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Review

Modern clinical management helps reducing the impact of type 1 diabetes in children

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ABSTRACT

Type 1 diabetes care may be very costly not only in terms of money but also in terms of psychological and therapeutic acceptance and compliance. Recently, a lot of new technologies have been introduced in the care of patients with type 1 diabetes that should allow them to achieve an improvement in glycemic control, quality of life and above all prevent long-term complications.

Combining continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion (CSII) provides a more useful tool for patients with type 1 diabetes, the sensor-augmented pump (SAP). The aim of the present review is to explore SAP efficacy and safety in young patients with type 1 diabetes. SAP demonstrated increased efficacy in lowering glycated hemoglobin when compared either to multiple daily injections or CSII alone. Its efficacy is positively associated with CGM use, baseline HbA1c and patients' age. According to currently available evidence, SAP seems sufficiently safe, effective and beneficial in improving glycemic control in pediatric patients with type 1 diabetes. Moreover, encouraging results using semi-closed loop systems are emerging, paving the way toward a fully automated artificial pancreas. As pediatric diabetologists we have the duty to offer our patients the best therapeutic option currently available, supported by evidence, to help them gain the best results with the fewest adverse effects (hypoglycemia and/or diabetic ketoacidosis), better if chomping a little piece of dark chocolate.

Contents

1. Introduction

Diabetes mellitus is one of the most common chronic diseases in the world, and continues to increase in numbers and significance [1]. Individuals with diabetes suffer from high morbidity and mortality rates due to complications that could be prevented with intensive therapy. The Diabetes Control and Complications Trial

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confirmed that tight metabolic control is regarded as crucial to prevent microvascular and macrovascular complication in type 1 diabetic patients [2].

Insulin remains the lifesaving treatment for type 1 diabetes and is also required by many patients with type 2 diabetes.

However, despite the recent advances in diabetes management, including the new long- and rapid-acting insulin analogs and insulin intensification strategies such as basal/bolus or insulin pump therapy, at least 50% of the type 1 diabetes patients in pediatric age exhibits poor glycemic control and fails to reach or maintain target glycosylated hemoglobin (HbA1c) values, putting them at increased risk for vascular complications [3].

Observational studies have clearly linked the quality of glycemic control (expressed as HbA1c) with the frequency of daily self-monitored blood glucose (SMBG) tests in insulin-treated patients [4]. Usually, type 1 diabetes patients carry out between 4 and 8 finger-prick measurements per day, or less, and rarely monitor their blood glucose level at night. This is the cause of overlooking blood glucose excursion, and possibly postprandial hyperglycemia, asymptomatic hypoglycemia, and glucose fluctuation during the night.

In the last several years, continuous glucose monitoring (CGM) has developed as a major technological help that can provide detailed information on glucose patterns and trends, thus allowing the diabetes team, and especially the patient, to manage diabetes more effectively.

Combining CGM and continuous subcutaneous insulin infusion (CSII), a now well-established way to insulin delivery [5], provides a more useful tool for patients with type 1 diabetes, the sensor-augmented pump (SAP). Adding CGM to CSII arrange for an even better insight into glycemic profiles, which can have many benefits both in patients in poor glycemic control than in those with frequent severe hypoglycemia.

The aim of the present review is to explore SAP efficacy and safety in pediatric patients with type 1 diabetes.

2. Glycemic control

The system uses a wire-type glucose sensor implanted in the subcutaneous tissue to monitor the glucose concentration of interstitial fluid in people with type 1 diabetes. Early CGM systems were first introduced in 1989, only providing data for brief periods for retrospective analysis and review of glucose traces. This allowed healthcare professionals to advice on changes in therapy. These devices were quickly followed by real-time CGM (RT-CGM) systems for personal daily use by patients at home, providing information on direction, magnitude, frequency and duration of glycemic oscillations on a moment to moment basis to aid control of diabetes by patients themselves.

Great effort has been expended over the past years to determine the effectiveness of CGM in allowing a greater proportion of type 1 diabetes patients to achieve and maintain target HbA1c levels without increasing the risk of severe hypoglycemia. Evidence from randomized controlled trials for the effectiveness of continuous glucose monitoring at improving glycemic control compared with SMBG has recently appeared. In these studies the mean reduction in HbA1c percentage with CGM vs. SMBG has ranged from about 0.1% to 0.6%, depending on age [5] and percentage of time wearing CGM, with the best HbA1c reduction when using the CGM for more than 70% of the time [6–8]. In 2006, the Guard Control Study conducted in 161 patients including 81 adults with poor metabolic control (HbA1c > 8.1%) evaluated the impact of CGM worn intermittently (3 days every 2 weeks) or continuously. Compared with the control group, the group with consistent CGM using obtained a 0.6% HbA1c decrease after 3 months, while no benefits was obtained by the group wearing sensors only intermittently [6]. In the study of Hirsh et al. [7], a sensor usage of more than 60% of the time was associated with a significant HbA1c reduction ($p = 0.046$). In 2008, the JDRF CGM controlled trial (RCT) showed that adults with type 1 diabetes had a greater reduction in HbA1c levels with use of RT-CGM and SMBG than with SMBG alone [5]. At 6 months the same study demonstrated in patients using RT-CGM system a greater HbA1c decrease (−0.53%, $p < 0.001$) when compared to controls, confirming that compliance with the device usage correlated with its effectiveness. Furthermore, after 12 months, the same study confirmed an HbA1c level reduction of −0.4% from baseline ($p < 0.001$) and a median CGM usage of 6 days or more per week [8]. The JDRF study examined also the impact of CGM in 114 children over 8–12 years and 110 adolescents 13–18 years with basal HbA1c level greater than 7%. After 6 months of use, the HbA1c reduction was modest (−0.2 to −0.3%) in children wearing the CGM when compared to the control group. Nevertheless, those who wore the CGM device 6–7 days per week during the first 6 months of the study showed a HbA1c levels decrease of 0.8% without any increase in hypoglycemia [5]. Unfortunately only 21% of the pediatric cohort maintained a frequent use of sensor for the whole study period (12 months), and those that reverted to less frequent sensor usage during the second 6 months of the study lost the HbA1c benefits observed in the first 6 months [8].

3. Sensor-augmented pump

O'Connel et al. conducted a study to assess the impact of sensor-guided pump management on glycemic control compared with standard insulin pump therapy. The study showed an improvement in HbA1c levels (−0.43%) only in the SAP group and not in the group using insulin pump only [9]. When the sensor usage was more than 70% of the time, HbA1c improvement was even higher (−0.51% vs baseline) [9]. The RealTrend study, conducted both in children and in adults, assessed the impact of CGM use in poor metabolic controlled patients (HbA1c ≥ 8%). After switching to insulin pump therapy at the start of the study, after 6-month follow-up, a significant decrease in HbA1c (−0.68%, $p < 0.001$) was observed in those patients who wore the device >70% of the time in comparison with the ones who used the sole insulin pump [10].

The largest and longest SAP RCT study to date (STAR 3 Study), confirmed the advantage when using the SAP when compared to multiple daily injections, and showed its long term beneficial effect over a 12 months study period [11]. The study involved children, adolescents and adults with type 1 diabetes. In the SAP group, pump therapy was started first and RT-CGM initiated 3–4 weeks later. After 3 months a clinically and statistically significant decline in HbA1c levels was observed in the SAP group compared to MDI group (7.5% vs. 8.1%, $p < 0.001$), with no differences among groups (children, adolescents and adults). Furthermore, the glycemic improvement observed was maintained 1 year later. The percentage of patients reaching a recommended HbA1c target <7% (American Diabetes Association), was significantly greater in the SAP group than in the MDI group (27% vs. 10%, respectively).

Hermanides et al. [12] compared the efficacy of SAP therapy compared to multiple daily injections in adult patients with poorly controlled type 1 diabetes. The study randomized 83 patients, aged 18–65 years (with HbA1c ≥ 8.2%) to 26 weeks of treatment with either SAP therapy or multiple daily injections. Mean difference in HbA1c change after 26 weeks was −1.21% (7.2% vs. 8.5%, $p < 0.001$) in favor of the SAP therapy group. Noteworthy, the glycemic improvement observed was not accompanied by an increase in the number of hypoglycemic episodes.

The Onset Study [13] evaluated the impact of initiating SAP vs. pump-only therapy at the onset of diabetes in 160 children and

adolescents aged 1–16 years. After 12 months, an improvement in HbA1c level (−0.5%, $p < 0.05$) was observed in children wearing CGM regularly, and a decrease of glycemic variability and hypoglycemic events were also showed. Once again benefits of SAP therapy appeared to be due to a regular use of CGM. Moreover, a re-examination of 131/151 24 months after type 1 diabetes onset showed that SAP therapy from onset of diabetes may lead to better long-term glycemic control and help to preserve endogenous β-cell function, if patients comply with frequent use of CGM [14].

Mauras et al. published a trial assessing CGM benefit in 146 young children with type 1 diabetes, aged 4–9 years, randomly assigned to CGM or to usual care [15]. After 26-week follow-up, CGM group fails to show a better glycemic control compared to controls, despite CGM wearing was well tolerated, and parental satisfaction with CGM was high. However, sensor usage decreased over time, with only 41% averaging at least 6 days/week at 26 weeks, explaining at least in part the reason of the results observed.

A meta-analysis by Pickup et al. showed an overall −0.3% HbA1c reduction in CGM users ($n = 449$) vs. patients using SMBG ($n = 443$). The paper confirmed also that the improvement in glycemic control wearing CGM was greatest in those with the highest baseline HbA1c and those who used the sensor most frequently, with an additional 0.15% decrease of HbA1c for every one day increase of sensor usage per week [16].

The INTERPRET study, the largest and longest multicenter prospective observational study providing real-life data on SAP to date confirmed these data. Factors associated with improvement in HbA1c after 12 months in patients with baseline HbA1c ≥7% were high baseline HbA1c ($p < 0.001$), older age group ($p < 0.001$), and more frequent sensor use ($p = 0.047$), with a mean sensor usage for 12 months of 30% (range, 0–94%), and sensor use decreasing with time (first 3 months, 37%; last 3 months, 27%) [17].

4. Hypoglycemic episodes

Several studies demonstrated improvements of glycemic control with the use of CGM with no increase in episodes of hypoglycemia [9–12]. Rates of severe hypoglycemia and diabetic ketoacidosis were low and did not differ between CGM or SAP groups and SMBG and/or MDI therapy groups. In particular the JDRF study group conducted a trial in 129 patients with fair metabolic control (HbA1c < 7%) in order to evaluate the efficacy of CGM in reducing hypoglycemia episodes. The study showed a reduction in time spent in hypoglycemia (<60 mg/dl) related to CGM use (18 min vs. 35 min per day, $p < 0.05$), even if the rate of hypoglycemia was not influenced by CGM use [18]. On the other side, CGM does not seem to prevent severe hypoglycemia in this study. Also Mauras et al. [15] observed no differences in severe hypoglycemia rates in CGM vs. control group in children with type 1 diabetes.

Hermanides et al. [19] speculated it could be due to a relative CGM inaccuracy compared to plasma glucose values, higher in the hypoglycemic range or during rapid rise and fall of the plasma glucose. Furthermore during severe hypoglycemia, the decline of cognitive function makes patients unable in responding to acoustic or vibration alarms [19]. Finally during sports, when the risk of severe hypoglycemic events is higher, the CGM device is more likely to be put aside. However few trials were specifically designed and powered to investigate CGM in relation to prevent severe hypoglycemia and new controlled trials are needed to learn how to avoid severe hypoglycemia.

In his meta-analysis, Pickup et al. confirmed this data: the improvement in HbA1c level with CGM was accompanied by a small reduction in exposure to hypoglycemia [16].

Battelino et al. studied the influence of CGM on hypoglycemia in type 1 diabetes patients with a baseline HbA1c <7.5%. In this trial were enrolled 120 patients, 58 using CGM and 62 SMBG for a 26-week period. CGM was associated with reduced time spent in hypoglycemia and a concomitant decrease in HbA1c in children and adults with type 1 diabetes [20].

Better results have been reached using a new feature of some sensor-augmented pumps in the market (low glucose suspend, LGS). The low glucose suspend system allows the basal rate of the patient's pump to be suspended for up to 2 h if the patient fails to respond to the sensor's low glucose alarm.

Danne et al. investigated the effect of the LGS algorithm on the frequency of hypoglycemia in 21 children and adolescents with type 1 diabetes under real-life condition. The number of hypoglycemic excursions (average/day) was reduced during SAP + LGS (<70 mg/dl, 1.27 ± 0.75 vs. 0.95 ± 0.49, $p = 0.010$; ≤40 mg/dl, 0.280.18 vs. 0.13 0.14, $p = 0.005$) as was the time spent in hypoglycemia (average minutes/day, 101 ± 68 vs. 58 ± 33, $p = 0.005$) [21]. In a large randomized crossover study, the ASPIRE study, subjects used SAP system with LGS that automatically stopped insulin delivery for 2 h following a sensor glucose value ≤70 mg/dl [22]. Results confirmed that hypoglycemia duration and severity were significantly reduced by the automatic suspension of insulin delivery system, without any rebound hyperglycemia.

Ly et al. recently demonstrated that SAP therapy with automated insulin suspension, in patients with type 1 diabetes at high risk for severe hypoglycemia, reduced the combined rate of severe and moderate hypoglycemia in patients with type 1 diabetes, reducing to 0 (zero) the rate of severe hypoglycemia [23].

5. Quality of life

Despite of glucose sensors alarms and the discomfort of the device itself, CGM seems to have a positive impact on patient-reported outcomes. In the JDRF study, general-related and diabetes-specific questionnaires investigated the impact of CGM on quality of life (QoL), showing a significant decrease of anxiety and improved ability to avoid hypoglycemic events in the CGM group ($p < 0.05$) [24]. In the trial by Kordonouri et al. [13], questionnaires evaluating patients QoL and their caregivers' impressions, found scores for physical, psychological, social support and school significantly improving throughout the study when using the CGM.

In the study by Peyrot et al. [25] an "online" internet study about medical devices was conducted in 311 type 1 diabetes patients treated with SAP ($n = 162$) or SMBG ($n = 149$). Level of satisfaction, the impact of the device on daily life, blood glucose monitoring, social events, and diabetes-related worries were significantly more positive in the SAP arm than in the control arm.

In the INTERPRET study [17], increased treatment satisfaction, and reduced fear of hypoglycemia were reported after 12 months of SAP.

In a study recently published, SAP therapy in preschool children with type 1 diabetes, the greatest perceived benefit was the reduced fear of hypoglycemia, with a positive impact on QoL and not only HbA1c [26].

6. Recommendations

International guide lines [27] recommend different categories of patients that can benefit using CGM especially if associated with current open-loop basal/bolus insulin replacement, including: (1) improving overnight control with hypoglycemia alarms, particularly if using the LGS feature; (2) improving daytime bolus dosing with trend arrows and hyper- and hypoglycemia alarms for real-time adjustments, and retrospective data to optimize carbohydrate ratios and correction doses; (3) enhanced understanding of diabetes management teaching to understand effects of different

foods, exercise, stress, and menstrual cycles on glucose excursions; (4) improving management of acute illnesses.

CGM should be considered for therapeutic use (continuous use) in children and adolescents with type 1 diabetes in the following conditions: (a) patients who are doing frequent blood glucose testing; (b) patients who have severe hypoglycemic episodes; (c) patients who have hypoglycemic unawareness especially in young children; (d) patients who have nocturnal hypoglycemia; (e) wide glucose excursions regardless of HbA1c levels; (f) young children with diabetes with large blood glucose variability and difficulty in identifying hypoglycemic episodes; (g) patients who have suboptimal glycemic control with HbA1c exceeding target range; (h) patients with type 1 diabetes and HbA1c levels <7% (with the aim to maintain target glycemic control, while limiting the risk of hypoglycemia).

According to the international guidelines, recently the Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetology published its own recommendations about self-monitoring, including the use of CGM, endorsing its usage to obtain better compliance to insulin therapy, independently of the HbA1c values, and in order to avoid patients' glycemic values cheating [28].

Evidence from RCT studies for the effectiveness of CGM plus insulin pump to improve glycemic control in type 1 diabetes compared with conventional SMBG has only recently appeared [29], with a mean HbA1c improvement of −0.3% for the pump alone, and −0.68% in patients using SAP vs. multiple daily injections plus SMBG, suggesting a usage time of the sensor of more than 70% of the time.

The failure to find a greater effect of CGM on the area under the curve of reduction in hypoglycemia with increased sensor use, in contrast to the greater effectiveness on reduction of HbA1c observed in frequent sensor users is of interest.

Possibly, the reduction of hypoglycemia in those using CGM was not obtained by adjusting insulin dosages or taking extra carbohydrate based on CGM data, but by general behavioral changes, such as increased general confidence to manage diabetes afforded by the use of CGM. This prospect underlines the belief that CGM is a highly complex therapy that involves interacting behaviors, learning, and decisions. Effective sensor use is likely to be a combination of frequency of sensor wear, amount and quality of education and training, and ability of patients to use the data.

Many studies to date have suggested that patients who used SAP therapy with adherence to CGM had improved HbA1c levels without an increased rate of hypoglycemia. Bergenstal et al. [11] found that both adults and children using SAP had a decrease in HbA1c levels from baseline to 3 months and it persisted lower for the remainder of the study. The same did not occur in patients using multiple daily injection and SMBG. Moreover, an increased frequency of sensor use was associated with a greater HbA1c reduction at 1 year. The proportion of patients reaching target HbA1c was greater in the pump therapy group than in the multiple daily injection group, both in adults and children.

7. Prescribing sensor-augmented pump therapy

The adoption of CGM, and especially SAP, in clinical practice has been limited to date because the evidence of its effectiveness has been reported only in the last few years, and it is still controversial.

As a result, funding from national health services and insurance reimbursement has been restricted, although use and reimbursement are now increasing.

Pickup et al. [16] in their meta-analysis high lightened the fact that the cost effectiveness of CGM may be calculated for different patient groups according to their baseline HbA1c value, sensor usage, and age.

It is important to note that unfortunately CGM is not yet a replacement for, but a supplement to SMBG, since at the moment SMBG needs to be used to calibrate the sensor and to verify sensor values, especially if in the hypoglycemic range [28]. Such costs must be considered when estimating cost effectiveness.

The most cost effective and most appropriate use of CGM in everyday clinical practice is likely to be when targeted at those people with type 1 diabetes who have steadily constant HbA1c levels above target and, probably even more important, who are willing to use CGM frequently (i.e., more than 70% of the time).

Recently, in patients with type 1 diabetes who have impaired awareness of hypoglycemia, a clinical trial-based economic evaluation was performed in which the net costs and effectiveness of the two treatment modalities (SAP therapy with LGS functionality versus standard pump therapy with SMBG) were calculated and expressed as an incremental cost-effectiveness ratio. The clinical outcome of interest for the evaluation was the rate of severe hypoglycemia in each arm of the LGS study. After 6 months, the use of SAP therapy with LGS significantly reduced the incidence of severe hypoglycemia compared with standard pump, making the SAP with LGS be considered a cost-effective alternative to standard pump therapy with SMBG in hypoglycemia unaware patients with type 1 diabetes [30].

8. Discussion

CGM helps to lower HbA1c without increasing the incidence of severe hypoglycemic episodes in patients with type 1 diabetes who use the device more than 70% of the time. Data suggest that initiating CGM treatment might even be more effective when combined with the initiation of insulin pump therapy. Moreover CGM seems to have a positive impact on quality of life.

Treating children adolescents with CGM and/or SAP requires additional attention, since these patients are often non-compliant using the CGM an adequate amount of time (usually <70% of the time), so its value in this patient group may be limited only to the most motivated patients [5,8].

Optimal training regimens for these new tools remain unclear, but the need for routine use of the sensor to optimize glycemic control must be emphasized. This aspect could be also important to reduce drop-out and failure rates.

For all these reasons CGM and/or SAP (especially for their reimbursement), even if might be used by all patients with type diabetes because their proven outcome, are not for everyone and a careful selection of the patients is needed.

In fact, if it can be assumed that CGM and/or SAP would be cost-effective in poorly controlled type 1 diabetes patients because of the gain in long-term health benefits, the cost-effectiveness of CGM in preventing hypoglycemia is hard to assess because of the existing lack of evidence in some studies.

Finally, SAP is a crucial step in the direction of a close-loop system or artificial pancreas. Many studies have been performed to develop and improve control algorithms that automatically regulate insulin infusion rates through the pump based on sensor glucose readings. From the very first studies [31–33], in which closed-loop systems were studied mostly overnight, after meal and after exercise, we start to have the promising results of the first experiences run in outpatient's settings, such as at home [34,35].

Beside technological improvement, we can also address some future directions especially in the field of immunotherapy [36–38] and of stem cells [39,40]. One of the most promising is cord blood stem cells that have been demonstrated to became a powerful tool not only for regenerative medicine but for autoimmune (e.g., type 1 diabetes) and inflammatory diseases as well [39]. Recently, a novel hematopoietic stem cell-based strategy has been tested

in individuals with new-onset type 1 diabetes, suggesting that remission of the disease is possible by combining hematopoietic stem cell transplantation and immunosuppression, but that safer hematopoietic stem cell-based therapeutic options are required [40].

Looking at all these data from the most recent studies in the field of advanced therapy for children with diabetes we would like to conclude that continuous insulin infusion and continuous glucose monitoring alone might not be enough to give our patients the possibility to reach and maintain target HbA1c in order to avoid micro and macro vascular complications. What they also need is continuous education (giving rise to what we call the '3C paradigm').

Indeed, even if insulin pump therapy and CGM are now a validated therapeutic option for children with type 1 diabetes, we are still far from achieving optimal metabolic outcome for everyone [29,41–43]. Fine-tuning insulin pump therapy has become an important factor to consider, and the right time to administer bolus insulin [44], the proper type of bolus according to different meals [45], and the infusion site need to be taken into account [46]. And this mean keep learning from our patients and teaching them how to behave every day healthier and more effective, better if chomping on a small piece of dark chocolate that seems to help to have lower values of HbA1c [47].

Contributors

AES, and GVZ conceived and designed this paper and drafted the report. All authors participated in critical review of the report, and all have seen and approved the final version.

Conflict of interest

We declare none of us has any competing interest.

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