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Effect of CGM in the HbA1c and Coefficient of Variation of glucose in a pediatric sample

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ABSTRACT

Aim of the study: Previous studies have found no significant improvements in glycated hemoglobin (HbA1c), while using Continuous Glucose Monitoring (CGM), with children and adolescents. The aim of this paper is to measure the change in HbA1c, and the Coefficient of Variation in glucose levels, when using CGM, once the effect of other relevant variables, such as gender, actual age, the years the patient has had diabetes, use of an insulin pump, the presence of autoimmune disease, other associated pathologies, and weekly hours of exercise, are controlled for.
Methods: This is a retrospective study that uses a linear regression model. Data was collected from Type 1 Diabetes Mellitus (T1DM), children diagnosed between 2003 and 2017 in the Pediatric Unit for Diabetes in Zaragoza, Spain. We used a linear regression and the method of estimation is Ordinary Least Squares.
Results: Results show that the use of CGM decreased the HbA1c value by 3.5% and the Coefficient of Variation by 14%.
Conclusions: The implication of these results is that this device helped in the management of diabetes, although more research is needed to distinguish between different devices in terms of their efficacy.

1. Introduction

There are two steps to maintain blood glucose within optimal range for a Type 1 Diabetes Mellitus patient: (1) To know the value in real time and (2) to provide the necessary insulin. The main advantages of Continuous Glucose Monitoring (CGM) are the continuous measurement of glucose, which shows all the peaks in values not seen with discontinuous measures, as well as decreasing the number of skin punctures [1], and increasing patient satisfaction [2]. The main disadvantage is a lack of accuracy which has been noted in several articles [3], although new models and algorithms have improved precision [4]. One key factor in the use of CGM is patient education, so patients with varying levels of expertise in diabetes care can present different results, independent of the glucose-measuring device used [5].

The result of a good control for diabetes in the long-term is quantified through a low value of HbA1c, although new research also takes into consideration a low Coefficient of Variation of glucose levels [6].

Despite the fact that many recent papers find a high correlation between the use of CGM and the value of HbA1c [7], some studies have reached different conclusions [8]. However most of them have used descriptive statistics to reach this conclusion [9].

Given that the HbA1c levels and the Coefficient of Variation in the child population are related to variables such as age, sex, and years of experience with diabetes [10], among others, the improvement in HbA1c levels in this population is also due to the effect of these variables in addition to the use of the CGM itself. For this reason, by means of a linear regression model, we planned to study the effect of the use of CGM in the improvement of the metabolic control of children with type 1 diabetes, isolating the effect of other variables such as gender, age, years the patient has had diabetes, use of an insulin pump, the presence of autoimmune disease, other associated pathologies, and weekly hours of exercise.

The aim of the paper is to measure the effect of using CGM on changes in HbA1c and the Coefficient of Variation in the Pedi-

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atric Unit of Aragón. The plan to introduce this device in the Public Regional Health System made it necessary to evaluate the results. The CGM devices were used by some of the patients in the sample (who paid their own costs), and the regional government's project was to finance the use by the Regional Health System for pediatric patients without additional cost to the patients.

The paper is organized as follows. Section 2 presents the database and methodology on which we based the empirical study. Section 3 presents the regression model. In Section 4, we summarize the main conclusions.

2. Materials and Methods

2.1. Database

The database consists of data collected from September to December 2017 from patient-and-family clinical data, for subjects diagnosed with Type 1 Diabetes Mellitus, between 2003 and 2017, in the Pediatric Unit for Diabetes in Zaragoza, Spain. This Unit controlled the training of patients and their families, all of whom participated in the same training courses and received the same guidelines to manage the device. Questionnaires were completed by doctors and patient-caregivers and the information was summarized in an anonymized database. Parents of patients were fully informed and gave their consent. The data showed that more than 50% of children used CGM in the Diabetic Pediatric Unit of Aragón, and almost all of them used it routinely.

A statistical summary of the variables used in our study can be found in Table 1. The variables considered were reported by doctors and by a glucose meter, except for the time devoted to exercise, while hypoglycemic information was provided by patient-caregivers. Despite the potential time lag these measures present with respect to the medical variables, they can still be considered a good proxy in the regression analysis. We considered two types of patients: (1) those with CGM whose information corresponds to the time when each patient began to use the device (previous variables are 6 and 3 months before that time, and post variables are 3 and 6 months after the use of CGM); (2) those without CGM whose information relates to the moment the questionnaire was completed (previous variables are the two last values collected, from September to December 2017). For the analysis, age and experience over time were categorized with similar ranges used in previous papers. [11]

The questions were answered by 120 individuals, from a target population of 256. The Pediatric Unit treats approximately 85% of the children diagnosed with Type 1 diabetes in this geographic area. For the regression model, weights were used to adjust for differences in age, sex and experience over time between the sample and the target population.

In order to capture the evolution of HbA1c we created two variables for every child in the sample: HbA1cPre and HbA1cPost. HbA1cPre is the mean of the two HbA1c values prior to the use of CGM for those using the continuous device, and the last value of HbA1c before answering the questionnaire for those without CGM. HbA1cPost is the mean of the two HbA1c values after using CGM, and the value of HbA1c collected from September to December 2017 for those without CGM. The ratio between both variables, HbA1CPost over HbA1CPre, measures the difference between them in relative terms and allows us to measure the growth for every patient. For those with CGM it captures the changes produced by the use of CGM, and for those without CGM it allows us to capture the variability of this parameter (HbA1c differs for each patient in different time periods).

We have used the Coefficient of Variation provided by the doctors that took the data from the glucose meter. For those patients with CGM, it is the variation coefficient after 6 months of using CGM, or after three months if that information was not available.

2.2. Statistical and regression analysis

Data were analyzed with the statistical package STATA 14 [12]. We used a linear regression and the method of estimation was Ordinary Least Squares (OLS), which allowed us to measure the isolated effect of the CGM, taking into account that the sample is heterogeneous in terms of age, gender, and other characteristics. Two models were used: one to explain the HbA1c change and a second to explain the Coefficient of Variation of glucose levels. The coefficients associated with all the explanatory variables considered: gender, age, years the patient has had diabetes, that is years of experience with diabetes [13], type of treatment [14] time spent on exercise, other pathologies, and the use of CGM. We measured the effect of each explanatory variable on the endogenous variables (HbA1c change and Coefficient of Variation), in order to control for the effect of the other variables.

The two models fulfilled our main requirements: normality of residuals, no misspecification of the model, and coefficients robust to heteroskedasticity.

3. Results

Table 2 shows the coefficients, Coef, for the same exogenous variables used to explain the two endogenous variables: HbA1c Ratio and Coefficient of Variation, along with the p-value, P>|t|, to measure the significance of the coefficient. The Coefficients of Variation use logarithms in order to interpret the rate of growth. For categorical exogenous variables (insulin pump use, CGM, autoimmune diseases and associated pathology), the corresponding coefficient explains the variation in the ratio due to having that characteristic vs. not having it (for example, how much the HbA1c ratio varies when wearing an insulin pump vs. not wearing a pump). Regarding the gender variable, the reference group is male, so the coefficients explain how the dependent variables vary when the patient is female versus male. Finally, for age and years of experience with diabetes, which are categorical variables with more than two categories, the lower levels of these variables (the patient's age from 0 to 5 years and less than one year of disease evolution) have been used as reference ranges in the models. Thus, in these variables the coefficients indicate how the dependent variables (HbA1c of Coefficient of Variation) vary when comparing the reference range with the other categories (for example, how much would the HbA1c ratio vary in patients between 1 and 6 years old with respect to those from 0 to 5 years, if all the other exogenous variables remained stable).

Gender, any associated pathology, and hours of weekly exercise had no significant effects on the HbA1c Ratio, nor on the Coefficient of Variation when the other explanatory variables were introduced into the model, as shown by the significance of the coefficients in column P>|t|.

The model indicated that being in the age range of 6 to 10 years old increased the HbA1c Ratio by 0.15, while being more than 10 years old increased that same ratio by 0.12. Age did not affect the Coefficient of Variation.

Those patients who had had the condition for up to five years showed an improvement of 19% in the Coefficient of Variation, relative to those patients in their first year of diabetes.

Paradoxically, the use of an insulin pump increased the Coefficient of Variation. Perhaps it is because the pump is more strongly recommended for patients with a history of poor diabetes control in the Pediatric Diabetes Unit of Zaragoza.

Table 1
Summary statistics.

Metabolic variables	Obs	Mean	Std. Dev.	Min	Max
HbA1cPOST (%[mmol/mol])[a]	117	7.3%	0.9112	5.1[33]	10.4 [90]
HbA1cPRE(%[mmol/mol])[b]	118	7.4%	1.0217	5.4 [36]	12.1 [109]
HbA1cRatio[c]	117	0.99	0.0831	0.63	1.19
HbA1cPOST- HbA1cPRE	117	−0.14	0.7273	−4.5	1.1
HbA1c growth	117	−1.36%	8.3138	−37.19%	18.97%
Coefficient of VariationPOST[d]	72	41.37	7.2436	23.03	65.08
Coefficient of VariationPRE[e]	72	41.51	7.7353	13.01	57.58
Mean GlycaemiaPOST[f] (mg/dl)	88	165	23.4427	115	271
Mean GlycaemiaPRE[g] (mg/dl)	88	166	24.0713	115	246
Personal variables					
		Female	Male		
Gender	120	43.33%	56.67%		
		from 0 to 5	**from 6 to 10**	**more than 10**	
Age	119	10.92%	34.45%	54.62%	
		less than 1	**from 1 to 5**	**from 6 to 10**	**more than 10**
Years of experience	119	5.04%	67.23%	19.33%	8.40%
		Medtronic	**Dexcom**	**Freestyle**	**No CGM**
CGM	120	15.00%	9.17%	28.33%	47.50%
Weekly exercise (hours)	109	Mean = 6	Std. Dev. = 3.8489		
		Yes	**No**		
CGM	120	52.50%	47.50%		
Insulin pump	120	26.67%	73.33%		
Autoimmune diseases	118	11.86%	88.14%		
Associated pathology	120	14.17%	85.83%		

[a] HbA1c after CGM use or last value for those not using CGM.
[b] HbA1c prior to CGM use or prior to last value for those not using CGM.
[c] Ratio between HbA1cPOST and HbA1cPRE
[d] Coefficient of Variation after CGM use or last value for those not using CGM.
[e] Coefficient of Variation prior to CGM use or prior to last value for those not using CGM.
[f] Mean glycaemia after CGM use or last value for those not using CGM.
[g] Mean glycaemia prior to CGM use or prior to last value for those not using CGM.

Table 2
OLS model: endogenous variables: HbA1c ratio and Coefficient of Variation of glucose.

	HbA1c ratio[a]			Coefficient of Variation[b]		
	Coef	P > |t|		Coef	P > |t|	
Female	−0.0081	0.651		−0.0533	0.175	
Age (reference range 0–5 years)						
From 6 to 10 years old	0.1487	0.009	***	−0.0008	0.992	
More than 10 years old	0.1236	0.036	**	0.0258	0.723	
Years of experience (reference range > 1 years)						
From 1 to 5 years	0.0338	0.571		−0.1667	0.061	*
From 6 to 10 years	0.0114	0.851		−0.1226	0.205	
More than 10 years	0.0027	0.967		−0.0747	0.484	
Insulin pump	0.0282	0.105		0.0975	0.059	**
CGM	−0.0359	0.019	**	−0.1402	0.002	***
Autoimmune diseases	−0.0491	0.002	***	0.1461	0.003	***
Associated pathology	0.0267	0.108		−0.0333	0.29	
Hours of weekly exercise	−0.0006	0.752		−0.0065	0.24	
cons	0.8594	0	***	3.9310	0	***

* p < 0.10.
** p < 0.05.
*** <0.01.
[a] N = 106; F (11, 94) = 4.91; R^2 = 0.28; Ramsey Ho: no misspecification (p-value) = 0.06; Skewness/Kurtosis tests for normality (p-value) = 0.11.
[b] N = 69; F (11, 57) = 2.78. R^2 = 0.33; Ramsey Ho: no misspecification (p-value) = 0.07; Skewness/Kurtosis tests for normality (p-value) = 0.1.

The presence of an autoimmune disease decreased the HbA1c Ratio by 0.05, but increased the Coefficient of Variation by 15%.

Finally, the use of CGM decreased the HbA1c Ratio by 0.036, which can be interpreted as a change of -3.6%, and the Coefficient of Variation decreased by 14% when gender, age, years of experience with diabetes, insulin pump use, other pathologies, and exercise were considered as explanatory factors.

4. Conclusion

There were variations in the HbA1c or Coefficient of Variation of glucose levels by age, by years of experience with diabetes, and by gender. Using a regression model, it was possible to establish a fixed value for the variables that affected the HbA1c and the Coefficient of Variation of glucose, in order to isolate and measure the effect of the CGM device.

This study demonstrates the positive effect of using CGM in children with T1DM, in terms of improving the HbA1c and the Coefficient of Variation supporting the addition of these devices to the services provided by the Regional Health System. Better control of diabetes leads to a lower probability of costly complications (retinopathy, nephropathy, renal failure, etc).

The study has certain limitations:

- There are no values for the Coefficient of Variation and Mean Glucose for the whole sample, because not all patients in the sample had a blood glucose meter that provided a mean and a standard deviation necessary to make those calculations.
- There are insufficient observations of patients using the three CGM devices, Freestyle, Dexcom and Medtronic, to pursue a more specific analysis for each brand. A broader sample would allow us to evaluate the effectiveness of each device in isolation, rather than taking an aggregate evaluation that could be masking important differences between these devices.

5. Discussion

With respect to HbA1c improvements, some prior studies, [8] find no significant differences in results, while using CGM, for patients in the age range of 4 to 9. In our work, a more detailed age range for children is used and the improvement was general for all ages considered. The papers that concluded that HbA1c did not decrease in children could be capturing the effect of age, rather than that of the use of CGM, so it was necessary to control for a range of variables in order to isolate the effect of CGM. Another reason for a different result could be that more than 94% of our sample used CGM routinely, and some papers associate improvement in HbA1c with the continuous use of CGM devices [15]. Considering the Coefficient of Variation, certain studies relate the use of CGM to a decrease in the Coefficient of Variation [16]. Our results were similar for the Coefficient of Variation: when other related factors (gender, age, pathologies, habits, and so on) are considered, the Coefficient of Variation decreases.

Conflict of interest

None.

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The study complies with the ethical guidelines and has been approved by the corresponding ethics committee (CEICA) on May 23, 2018.

References

[1] L. Van den Boom, K. Kostev, Changes in the utilization of blood glucose test strips among patients using intermittent-scanning continuous glucose monitoring in Germany, Diabetes Obes. Metab. (2020), forthcoming.
[2] S. Twigg, et al., Flash continuous glucose monitoring and its IMPACT to REPLACE blood glucose monitoring in the management of type 1 and type 2 diabetes, US Endocrinol. 13 (2017) 57–62.
[3] B. Kovatchev, et al., Comparison of the numerical and clinical accuracy of four continuous glucose monitors, Diabetes Care 31 (6) (2008) 1160–1164.
[4] L. Laffel, Improved accuracy of continuous glucose monitoring systems in pediatric patients with diabetes mellitus: results from two studies, Diabetes Technol. Ther. 18 (S2) (2016) 223–233.
[5] H. Wolpert, Use of continuous glucose monitoring in the detection and prevention of hypoglycemia, J. Diabetes Sci. Technol. 1 (2007) 146–150.
[6] G. Sartore, et al., The importance of HbA1c and glucose variability in patients with type 1 and type 2 diabetes: outcome of continuous glucose monitoring (CGM), Acta Diabetol. 49 (1) (2012) 153–160.
[7] A. Burden, ACP journal club review: continuous glucose monitoring reduces HbA1c more than self-monitoring in type 1 diabetes, Ann. Intern. Med. 158 (6) (2013) 1–6.
[8] N. Mauras, et al., A radonmized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to 10, Diabetes Care 35 (2) (2012) 204–210.
[9] K. Lewis, S. McCrone, P. Deiriggi, S. Bendre, Efeectiveness of continuous glucose monitoring in children, adolescents, and young addults with poorly controlled type 1 diabetes, J. Specialists Pediatr. Nurs. 22 (1) (2017) 1–10.
[10] O. Pinhas-Hamiel, U. Hamiel, V. Boyko, C. Graph-Barel, B. Reichman, L. Lerner-Geva, Trajectories of HbA1c levels in children and youth with type 1 diabetes, PLoS One 9 (10) (2014), e109109.
[11] J. Rosenbauer, et al., Improved metabolic control in children: a trend analysis using prospective multicenter data from Germany and Austria, Diabetes Care 35 (1) (2012) 80–86.
[12] M.B. Abraham, et al., ISPAD Clinical Practice Consensus Guidelines 2018: assessment and management of hypoglycemia in children and adolescents with diabetes, Pediatr. Diabetes 19 (27) (2018) 178–192.
[13] A.C. Cameron, P.K. Trivedi, Microeconometrics Using Stata, StataCorp, Texas, 2009.
[14] C. Hochhauser, et al., Age at diagnosis, gender and metabolic control in children with type 1 diabetes, Pediatr. Diabetes 9 (4pt1) (2008) 303–307.
[15] T. Battelino, et al., Routine use of continuous glucose monitoring in 10 501 people with diabetes mellitus, Diabet. Med. 32 (2015) 1568–1574.
[16] J. Wong, et al., Real-time continuous glucose monitoring among participants in the TiD exchange clinic registry, Diabetes Care 37 (10) (2014) 2702–2709.