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Comparison of flash glucose monitoring with real time continuous glucose monitoring in children and adolescents with type 1 diabetes treated with continuous subcutaneous insulin infusion

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ABSTRACT

Aims: In 2016 intermittently scanned continuous glucose monitoring (isCGM) became the first reimbursed CGM system in Belgium. Many children with type 1 diabetes (T1D) treated with multiple daily injections as well as with continuous subcutaneous insulin infusion (CSII) switched from self-monitoring of blood glucose to isCGM to monitor their treatment. In 2017 the Enlite® real-time CGM (rtCGM) system was reimbursed enabling its use with the Minimed® 640G insulin pump with integrated SmartGuard technology. In this study we compared the metabolic control during CSII with isCGM with that during rtCGM. Patient's satisfaction and side effects of the rtCGM system were also evaluated.

Methods: 20 children with T1D, aged 5–16 years, were included. Metabolic control during the last month of isCGM use was compared to that during the 3rd and 6th month of rtCGM.

Results: Three patients stopped early rtCGM mainly due to calibration burden. The HbA1c level and the mean glucose value in the other patients did not change after switching to the rtCGM system. Glucose variability was smaller (46.2% vs 38.4% and 36.4%, $p = 0.000$). Time in hypoglycemia (<70 mg/dl) was lower (7.4% vs 1.6% and 1.5%, $p = 0.000$). The main patient inconvenience was the sensor calibration.

Conclusions: Our data show that during Enlite® rtCGM with the Minimed® 640G pump system glucose variability was smaller and the patients spent less time in hypoglycemia than during isCGM. The need for timely calibrations is considered as the main drawback of the system.

1. Introduction

Strict glycemic control with near-normal blood glucose (BG) levels from the early stages of the disease is desirable in children with type 1 diabetes mellitus (T1D) to reduce the risk of developing micro- and macrovascular diabetes complications [1,2]. Advanced diabetes technologies like continuous glucose monitoring (CGM) devices provide patients, caregivers and

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healthcare professionals information on real-time glucose data and trends facilitating the (self-)management of the disease [3,4]. Currently available CGM systems measure interstitial fluid glucose concentrations utilizing subcutaneously placed enzyme-tipped electrodes [4]. Known benefits of CGM include reduced HbA1c, glucose variability and hypoglycemia, and improved quality of life [3,5,6].

Current CGM systems encompass real-time CGM (rtCGM) and intermittently scanned or flash CGM (isCGM) [4]. Real-time CGMs provide at 5 min intervals numerical and graphical information about the current interstitial glucose level, glucose trends, and the direction and rate of change of glucose [3,4]. They utilize alarms for thresholds and predictions of hypo- and hyperglycemia, as well as rate of change alarms for rapid glycemic excursion [4]. The new generation Enlite® CGM sensor (Medtronic MiniMed, Inc., Northridge, CA) [7,8] benefits from an enhanced signal processing algorithm (SmartGuard technology) and is used with the Minimed® 640G insulin pump (Medtronic MiniMed, Inc., Northridge, CA) resulting in sensor augmented pump (SAP) therapy with predictive low glucose suspend [9]. The Minimed® 640G SAP system automatically suspends the insulin infusion when a low glucose concentration is predicted and resumes the infusion once this risk has been overcome [10–14]. Disadvantages of this system are the short sensor working life (6 days), frequent systems alarms and the necessity of at least twice daily capillary BG measurements for calibration [15,16].

In 2013, isCGM was introduced as the FreeStyle® Libre Flash Glucose Monitoring System (Abbott Diabetes Care, Alameda, California, USA) [17]. In contrast to rtCGM the isCGM does not automatically display glucose readings at regular intervals, but reports glucose levels only when the user scans the sensor by holding a special hand-held scanner, or a compatible cell phone, close to the sensor [4]. The real-time interstitial glucose level, a glucose trend arrow and a graph of the preceding 8 h stored glucose readings are provided on demand [4,18]. Advantages are that the sensor can be worn for up to 2 weeks and that the sensor is factory calibrated [19], eliminating the need for recalibration and increasing the ease of use. Disadvantages are that isCGM lacks alarm features and connectivity with insulin pumps [18,20].

Since August 1, 2016 the isCGM is reimbursed by the health insurance system in Belgium for children older than 4 years and adults with T1D. Many patients treated with multiple daily injections (MDI) as well as with continuous subcutaneous insulin infusion (CSII) switched from self-monitoring of blood glucose (SMBG) to isCGM [21,22]. In the spring of 2017 the Enlite® rtCGM system was reimbursed and became available for wider use in the Guardian™ Connect CGM system (Medtronic MiniMed, Inc., Northridge, CA) [23] or in connection with the MiniMed® 640G pump enabling the suspend before low function. Patients were allowed to switch from isCGM to rtCGM with the Enlite® sensor, and patients using older insulin pumps, i.c. Paradigm® Veo™ insulin pump (Medtronic MiniMed, Inc., Northridge, CA), could switch at the same time to a MiniMed® 640G insulin pump taking profit of the Smartguard technology.

In the present study we compared in children and adolescents with T1D treated with CSII who switched from isCGM to rtCGM the metabolic control during the last month of the use of isCGM and a Paradigm® Veo™ insulin pump with the metabolic control during the third and sixth month of use of the SAP Minimed® 640G insulin pump. The usability and acceptability of the Enlite® sensor was evaluated after one month of use and the occurrence of side effects were registered during the study period.

2. Materials and methods

2.1. Study design

A prospective, nonrandomized, nonblinded single arm study was performed. The study protocol (NCT03249974) and informed consent forms were approved by the Ethics Committee of the Jessa Hospital. The study was performed according to Good Clinical Practice and the Principles of the Declaration of Helsinki. The manufacturers of the isCGM system and of the Enlite® rtCGM system were not involved in the design or conduct of the study, neither was there any financial or in-kind support.

The primary endpoints were the level of metabolic control as reflected by the HbA1c, eA1c, the mean glucose level and the glucose variability evaluated by coefficient of variation (standard deviation divided by the mean). Secondary endpoints were the time of the day spent in range (values between 70 and 140 mg/dl and between 70 and 180 mg/dl), in hypoglycemia (values <70 mg/dl and <54 mg/dl), and in hyperglycemia (values >180 mg/dl and >250 mg/dl). In addition patients' satisfaction with the Enlite® rtCGM system and side effects were evaluated.

2.2. Patients

Children and adolescents aged 5–16 years with T1D for at least 6 months and treated with CSII with a Paradigm® Veo™ insulin pump and evaluating their metabolic control with isCGM were eligible to participate to the study. The patients were followed at the childhood diabetic center of the Jessa Hospital, Hasselt, Belgium. Informed and written consent was obtained from all caregivers and participants older than 12 years prior to participation in the study.

2.3. Study procedures

2.3.1. Preliminary visit

During a routine visit at the outpatient pediatric diabetic clinic the possibility to switch to the Enlite® rtCGM system and Minimed® 640G insulin pump with the SmartGuard integrated system was proposed to all (n = 30) patients (and their caregivers) treated with a Paradigm® Veo™ insulin pump and controlling their glucose levels with isCGM. The advantages of the SmartGuard integrated system (e.g. alerts, stop before low) and disadvantages (e.g. calibration) were discussed. Subjects who agreed to switch were invited to participate in the study.

2.3.2. Study visit 1

Study participants who agreed to switch to the Enlite® rtCGM system and Minimed® 640G insulin pump were admitted to

the hospital for two days (one night). The readings of the FreeStyle® Libre Flash glucose scanner were downloaded to the Diabass Pro software program (version 17.1.0.1) and a blood sample for determination of HbA1c was collected. A new infusion set was inserted and the Minimed® 640G insulin pump was attached; the same device settings for insulin delivery as used with the Paradigm® Veo™ insulin pump were programmed. The Enlite® sensor was inserted on the abdomen or buttock, as instructed by the company, and activated by the Guardian™ 2 Link transmitter. After the warming up period the sensor was calibrated two and six hours after insertion, and thereafter at least twice daily by capillary BG values measured with the Contour® Next Link (Bayer/Ascensia) glucometer that communicates with the Minimed® 640 insulin pump. Patients and their caregivers were intensively trained in the use of the Enlite® rtCGM system and Minimed® 640G insulin pump by the diabetes educators of the Pediatric Diabetes Unit. At the start of the use of the Enlite® rtCGM system the threshold for 'suspend before low' was set to 70 mg/dl as proposed in a recently published protocols [9,12] and the alert level for hypoglycemia was set to 70 mg/dl. All other glucose alerts were disabled.

2.3.3. *Intermediate visit*

Patients and their caregivers were seen at the out-patient clinic about four weeks after the start of Enlite® rtCGM system and Minimed® 640G insulin pump. Subjects and their caregivers' experience with the Enlite® rtCGM system was evaluated by a 5-point Likert scale questionnaire to assess their satisfaction with insertion, comfort and usability. The used questionnaire was an adaptation of previously published questionnaires [21,24]. The sensor insertion site was examined for skin reactions as e.g. infection, inflammation or bleeding. During this visit the high glucose alert was activated at 250 or 300 mg/dl and the suspend before low and lower limit were decreased to 60 or 65 mg/dl. These limits were determined after deliberation with the patients and their caregivers in order to provide them with the most comfortable feeling.

2.3.4. *Study visit 2 and 3*

Patients and their caregivers were seen at the out-patient clinic about 3 (study visit 2) and 6 (study visit 3) months after the initiation of the Enlite® rtCGM system and Minimed® 640G insulin pump. The data from the insulin pumps were uploaded to the CareLink™ therapy management software. A blood sample for the determination of HbA1c was taken. The sensor insertion sites were examined for skin reactions.

2.4. *Data analysis*

The evaluation of the results was done based on continuous recording of glucose profiles from the isCGM system (every 15 min) and rtCGM component of the Enlite®/MiniMed® 640G system (every 5 min). The glucose data of the isCGM reader downloaded to the Diabass Pro software program were exported to an excel file. Only the 'no scan' data of the last 28 days before the start of the study were used in the analyses. As the upper limit of the Enlite® rtCGM system is 400 mg/dl, data from the isCGM system were censored by setting all values above 400 mg/dl to 400 mg/dl. Data of the Enlite® rtCGM system uploaded to the Carelink™ therapy management software were also exported to an excel file. The glucose data of the 28 days before the HbA1c blood sampling were used for study visit 2 and 3. The following comparisons were made between isCGM system and the Enlite® rtCGM system readings: mean blood glucose (mg/dl), glucose coefficient of variation (%, SD/mean blood glucose × 100), percentage of glucose measurements above 250 mg/dl, above 180 mg/dl, between 70 and 180 mg/dl, between 70 and 140 mg/dl, below 70 mg/dl and below 54 mg/dl, low blood glucose index (LBGI) and high blood glucose index (HBGI) [25]. In addition, the estimated HbA1c (eA1C) was calculated according to the formula provided by Beck *et al.* [26]. The active sensor wear duration was also compared between the three periods.

Results are expressed as median (IQR). Results at the three study visits were compared by the nonparametric Friedman test. In case of a statistically significant difference post hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied, resulting in a significance level set at $p < 0.017$. The statistical analyses were done with IBM SPSS® Statistics 25 (IBM SPSS Statistics for Windows, Chicago, IL, USA).

3. Results

3.1. *Patients*

Between May 1st and October 31th 2017 20 children and adolescents (7 boys) switched to Enlite® rtCGM system and Minimed® 640G insulin pump. Three girls interrupted the use of the Enlite® rtCGM system early after respectively 38, 44 and 60 days of use. Reasons for switching back to the isCGM were non compliancy with the calibrations and alarm fatigue. Hence, the data of 17 patients were included in the present analysis.

Median (IQR) age of the patients at the start of the study was 10.4 (8.1–13.2) years. Diagnosis was made at 4.6 (2.6–7.9) years; the disease duration was 5.6 (2.3–7.0) years. The median time of CSII use before starting Enlite® rtCGM system and Minimed® 640G insulin pump was 3.1 (0.8–6.0) years and the time of isCGM use was 0.8 (0.7–1.0) years.

3.2. *Glucose parameters*

Parameters of glycemic control were collected at visit 1 (isCGM data) and 84 (51–93) days (visit 2) and 203 (176–217) days (visit 3) after the start of the Enlite® rtCGM system and Minimed® 640G insulin pump (rtCGM data). Time of sensor use was not different between the evaluation periods: visit 1 (isCGM system) 94.3 (89.2–96.5) %; visit 2 94.0 (91.1–96.0) % and visit 3 92.5 (89.6–97.1) % for the rtCGM system. Results for the glycemic parameters are shown in Table 1. The HbA1c level, the eA1c and the mean glucose value did not change during the use of the Enlite® rtCGM system. There was a statistically significant difference in the coefficient of variation (CV) between the observation periods ($\chi^2 = 25.529$, $p = 0.000$). Post hoc analysis with Wilcoxon signed-rank tests showed

Table 1 – Comparison of glycemic parameters during the three study periods.

Characteristic	isCGM	rtCGM 3 months	rtCGM 6 months	χ^2	P
HbA1c (%)	7.7 (6.8–8.0)	7.5 (7.2–8.0)	7.4 (7.2–7.9)	0.406	0.816
HbA1c (mmol/mol)	60 (51–64)	58 (56–62)	58 (55–63)	0.123	0.940
eA1c (%)	7.6 (7.0–8.0)	7.4 (7.3–7.6)	7.5 (7.2–8.0)	0.118	0.943
eA1c (mmol/mol)	60 (52–64)	58 (56–60)	58 (55–64)	0.118	0.943
mean (mg/dl)	183 (153–198)	172 (165–181)	175 (164–196)	0.118	0.943
CV (%)	46.2 (42.2–49.5)	38.4 (35.3–40.4)	36.4 (34.3–40.9)	25.529	0.000
>250 mg/dl (%)	18.6 (12.2–30.2)	12.5 (10.3–16.7)	15.3 (9.7–21.9)	8.941	0.011
>180 mg/dl (%)	45.5 (30.5–54.9)	39.8 (35.1–46.0)	44.4 (34.3–55.4)	0.000	1.000
70–180 mg/dl (%)	47.1 (38.2–55.6)	56.9 (52.6–63.0)	52.5 (43.6–63.9)	4.507	0.105
70–140 mg/dl (%)	29.2 (22.6–37.5)	34.4 (29.1–42.0)	39.9 (24.4–40.8)	0.567	0.753
<70 mg/dl (%)	7.4 (5.3–8.7)	1.6 (0.5–3.1)	1.5 (0.8–2.9)	20.485	0.000
<54 mg/dl (%)	2.8 (1.3–4.7)	0.2 (0.0–0.7)	0.2 (0.0–0.5)	18.794	0.000
LBGI	1.8 (1.2–2.3)	0.5 (0.3–0.9)	0.5 (0.3–0.8)	22.531	0.000
HBGI	11.4 (7.6–15.6)	8.9 (8.1–10.7)	9.9 (7.9–13.2)	3.667	0.160

that the CV was lower after three months (Z = -3.621, p = 0.000) and after six months (Z = −3.621, p = 0.000) of rtCGM compared to isCGM. During isCGM none of the patients had a CV below 36%, whereas after three months rtCGM six (35%) and after six months rtCGM seven (41%) of the subjects had a CV below 36%. The percentage of time in the three main glycemic zones is shown in Fig. 1. Time in range (70–180 mg/dl) was not different between the three observation periods. There was a significant difference in time spent in hypoglycemia (<70 mg/dl) and in severe hypoglycemia (<54 mg/dl). Post hoc analysis showed that the time spent in hypoglycemia (<70 mg/dl) was lower after three months (Z = −3.575, p = 0.000) and after six months (Z = −3.574, p = 0.000) of rtCGM compared to isCGM. Time spent in severe hypoglycemia (<54 mg/dl) also was lower after three months (Z = −3.464, p = 0.001) and after six months (Z = −3.464, p = 0.001) of rtCGM. LBGI was lower after three months (Z = −3.517, p = 0.000) and after six months (Z = −3.576, p = 0.000) of rtCGM. During isCGM 11 patients (64%) had a LBGI $\geq$ 1.5, whereas during rtCGM LBGI was <1.5 in all subjects. Time spent in severe hyperglycemia (>250 mg/dl) was lower after three months (Z = −2.604, p = 0.009) and after six months (Z = −2.367, p = 0.018) of rtCGM. There were no differences in the glycemic parameters between three and six months of rtCGM use.

3.3. *Application and usability*

Study subjects and/or their caregivers rated their experience with the Enlite® rtCGM system on a scale of 1 (strongly agree) to 5 (strongly disagree). Fig. 2 summarizes the responses about sensor application and wear, and the comparison to isCGM. The majority of the participants (66.7%) agreed that it was easy to put the sensor on and that it did not hurt when the sensor was put on (72.2%). Most statements about sensor wear and use (61.1–100.0%) were rated favorable (1 or 2). The most encountered inconveniences (4 or 5) were the calibration of the sensor (41.1%) and the sensor alarms (35.3%). In comparison with the isCGM most of the participants agreed that it was easier and more private to measure glucose levels, and that the Enlite® rtCGM system gives more information.

3.4. *Safety and skin reactions*

None of the patients experienced any serious adverse event (severe hypoglycemia, diabetic ketoacidosis) during the study period. Ten patients complained of itching during the wearing of the Enlite® sensor and nine showed signs of skin irritation/inflammation after removal of the sensor. Two patients developed serious skin lesions compatible with contact dermatitis. The symptoms disappeared after replacing the Enlite® plaster with Opsite◇ Flexiflix◇ (Smith & Nephew, USA).

4. Discussion

In the present study we compared in a cohort of diabetic children and adolescents with T1D treated with CSII the metabolic control during the use of isCGM with a Paradigm® Veo insulin pump with that during the use of the Enlite® rtCGM with the Minimed® 640G pump. To the best of our knowledge this is the first study that compares isCGM in combination with a Paradigm® Veo pump with Enlite® rtCGM with the Minimed® 640G pump. Our data show that although the HbA1c and eA1c levels and mean glucose value were comparable glucose variability was smaller and the patients spent less time in hypoglycemia and severe hyperglycemia after switching to the Enlite® rtCGM with the Minimed® 640G pump stressing the superiority of the latter system.

When in the summer of 2016 the isCGM became reimbursed by the health insurance system in Belgium many patients with T1D treated with MDI as well as with CSII changed from SMBG to isCGM [21,22]. Although the patients in our clinic treated by CSII used the Paradigm® Veo insulin pump with the possibility of SAP low glucose suspend rtCGM, this pump was not used in connection with rtCGM because the Enlite® sensors were not reimbursed and too expensive to buy. The ease of use of isCGM without the need for calibration by finger stick BG is the main advantage of this system. We and others previously reported a limited accuracy of isCGM, especially in the hypoglycemic range [21,27,28]. Moreover, with ongoing use several children using isCGM developed severe contact dermatitis necessitating ending the use of isCGM [29,30]. Other limitations of the isCGM are the need to scan at

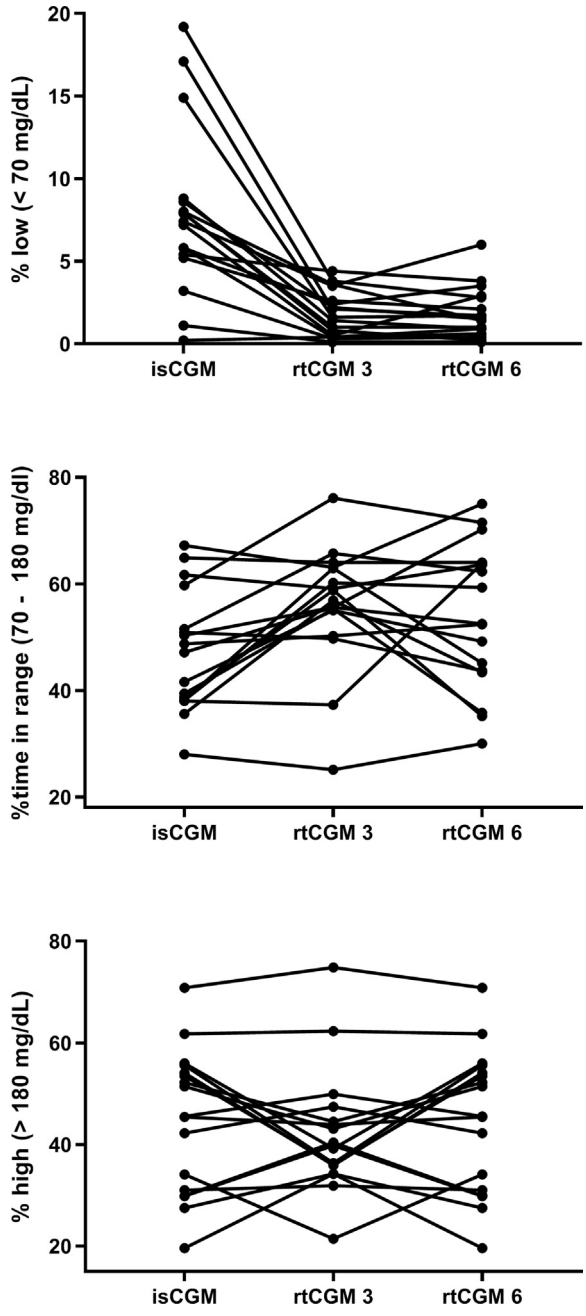

Fig. 1 – Comparison of time spent in hypoglycemia (upper panel), in range (middle panel) and in hyperglycemia (lower panel) between isCGM and the two periods of rtCGM (n = 17).

least 8-hourly in order not to lose information and the lack of alarms and connection with an insulin pump.

In the spring 2017 the Enlite® rtCGM was reimbursed for T1D patients and became available for wider use in connection with the Guardian™ Connect CGM system (Medtronic MiniMed, Inc., Northridge, CA) [23] or in connection with the MiniMed® 640G pump enabling the suspend before low function. A major characteristic of this sensor system is that it communicates with the MiniMed® 640G pump enabling hypo- and hyperglycemic alarms and in connection with the SmartGuard technology enabling the stop before low function [10–14]. Two drawbacks of the Enlite® rtCGM systems, however, are the working life of 6 days of the sensor and the need for timely calibration [31]. With a working life of 6 days the sensor has to be replaced on a different day of the week which often is problematic on schooldays. Moreover the calibration has to be done only with stable BG (not rising or falling) to maximize accuracy which is often difficult to achieve in children [16]. If the sensor is not timely calibrated it will stop functioning with loss of signal. Although in our diabetic clinic the advantages of the Enlite® rtCGM system in combination with the Minimed® 640G insulin pump were explained in detail to the patients treated with SCII and their caregivers only two third of them decided to switch from isCGM to rtCGM. Moreover, three patients discontinued early the use of the Enlite® rtCGM system. The need to calibrate the sensor and the short sensor working life (6 days instead of 2 weeks) retained these patients to switch to or to continue the Enlite® rtCGM system.

Although the HbA1c, eA1c and mean glucose values were not different between the time periods of use of isCGM or rtCGM the glucose variability was lower in all patients, with one third of the patients having a CV below 36%, which is defined as the threshold between low and high glucose variability in T1D [3,32,33]. The lower CV indicates smaller glucose excursions or less glucose variability, which is considered as a risk factor for the development of vascular complications in diabetes [34 –36]. It has been shown that large glucose excursions induce more free radical generation than chronical hyperglycemia suggesting that oxidative stress plays a role in inducing the complications linked to glucose variability [37].

Compared to the last month of isCGM use during the use of the Enlite® rtCGM system the studied patients spent much less time in hypoglycemia. In our study, 82% of the patients spent more than 5% of the time in hypoglycemia (<70 mg/dl) during isCGM whereas with the Enlite® rtCGM all but one patient spent less than 5% of the time in hypoglycemia. As this is inherent to the Smartguard technology it is no surprise that the patients spent less time in hypoglycemia as the insulin pump will stop timely the insulin administration. With the Smartguard technology the Minimed® 640G insulin pump automatically suspends basal insulin delivery for at least 30 min and up to maximum 120 min if the interstitial glucose level is predicted to drop to 20 mg/dl above the pre-established threshold limit within 30 min and the blood glucose level is 70 mg/dl or less above the established limit. Basal insulin delivery automatically resumes when the interstitial glucose level is 20 mg/dl above the pre-established threshold limit, is predicted to be 40 mg/dl above that threshold within 30 min, and the insulin infusion has been stopped for at for at least 30 min [9,10]. Our findings are in line with those of previous studies evaluating the Minimed® 640G SAP system [10–14]. The lesser time spent in hypoglycemia not only reduces the acute complications [38] and improves quality of life with less fear of hypoglycemia [39], but also reduces the development of diabetic cardiovascular complications [40].

In line with previous studies most of the patients considered the use of the Enlite® sensor as easy and comfortable [31,41]. The most common reported inconveniences were the sensor calibration and the alarms [16,41]. Future develop-

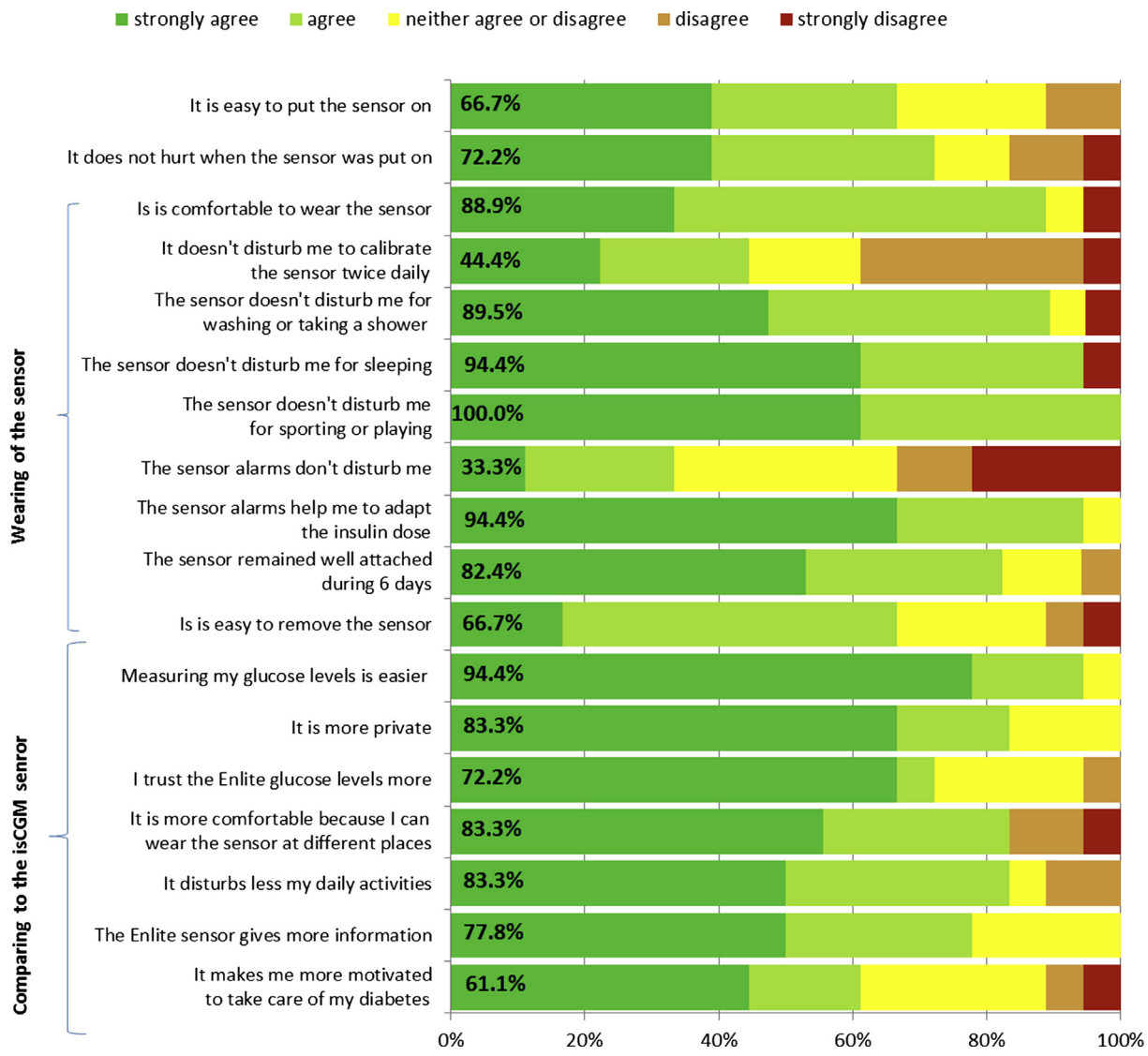

Fig. 2 – User acceptability with participants/caregivers responses to usability questionnaire. Listed percentages are the sum of agree and strongly agree.

ments in sensor technology will hopefully overcome this limitations.

Skin issues as irritation/inflammation and allergic reactions to adhesives used for diabetes medical devices are reported more and more, especially with a longer wearing time of the sensor [30,42,43]. In our cohort more than half of the patients developed some degree of skin irritation and two patients developed contact dermatitis to the Enlite® sensor. Special care should be taken to prevent skin irritation and sensor manufacturers should urgently investigate this problem and adapt the adhesives to prevent skin reactions especially in the perspective of sensor use for many years.

Strengths of this study are that it was performed fully independently of the device manufacturers and that is was performed in the home environment of the patient. The study has several limitations. First of all, the number of studied patients is small. Secondly, the patients participating in this study were those who were convinced of the advantages of the rtCGM in connection with the Minimed® 640G insulin pump, which may induce a selection bias. In addition, patients' satisfaction with the Enlite® rtCGM system was evaluated by means of a by the authors developed questionnaire which might have led to bias in favor of the Enlite® rtCGM system. Larger studies comparing T1D children and adolescents treated with SCII in combination with isCGM and rtCGM are needed.

In conclusion, this prospective study confirms that in comparison with isCGM the use of the Enlite® rtCGM system in combination with the Minimed® 640G insulin pump ameliorates metabolic control in children and adolescents with T1D with lower glucose variability and less time spent in hypoglycemia and extreme hyperglycemia. Nevertheless the system has some practical limitations causing patients to stop using the system. Amelioration of the system to a work-

ing sensor life of seven days and more flexible calibration will certainly stimulate the use of it. In addition, continuous patient education and support remain mandatory.

Contributors

GM and RZ contributed to the study concept and design, and supervised the study. IG, EB and AW collected data. All authors participated in data analysis and interpretation. The manuscript was drafted by GM and RZ and reviewed by IG, EB and AW. All contributing authors approved the final version of the manuscript. GM is the guarantor of the study and takes full responsibility for the work as a whole, including the study design, access to data and the decision to submit and publish the manuscript.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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