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ORIGINAL ARTICLE

Impact on variables of severe hypoglycaemia and healthcare costs of the use of the FreeStyle system in paediatric population with type 1 diabetes mellitus

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Abstract
Introduction: Analysis of the impact on severe hypoglycaemia and direct costs of the introduction of the FreeStyle Libre sensor in paediatric population with type 1 Diabetes Mellitus.
Material and methods: Ambispective single-centre study to assess the impact on severe hypoglycaemia and direct costs, focusing on consumption of materials, in paediatric population with type 1 Diabetes Mellitus before and after introduction of the FreeStyle Libre 1 sensor.
Results: A significant decrease was found in episodes of severe hypoglycaemia, with 4.2 episodes of severe hypoglycaemia per 100 patients under follow-up versus 0.25 episodes per 100 patients a year after introduction of the system. This represents a cost difference for severe hypoglycaemia, estimated at €6559.52 before introduction and €409.97 after introduction of the FreeStyle Libre sensor. We found a decrease in the daily consumption of capillary blood glucose strips, which translates as a decrease in the cost of materials and helps mitigate the cost of the sensor. The cost in materials for the patient with FreeStyle Libre was €185.13 per patient and year higher than conventional control with capillary blood glucose strips.

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PALABRAS CLAVE
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Impacto en hipoglucemia grave y costes sanitarios del uso del sistema FreeStyle en población pediátrica con diabetes mellitus tipo 1

Resumen
Introducción: Análisis del impacto en hipoglucemia grave y costes directos de la implantación del sensor Free Style libre en población pediátrica con Diabetes Mellitus tipo 1.
Material y métodos: Estudio unicéntrico ambispectivo de valoración de impacto en hipoglucemia grave y costes directos centrados en consumo de material en población pediátrica con Diabetes Mellitus tipo 1 antes y después de la implantación de sensor Free Style Libre 1.
Resultados: Se evidencia un relevante descenso de episodios de hipoglucemia grave con 4.2 episodios de hipoglucemia grave por cada 100 pacientes en seguimiento versus 0.25 episodios por cada 100 pacientes en seguimiento y año tras su implantación. Este hecho representa una diferencia de coste por hipoglucemia grave estimado antes de la implantación de 6.559,52€ y tras la implantación de sensor Free Style libre de 409.97€. Se evidencia un descenso en el consumo de tiras de glucemia capilar al día, lo que condiciona un descenso en el coste de material centrado en tiras de glucemia capilar que amortigua el coste del sensor, siendo la diferencia de coste en material del paciente con FreeStyle Libre versus control convencional con tiras de glucemia capilar de 185,13€ por paciente y año superior en el paciente con FreeStyle Libre versus control convencional.

Introduction

Type 1 diabetes mellitus (T1DM) is one of the most common chronic diseases in childhood. Starting at a young age, affected individuals spend many years living with the disease. This represents a major burden in terms of morbidity and mortality, since both short-term and long-term complications can occur.

Severe hypoglycaemia is the most common acute complication in paediatric patients with T1DM. It is defined as blood glucose levels below 70 mg/dl associated with loss of consciousness or seizure, requiring outside help through glucagon administration[1]. Reports on the impact of severe hypoglycaemia on neurodevelopment are mixed and include alteration of specific areas such as memory, psychomotor activity and attention[2,3]. Its effects on quality of life for patients and their main caregivers, as well as its effects on direct and indirect healthcare costs, are also not to be overlooked[4].

The chronic nature of T1DM itself, its common short-term and long-term complications, prolonged hospital admissions associated with it and the use of technology to optimise metabolic control of the disease entail high costs, both direct and indirect.

The introduction in October 2014 of an on-demand interstitial fluid glucose monitoring system represented a turning point in the management of the disease. This system enjoyed prompt acceptance and is increasingly widely used. The FreeStyle interstitial fluid glucose monitoring flash system was funded by the Management Directorate of the Andalusian Health Department in 2018; this allowed for its inclusion in the Basic Portfolio of Services of the Spanish National Health System for all patients with T1DM 4–18 years of age — both those whose disease is managed with multiple dose insulin (MDI) therapy and those who use any continuous subcutaneous insulin infusion (CSII) pump (Resolution of 26 April 2018, of the General Directorate of the Basic Portfolio of Services of the Spanish National Health and Pharmacy System, publicising the agreement of the Benefits, Insurance and Funding Commission, of 5 November 2018 and 28 March 2019).

In the Autonomous Community of Andalusia, the incidence of T1DM in individuals under 18 years of age is 20.76 cases per 100,000 population-years (0–4 years: 14.34 per 100,000 population-years; 5–9 years: 23.46 per 100,000 population-years; 10–18 years: 25.15 per 100,000 population-years). The prevalence of T1DM in Andalusia is 17 cases per 100,000 population, and the number of patients under age 14 with this disease has been estimated at 2550[5].

At the time this device started to be used in the paediatric population in Andalusia, there was no scientific evidence on it; for this reason, we tied our implantation thereof to follow-up with data collection to assess the impact of this technology on acute episodes of decompensation such as severe hypoglycaemia as well as its impact on direct healthcare costs through a research project funded by the Andalusian Ministry of Health and Families (PIGE 0533-219).

Methods

This ambispective study analysed data following implantation of a flash system for interstitial blood glucose monitoring (FreeStyle 1®) on a paediatric endocrinology unit at Hospital Regional de Málaga [Málaga Regional Hospital], a tertiary hospital, from June 2018 to June 2019. These data

were compared to the data collected the year prior to the implantation of this device, from June 2017 to June 2018.

The study was approved by the Hospital Regional de Málaga Independent Ethics Committee.

Training in the device was provided by an educator and a device technician in group sessions with 10 patients.

In-person follow-up consisted of four visits the year before implantation with subsequent follow-up every three months ending 12 months after implantation. An episode of severe hypoglycaemia was defined as follows: blood glucose levels below 70 mg/dl associated with loss of consciousness or seizure, requiring outside help through glucagon administration[1]. In each in-person visit, patients were asked about episodes of severe hypoglycaemia, and their reports were documented in their electronic records both prior to implantation and a year thereafter.

Numbers of capillary blood glucose checks were measured by downloading them from the device on the LibreView® platform, then added to patients' electronic records; those documented both prior to implantation and a year thereafter were analysed.

Glycosylated haemoglobin (HbA1c) was determined in a capillary blood sample using the DCA Vantage analyser system (immunoassay technique), performed in the laboratory at Hospital Regional de Málaga.

The results were analysed using different tests depending on the nature of the data. For two data samples, if the data were normal, Student's *t*-test was used, and if they were not normal, the Wilcoxon rank test was used. Normality was confirmed using the Anderson–Darling test, and homoscedasticity was verified using the Fligner–Killeen test.

Results

A total of 357 patients with T1DM were followed up. Their mean age was 11.36 years (SD: 3.06), and their mean time since disease onset was 5.2 years (SD: 3.2). With respect to type of treatment, 17.9% were being treated with CSII and 82.1% were being treated with MDI.

Impact on severe hypoglycaemia

On our unit, numbers of episodes of severe hypoglycaemia in the year prior to implantation of the FreeStyle Libre sensor (June 2017 to June 2018), were evaluated; 4.2 episodes of severe hypoglycaemia per 100 patients in follow-up were documented. One year after implantation of the FreeStyle system, episodes of severe hypoglycaemia were measured, with detection of 0.25 episodes per 100 patients in follow-up.

Impact on glycosylated haemoglobin

No significant differences in HbA1c were found before or after the use of FreeStyle Libre. Significant differences were found when the groups were stratified by two variables: a) metabolic control prior to sensor implantation (prior HbA1c exceeding 7.5% versus prior glycosylated haemoglobin less than or equal to 7.5%), and b) type of treatment used (CSII versus MDI).

The greatest drop in HbA1c was detected in the group of patients with previously poor control (HbA1c exceeding 7.5% before implantation of the FreeStyle Libre sensor) being treated with MDI. This group showed a −1.96% drop with statistical significance ($p = 0.04$) after the Wilcoxon test was performed.

Patients with previously good control (HbA1c below 7.5% before implantation of the FreeStyle Libre sensor) being treated with MDI showed a slight increase in HbA1c (+0.37%), which was statistically significant ($p < 0.001$).

Impact on direct costs

Number of capillary blood glucose strips used before FreeStyle sensor implantation was evaluated with a sample size of 357 patients, yielding a mean of 7.996 (SD: 1.325) capillary blood glucose checks per day.

After one year of sensor use, mean numbers of capillary blood glucose checks performed were 1.066 (SD: 1.727) per day.

The data published the year prior to implantation of the FreeStyle Libre sensor corresponding to the direct healthcare costs of paediatric patients with T1DM in Andalusia were used to evaluate direct healthcare costs[6].

Said data were collected from six hospitals in Andalusia, including this study's hospital; mean annual costs per patient were estimated at €4720.

These costs could be broken down as follows:

- Insulin-associated costs: €2212.90.
- Medication (drugs other than insulin): €36.40.
- Diagnostic tests: €186.40.
- Hospital visits: €766.70 (including hospital visits, non-hospital visits, hospitalisations and accident and emergency department visits).
- Supplies: €1518.00. These included strips for blood glucose and blood ketones and systems for insulin infusion and glucose monitoring (16.2% of the total).

Total costs were lower in the group of patients with MDI (€4141.80) compared to CSII (€8188.70); differences in supplies costs were statistically significant (€945.10 in patients with MDI versus €5378.90 in patients with CSII).

The €945.10 essentially covered the use of capillary blood glucose strips, considering the cost of the capillary blood glucose strip (€0.32) and not the lancet.

Analysis of this last bit of information following the use of the FreeStyle Libre sensor and the change in numbers of capillary blood glucose strips revealed that costs of supplies (blood glucose strips) had been reduced to €130 per patient.

The use of the FreeStyle Libre sensor accounts for supplies costs of €43.27 per sensor (value-added tax [VAT] not included), with 26 sensors required per year, amounting to costs of €1011.92 per patient per year. If the cost of an additional capillary blood glucose strip is added to this, then the total cost is €1188.63 per patient per year.

In patients who do not use the FreeStyle Libre system, capillary blood glucose strips account for €945.10 and lancets (€0.16 per lancet), using one lancet per blood glucose check, account for €58.40, for a total of €1003.50 per patient per year. The difference in supplies costs for

the patient with FreeStyle Libre compared to conventional management with capillary blood glucose strips is €185.13 per patient per year more in the patient with FreeStyle Libre (€1188.63 per patient per year versus 1003.50 per patient per year).

Regarding severe hypoglycaemia, there would be a change in costs related to severe hypoglycaemia on the unit, using data from Reviriego et al. to measure costs of severe hypoglycaemia as a reference[7].

- Before implantation of the FreeStyle Libre sensor: €6559.52.
- After implantation of the FreeStyle Libre sensor: €409.97.

Thus, implantation of this system represented an annual saving of €6149 in the follow-up of 357 patients included in the study.

Discussion

The FreeStyle Libre 1® system consists of an electrochemical sensor that operates by means of a glucose oxidase reaction and an on-demand reader/receiver of the measurements taken. It is currently approved for use in measuring interstitial glucose (IG) levels in people four years of age and older. The indication for children and adolescents 4–17 years of age is limited to supervision by a caregiver over 18 years of age who will be responsible for managing and interpreting the system's readings. The approval of this device gave rise to high expectations. Nevertheless, there are few studies with scientific evidence on its use in children and its impact on acute episodes of decompensation and healthcare costs.

The incidence of severe hypoglycaemia, frequently documented in the literature in paediatric units, is 5–20 episodes per 100 patients in follow-up per year; undoubtedly, lower numbers of these events represent a quality marker on diabetes units. The drop to 0.25 episodes per 100 patients recorded at our hospital reflected low figures for severe hypoglycaemia.

A reduction in the risk of level 3 hypoglycaemia in children and adolescents with T1DM was published in a single study that found a reduction by 53% after 12 months of follow-up in 278 subjects subsequent to a switch from capillary blood glucose strips to FreeStyle Libre implantation[8].

Regarding the impact on healthcare costs of severe hypoglycaemia, a 2016 study in nine European countries, including Spain[9], presented a report of healthcare costs per event of severe hypoglycaemia by type of care received:

- €1076.05 if hospital treatment was required.
- €209.28 if non-hospital healthcare was required.
- €0.46 if the family provided treatment.

Reviriego et al.[7] reported a mean cost per episode of €409.97; we used this figure in our study to extrapolate costs at our hospital, yielding total costs on the unit of €6,559.52 prior to sensor implantation. In a study by Reviriego et al.[7], of the €409.97 reported per episode of hypoglycaemia, 65.40% corresponded to direct costs and 34.60% to indirect costs. Barranco et al.[10], for their part, estimated the mean cost of hypoglycaemia in those under 17 years of age to be €984.

In our case, taking into consideration direct costs of an episode of severe hypoglycaemia by extrapolating the data from the literature, we found a mean cost per episode of €409.97, compared to the €6559.52 recorded prior to the use of the flash system. This represented a decrease in costs related to severe hypoglycaemia.

In the paediatric population, these events are not always visible in healthcare costs, since in most cases they are resolved at home by primary caregivers with no healthcare support but with significant long-term consequences with respect to morbidity.

This economic impact is higher in adults, who lack a primary caregiver to render healthcare costs invisible. Some studies in adult populations have affirmed that the use of FreeStyle Libre would be associated with a decrease in costs of managing episodes of hypoglycaemia by €1,911 per patient-year (a saving of 43.1%), and a decrease in costs deriving solely from episodes of hypoglycaemia prevented following its use by €1,887 per patient-year[11].

Compared to these studies, our study reported a saving of €6149 per year. Undoubtedly, this saving would be higher on units with worse healthcare quality markers (high number of episodes of severe hypoglycaemia) and in risk groups (less effective primary caregivers).

Moreover, hypoglycaemia was the most significant limiting factor in the management of the paediatric population with T1DM and represented a close link to long-term complications, such as cardiovascular risk[12]. Preventing hypoglycaemia not only enabled suitable adjustment on the part of patients and caregivers to their day-to-day life and protection of neurodevelopment, but also a drop in cardiovascular risk. Paediatric onset of T1DM already carries an ominous prognosis, with a loss of up to 17 years lived in relation to cardiovascular risk[13]; this calls for ongoing pursuit of improvements with new treatments that modify the outcomes observed to date.

Traditionally, blood glucose checks in the paediatric population with T1DM have been performed using capillary blood glucose strips, with a positive correlation between higher numbers of capillary blood glucose checks and metabolic control. Clinical practice guidelines have recommended 8 to 10 capillary blood glucose checks per day to achieve the targets established. Paediatric patients with T1DM performed more than eight capillary blood glucose checks per day for metabolic control, with physical deterioration (skin of the hands) and the social stigma that ongoing blood checks entail.

Supplies costs for patients with FreeStyle Libre compared to conventional management with capillary blood glucose strips were €185.13 higher per patient per year with FreeStyle 1. The lack of accuracy of the FreeStyle system in certain situations (the first 24 h during which it is used) and extreme values (hyperglycaemia and hypoglycaemia) required simultaneous prescription of capillary blood glucose strips following FreeStyle Libre sensor implantation[14]. Up to now, numbers of capillary blood glucose strips required by paediatric patients with T1DM concomitant to the use of the FreeStyle system were unknown. However, given the savings seen in our sample, these numbers should be much lower than those used prior to the use of the flash sensor.

Our study found a clinically significant drop in HbA1c in patients with higher costs, such as those with worse HbA1c control and those with lower costs invested as they were being treated with MDI[15].

The Freestyle Libre 2 with its greater accuracy probably reduced the need for capillary checks at times when symptoms were not consistent with readings; therefore, future studies must evaluate whether the reduction in the need for self-testing could be even higher than that detected.

One of the limitations of this study was that it did not measure additional costs corresponding to device training carried out on the unit. Another was that it was not possible to have a control group. Long-term multicentre studies with larger sample sizes in the paediatric population are needed to enable assessment of reductions in direct and indirect healthcare costs, as well as quality-adjusted life years (QALYs) in the paediatric population with T1DM following the use of this technology.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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