

# Real-Time Glucose Sensors in Children and Adolescents with Type-1 Diabetes

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## Key Words

Glucose sensors, real-time · Diabetes therapy

## Abstract

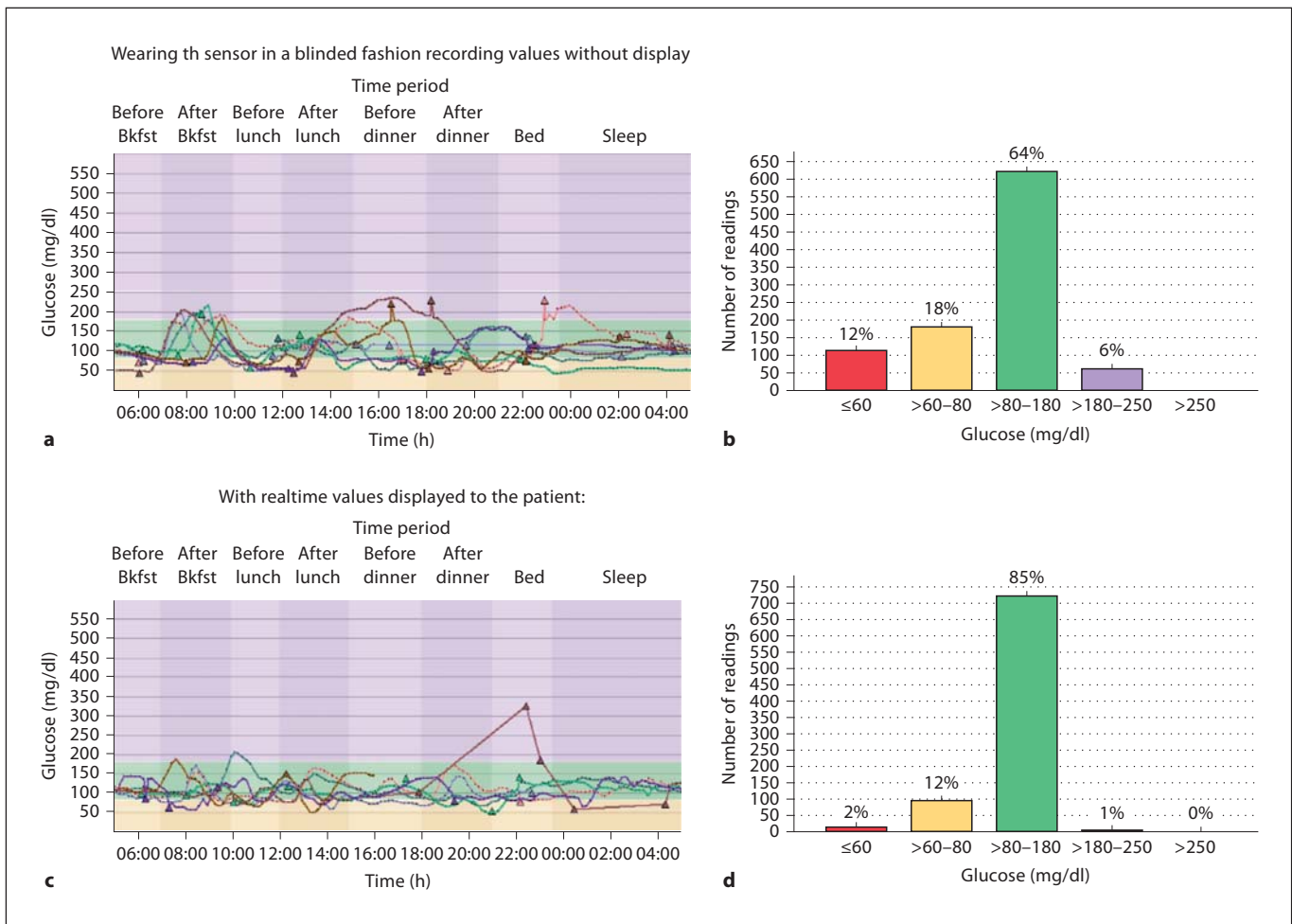
The increased availability of continuous glucose sensors is likely to have a significant impact on pediatric diabetes therapy and education in the future. While a recent meta-analysis of retrospective first-generation Holter-type sensors was not able to show advantages compared to self-monitoring of blood glucose levels, this review focuses on current real-time sensors. Our own experience with 23 children aged 10 (3–15) years with sensor-augmented pump therapy showed high ratings for overall satisfaction and ease of use of the system (5.8 on a 7 point Likert scale). The results of our ongoing international pediatric ONSET trial will show the impact of this technology on learning to live with diabetes by having the biofeedback of glucose excursions from the onset of diabetes. Families previously relying on self-monitoring of blood glucose need to understand the difference between estimating the absolute blood glucose value (point accuracy) and the change in blood glucose (rate accuracy), and how to take into consideration the inherent interstitial time lag. Selection of patients capable and motivated to use continuous sensors accompanied with proper age-appropriate education remain key factors for the long-term success of these new technological advances in diabetes therapy as long as closed loop systems are not available.

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## Introduction

While HbA1c for the time being remains the gold standard for assessing the risk for late complications also in pediatric patients [1, 2], it has obvious limits as it is only a parameter for average glucose levels. There is substantial variability in individual mean glucose concentrations for a given A1c. Utilizing continuous glucose monitoring (CGM) data to examine the relationship between A1c and glucose levels in 48 youths with type-1 diabetes found a slope of mean glucose over the previous 3 months vs. A1c of only 18 mg/dl per 1.0% A1c [3].

Evidence is building relating to the importance of glycemic variability for various outcomes in type-1 diabetes. For example, in a recent meta-analysis of four trials with the long-acting insulin detemir, a significant correlation between the inpatient variability (coefficient of variation) of fasting blood glucose and the rate of hypoglycemia was found [4]. In patients with type-2 diabetes a significant association of the mean amplitude of glycemic excursions (MAGEs), an established parameter for glycemic variability [5], and urinary 8-iso-PGF<sub>2</sub>α, a parameter related to superoxide overproduction, and the subsequent development of later complications was reported [6]. This suggests that different therapeutic strategies now in use [7] should be evaluated for their potential to minimize glycemic excursion, as well as their ability to lower A1c. Therefore, wider use of real-time CGM in clinical practice would provide the required monitoring tool to mini-



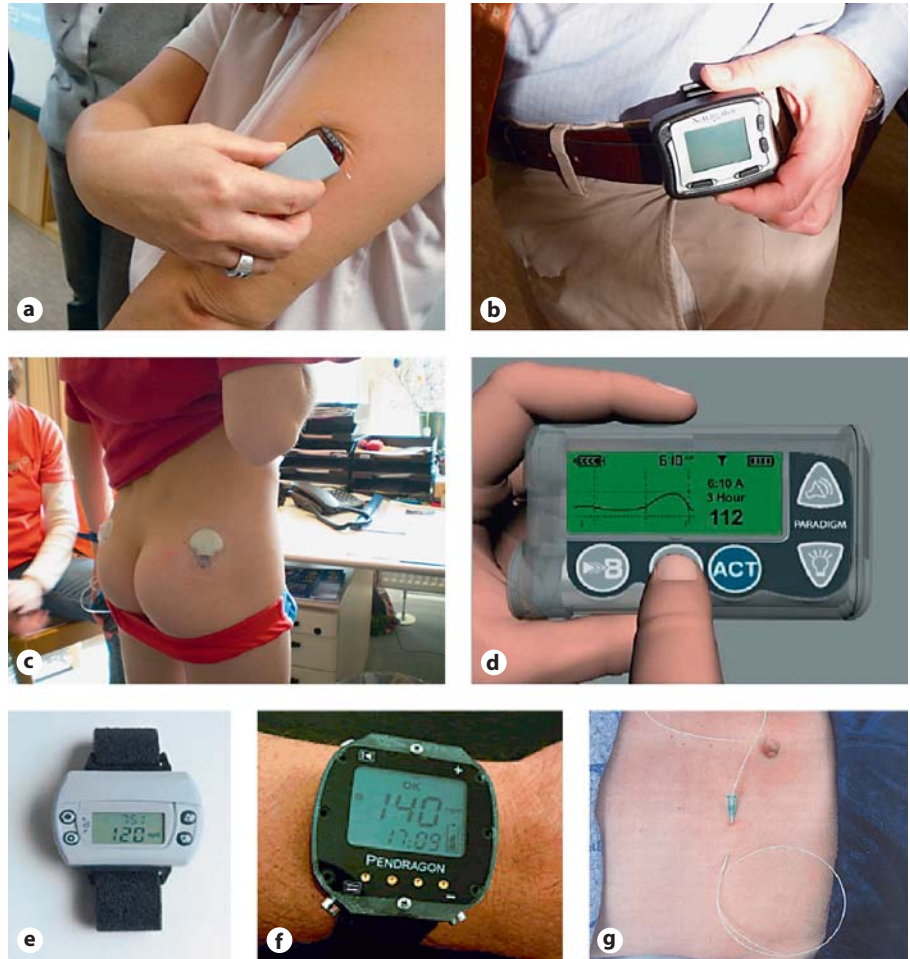
**Fig. 1.** Clinical benefit of 6 weeks realtime CGM with the Freestyle Navigator (Abbott Diabetes Care) in a patient with type 1 diabetes and hypoglycemia unawareness. Although the HbA1c remained stable (6.0 vs. 5.8%) the patient experienced significantly less time

in the hypo- and hyperglycemic range with a realtime display of glucose values (**c, d**) than during a previous 2-week period wearing the sensor in a blinded fashion (**a, b**).

mize glycemic variability [8]. A new measure of glycemia, derived from the duration of normal, low, and high readings, could supplement HbA1c as an integrated measure of control. Furthermore, measurements of MAGE [9], composite hypoglycemic score [10], and lability index [10] could provide information about the tendency for a mean blood glucose level to be comprised of stable or labile data points. For some patients, a decreased amount of glycemic instability alone, even without any improvement in HbA1c, might represent an improved outcome (fig. 1). This mini-review describes the currently available technology and relevant pediatric studies of CGM on the basis of a Medline search (search strategy: CGM, children, diabetes).

### Types of Sensors

Several CGMs have been approved by the US Food and Drug Administration (FDA) for use in the US or carry Conformité Européenne (CE) marking for use in Europe. They are the Continuous Glucose Monitoring System Gold (CGMS Gold; Medtronic MiniMed, Northridge, Calif., USA) [11], the GlucoWatch G2 Biographer (GW2B; Cygnus, Redwood City, Calif., USA) [12], the Guardian Telemetered Glucose Monitoring System (Medtronic MiniMed) [13], the GlucoDay (A. Menarini Diagnostics, Florence, Italy) [14], the Pendra (Pendragon Medical, Zurich, Switzerland) [15], the FreeStyle Navigator Continuous Glucose Monitor (Abbott Laborato-



**Fig. 2.** Examples of CGM in the everyday practice. Placement of the sensor unit of the Freestyle Navigator (a) and wearing the receiver (b); placement of the Medtronic MiniLink (right) (c) and display of the Paradigm Realtime pump (d); the GlucoWatch Biographer (e); the Pendragon watch (f); placement of the dialysis catheter of the Glucoday (g).

ries, Alameda, Calif., USA) [16] and the DexCom STS [17] (fig. 2, 3).

Particularly the development of the Pendra also shows the problem in evaluating these new technological approaches. In 2000 the Pendragon Medical Company introduced a truly noninvasive CGM device. This system was supposed to work through so-called impedance spectroscopy. Pendra was CE approved in May 2003. For a short time Pendra was available on the direct-to-consumer market. However, a post-marketing reliability study showed that several readings were erroneous [18] and potentially harmful to patients. Apparently marketing strategies had overtaken scientific progress in this device, contributing to the eventual disappearance of this monitor from the field. Currently four different systems are available outside the research setting (fig. 3).

### Where Is Glucose Measured?

All designed prototypes or commercially available systems can be divided into three groups based on the way glucose measurement is carried out: noninvasive, minimally invasive, and invasive systems. Noninvasive devices use light or electromagnetic waves to measure glucose without penetrating the skin. Minimally invasive sensors measure the glucose concentration in the interstitial fluid of the skin or subcutaneous tissue.

### Noninvasive Glucose Sensors [19]

While most wavelengths are absorbed through the skin [20], certain wavelengths can interact with the glucose molecule to allow optical [21] or near-infrared spec-

	Guardian® REAL-Time	Paradigm® REAL-Time	DexCom STS™	FreeStyle® Navigator
Sensor size	23 Gauge (= 0,6 mm)	23 Gauge (= 0,6 mm)	25 Gauge (= 0,5 mm)	22 Gauge (= 0,7 mm)
Sensor length	12,7 mm	12,7 mm	13 mm	6 mm
Angle of placement	45 °	45 °	45 °	90 °
Duration	72 h	72 h	7 days	5 days
Time from placement to display	2 h	2 h	2 h	10 h
Calibration	2, 8, then every 12 h	2, 8, then every 12h	1, 1.5, every 12 h	10, 12, 24, 72 h
New readings	every 5 min	every 5 min	every 5 min	every minute
Display options	3, 6, 12, 24 h	3, 6, 12, 24 h	1, 3, 9 h	2, 4, 6, 12, 24 h
Data download	possible	possible	possible	possible



**Fig. 3.** Overview of the features of the continuous sensor systems that are commercially available.

troscopy [22]. Although some studies provide evidence for the good clinical correlation between blood glucose and spectroscopic results [23, 24], ultrasound [25] or photoacoustic measurements [26], the limited strength of the signal and the low reliability of the measurement make the use of this approach currently impossible for clinical use [27].

Enzymatic glucose sensors are based on the enzyme-promoted oxidation of glucose, with a generated signal that is proportional to the glucose concentration in the sensor environment. However, sensor accuracy can be impaired by oxygen deficit, chemical interference, enzyme inactivation and disturbances in the diffusion field in front of the sensor.

The minimally invasive device, called GlucoWatch™ Biographer (Cygnus, Redwood City, Calif., USA), is based on the principle of reverse iontophoresis, with generation of a signal in proportion to the interstitial glucose level [28]. The device provided near-continuous monitoring of glucose values in near real-time, and it is equipped with two types of alarms to detect hypoglycemia. It took a blinded phase of about 12 h to get a stable signal, displaying glucose values every 20 min for approximately the same time period thereafter. Skin reactions at the site of electrodes led to decreasing sensor use

over time [29]. A clinical study of 89 children and adolescents using the GlucoWatch™ Biographer demonstrated an acceptable accuracy that may have been sufficient for detecting trends and modifying diabetes management [30]. However, use of the GlucoWatch™ Biographer in addition to standard glucose monitoring was not found to improve glycemic control or reduce the frequency of severe hypoglycemia over 6 months in 200 youths with type-1 diabetes when compared to results obtained with standard glucose monitoring alone. Despite its innovative technology, this monitor is currently no longer available.

### Microdialysis

Systems with microdialysis are more or less invasive due to the introduction of the dialysis catheter into the tissue. They have been tried extensively for many years [31–33] with the Glucoday system having been most widely used. However, the subcutaneous insertion of the dialysis catheter and the size of the dialysis unit have limited the widespread use of this technology in children.

## Subcutaneous Sensors

Three subcutaneous enzymatic sensors in four systems are currently available. They differ in needle length, sensor wear, number of calibrations and time from placement to display (fig. 3). The Continuous Glucose Monitoring System (CGMS) by Medtronic-Minimed (Northridge, Calif., USA), was the first system approved by the FDA. The sensor is introduced through the skin and connected to a portable pager-size monitoring unit that records the sensor signal for several days [34]. The monitor records the signal from the sensor every 10 s, then uses these readings to calculate and store the average value every 5 min. Data are downloaded onto a computer and are presented as a continuous glucose level. The sensor signal must be calibrated against capillary blood glucose at least 3 times/day to match up correctly with blood glucose levels. The accuracy of the CGMS was assessed in 200 children and adolescents with type-1 diabetes when compared with reference serum glucose levels from a home glucose meter [35].

### The Old Technology – Holter-Type Retrospective Sensors

The CGMS has been reported to serve as a tool to reveal daily glucose trends missed by self-monitoring of blood glucose (SMBG), to serve as an educational tool to improve metabolic control, and to decrease the rate and magnitude of hypoglycemia in young patients with type-1 diabetes [36]. However, a recent meta-analysis [37] of five randomized pediatric studies [38–42] has indicated that the technology did not allow real-time assessment of glycemia by the patient, and that a retrospective analysis by the doctor also does not lead to a significant improvement in HbA1c. Nevertheless, the trials have already led to considerable practical experience with this technology. Age does not appear to be a limiting factor as these systems can also be applied in the preschool group [43]. Fourteen toddlers (age  $3.9 \pm 0.8$  years) using CGM quarterly for 1 year when transitioned from multiple daily insulin with bedtime glargine to continuous subcutaneous insulin infusion (CSII) did not improve in A1c, whereas MAGE was reduced on CSII ( $210 \pm 31$  vs.  $168 \pm 22$  mg/dl,  $p < 0.005$ ). Although this study confirms that CSII improved glycemic instability without reducing HbA1c, the quarterly application of CGM is not sufficient to improve overall control [44]. However, others have reported its usefulness in the management of individual patients,

particularly adolescents experiencing difficulties with adherence to diabetes management and in detecting unrecognized hypoglycemia [45]. CGM can also be used to compare the effectiveness of various therapeutic strategies in research settings [46].

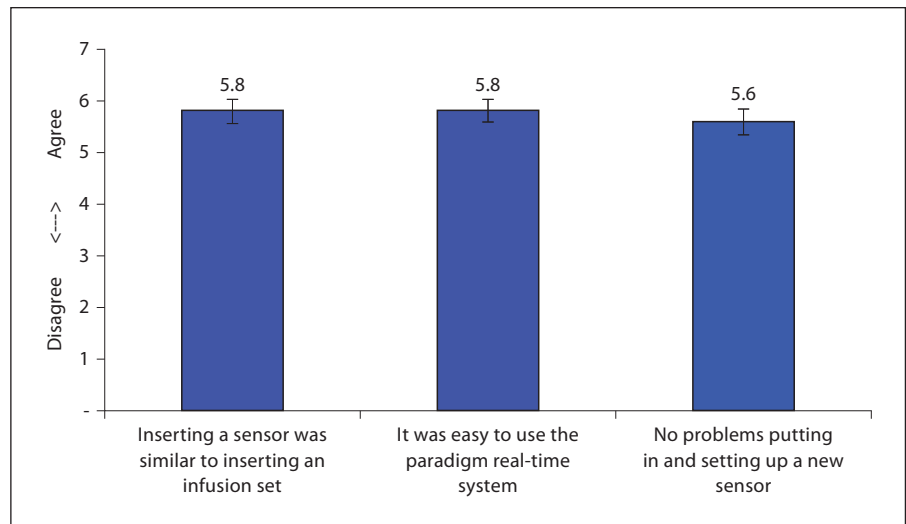
The power of CGM as a research tool was demonstrated by providing proof of the association of fluctuating blood glucose levels and behavioral changes that parents frequently report in their diabetic children. Comparing the results of a continuous glucose monitor over a 72-hour period and a Behavior Assessment System for Children completed by the parents found a decrease in the externalizing behavior score of 1.0 for every 5% increase in time in the normal glycemic range, and for every 5% increase in time in the high glycemic range there was an increase in the externalizing behavior score of 1.0. There was no significant association between the monitoring of blood glucose and the mean internalizing behavior score. These findings underscore the importance of understanding the mechanisms of this association and how it might impact ultimate diabetes outcomes [47].

### The New Technology – Real-Time Sensors

In contrast to the physician-based analysis of retrospective data on the Holter-type sensors, the real-time sensors shift the focus to the patient and the family, enabling them to react to subcutaneous glucose readings in a 'biofeedback' fashion. In a multicenter study with adult and pediatric participants [48] the efficacy of REAL-Time CGMS using the Guardian<sup>®</sup> RT system was evaluated in 81 children and adolescents with type-1 diabetes in whom glycemic control was suboptimal despite intensive insulin therapy. Patients were randomized to 1 of 3 groups: use of the sensor continuously; use for 3 days bi-weekly, or conventional SMBG (the control group). Treatment adjustments were made by physicians and patients on the basis of SMBG in the control group and on REAL-Time glucose profiles and alarms (of hypo- and hyperglycemia) in the 2 sensor groups. The results of the study demonstrated that REAL-Time CGMS using the Guardian<sup>®</sup> RT system improved glycemic control when compared with SMBG, especially in the group using the system continuously [48]. The continuous availability of glucose measurements permitted the patients to adjust their own insulin doses, food intake and physical activity and, thus, improve their glycemic control [49].

The Paradigm<sup>®</sup> 522/722 sensor-augmented insulin pump system is a fully external system designed to utilize

**Fig. 4.** User evaluation on a seven-point Likert scale of an Integrated Insulin Pump and Real-Time Continuous Glucose Monitoring System in German pediatric and adult patients with type-1 diabetes [51].



a subcutaneous glucose sensor, which is easily inserted under the skin, to continuously record blood sugar readings for up to 3 days. The system’s transmitter is designed to send continuous glucose readings via radiofrequency to the pump, which is expected to display real-time glucose readings every 5 min and to provide trend graphs as well as hypoglycemia and hyperglycemia alerts to patients, allowing them to monitor trends in their blood sugar levels and make immediate corrective adjustments using their insulin pump.

A pilot trial of 1 month in 10 type-1 diabetic children was reported in which the real-time CGMS and the insulin pump were combined into a sensor-augmented pump system [50]. In this short-term trial the system allowed access to real-time glucose values, trend data, and hypoglycemic and hyperglycemic alerts so that patients/parents, with the aid of the diabetes team, could adjust insulin doses, energy intake, and activity pattern to improve HbA1c level, and to reduce the frequency of episodes of hypoglycemia and hyperglycemia. This system was developed further and combined with an insulin pump in the Paradigm Realtime pump which we used in an user evaluation of 35 patients, 23 of them children, for 4 weeks (median age 10.5, range 3–15 years; diabetes duration 2, range 1–9 years; CSII experience 1, range 0.2–3 years) [51]. 35 patients completed the 1-month evaluation, providing data from more than 1,000 patient-days. Patients ratings were high for overall satisfaction and ease of use of the system (fig. 4). The information given by the system was highly valued and demonstrated the feasibility of sensor-augmented pump therapy for all pediatric age groups.

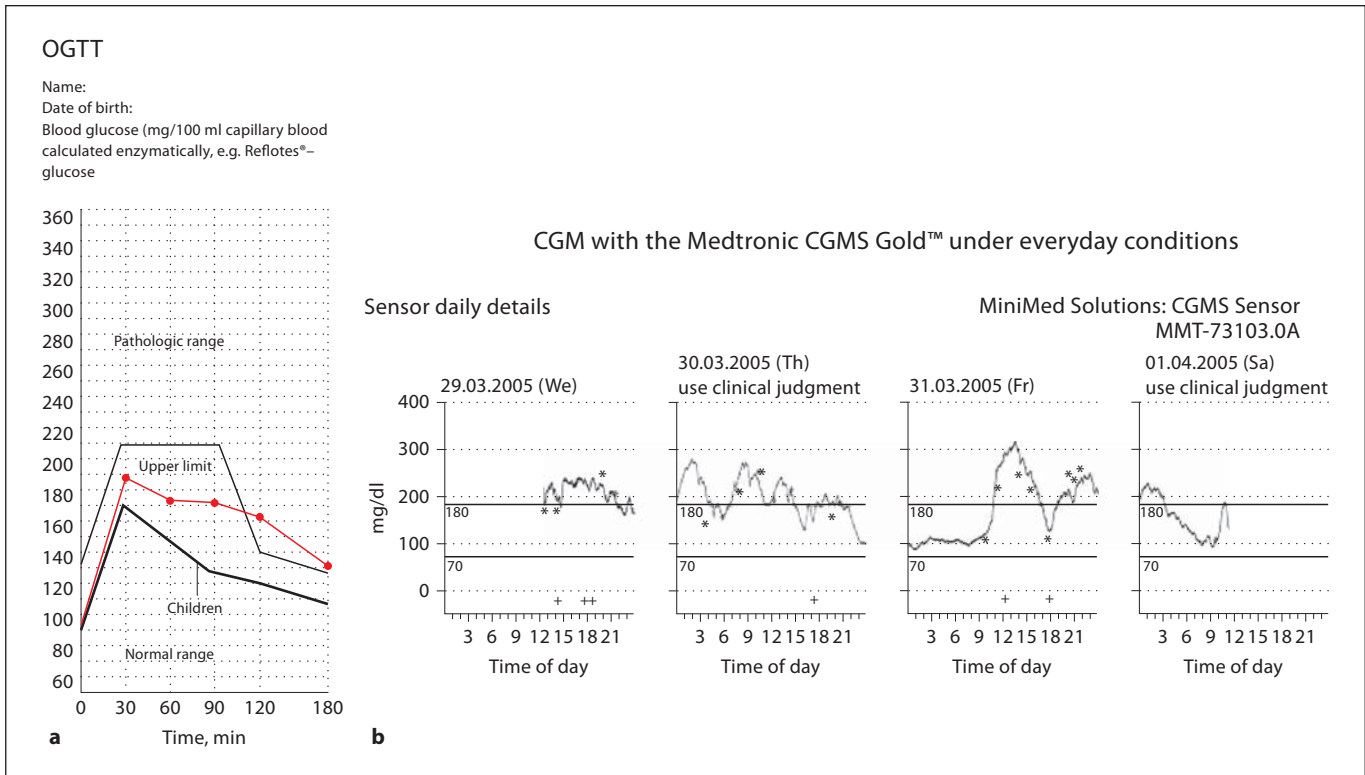
This has led to the conception of the ONSET-Trial. This international multicenter trial will compare the effect of conventional CSII with sensor-augmented pump therapy during the first year after onset of diabetes in 160 pediatric patients in a randomized prospective trial.

Pediatric experience is also available for the FreeStyle Navigator [52]. 30 insulin pump users with type-1 diabetes (average age 11.2 years) logging between 134 and 149 h/week of Navigator use improved their A1c from 7.1% at baseline to 6.8% at 13 weeks ( $p = 0.02$ ), and the percentage of glucose values between 71 and 180 mg/dl increased from 52 to 60% ( $p = 0.01$ ) [53]. The Navigator was similarly tolerated over 13 weeks in 27 children aged 4–17 years using glargine-based multiple daily injection insulin regimens. Subjects averaged >100 h/week of Navigator use. Mean HbA1c fell from  $7.9 \pm 1.0\%$  at baseline to  $7.3 \pm 0.9\%$  at 13 weeks ( $p = 0.004$ ) [54].

The benefits of CGM are not limited to type-1 diabetes, but may also be helpful in type-2 diabetes (fig. 5) or other metabolic disorders [55]. Also, Guardian RT real-time subcutaneous blood glucose measurement is safe and potentially useful for CGM in critically ill children [56].

#### Education: Time Lag, Calibration and Algorithms

Teaching patients to determine what to do with all of the data provided by CGM remains challenging. Families previously relying on SMBG need to understand the difference of estimating the absolute blood glucose value



**Fig. 5.** Decision to intensify treatment in an 12-year-old obese boy (BMI 46 kg/m<sup>2</sup>) suspected of having type-2 diabetes despite a normal oral glucose tolerance test (OGTT; **a**). The CGMS readings (Medtronic; **b**) were in the diabetic range under everyday eating

conditions. Metformin was started after CGM in connection with the laboratory results (HbA1c 6.3%, insulin basal 95.5 (normal 5–30.0) mU/l, after 60 min 81.2 mU/l).

(point accuracy) and change in blood glucose (rate accuracy) and how to take into consideration the inherent interstitial time lag. All of the available sensors show a lower point accuracy compared to SMBG. However, a patient able to read trends in CGM will be able to live easily with this limitation when sufficient experience in analyzing glucose trends is available. Practical algorithms need to be developed to calculate the current and future insulin infusion/injection rates. Patient variability in assessing the glycemic excursion of the meal may also affect the function of such an open-loop system.

From the very beginning it is critical to understand the reasons for delays between glucose changes and a displayed value. For reasons that are currently not completely understood all subcutaneous sensors need a certain time after placement before they give a stable signal. Apparently, the trauma associated with subcutaneous insertion impairs glucose measurement for some time before reaching an equilibrium. Depending on the system this 'blind period' between placement and display of values

ranges from 2 to 10 h. In addition two further reasons for delay need to be considered: time for transfer of sample to detection site (i.e. microdialysis), and secondly time for analysis of the samples. A desired high frequency of glucose measurements, allowing detection of changes of 10 mg/dl in 5 min, is thought to be clinically relevant.

Even after an initial stable signal is reached, the reaction of the surrounding tissues with the sensor surface continues leading to changes in the sensor signal over time ('drift'). Repeated calibration may allow adjustment for drift for a certain period. Patients need to understand that the glucose measurements are in the interstitial fluid, and the lag time between blood and interstitial fluid sampled glucose levels may be in the range of 5–10 min.

Although accuracy has slightly improved with more calibrations, the timing of the calibrations appears more important. Modifying the algorithm to put less weight on daytime calibrations for nighttime values and calibrating during times of relative glucose stability may have greater impact on accuracy [57].

## Selecting the Right Patients for CGM

In addition to proper education, patient selection may be a key to CGM success. The key to sensor success is the motivation to use it continuously. Already in early studies with the Glucowatch, more frequent use over a 6-month period was found among youths whose parents reported higher scores for treatment adherence and diabetes-related quality of life (QoL) at baseline. The study illustrates the empiric assessment of the psychological context of CGM use [58]. In a recent study of sensor-augmented pump therapy (SAP) in 40 CSII-experienced adolescents with HbA1c above 7.5%, the improvement in HbA1c in the SAP group overall was not so different from controls: HbA1c baseline to 26 weeks  $8.8 \pm 1.1$  to  $8.0 \pm 1.1$  vs. control  $8.6 \pm 0.8$  to  $8.2 \pm 1.0$ . However, if the improvement in HbA1c was analyzed in relation to sensor wear, a close association was seen: HbA1c difference with <60% compliance (n = 2)  $-0.3\%$ ; 60–80% (n = 5)  $-0.7\%$ ; >80 (n = 10)  $-1.0\%$  (p = 0.0008) [59]. Therefore, psychological assessments about adherence with CGM may demonstrate the power of this technology much better than an uncritical application in unselected patients not all of whom use the information continuously. This observation is summed up in the phrase ‘an expensive watch is not going to make you punctual unless you use it!’.

## Psychosocial Aspects of Sensor Use in Children

In evaluating the psychosocial consequences of continuous use of sensors, the beneficial as well as adverse aspects for children and parents have to be assessed. CGMs could yield educational and motivational benefits or may lead to feelings of learned helplessness and frustration by information overload and continuous worries about the blood glucose level. These aspects have to be assessed by psychological questionnaires including the health-related QoL of the children, the parents’ perception of their child’s health-related QoL and the parents’ own QoL or wellbeing, diabetes-related anxiety, treatment burden and parental stress. In addition the possible effects on behavioral problems, diabetes self-management skills and behavior, treatment satisfaction/tolerance of the sensor, and consequences for the mothers’ or fathers’ occupational situation should be considered.

One small study indicated a positive effect on the QoL of young children as judged by their parents through CGM. Particularly fear and behavior issues were influenced [44]. In another study [58] of older children and

adolescents using the GlucoWatch G2, no significant effects on QoL or burden of the disease could be identified with the instruments used in that study. One has to take into consideration that in this study the CGM was used discontinuously and selected patients with a very good situation at baseline were studied. It remains to be clarified if conventional measures of fear, burden of the disease and QoL are sensitive enough to detect potential effects of CGM on psychosocial variables. Longer studies with continuous use of real-time sensors and sufficient power are currently lacking to evaluate the likely effects of sensor use on psychosocial aspects in children and their families.

## Closed Loop

Several approaches have been used in the search for an ‘artificial pancreas’ [60–62]. The time lag remains also one of the major problems on the road to an artificial pancreas. In a research center setting a meal detection algorithm for 19 children 1–6 years old detected a meal at a mean time of 30 min from the onset of eating, at which time the mean serum glucose was 21 mg/dl above baseline (range 2–36 mg/dl), although more than 90% of the meals were detected before the glucose had risen 40 mg/dl from baseline [63]. In combination with the delay of subcutaneous insulin infusion, such a time lag remains a problem for automated insulin dosing in response to meals and ultimately the development of a closed loop system.

## Conclusions

Nevertheless, it is our prediction that real-time CGM will become the standard of care for the treatment of pediatric patients with type-1 diabetes within the next 5–10 years [64]. However, in order to scientifically provide the promise of continuous sensing in children with type-1 diabetes, appropriate randomized prospective studies assessing this new technology in selected patients are needed. Psychological evaluation may be a key in identifying patients likely to wear a sensor continually. If the HbA1c is high at baseline, families may not be using the current tools adequately, and possibly sensor technology may be better for those with only modest A1c elevations. The ONSET trial will provide evidence for advocating this technology from the onset and thereby learning about diabetes in a feedback fashion. Early feedback from

the first families to complete this study during the first year after the onset of diabetes shows that those families wish to continue with continuous real-time use after completion of the study and can easily imagine life-long use of continuous sensors. All in all, the emerging evi-

dence for glycemic variability playing a role in such different areas as behavioral changes in children and the development of vascular complications underscores that additional endpoints to HbA1c need to be considered in future studies.

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