6±6.7	37.3±6.1	39.0±5.8	0.9	0.8	0.8	0.37	0.25
GMI%	9.5±1.6	7.0±0.5	7.2±0.3	7.5±0.5	**0.000**	0.1	**0.000**	**0.000**	0.35

C

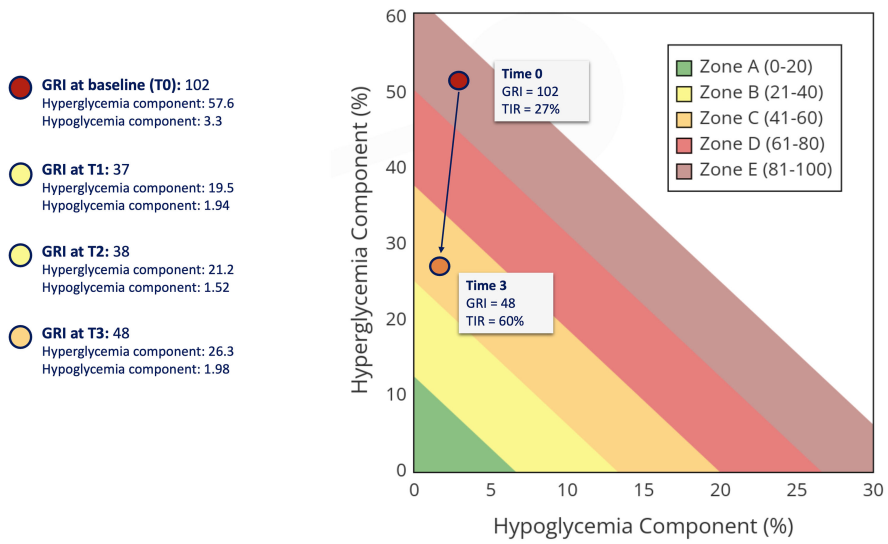


FIGURE 1
(A) Glucometric profile of the study population at baseline, after 2 weeks, 1 month, and 6 months of AHCL use. **(B)** Glucose oucomes of study population at baseline (TO), after 2 weeks (T1), after 1 month (2), and after 6 months (T3) of CIQ use. TIR, time in range; TAR, time above range; TBR, time below range; SD, standard deviation; CV, coefficient of variation; GMI, glucose management indicator. **(C)** GRI (Glycemia Risk Index) at baseline (TO) and after 6 months of CIQ technology.

authors demonstrated that AHCL confers significant benefits in terms of glycemic control beyond those that can be achieved with multiple daily injections and suggest that AHCL should be considered at the early stages in the T1D treatment pathway (REF). Similarly, Lombardo et al. demonstrated the successful use of the AHCL system in a real-world study. The authors described the 6-month impact of the advanced automated functions of MiniMed™ 780G on GRI in a large cohort of children and adolescents with T1D also documenting the effectiveness and safety of AHCL technology in the pediatric population (REF).

Therefore, AHCL technology significantly, quickly, and safely improves glucose control, even in adolescents with poor glucose control, representing a turning point for technology that used to favor mainly those who were already compliant.

Our results, although possibly biased by the relatively short follow-up, suggest that even non-compliant adolescents with T1D

can significantly benefit from AHCL in terms of reducing the burden and risk of future complications (9).

Although the use of an AHCL in our cohort has led to a reduction in mean glucose and SD, the fact that the CV has not significantly changed may suggest that, relative to the mean glucose level, the spread or dispersion of glucose levels has not altered significantly.

This could potentially happen for several reasons. For instance, it is possible that while the mean glucose level and SD improved, they did so in a manner that maintained a relatively constant ratio, leading to a consistent CV. Another possibility is that the AHCL system has effectively reduced both extreme high and low glucose readings, causing improvements in mean glucose and SD, but still preserving some degree of glucose variability that is reflected in the CV. It is also worth noting that while we aim for lower variability in glucose management, some level of variability is natural and expected, especially in particular populations such as non-compliant adolescents, even with advanced management systems.

Safety is an essential component of AHCL technology in this population. No severe hypoglycemia was documented, which is consistent with other similar studies (4, 10); two episodes of moderate DKA occurred due to infusion set occlusion. Infusion set failure or occlusion is a well-documented complication of all insulin pump therapies, with higher rates seen in younger users (11). Therefore, frequent anticipatory education to avoid and manage infusion set issues remains crucial.

Limitations of our study include the small number of patients and the absence of a control group. The duration of the follow-up did not permit long-term conclusions; however, all enrolled adolescents will be followed for additional months to evaluate whether outcomes are confirmed.

For less complex T1D populations, closed-loop systems are already the gold standard therapeutic option (12). AHCL technology, combined with adequate training and clinical support, should now be considered a first-line approach for those with the most to gain, namely, non-compliant adolescents with T1D.

In conclusion, the pivotal role of AHCL technology in glucose control management is undeniable, demonstrating striking improvements even in non-compliant adolescents with T1D. Our study sheds new light on the immense potential of this technology, which could indeed be a game changer, a true turning point for those most in need of such assistance. Despite the challenging landscape of T1D management, particularly among non-compliant adolescents, our results point towards a path of improved quality of life and a future with fewer complications. This is not just a technological advancement, but a lifeline for these delicate subset of patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Comitato Etico - San Raffaele. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GF conceived the design of the work. VC collected data. GF, VC and AR drafted the article. All the authors contributed to the revision and approval of the final version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Leelarathna L, Choudhary P, Wilmot EG, Lumb A, Street T, Kar P, et al. Hybrid closed-loop therapy: Where are we in 2021? *Diabetes Obes Metab* (2021) 23(3):655–60. doi: 10.1111/dom.14273

2. Ferrito L, Passanisi S, Bonfanti R, Cherubini V, Minuto N, Schiaffini R, Scaramuzza A. Efficacy of advanced hybrid closed loop systems for the management of type 1 diabetes in children. *Minerva Pediatr (Torino)* (2021) 73:474–85. doi: 10.23736/S2724-5276.21.06531-9

3. 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. doi: 10.1089/dia.2018.0384

4. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. Children and adolescents: standards of care in diabetes-2023. *Diabetes Care* (2023) 46 (Suppl 1):S230–53. doi: 10.2337/dc23-S014

5. Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC, et al. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. *N Engl J Med* (2019) 381(18):1707–17. doi: 10.1056/NEJMoa1907863

6. Tauschmann M, Thabit H, Bally L, Allen JM, Hartnell S, Wilinska ME, et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. *Lancet* (2018) 392(10155):1321–9. doi: 10.1016/S0140-6736(18)31947-0

7. Burnside MJ, Lewis DM, Crocket HR, Meier RA, Williman JA, Sanders OJ, et al. Open-source automated insulin delivery in type 1 diabetes. *N Engl J Med* (2022) 387 (10):869–81. doi: 10.1056/NEJMoa2203913

8. Boucsein A, Watson AS, Frewen CM, Sanders OJ, Haszard JJ, Jones SD, et al. Impact of advanced hybrid closed loop on youth with high-risk type 1 diabetes using multiple daily injections. *Diabetes Care* (2023) 46(3):628–32. doi: 10.2337/dc22-1971

9. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* (1993) 329(14):977–86. doi: 10.1056/NEJM199309303291401

10. Bergenstal RM, Nimri R, Beck RW, Criego A, Laffel L, Schatz D, et al. A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial. *Lancet* (2021) 397 (10270):208–19. doi: 10.1016/S0140-6736(20)32514-9

11. Ross PL, Milburn J, Reith DM, Wiltshire E, Wheeler BJ. Clinical review: insulin pump-associated adverse events in adults and children. *Acta Diabetol* (2015) 52 (6):1017–24. doi: 10.1007/s00592-015-0784-2

12. Boughton CK, Hovorka R. The artificial pancreas. *Curr Opin Organ Transplant* (2020) 25(4):336–42. doi: 10.1097/MOT.0000000000000786

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Efficacy and safety of advanced hybrid closed loop systems in children with type 1 diabetes younger than 6 years

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Background: Tight glycemic control is essential for the normal growth and development of preschool children. The aim of our study was to evaluate the impact of advanced hybrid closed loop (AHCL) systems in a real-life setting in children younger than 6 years.

Methods: We conducted a two-center prospective study. We enrolled 19 patients with a median age at disease onset of 2.6 years [interquartile range (IQR) 1.6; 4.4] and a median disease duration of 1.4 years (IQR 0.9; 2.8) who were switched to AHCL from multiple daily injections or open-loop insulin therapy and with a 6-month follow-up. Clinical data, sensor glycemic metrics, and pump settings were collected and analyzed.

Results: After 6 months of follow-up, there was a significant reduction in median HbA1c (p = 0.0007) and glucose management indicator (p = 0.03). A reduction in both mild (>180 mg/dL) (p = 0.04) and severe (>250 mg/dL) (p = 0.01) hyperglycemia was observed after 1 month of auto mode, and in mild hyperglycemia, it persisted up to 6 months (p = 0.02). A small increase in time below range (<70 mg/dL) was observed (p = 0.04) without a significant difference in time <54 mg/dL (p = 0.73). Time in range increased significantly, reaching a 10% increment (p = 0.03) compared with baseline. A significant reduction in the average sensor glucose was observed (p = 0.01) while coefficient of glucose variability (CV%) remained stable (p = 0.12). No episodes of ketoacidosis or severe hypoglycemia have been recorded.

Conclusion: AHCL systems are effective and safe for children younger than 6 years and should be considered as a valid therapeutic option from diabetes onset.

KEYWORDS

T1D (type 1 diabetes), CSII (continuous subcutaneous insulin infusion), children, insulin, AHCL

Introduction

Glycemic control in preschool children is challenging and glucose management is burdened by high glycemic variability (1) due to the reduced predictability of daily activities and meals. Tight glycemic control is mandatory, as toddlers diagnosed with type 1 diabetes (T1D) are expected to be exposed to long diabetes duration to reduce complications (2, 3), minimizing at the same time the hypoglycemic risk (4). Furthermore, neuroimaging studies identified alterations particularly affecting white matter, suggesting that during toddler and preschool years, the brain is highly sensitive to metabolic disturbances (both hypo- and hyperglycemia) (5) with implications for cognitive and executive functions, intelligence quotient, delayed memory, and processing speed (6). Advanced hybrid closed loop (AHCL) devices have proven useful in improving disease management and time in range (TIR) (7), but they have been currently approved above 6 or 7 years of age with a minimum total daily dose (TDD). The aim of our study was to evaluate the impact of AHCL on glycemic control over time in children younger than 6 years in a real-life setting, compared to the previous conventional multiple daily injection (MDI) insulin therapy and open-loop continuous subcutaneous insulin infusion (CSII) treatment [with or without a sensor augmented pump (SAP)].

Methods

We enrolled 19 pediatric patients (11 boys; 8 girls) with T1D {with a median age at disease onset of 2.6 [interquartile range (IQR) 1.6; 4.4] years and a median disease duration of 1.4 (IQR 0.9; 2.8) years} from the Bambino Gesù Children's Hospital Diabetes Unit in Rome and at the Viterbo Pediatric Diabetes Unit, Italy, between January 2021 and June 2023. All involved families gave their consent for the use of algorithm-driven automated insulin delivery, although this therapeutic approach is currently approved in children at the age of 6 years or above with a minimum TDD of 10 units or >25 kg of weight (Tandem t:slim X2 Control-IQ) and above the age of 7 years with a minimum TDD of 8 units (Medtronic MiniMed™ 780G).

We considered the following inclusion criteria:

- age < 6 years
- diagnosis of T1D according to ISPAD guidelines (8)
- being monitored by isCGM (intermittent scanning continuous glucose monitoring) or rtCGM (real time continuous glucose monitoring) at baseline
- being on MDI insulin therapy or open-loop CSII treatment

Exclusion criteria were as follows:

- conditions or use of medications known to affect glycemic levels
- being already on the AHCL system

The study was approved by the Institutional Ethics Committees of participating centers, and all participants' parents provided informed consent.

Weight (kg), height (cm), body mass index (BMI), glycated hemoglobin (HbA1c), and TDD in international units per body weight (IU/kg) have been evaluated. Participants' demographic and anthropometric characteristics are shown in Table 1.

Sensor glucose reading data for 30 days were collected from rtCGM, and glycemic control was evaluated, analyzing data obtained from Carelink and Glooko platforms, considering percentage of TIR (TIR%, between 70 and 180 mg/dL), time above range in mild (TAR% >180 mg/dL) and severe (TAR% >250 mg/dL) hyperglycemia, and time below range in mild (TBR % <70 mg/dL) and very low (TBR% <54 mg/dL) hypoglycemia (9). Glucose management indicator (GMI), glucose average (mg/dL), coefficient of variability (CV%), and recorded dietary carbohydrate (9) were also evaluated.

All participants reported >90% of time with sensor in use.

The last available 30 days of sensor glucose data on MDI treatment or the open-loop system, before switching to AHCL, were considered as baseline, and 30 days of sensor glucose data were considered for each of the other time points (1, 3, and 6 months) during the follow-up period.

During follow-up, nine patients used Tandem t:slim X2 in Control-IQ mode, nine used MiniMed 780G with SmartGuard mode, and one shifted from MiniMed 640G to MiniMed 670G.

The MiniMed 780G pump was initially used in manual mode for 2 weeks before switching to auto mode with a 120 mg/dL glycemic target and a 100 mg/dL glycemic target after 3 months with a mean active insulin time of 2 h.

After switching to AHCL systems, subjects were followed up for 6 months and glycemic metrics were recorded after 1, 3, and 6 months. At each visit, the family was asked whether ketoacidosis or severe hypoglycemia occurred during the reported period. Furthermore, differences in anthropometric parameters were analyzed (weight, height, and BMI) as well as the HbA1c level at the beginning and at the end of the follow-up (Table 2).

TABLE 1 Participants' demographic and anthropometric characteristics.

	Median (IQR)
Number of patients	19
M/F	11/8
Duration of the disease (years)	1.4 (0.9, 2.8)
Age at disease onset (years)	2.6 (1.6, 4.4)
Age at start of AHCL (years)	4.8 (4.4, 5.5)
Weight (kg)	19 (1.2, 19.9)
Height (cm)	109 (102, 111.3)
BMI (kg/m2)	16.2 (15.6, 17.5)

Statistical analysis

Participants' characteristics are reported as median and IQR for continuous variables and as absolute frequency and percentage for categorical variables.

We performed Wilcoxon signed-rank test to check whether the differences between paired data were statistically significant. We considered *p*-value below 0.05 as statistically significant.

Analyses were performed using GraphPad Prism ver. 9.00.

Results

After 6 months of follow-up with the AHCL systems, there was a significant reduction in both median HbA1c from 56.3 (52, 62.5) to 55 (44.8, 58.7) mmol/mol (Figure 1A) ($p = 0.0007$) and median GMI from 7.2 (6.9, 7.8) to 7 (6.8, 7.2) % ($p = 0.03$) without changes in BMI ($p = 0.27$, not shown).

Time in range (TIR%) increased significantly during the 6 months of follow-up, reaching a difference from baseline of +10% ($p = 0.03$) and +6% after the first ($p = 0.007$) and after the third ($p = 0.03$) month of use (Figure 1B). Insulin requirement presented a slight increment at 1 and 3 months ($p = 0.02$ and $p = 0.004$), without a significant change at the end of follow-up period compared to baseline (0.6 IU/kg/day, $p = 0.4$).

A significant reduction in the glucose average was observed, during the entire 6 months ($p = 0.01$) (Figure 1C).

A reduction in both mild (>180 mg/dL) ($p = 0.04$) and severe (>250 mg/dL) hyperglycemia ($p = 0.01$) was observed 1 month after AHCL systems, which persisted up to 6 months for mild hyperglycemia ($p = 0.02$) (Figure 1D).

Furthermore, time below range <70 mg/dL presented a small increment ($p = 0.04$) (Figure 1E) from baseline to 6 months without a significant difference in time <54 mg/dL ($p = 0.73$).

No significant differences were found in CV during follow-up ($p = 0.12$).

Recorded carbohydrates per day remained stable during the study period ($p = 0.12$, 0.43, and 0.62, respectively) with a significant reduction between 3 and 6 months ($p = 0.02$).

Both AHCL systems have always worked in auto mode during the observational period despite the low insulin demand (the minimum reported daily dose was 6 IU).

No episodes of ketoacidosis or severe hypoglycemia were reported during follow-up.

Discussion

Our study, involving preschool children with T1D treated with AHCL systems for a follow-up period of 6 months, showed a +10% increment of TIR from baseline, reflecting a reduction of 2.5 h per

TABLE 2 Participants' glycemic metrics at baseline and during follow-up.

	Baseline, median (IQR)	1 month follow-up, median (IQR)	*p*-value	3 months follow-up, median (IQR)	*p*-value	6 months follow-up, median (IQR)	*p*-value
HbA1c (mmol/mol)	56.3 (52, 62.5)					55 (44.8, 58.7)	**0.0007**
TDI (units/kg/day)	0.6 (0.5, 0.8)	0.7 (0.6, 0.8)	**0.02**	0.8 (0.7, 0.8)	**0.004**	0.6 (0.5, 0.7)	0.4
Bolus/TDI (%)	47.1 (45, 55.3)	56.6 (52, 60.2)	**0.009**	54.4 (52.2, 62.4)	0.16	54.7 (50.4, 58.8)	0.22
CHO (g)/day Recorded dietary carbohydrate	140 (112, 170)	152 (138.9, 206.6)	0.12	153 (122, 192.5)	0.43	142 (93, 167)	0.62
TBR (<54 mg/dL) %	0 (0, 1)	0 (0, 1)	0.36	0 (0, 1)	0.99	0 (0, 1)	0.73
TBR (54–70 mg/dL) %	2 (1, 3)	3 (2, 3)	0.69	2 (2, 4)	0.34	2.5 (2, 4)	**0.04**
TIR (70–180 mg/dL) %	60 (50, 59.5)	66 (72, 70.5)	**0.007**	66 (61, 70.5)	**0.03**	70 (61.3, 72.8)	**0.03**
TAR (180–250 mg/dL) %	25 (21, 27.5)	22 (19, 26)	**0.04**	22 (20.5, 24.5)	**0.01**	21 (18.3, 23.8)	**0.02**
TAR (>250 mg/dL) %	11 (6, 19.5)	9 (6, 11.5)	**0.01**	10 (6, 12)	0.09	7 (5, 9.8)	0.06
Mean glucose (mg/dL)	161.5 (150.5, 187.8)	158 (146, 165)	**0.006**	157 (150, 167.5)	**0.04**	153.5 (146, 163.8)	**0.01**
CV%	37.6 (35.8, 40)	38.1 (36.6, 40.1)	0.41	39 (35.6, 41.4)	0.29	38.3 (34.9, 41.9)	0.12
GMI%	7.2 (6.9, 7.8)	7.1 (6.8, 7.3)	**0.01**	7.1 (6.9, 7.3)	**0.03**	7 (6.8, 7.2)	**0.03**

HbA1c, glycated hemoglobin; TDI, total daily insulin; CHO, carbohydrate; TBR, time below range; TIR, time in range; TAB, time above range; CV, coefficient of variation; GMI, glucose management indicator.
All p-values are compared to baseline.
In bold the values statistically significant.

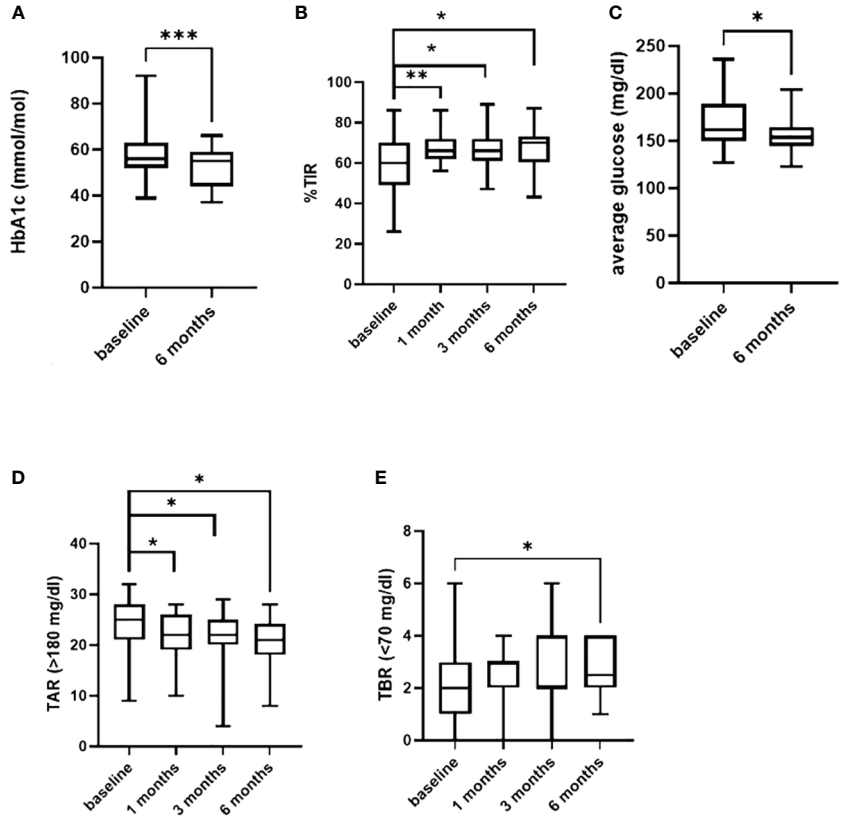

FIGURE 1
In **(A)** difference in HbA1c from baseline and 6 months of follow-up. Difference in TIR, in TAR (>180 mg/dl) and in TBR (<70 mg/dl) from baseline and 1-3-6 months follow-up are shown in **(B, D, E)**. In **(C)** difference in the average of sensor glucose. *=p<0.05; **=p<0.001; ***=p<0.0001.

day spent in a hyperglycemic state. Interestingly, improvement in TIR was already evident after 1 month and was sustained during the 6-month period, suggesting a precocious and stable effect of these systems on glycemic control. Furthermore, they led to a reduction in HbA1c, which was more evident for individuals with worse baseline levels.

We also observed an important reduction of time spent in hyperglycemia using AHCL systems, compared to baseline MDI or SAP therapy.

These results are relevant whereas detectable changes in brain volumes and cognitive scores in children with T1D are associated with hyperglycemic metrics (10).

Literature confirms these results. Recently, a 12-week open-label prospective study with MiniMed 780G™ in children 2–6 years old (TDD ≥8 IU/day) demonstrated that this device is also safe in this age group, improving glycemic control and reducing parental distress (11).

Similar lines of evidence were gathered from a retrospective analysis conducted by Tornese et al. on 12 children <7 years (minimum TDD 4 IU/day) with MiniMed 780G™ with SmartGuard who have been followed up for 12 months (12).

In another multicenter 13-week trial with Tandem t:slim X2 insulin pump with Control-IQ Technology, 102 children with a mean age of 4 years (TDD ≥5 IU/day) were assigned to receive an advanced hybrid closed-loop system of insulin delivery or standard care. TIR increased from 56.7% ± 18.0% to 69.3% ± 11.1% during follow-up in the closed-loop group. There was also a significant reduction of TAR and HbA1c, while TBR remained stable (13).

Consistent with these data, we did not observe a reduction of TBR. This finding could be explained by the fear of hypoglycemia in very young children, which led the caregivers to try to maintain a strict control on low glucose values. These systems, however, allow parents to become more confident, thanks to the automatic insulin delivery suspension, leading to a reduction of excessive sugar correction and, consequently, a reduction in time spent in hyperglycemia as well.

CV, above the threshold already at baseline, showed a slight increasing trend, similar to the results of Tornese et al. (12) at the end of the follow-up. The median values above the threshold could be attributed to the unpredictability of meals and activity in this age group while the increasing trend could be due to more frequent bolus performed by the pump.

Because of this variability, even if 48 h is sufficient, we decided to prolong the manual period before transitioning to auto mode with MiniMed 780G until 14 days to allow the algorithm to calculate a more precise basal rate.

The strengths of our study include the real-world setting and the evaluation of two different AHCL systems. A limitation of this 6-month study was its relatively short duration of follow-up, although it seems clear that the benefits on glycemic control persist.

Another limit is the small sample size. Our data should be confirmed and further assessed in other studies with extended follow-up periods and more participants.

Conclusion

Our results confirm that AHCL systems are effective in improving glycemic control in preschool children as already shown in previous studies.

Furthermore, these pumps have proven to be safe tools, improving TIR and TAR, working in auto mode also with a TDD <8 IU/day.

In conclusion, AHCL systems, such as MiniMed 780G with SmartGuard and Tandem t:slim X2 with Control-IQ technology, are an effective therapeutic option for children younger than 6 years.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Ospedale Pediatrico Bambino Gesù, Rome. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

NR: Conceptualization, Supervision, Writing – original draft. MM: Formal analysis, Methodology, Writing – original draft. CA: Data curation, Investigation, Writing – review & editing. AD: Writing – review & editing, Supervision. LA: Data curation, Formal analysis, Writing – original draft. MA: Conceptualization, Investigation, Writing – review & editing. PC: Supervision, Writing – review & editing. VP: Conceptualization, Validation, Writing – review & editing. AL: Data curation, Writing – original draft. DT: Data curation, Writing – original draft. SC: Resources, Supervision, Writing – review & editing. RS: Conceptualization, Data curation, Resources, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Daneman D, Frank M, Perlman K, Wittenberg J. The infant and toddler with diabetes: challenges of diagnosis and management. *Paediatr Child Health*. (1999) 4:57–63. doi: 10.1093/pch/4.1.57

2. Sundberg F, de Beaufort CE, Krogvold L, Patton S, Piloya T, Smart C, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Managing diabetes in preschoolers. *Pediatr Diabetes*. (2022) 23:1496–511. doi: 10.1111/pedi.13427

3. Nathan DM. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care*. (2014) 37:9–16. doi: 10.2337/dc13-2112

4. Barnard K, Thomas S, Royle P, Noyes K, Waugh N. Fear of hypoglycaemia in parents of young children with type 1 diabetes: a systematic review. *BMC Pediatr*. (2010) 10:50. doi: 10.1186/1471-2431-10-50

5. Barnea-Goraly N, Raman M, Mazaika P, Marzelli M, Hershey T, Weinzimer Stuart A, et al. Alterations in white matter structure in young children with type 1 diabetes. *Diabetes Care*. (2014) 37:332–40. doi: 10.2337/dc13-1388

6. Gaudieri PA, Chen R, Greer TF, Holmes CS. Cognitive function in children with type 1 diabetes: a meta-analysis. *Diabetes Care*. (2008) 31:1892–7. doi: 10.2337/dc07-2132

7. American Diabetes Association. Diabetes technology: standards of medical care in diabetes—2022. *Diabetes Care*. (2022) 45:S97–S112. doi: 10.2337/dc22-S007

8. Libman I, Haynes A, Lyons S, Rwagasor E, Yuet-ling Tung J, Jefferies Craig A, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr Diabetes*. (2022) 23:1160–74. doi: 10.1111/pedi.13454

9. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. (2019) 42:1593–603. doi: 10.2337/dci19-0028

10. Mauras N, Buckingham B, White NH, Tsalikian E, Weinzimer SA, Joet B, et al. Impact of type 1 diabetes in the developing brain in children: A longitudinal study. *Diabetes Care*. (2021) 44(4):983–92. doi: 10.2337/dc20-2125

11. Pulkkinen MA, Varimo TJ, Hakonen ET, Harsunen MH, Hyvönen ME, Janér JN, et al. MiniMed 780G™ in 2- to 6-year-old children: safety and clinical outcomes after the first 12 weeks. *Diabetes Technol Ther*. (2023) 25(2):100–7. doi: 10.1089/dia.2022.0313

12. Tornese G, Carletti C, Lanzetta MA, Tamaro G, Barbi E, Faleschini E, et al. Safety of real-life usage of advanced hybrid closed-loop system miniMed 780G in children with type 1 diabetes younger than 7 years old. *Diabetes Care*. (2023) 46:e123–5. doi: 10.2337/dc22-2046

13. Wadwa RP, Reed ZW, Buckingham BA, DeBoer DM, Ekhlaspour L, Forlenza GP, et al. Trial of hybrid closed-loop control in young children with type 1 diabetes. *N Engl J Med*. (2023) 388:991–1001. doi: 10.1056/NEJMoa2210834

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Efficacy of advanced hybrid closed loop systems in cystic fibrosis related diabetes: a pilot study

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Background and aims: Cystic fibrosis related diabetes (CFRD) is correlated with worsening of nutritional status and greater deterioration of lung function. The role of new technologies for the treatment of CFRD is little explored. The aim of the study was to evaluate the efficacy of Advanced Hybrid Closed Loop (AHCL) systems on glycemic control in CF patients.

Methods: A single-center retrospective study on CFRD patients using AHCL systems was performed. Glycated hemoglobin (HbA1c) values and Continuous Glucose Monitoring (CGM) metrics were collected at T0 (AHCL placement), T1 (1-month), T2 (6-months) and T3 (1-year) to evaluate glycemic control.

Results: 10 patients were included in the study. Data showed a reduction of HbA1c value (7.31 ± 0.34 to 6.35 ± 1.00; p=0.03), glycemic variability (p=0.05) and insulin requirement (p=0.03). The study population reached American Diabetes Association (ADA) recommended glycemic targets at 1-year. An increase in the Time in Range (TIR) and a reduction in time in hyperglycemia were also observed, although not statistically significant.

Conclusions: In patients with CFRD, the use of AHCL leads to an improvement in glycemic control in terms of HbA1c and glycemic variability. The increase in TIR and the reduction of time in hyperglycemia, although not statistically significant, are extremely encouraging from a clinical point of view. Further studies with a larger population and a longer follow-up are needed. The results of this study demonstrate the importance of proposing the use of AHCL even in CF patients, who could benefit from glycemic improvement also in terms of nutritional status and respiratory function.

KEYWORDS

AHCL (Advanced Hybrid Closed Loop), cystic fibrosis, CFRD (cystic fibrosis related diabetes), CGM (continuous glucose monitoring), insulin pumps, time in range (TIR)

1 Introduction

Cystic fibrosis-related diabetes (CFRD) is one of the most common extrapulmonary manifestations of cystic fibrosis (CF) which affects up to 20–30% of adolescents and 30–50% of young adults living with CF (1, 2). The diagnosis of CFRD can be made in CF patients according to the American Diabetes Association (ADA) criteria. ADA Clinical Practice Guideline recommends patients with cystic fibrosis to perform CFRD annual screening with oral glucose tolerance test (OGTT), starting from the age of 10 (3). A poor glycemic control has been related to a more severe clinical outcome, characterized by the progression of lung function deterioration and poorer nutritional status, resulting in a higher risk of recurrent pulmonary exacerbations, chronic growth of respiratory pathogens and earlier mortality (4–6).

Cornerstones of CFRD management are glucose monitoring and insulin therapy, which is the only treatment currently approved for CFRD (7). Self-monitoring of blood glucose (SMBG) multiple times a day can be burdensome and difficult for many patients (8).

Huge technological advancements in diabetes management have been achieved during the past decade, such as the development of the modern flash/continuous glucose monitoring (FGM/CGM), insulin pumps, and automated insulin delivery (AID) systems, creating a paradigm shift in Type 1 Diabetes Mellitus (T1DM) standards of care (9), although the impact of these devices in individuals with CFRD is less clear (10). FGM and CGM systems are minimally invasive devices tracking glucose levels continuously. Glucose readings are sent to a smart device in real-time for CGM or on-demand for FGM. CGM allowed the development of the Sensor Augmented Pump (SAP), consenting the association of the two systems without providing any interaction between glucose sensor and insulin pump. Subsequently, SAPs were developed with the Low Glucose Suspend (LGS) and Predictive Low Glucose Suspend (PLGS) function, automatically interrupting the basal insulin infusion in case of hypoglycemia or predicted hypoglycemia. In 2015 Hybrid Closed Loop (HCL) systems were introduced as integrated algorithms which automatically regulate basal insulin delivery based on CGM glucose values. In 2019 the Advanced Hybrid Closed Loop (AHCL) were developed combining automated basal rate and correction boluses to keep glycemic values in a target range (11).

The application of diabetes technology in CF patients has consistently increased during the last years. In 2009, CGM systems were validated for this population of patients (12). Subsequent studies demonstrated that CGM measurements of hyperglycemia and glycemic variability were superior to HbA1c in distinguishing patients with and without CFRD (13). Adjustment of insulin treatment based on CGM metrics was associated with improvements in lung function, weight and reduced pulmonary function decline (14). Regarding use of insulin pumps in CFRD, there is lack of evidence. The studies performed, excluding case reports (15, 16), demonstrated CSII and SAP safety and efficacy for treatment of CFRD (17, 18). There are no studies exploring the benefit of LGS or PLGS systems in CFRD (10).

In the last two years, the use of AHCL systems, initially developed for T1DM treatment, has been extended to other forms of diabetes and special populations, such as patients affected by CFRD (11). A small pilot study on three patients showed treatment satisfaction, reduced burden of diabetes care and a reduction in glycemic variability (19). The first study to report a beneficial effect of AHCL technology (Tandem Control-IQ algorithm) on glycemic control in adults and adolescents with CFRD was performed by Scully et al. in 2022. An improvement in glycemic control as well in glycemic variability were observed (20).

2 Methods

2.1 Aims of the study

The aim of this study was to evaluate the efficacy of AHCL systems in CF patients in terms of HbA1c and CGM metrics over a 1-year follow-up period.

The primary aim was to evaluate the improvement of glycemic control in terms of glycated hemoglobin (HbA1c) in CFRD patients using AHCL. Secondary aims were the evaluation of the improvements in CGM metrics, the evaluation of changes in weight, BMI, insulin requirement and FEV1%, the achievement of ADA recommended targets and the safety of the system in terms of occurrence of severe hypoglycemia (SH) episodes.

2.2 Population characteristics

A retrospective single center study involving a cohort of patients affected by CFRD followed by the Regional Cystic Fibrosis Center and Regional Pediatric Diabetes Center of IRCCS Giannina Gaslini (Genoa) was performed. All patients affected by CFRD using AHCL systems for at least 1-year, independently from previous therapy, were included. Data collection and subsequent analysis were conducted in 2022–2023.

Because of the retrospective nature of the study the ethic approval and informed consent already signed by patients at the disease onset and renewed yearly, in which they agree on the use of clinical data for research purposes, were used. In addition, all patients provided a specific informed consent for the collection of data.

2.3 AHCL systems

Two different AHCL systems were used by the study population: the Tandem t:slim X2 Control IQ™ system (Tandem Inc., San Diego, California) and the Minimed™ 780G system (Minimed Medtronic, Northridge, California). The two systems differ in the type of algorithm and in some features, but both are able to automatically adjust basal insulin delivery in relation to the glucose level detected by the CGM, suspend insulin delivery in the event of hypoglycemia (current or predicted) and deliver automatic corrective boluses in case of hyperglycemia. The use of AHCL systems in patients affected by CFRD is part of our clinical practice and the choice of the device depends on the specific needs of the single patient. For this reason and given the retrospective nature of the study, a single AHCL system was not used for the study.

2.4 Clinical and CGM data collection

Data were collected at T0 (starting of AHCL system), T1 (1-month after starting AHCL system), T2 (6-months after starting AHCL system) and T3 (1-year after starting AHCL system). Clinical data were collected from electronic clinical records of regular follow-up visits and included age, gender, age at CFRD diagnosis, age at insulin therapy initiation, duration of CFRD, bacterial colonization, FEV1% predicted, weight, BMI, eventual therapy with CFRD modulator drugs or glucocorticoid, lung transplant status, pancreatic insufficiency, previous diabetes treatment, insulin requirement and glycated hemoglobin (HbA1c). Where possible, FGM or CGM data were obtained in a 14-day period within one month from T0.

FGM/CGM metrics included: Time in Range (TIR, 70–180 mg/dl), Time above Range (TAR, 180–250 mg/dl), TAR>250 (>250 mg/dl), Time below Range (TBR, 54–70 mg/dl) and TBR<54 (<54 mg/dl), average glucose (AG) value, standard deviation (SD), glucose coefficient of variation (CV) and percentage of sensor use (%). FGM/CGM and insulin pump data were collected remotely, with real time glucose data sharing dedicated platforms or by downloading them and storing them on cloud platforms available at our center.

Data collected at T1, T2 and T3 were HbA1c and CGM metrics. Additionally, at T2 and T3 weight, BMI, insulin requirement (total daily insulin dose - U/kg/day) and FEV1% predicted were collected. Hospitalization in the 1-year period before T0 and T3 were recorded.

2.5 Statistics

Data are described as mean and standard deviation (SD) or median and range for continuous variables, and as absolute and relative frequencies for categorical variables. The Kolmogorov-Smirnov test was used to establish the normality of continuous variables. Comparisons between T0, T1, T2 and T3 to examine continuous variables were performed using Paired Wilcoxon test. P values ≤ 0.05 were considered statistically significant, and all P values were based on two tailed tests. Statistical analysis was performed using SPSS for Windows (SPSS Inc, Chicago, Illinois USA).

3 Results

Population characteristics at baseline are summarized in Table 1. Ten patients with CFRD, on insulin therapy with AHCL systems (5 on Tandem Control IQ™ and 5 on Minimed™ 780G) were included in the study, 3 (30%) of them were female and 7 (70%) had at least one copy of F508del mutation. Mean age was 39.3 years (range 18.4–50.1 years), mean FEV1 was 80% ± 29.6% and 9 patients (90%) had a mild or moderate lung disease (FEV1 > 80% of predicted as mild disease and FEV1 between 50% and 80% for moderate lung disease). Three patients had previously undergone a lung transplant and were on corticosteroid therapy; none of the

TABLE 1 Population characteristics at baseline (T0).

	Total (n = 10)
Age (years)	39.3 ± 12.7
Female	3 (30%)
B.M.I. (Kg/m^2)	22.9 ± 3.1
Age at CFRD diagnosis (years)	21.3 ± 7.9
Duration of CFRD (years)	17.8 ± 10.6
HbA1c (%)	7.31 ± 0.34
Genotype	
F508del homozygous	5 (50%)
F508del heterozygous	2 (20%)
Other	3 (30%)
Bacterial colonization	
OXA-S *S. aureus*	5 (50%)
P. aeruginosa	2 (20%)
OXA-S *S.aureus and P. aeruginosa*	2 (20%)
OXA-S *S.aureus and B. cepacia*	1 (10%)
Pancreatic insufficiency	10 (100%)
CF-related liver disease	0 (0%)
Lung Transplant (on CCS therapy)	3 (30%)
FEV 1 (% predicted)	79.90 ± 29.62
Hospitalizations due to CF exacerbations in the previous 12 months	6 (60%)
CFTR modulator therapy	
None	5 (50%)
Ivacaftor–Lumacaftor	2 (20%)
Elexacaftor–Tezacaftor–Ivacaftor	3 (40%)
Diabetes treatment	
MDI	4 (40%)
Conventional insulin pump	3 (30%)
PLGS	3 (30%)
Glycemic monitoring	
SMBG	1 (10%)
FGM	5 (50%)
CGM	4 (40%)

BMI, Body Mass Index.
CFRD, Cystic Fibrosis Related Diabetes.
HbA1c, Glycated hemoglobin.
OXA-S, Oxacylline sensible.
MFDI, Multiple Daily Injections.
PLGS, Predictive Low Glucose Suspend.
SMBG, Self Monitoring Blood Glucose.
FGM, Flash Glucose Monitoring.
CGM, Continuous Glucose Monitoring.
CCS - Corticosteroids.

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other patients were on steroid therapy during the study period. Mean HbA1c value was 7.31% ± 0,34%, only 2 patients (20%) met recommended value of <7.0%.

Table 2 reports HbA1c, weight, BMI, insulin requirement and CGM metrics expressed as mean values and standard deviations (SD), at baseline and at 1-month, 6-months, and 1-year from transition to AHCL system. CGM metrics at baseline were available for 8 patients, one patient did not have available 1-month follow-up data and one patient did not have available 1-year follow-up data. HbA1c value of one patient was only recorded at twelve months.

HbA1c showed a statistically significant reduction over the 1-year study period (7.31 ± 0.34 to 6.57 ± 0.85 at T2; p=0.01, to 6.35 ± 1.00 at T3; p=0.03). CV showed a statistically significant reduction at 1-month, 6-months, and 1-year from starting of AHCL (39.00 ± 5.63 to 31.44 ± 3.44 at T2; p=0.04, to 30.23 ± 4.16; p=0.05). Total daily insulin requirement (U/kg/day) decreased significantly during the study period (0.59 ± 0.29 to 0.51 ± 0.21 at T2; p=0.03, to 0.50 ± 0.21 at T3; p=0.03). A trend in increase in TIR during the one-year study period was observed (60.0 ± 20.0 to 76.29 ± 13.30 at T2; p=0.06, to 76.17 ± 13.66 at T3; p=0.34). In addition, we reported a trend in reduction in % time in hyperglycemia > 250 mg/dl (15.0 ± 9.93 to 4.29% ± 3.64 at T2; p=0.06, to 3.83 ± 4.07 at T3; p=0.07). No significant difference of time in hypoglycemia was observed from baseline to 1-year. After 6-month and 1-year from transition to AHCL system, the study population (expressed as mean values) achieved ADA-recommended CGM-based glycemic targets (21), only minimally reached at T0 (Table 3). Supplementary Table 1 shows the increase in the number of patients reaching the over mentioned targets. Variation in HbA1c and CGM metrics across the six-month study period are presented for each patient in Figure 1. No significant differences were found between T0 and T3 in terms of FEV1%, and BMI. However, BMI increased from 22.95 ± 3.08 to 23.38 ± 2.91 (p=0.17). The number of hospitalizations per patient for CF exacerbations decreased from 0.56 ± 0.73 in the year before T0 to 0.11 ± 0.33 during the 1-year follow-up period (p=0.05). No severe hypoglycemia (SH) events occurred between T0 and T3. At the time of data analysis, all the participants were still on AHCL therapy, with a median of duration of use of 26.23 months (range 17.39 – 37.65 months). The results stratified by type of AHCL used (Minimed 780G and Tandem Control-IQ) are shown in Supplementary Table 2.

4 Discussion

This study suggests that AHCL systems are effective in improving glycemic control in CFRD patients, reducing HbA1c, CV values and insulin requirement and increasing the proportion of patients reaching ADA recommended CGM-based targets. The efficacy of insulin pumps and AHCL in T1DM are widely described and a consistent number of real-world data studies are available (11). Conversely, few studies exploring the efficacy and safety of insulin pumps in the

TABLE 2 CGM metrics, HbA1c, weight, BMI, FEV1 and insulin requirement at T0, T1 (1 month), T2 (6 months) and T3 (1 year) after initiation of AHCL system.

	T0	T1	*p (T1vsT0)*	T2	*p (T2vsT0)*	T3	*p (T3vsT0)*
HbA1c %	7.31 ± 0.34	6.81 ± 0.42	0.07	6.57 ± 0.85	**0.01**	6.35 ± 1.00	**0.03**
TIR% (70–180 mg/dL)	60.0 ± 20.0	68.71 ± 16.91	0.17	76.29 ± 13.30	0.06	76.17 ± 13.66	0.34
TAR% (181–250 mg/dL)	22.71 ± 9.39	22.43 ± 10.01	0.53	18.71 ± 10.14	1	18.67 ± 11.55	0.60
TAR% (>250 mg/dL)	15.00 ± 9.93	8.43 ± 8.14	0.14	4.29 ± 3.64	0.06	3.83 ± 4.07	0.07
TBR% (55–69 mg/dL)	1.71 ± 2.14	0.29 ± 0.49	0.07	0.57 ± 0.53	0.13	0.83 ± 0.75	0.27
TBR% (<54 mg/dL)	0.43 ± 0.79	0	0.18	0.03 ± 0.07	0.28	0.33 ± 0.52	0.70
AG (mg/dL)	169.71 ± 32.4	158.86 ± 27.46	0.61	147.57 ± 21.4	0.13	149.0 ± 25.27	0.50
SD (mg/dl)	66.0 ± 17.78	53.50 ± 12.45	0.07	53.67 ± 7.57	0.28	47.00 ± 11.31	0.18
CV (%)	39.00 ± 5.63	33.31 ± 2.94	**0.02**	31.44 ± 3.44	**0.04**	30.23 ± 4.16	**0.05**
Weight (kg)	63.71 ± 11.63			65.69 ± 11.79	0.06	64.30 ± 1.16	0.11
BMI	22.95 ± 3.08			23.66 ± 3.08	0.08	23.38 ± 2.91	0.17
TDI dose (U/kg/day)	0.59 ± 0.29			0.51 ± 0.21	**0.03**	0.50 ± 0.21	**0.03**
FEV1% predicted	79.90 ± 29.62			79.40 ± 30.51	0.81	82.56 ± 30.23	0.81

HbA1c, Glycated Hemoglobin.
TIR, Time in Range.
TAR, Time Above Range.
TBR, Time Below Range.
AG, Average Glucose.
SD, Standard Deviation.
CV, Coefficient of Variation.
BMI, Body Mass Index.
TDI, Total Daily Insulin.
Bold, statistically significant.

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TABLE 3 Achieving ADA-Recommended Continuous Glucose Monitor Targets at Baseline and after 6 months and 1 year from starting AHCL system (20) presented as medium population values.

	Recommended	T0		T2		T3	
HbA1c	< 7%	7.31%	✗	6.57%	✓	6.35%	✓
TIR% (70–180 mg/dL)	> 70%	60%	✗	76.29%	✓	76.17%	✓
TAR% (>180 mg/dL)	< 25%	35.67%	✗	23%	✓	18.67%	✓
TAR% (>250 mg/dL)	< 5%	15%	✗	4.29%	✓	3.83%	✓
TBR% (<70 mg/dL)	< 4%	2.14%	✓	0.6%	✓	0.83%	✓
TBR% (<54 mg/dL)	< 1%	0.4%	✓	0.03%	✓	0.33%	✓
CV	< 36%	39%	✗	31.44%	✓	30.23%	✓

HbA1c, Glycated Hemoglobin.
TIR, Time in Range.
TAR, Time Above Range.
TBR, Time Below Range.
AG, Average Glucose.
SD, Standard Deviation.
CV, Coefficient of Variation.

management of CFRD are available. In 2009, Hardin et al. performed the first study to evaluate the efficacy of continuous subcutaneous insulin infusion (CSII) in a cohort of 9 CFRD adult patients. Results showed a significant improvement in fasting and post-prandial blood glucose levels, HbA1c, body weight and lean mass after 6-months of CSII use (17). In 2023, Grancini et al. demonstrated the improvement of glycemic control parameters and increase in fat mass in 20 patients after 24-months of SAP use (18).

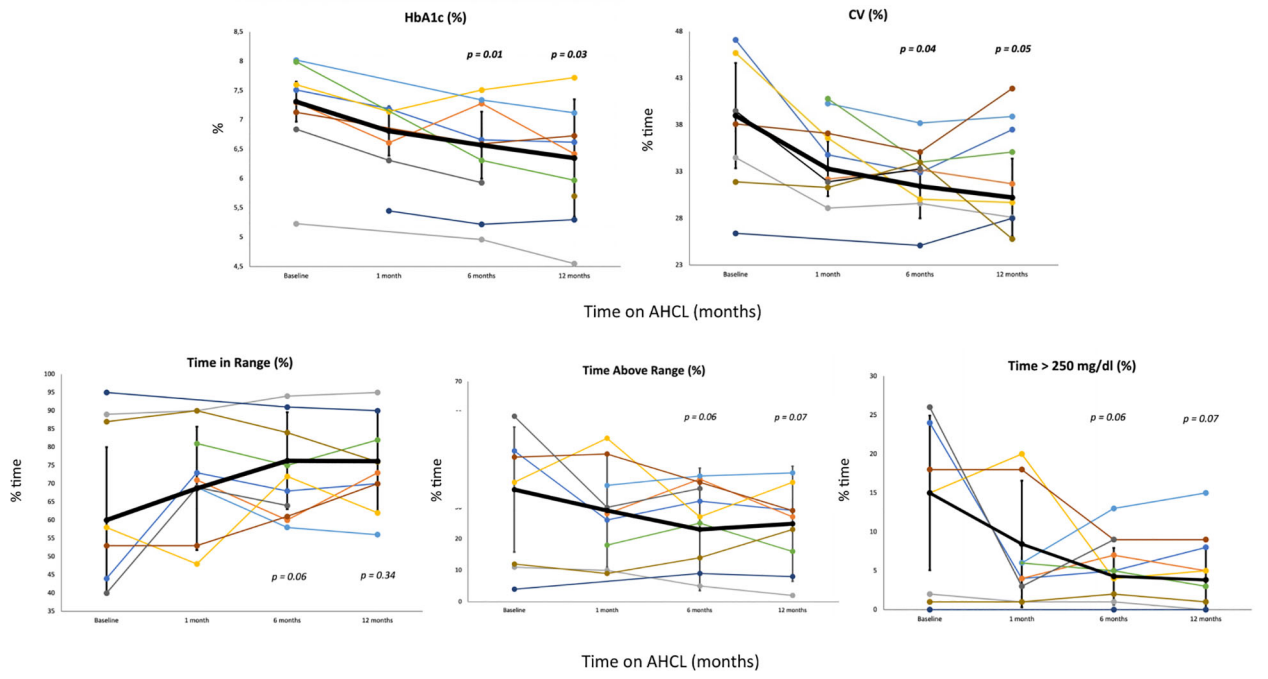

FIGURE 1
Change in key CGM measures from baseline to 1, 6 months and 12 months after starting AHCL. The figure depicts the change in five key glycemic variables (HbA1c, CV, % time in range, % time above range and % time > 250 mg/dl) with each patient represented by a different color. Thicker black lines represent the least LS mean across all subjects with the error bars depicting the SE. (HbA1c, glycated hemoglobin; CV, coefficient of variation CGM, continuous glucose monitor; LS, least squares; SE, standard error).

The first application of AHCL technology in CFRD was a three-arm random-order crossover pilot study. A closed loop artificial pancreas system, both in bihormonal (insulin+glucagon) and insulin-only configuration was compared with usual diabetes care in 3 adult patients. A non-significant reduction in glycemic variability with mean glucose levels <150 mg/dl and minimal hypoglycemia were observed. Patients reported improvements in treatment satisfaction and decreased treatment burden (19). In 2022 a multicenter retrospective study compared glycemic control at baseline and after one and three months from transition to the AHCL system Tandem t:slim X2 pump with Control IQ® technology in 13 patients with CFRD. A significant increase of 15.2% in Time in Range (TIR) was observed (54.3% to 69.5%, p = 0.001) as well as a decrease in hyperglycemia (TAR – time above range) and glycemic variability (CV – Coefficient of Variation). No significant differences in time spent in hypoglycemia were reported (20).

Given the limited data in literature on the efficacy and safety of AHCL in CFRD and differently from previous study, we performed a single center retrospective study among all CFRD patients referred to our Cystic fibrosis and Pediatric Diabetology center using AHCL systems, regardless of the type of system.

We chose the improvement of the HbA1c as primary outcome due to the availability of this data even for those who did not use CGM at T0. Data showed that the transition to an AHCL system is associated with a significant reduction in HbA1c and glycemic variability (CV). Clinically relevant trends in TIR improvement (+16%) and in reduction in TAR>250 mg/dl (-11%) were also observed, although probably due to the small sample size, results were next to statistical significance for both. Furthermore, the significant progressive reduction observed in insulin requirement (-0.09 U/kg/day, p = 0.03) demonstrates that the improvement in glycemic control is not due to an increase of TDI but rather to the optimization of insulin therapy. The use of insulin pumps leads to a reduction in daily insulin requirements also in T1DM (21). Nevertheless, after starting an AHCL systems the optimization of insulin therapy seems to be related to stability or increase in insulin requirement, in particular due to an increase in the percentage of bolus insulin and a reduction in the percentage of basal insulin dose (22, 23). The percentage of time in hypoglycemia did not increase with the introduction of the AHCL system in our cohort of patients, confirming not only the efficacy, but also the safety in the use of these devices in CFRD patients. Considering the average of the CGM metrics reached by the study population, the great efficacy of AHCL on glycemic control is demonstrated by the achievement of all CGM-based recommended targets at T2 and T3: TIR >70%, TAR<25% and TAR>250 mg/dL <5%, TBR< 4% and TBR<54 mg/dL <1% (24). Most recommended targets were not achieved with the other types of insulin therapy previously used (Table 3).

Considering how AHCL algorithms work, it is important to underline the pathophysiological differences of CFRD and T1DM in terms of insulin deficiency. In case of meal insulin bolus omission, the algorithm increases the insulin infusion rate driven by CGM sensor glucose value; it could also deliver a correction bolus in case the increment in basal insulin rate is not sufficient. This is effective for individuals with T1DM with complete insulin deficiency. CFRD is firstly characterized by impaired insulin secretion and progressive islet cell damage with insulin insufficiency developing over time. In addition, insulin resistance related to chronic inflammation, cyclic infections, glucocorticoid therapy and an association with genetic predictors of Type 2 Diabetes Mellitus (T2DM) is associated (25). In patients with CFRD, the residual endogenous insulin production alongside increased insulin delivered by the insulin pump can lead to reactive post-prandial hypoglycemia. Reactive hypoglycemia is a common side effect observed in CFRD, as a result of delayed first phase insulin secretion and late compensatory second phase insulin secretion (26). Pancreatic insufficiency, despite a correct enzyme replacement therapy, can lead to fat malabsorption, more rapid gastric emptying, and more significant post-prandial hyperglycemia (27). Further complicating CFRD management, gastroparesis has been estimated to occur in approximately one third of CF patients (28). Hence, in patients with CFRD it may be even more important to respect the correct timing of the bolus, which must always be performed before meals. In this regard, it would also be interesting to study the glycemic trend of CFRD patients using AHCL who omit meal boluses, as done for patients with T1DM (29). Some authors agree on starting an AID therapy with less aggressive correction if automated correction boluses are provided by the system (10). Lower basal rates in the overnight hours may also be required for CFRD patients with significant endogenous insulin secretion (30).

Time spent in hypoglycemia did not increase using AHCL and no cases of severe hypoglycemia (SH) occurred; these findings demonstrate the safety of these devices even in this form of diabetes which is different from T1DM.

Five patients were already on modulator therapy when they started AHCL systems, of whom three on elexacaftor-tezacaftor-ivacaftor (ETI). It is still controversial if and how much these therapies impact on CFRD. Preliminary data have shown improvements in average glucose levels and reduced CV following ETI treatment, but no significant changes in insulin total daily dose (31). An observational study of 134 adult patients treated with ETI found a random improvement of glucose and HbA1c levels in patients without CFRD but not in those with CFRD (32). Recently, Grancini et al. demonstrated a decrease of HbA1c and glycemic variability and an increase of fat mass after six months of ETI treatment (33). Due to the small number under treatment, this study could not contribute with regard to the effects of ETI on glycemic improvements.

Even though CFRD is the most common comorbidity in CF, many patients are unaware of the possibility to develop it and CFRD diagnosis may be seen as a further increase in therapy burden, which is already a complex, time-consuming medical regimen involving airway clearance, inhaled therapies and antibiotics, enzyme replacement and caloric supplementation (34, 35). The use of AHCL systems in T1DM has been associated with an improvement in Quality of Life (QoL), quality of sleep and reduced impact of diabetes on daily life (36, 37). Despite perceived benefits, the use of diabetes technology in people with Cystic Fibrosis is still low and related patients' perception is still understudied. In a 2021 survey of CFRD patients in the United States, 75% of youth and adults reported CGM use, similar to T1DM patients, while only 29% reported insulin pump use (38). A significant benefit from CGM use was reported, but also a greater burden from insulin pump use. In addition, high device discontinuation rates were observed: 19% for CGM and 28% for insulin pump, most commonly due to increased concerns about

glycemia, cost and pain related to the device use. Considering our study population all the participants were still on insulin therapy with AHCL and many of them over two years after the start of the system; the long-term adherence reported should be encouraging for CF centers to propose automated insulin delivery systems for their insulin-dependent patients. A prospective study evaluating AHCL treatment satisfaction in CF patients would be beneficial.

Advanced therapeutic solutions should be proposed to insulin-dependent CF patients by diabetologists experts in technological field, along with a close follow-up by a specialized multidisciplinary team with expertise in diabetes and CF; this approach can lead to a larger use of these advanced tools, an improvement of glycemic control and a low discontinuation rate in CF patients (39). As stated by "JDRF Barriers and Drivers to technology", the first reason for patients not using technological devices is that the clinician did not recommend it (40). Further studies with a greater number of patients and a longer follow-up period are needed; our results show the importance to offer AHCL systems to this population of patients which could benefit from glycemic improvement as well as in nutritional status and respiratory function.

The evaluation of treatment efficacy in terms of CGM metrics, the application of different AHCL systems and the single center data collection are the strengths of this study, although several limitations must be assessed. The relatively small number of patients and a low power of the study related with the low rate of use of technology in CFRD, although still adequate to detect significant changes in some glycemic measures, should be considered as a limitation. Furthermore, the retrospective nature of the study led to the difficulty to obtain complete clinical and CGM data at baseline in patients who were not on CGM prior to starting the AHCL system. A possible consequence of this limitation is the difference of statistical significance between the improvement observed in HbA1c values and CGM metrics.

5 Conclusions and future perspectives

In conclusion, AHCL systems showed to be effective in improving glycemic control in CFRD patients, reducing HbA1c, CV values and insulin requirement and increasing the proportion of patients reaching ADA recommended CGM-based targets. The long-term adherence to AHCL treatment observed in CF patients is encouraging for CF centers to propose these systems for their insulin-dependent patients. Multidisciplinary teams should support the use of technological devices for CFRD treatment, associated with a successful and close collaboration of each specialist during follow-up. Prospective study evaluating AHCL treatment satisfaction in patients affected by CFRD and evaluating the efficacy and safety of these systems on a higher number of patients and a longer follow-up would be very useful.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

MB: Writing – original draft, Conceptualization. DF: Writing – original draft, Data curation. FD: Writing – review & editing, Data curation. GS: Writing – review & editing, Data curation. FC: Writing – review & editing. GD: Writing – review & editing. GT: Writing – review & editing. MC: Writing – original draft, Formal Analysis. CC: Writing – review & editing, Supervision. NM: Writing – original draft, Supervision, Conceptualization. RC: Writing – review & editing, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1347141/full#supplementary-material

References

1. Foundation CF. *Cystic Fibrosis Foundation Patient Registry 2019 Annual Data Report*. Bethesda, Maryland (2020). Available at: https://www.cff.org/.

2. Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. *Diabetes Care*. (2009) 32:1626–31. doi: 10.2337/dc09–0586

3. Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care*. (2010) 33:2697–708. doi: 10.2337/dc10–1768

4. Prentice B, Nicholson M, Lam GY. Cystic fibrosis related diabetes (CFRD) in the era of modulators: a scoping review. *Pediatr Respir Rev*. (2022). 46:23–29. doi: 10.1016/j.prrv.2022.11.005

5. Olesen HV, Drevinek P, Gulmans VA, Hatziagorou E, Jung A, Mei-Zahav M, et al. Cystic fibrosis related diabetes in Europe: Prevalence, risk factors and outcome; Olesen et al. *J Cyst Fibros*. (2020) 19:321–7. doi: 10.1016/j.jcf.2019.10.009

6. Lewis C, Blackman SM, Nelson A, Oberdorfer E, Wells D, Dunitz J, et al. Diabetes-related mortality in adults with cystic fibrosis. Role of genotype and sex. *Am J Respir Crit Care Med*. (2015) 191:194–200. doi: 10.1164/rccm.201403-0576OC

7. Moran A, Pillay K, Becker D, Granados A, Hameed S, Acerini CL. ISPAD Clinical Practice Consensus Guidelines 2018: Management of cystic fibrosis-related diabetes in children and adolescents. *Pediatr Diabetes*. (2018) 19 Suppl 27:64–74. doi: 10.1111/pedi.12732

8. Chan CL, Ode KL, Granados A, Moheet A, Moran A, Hameed S. Continuous glucose monitoring in cystic fibrosis - A practical guide. *J Cyst Fibros*. (2019) 18 Suppl 2: S25–31. doi: 10.1016/j.jcf.2019.08.025

9. Moon SJ, Jung I, Park CY. Current advances of artificial pancreas systems: A comprehensive review of the clinical evidence. *Diabetes Metab J*. (2021) 45:813–39. doi: 10.4093/dmj.2021.0177

10. Marks BE, Williams KM, Sherwood JS, Putman MS. Practical aspects of diabetes technology use: Continuous glucose monitors, insulin pumps, and automated insulin delivery systems. *J Clin Transl Endocrinol*. (2021) 27:100282. doi: 10.1016/j.jcte.2021.100282

11. Bassi M, Franzone D, Dufour F, Strati MF, Scalas M, Tantari G, et al. Automated insulin delivery (AID) systems: use and efficacy in children and adults with type 1 diabetes and other forms of diabetes in europe in early 2023. *Life (Basel)*. (2023) 13:783. doi: 10.3390/life13030783

12. O'Riordan SM, Hindmarsh P, Hill NR, Matthews DR, George S, Greally P, et al. Validation of continuous glucose monitoring in children and adolescents with cystic fibrosis: a prospective cohort study. *Diabetes Care*. (2009) 32:1020–2. doi: 10.2337/dc08–1925

13. Scully KJ, Sherwood JS, Martin K, Ruazol M, Marchetti P, Larkin M, et al. Continuous glucose monitoring and hbA1c in cystic fibrosis: clinical correlations and implications for CFRD diagnosis. *J Clin Endocrinol Metab*. (2022) 107:e1444–54. doi: 10.1210/clinem/dgab857

14. Frost F, Dyce P, Nazareth D, Malone V, Walshaw MJ. Continuous glucose monitoring guided insulin therapy is associated with improved clinical outcomes in cystic fibrosis-related diabetes. *J Cyst Fibros*. (2018) 17:798–803. doi: 10.1016/j.jcf.2018.05.005

15. Klupa T, Małecki M, Katra B, Cyganek K, Skupień J, Kostyk E, et al. Use of sensor-augmented insulin pump in patient with diabetes and cystic fibrosis: evidence for improvement in metabolic control. *Diabetes Technol Ther*. (2008) 10:46–9. doi: 10.1089/dia.2007.0238

16. Sulli N, Bertasi S, Zullo S, Shashaj B. Use of continuous subcutaneous insulin infusion in patients with cystic fibrosis related diabetes: three case reports. *J Cyst Fibros*. (2007) 6:237–40. doi: 10.1016/j.jcf.2006.07.005

17. Hardin DS, Rice J, Rice M, Rosenblatt R. Use of the insulin pump in treat cystic fibrosis related diabetes. *J Cyst Fibros*. (2009) 8:174–8. doi: 10.1016/j.jcf.2008.12.001

18. Grancini V, Alicandro G, Porcaro LL, Zazzeron L, Gramegna A, Morlacchi LC, et al. Effects of insulin therapy optimization with sensor augmented pumps on glycemic control and body composition in people with cystic fibrosis-related diabetes. *Front Endocrinol (Lausanne)*. (2023) 14:1228153. doi: 10.3389/fendo.2023.1228153

19. Sherwood JS, Jafri RZ, Balliro CA, Zheng H, El-Khatib FH, Damiano ER, et al. Automated glycemic control with the bionic pancreas in cystic fibrosis-related diabetes: A pilot study. *J Cyst Fibros*. (2020) 19:159–61. doi: 10.1016/j.jcf.2019.08.002

20. Scully KJ, Palani G, Zheng H, Moheet A, Putman MS. The effect of control IQ hybrid closed loop technology on glycemic control in adolescents and adults with cystic fibrosis-related diabetes. *Diabetes Technol Ther*. (2022) 24:446–52. doi: 10.1089/dia.2021.0354

21. Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. *Cochrane Database Syst Rev*. (2010) 1):CD005103. doi: 10.1002/14651858.CD005103.pub2

22. Henry Z, Villar Fimbel S, Bendelac N, Perge K, Thivolet C. Beneficial effects of automated insulin delivery over one-year follow-up in real life for youths and adults with type 1 diabetes irrespective of patient characteristics. *Diabetes Obes Metab*. (2024) 26:557–66. doi: 10.1111/dom.15344

23. Silva JD, Lepore G, Battelino T, Arrieta A, Castañeda J, Grossman B, et al. Real-world performance of the miniMed™ 780G system: first report of outcomes from 4120 users. *Diabetes Technol Ther*. (2022) 24:113–9. doi: 10.1089/dia.2021.0203

24. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. (2019) 42:1593–603. doi: 10.2337/dci19–0028

25. Moran A, Diem P, Klein DJ, Levitt MD, Robertson RP. Pancreatic endocrine function in cystic fibrosis. *J Pediatr*. (1991) 118:715–23. doi: 10.1016/s0022–3476(05)80032–0

26. Kilberg MJ, Harris C, Sheikh S, Stefanovski D, Cuchel M, Kubrak C, et al. Hypoglycemia and islet dysfunction following oral glucose tolerance testing in pancreatic-insufficient cystic fibrosis. *J Clin Endocrinol Metab*. (2020) 105:3179–89. doi: 10.1210/clinem/dgaa448

27. Perano SJ, Couper JJ, Horowitz M, Martin AJ, Kritas S, Sullivan T, et al. Pancreatic enzyme supplementation improves the incretin hormone response and attenuates postprandial glycemia in adolescents with cystic fibrosis: a randomized crossover trial. *J Clin Endocrinol Metab*. (2014) 99:2486–93. doi: 10.1210/jc.2013–4417

28. Corral JE, Dye CW, Mascarenhas MR, Barkin JS, Salathe M, Moshiree B. Is gastroparesis found more frequently in patients with cystic fibrosis? A systematic review. *Scientifica (Cairo)*. (2016) 2016:2918139. doi: 10.1155/2016/2918139

29. Tornese G, Carletti C, Giangreco M, Nisticò D, Faleschini E, Barbi E. Carbohydrate tolerance threshold for unannounced snacks in children and adolescents with type 1 diabetes using an advanced hybrid closed-loop system. *Diabetes Care*. (2022) 45:1486–8. doi: 10.2337/dc21–2643

30. Kilberg MJ, Sheikh S, Stefanovski D, Kubrak C, De Leon DD, Hadjiliadis D, et al. Dysregulated insulin in pancreatic insufficient cystic fibrosis with post-prandial hypoglycemia. *J Cyst Fibros*. (2020) 19:310–5. doi: 10.1016/j.jcf.2019.07.006

31. Scully KJ, Marchetti P, Sawicki GS, Uluer A, Cernadas M, Cagnina RE, et al. The effect of elexacaftor/tezacaftor/ivacaftor (ETI) on glycemia in adults with cystic fibrosis. *J Cyst Fibros*. (2022) 21:258–63. doi: 10.1016/j.jcf.2021.09.001

32. Petersen MC, Begnel L, Wallendorf M, Litvin M. Effect of elexacaftor-tezacaftor-ivacaftor on body weight and metabolic parameters in adults with cystic fibrosis. *J Cyst Fibros*. (2022) 21:265–71. doi: 10.1016/j.jcf.2021.11.012

33. Grancini V, Gramegna A, Zazzeron L, Alicandro G, Porcaro LL, Piedepalumbo F, et al. Effects of elexacaftor/tezacaftor/ivacaftor triple combination therapy on glycemic control and body composition in patients with cystic fibrosis-related diabetes. *Diabetes Metab*. (2023) 49:101466. doi: 10.1016/j.diabet.2023.101466

34. Mason KA, Marks BE, Wood CL, Le TN. Cystic fibrosis-related diabetes: The patient perspective. *J Clin Transl Endocrinol*. (2021) 26:100279. doi: 10.1016/j.jcte.2021.100279

35. Millington K, Miller V, Rubenstein RC, Kelly A. Patient and parent perceptions of the diagnosis and management of cystic fibrosis-related diabetes. *J Clin Transl Endocrinol*. (2014) 1:100–7. doi: 10.1016/j.jcte.2014.07.003

36. Pinsker JE, Müller L, Constantin A, Leas S, Manning M, McElwee Malloy M, et al. Real-world patient-reported outcomes and glycemic results with initiation of control-IQ technology. *Diabetes Technol Ther*. (2021) 23:120–7. doi: 10.1089/dia.2020.0388

37. Iturralde E, Tanenbaum ML, Hanes SJ, Suttiratana SC, Ambrosino JM, Ly TT, et al. Expectations and attitudes of individuals with type 1 diabetes after using a hybrid closed loop system. *Diabetes Educ*. (2017) 43:223–32. doi: 10.1177/0145721717697244

38. Marks BE, Kilberg MJ, Aliaj E, Fredkin K, Hudson J, Riva D, et al. Perceptions of diabetes technology use in cystic fibrosis-related diabetes management. *Diabetes Technol Ther*. (2021) 23:753–9. doi: 10.1089/dia.2021.0201

39. Scheuing N, Badenhoop K, Borkenstein M, Konrad K, Lilienthal E, Laubner K, et al. Why is insulin pump treatment rarely used in adolescents and young adults with cystic fibrosis-related diabetes? *Pediatr Diabetes*. (2015) 16:10–5. doi: 10.1111/pedi.12158

40. Bennett C, Hazelton DJDRF Diabetes – Type 1 diabetes Research, Advocacy, and Support. JDRF Barriers and drivers to technology. *Npf Synergy*. (2019). Available at: https://jdrf.org.uk/wp-content/uploads/2023/07/jdrf-pathway-to-choice-full-report-2020.pdf.

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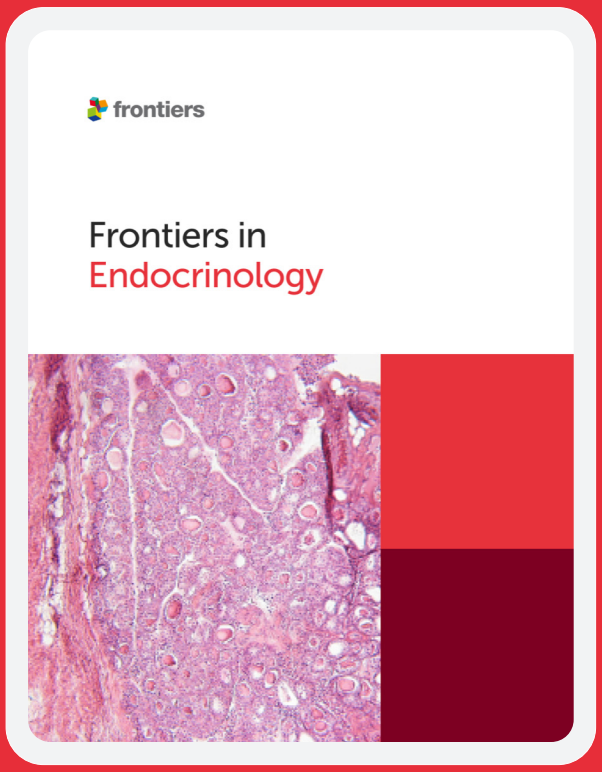

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