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RESEARCH LETTER

Impact of the basal/bolus ratio on continuous glucose monitoring parameters in patients with type 1 diabetes

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1 | BACKGROUND

Standard insulin therapy for type 1 diabetes (T1DM) combines the premeal use of rapid-acting prandial insulins with a longer-acting basal insulin.[1] Regimens with longer-acting insulin analogues (such as U-300 glargine and degludec, rather than U-100 glargine, detemir, or NPH insulin) and rapid-acting insulin analogues (such as aspart, lispro, and glulisine, rather than human insulin) carry a lower risk of hypoglycaemia.[1–4] This type of regimen is known as basal-bolus therapy.

In general, it is estimated that patients with T1DM require approximately 50% of their insulin as basal insulin and the remainder as prandial (bolus) insulin.[1] Few studies have evaluated the effect of the basal/bolus ratio on glycaemic control in patients with T1DM in terms of glycated haemoglobin (HbA1c), and these have reported inconsistent results.[5–7] To our knowledge, no study has investigated the influence of the basal/bolus ratio on glycaemic control in patients with T1DM in terms of continuous glucose monitoring (CGM) parameters. The aim of this study was to analyse the influence of the basal/bolus ratio on CGM parameters in patients with T1DM.

Elías Delgado and Edelmiro Menéndez-Torre contributed equally to this work.

2 | METHODS

This cross-sectional study was conducted at a university hospital in Spain. From a sample of 873 adults with T1DM using the Freestyle Libre 2 (FSL2; Abbott, USA) CGM devices described in a previous study that analysed the impact of the alarm thresholds on glycaemic control,[8] 629 patients (362 men; median age 48 years, range 18–90 years) on basal-bolus insulin therapy without non-insulin glucose-lowering medications were selected (Supplementary Figure S1). These patients were treated with U-300 glargine ($n = 450$) or degludec ($n = 179$) as basal insulins and lispro ($n = 147$), glulisine ($n = 65$), aspart ($n = 211$), faster-aspart ($n = 205$), or a combination of aspart and faster-aspart ($n = 1$; this patient used aspart insulin for breakfast and lunch and faster-aspart for dinner) as rapid-acting insulins in three daily prandial boluses. The basal/bolus ratio for each patient was the result of the insulin titration made throughout the duration of their T1DM (based on the American Diabetes Association adjustment recommendations)[1] by both physicians (who assessed patients 1–4 times/year, depending on their glycaemic control) and diabetes educators (who assessed patients 0–12 times/year, depending on their glycaemic control and diabetes knowledge), as well as by the patients themselves based on the diabetes education they received. Patients were also instructed on how to adjust their rapid-acting

insulin based on their preprandial blood glucose levels and their carbohydrate intake, according to their insulin-to-carbohydrate ratio.[1] The daily dose of basal and bolus insulin was recorded from the LibreView graph (for those patients who entered the insulin doses used in the FSL2 system; Supplementary Explanation in Data S1) or, if missing, from the clinical history (mean insulin doses the patient reported using during the data period). The percentage of basal insulin (PBI) was calculated (daily dose of basal insulin/[daily dose of basal insulin + daily dose of bolus insulin]), and patients were divided into three groups according to their PBI: (i) PBI <45%, (ii) PBI 45%–55% and (iii) PBI >55% (Table 1). Supplementary Figure S2 shows the distribution of patients according to the PBI. The effect variables were the usual CGM parameters of the FSL2 devices (from which the glycaemic risk index [GRI] was calculated)[9] and the number of days with nocturnal and diurnal hypoglycaemic episodes registered in the LibreView graph (these data were collected only in patients with a sensor usage ≥70%; Supplementary Explanation in Data S1) during a 14-day period between August 2022 and September 2023 (Table 1). The covariates are listed in Table 1. The study was approved by the institutional review board (code 2023.376).

3 | RESULTS

Table 1 shows the patients' glycaemic control (in terms of CGM parameters) and characteristics according to the PBI in the basal-bolus therapies, divided into the aforementioned three groups. The results showed that the higher the PBI, the lower the glucose variability (GV), and the lower the number of hypoglycaemic features (including a shorter duration of hypoglycaemic events, and fewer episodes of both diurnal and nocturnal hypoglycaemia). In contrast, the higher the PBI, the higher the percentage of time above range Level 1 and the higher the glucose management indicator (HbA1c estimator; Table 1). Patients in the three groups achieved time in range (TIR) goals (i.e., TIR >70%)[10] with similar frequency (Table 1). The number of scans per day and the GRI were similar in the three groups. The lower the PBI, the lower the daily doses of basal insulin and the higher the daily doses of rapid-acting insulin (Table 1). No other patient characteristic was associated with a higher or lower PBI (Table 1). Similar results were observed when selecting patients with a sensor usage ≥70% ($n = 539$; Supplementary Table S1) and when selecting patients with a TIR ≤70% ($n = 512$; Supplementary Table S2). However, when patients with a TIR >70% ($n = 117$) were selected, no differences in glycaemic control were observed among the three groups with different PBIs (Supplementary Table S3). No differences in any CGM parameter were observed when comparing faster-aspart users ($n = 205$) with other rapid-acting insulins users ($n = 423$; data not shown).

The correlation between the GV and the time below range (Rho = 0.644, $p < 0.001$) was stronger than the correlation between the GV and the time above range (Rho = 0.100, $p = 0.013$). There was a positive correlation between the total daily dose of rapid-acting insulin and the GV (Rho = 0.194, $p < 0.001$), but there was no correlation between the total daily dose of basal insulin and the GV (Rho = −0.001, $p = 0.976$).

4 | DISCUSSION

Our study showed that patients with a higher PBI are more prone to hyperglycaemia, and patients with a lower PBI have a higher GV and more hypoglycaemic features. After adjustment of the insulin doses by the physicians and the patients themselves, each patient had his/her own PBI (Supplementary Figure S2). Good glycaemic control in terms of TIR could be achieved with different PBIs, suggesting that each patient may require his/her individual basal/bolus ratio, adjusted to his/her lifestyle and personal characteristics. In patients achieving TIR goals, the basal/bolus ratio did not have a major impact on glycaemic control. However, our results have potential clinical implications, particularly for patients who do not achieve TIR goals: patients with high GV and/or frequent hypoglycaemia could benefit from increasing the PBI (i.e., reducing the dose of rapid-acting insulin), whereas patients with a tendency to hyperglycaemia could benefit from decreasing the PBI (i.e., increasing the dose of rapid-acting insulin) to achieve tighter glycaemic control.

The reasons why the PBI was associated with these outcomes are not entirely clear. The rapid-acting insulin dose had a greater correlation with the GV than the basal insulin dose, and the GV and hypoglycaemia were strongly correlated. This could explain why patients with a lower PBI (higher proportion of rapid-acting insulin) had a higher GV and more hypoglycaemia features, including nocturnal hypoglycaemia. The latter finding is noteworthy since the insulin that acts throughout the whole nighttime period is the basal insulin, although the new-generation basal insulins have a lower risk of nocturnal hypoglycaemia.[2] It is possible that patients with a lower PBI had a higher frequency of nocturnal hypoglycaemia because they had tighter glycaemic control during the day (Table 1), which has been observed in previous studies showing the influence of tight daytime glycaemic control on the development of nocturnal hypoglycaemia.[11] It should also be taken into account that, in Spain, people tend to eat dinner later than in other countries, so the nocturnal bolus of rapid-acting insulin could also trigger nocturnal hypoglycaemia.

Furthermore, our results might hide suboptimal titration of insulin therapy in some patients. It is possible that, when attending patients with global hyperglycaemia throughout the day, clinicians (or the patients themselves) may think that increasing the dose of basal insulin is an appropriate solution, as this is the insulin that acts throughout the whole day. This 'overbasalization'[1] of patients prone to hyperglycaemia would consequently increase the PBI, which may also explain some of our results. Ultimately, as mentioned above, it appears that these patients with global hyperglycaemia would benefit most from an increase in their rapid-acting insulin dose.

The number of scans per day was similar in patients with a lower PBI (prone to hypoglycaemia) to that in patients with a higher PBI (prone to hyperglycaemia), consistent with a previous study showing that both hypo- and hyperglycaemia trigger sensor scans.[8] Similarly, the GRI, an index that scores both hypo- and hyperglycaemia,[9] was similar in all groups according to the PBI.

The study has the strength of being a real-life study in a large sample of patients with T1DM, having excluded users of insulins at higher risk of hypoglycaemia.[1–4] The study also has limitations, including those inherent in its retrospective design. The recorded insulin

TABLE 1 Patients' glycaemic control characteristics according to the percentage of basal insulin in basal-bolus insulin therapies.

Variable	<45% basal insulin ($n = 160$)	45%–55% basal insulin ($n = 178$)	>55% basal insulin ($n = 291$)	*p* value
Glycaemic control in terms of continuous glucose monitoring parameters				
Time above range, Level 2 (>250 mg/dL), %	15.0 (14.0)	16.1 (14.7)	16.7 (15.5)	0.453
Time above range, Level 1 (181–250 mg/dL), %	23.0 (7.8)	24.8 (8.5)	26.0 (8.4)	<0.001
Time in range (70–180 mg/dL), %	56.7 (16.6)	55.3 (17.4)	53.8 (18.2)	0.117
Time below range, Level 1 (54–69 mg/dL), %	4.3 (4.0)	3.1 (2.8)	2.8 (2.9)	<0.001
Time below range, Level 2 (<54 mg/dL), %	0.7 (1.4)	0.4 (1.0)	0.4 (1.3)	0.005
Achievement of time in range goals: yes[a]	29 (18.1)	31 (17.4)	57 (19.6)	0.650
Achievement of time below range goals: yes[b]	80 (50.0)	107 (60.1)	194 (66.7)	<0.001
Glucose management indicator, %	7.3 (0.8)	7.5 (0.8)	7.5 (0.9)	0.045
Glucose variability, %	39.4 (6.4)	37.8 (7.1)	36.6 (6.1)	<0.001
Hypoglycaemic events, *n*	8.8 (7.5)	6.6 (5.3)	6.5 (5.9)	0.006
Days with nocturnal hypoglycaemic episodes, *n*[c]	3.5 (2.7)	2.5 (2.3)	2.3 (2.3)	<0.001
Days with diurnal hypoglycaemic episodes, *n*[d]	7.1 (3.6)	6.0 (3.5)	6.1 (3.4)	0.039
Duration of hypoglycaemia, min[e]	100 (42)	99 (57)	86 (39)	<0.001
Scans per day, *n*	8.9 (6.1)	9.9 (6.6)	9.3 (6.3)	0.778
Glycaemic risk index, score points	54.5 (22.4)	53.9 (22.7)	55.1 (23.8)	0.872
Patient characteristics				
Sex, men	89 (55.6)	101 (56.7)	172 (59.1)	0.455
Age, years	49 (14)	47 (16)	47 (14)	0.212
Duration of diabetes, years	21 (13)	21 (13)	22 (12)	0.141
Body mass index,[f] kg/m^2	26.5 (4.9)	26.8 (5.0)	26.5 (4.2)	0.912
Total daily dose of insulin,[g] IU/kg	0.7 (0.3)	0.7 (0.2)	0.6 (0.2)	0.870
Total daily dose of basal insulin,[g] IU/kg	0.2 (0.1)	0.3 (0.1)	0.4 (0.1)	<0.001
Total daily dose of rapid-acting insulin,[g] IU/kg	0.4 (0.2)	0.3 (0.1)	0.2 (0.1)	<0.001
Hypoglycaemia alarm set, yes	119 (74.4)	132 (74.2)	208 (71.5)	0.471
Hypoglycaemia alarm threshold,[h] mg/dL	73.7 (7.6)	74.0 (6.3)	75.0 (8.0)	0.209
Hyperglycaemia alarm set: yes	85 (53.1)	95 (53.4)	158 (54.3)	0.800
Hyperglycaemia alarm threshold,[i] mg/dL	234.8 (36.1)	241.6 (40.0)	234.1 (33.3)	0.484

Note: Data are expressed as mean and standard deviation (within parentheses) or as absolute numbers and percentage (within parentheses). *p* values were obtained with the Jonckheere-Terpstra test for trends (for numerical variables) and the chi-squared test for trends (for categorical variables). 1 mmol/L of glucose is equivalent to 18 mg/dL of glucose.

[a]A patient was considered to have achieved the time in range goals if his/her time in range was >70%.

[b]A patient was considered to have achieved the time below range goals if his/her time below range Level 1 was <4% and his/her time in range below range Level 2 was <1%.

[c]Number of nights (0:00 AM to 6:00 AM period) during the 14-day period in which the LibreView graph recorded at least one hypoglycaemic episode, regardless of its duration. Data available for 539 patients, as only patients with a sensor usage ≥70% were selected for this analysis.

[d]Number of days (6:01 AM to 23:59 PM period) during the 14-day period in which the LibreView graph recorded at least one hypoglycaemic episode, regardless of its duration. Data available for 539 patients, as only patients with a sensor usage ≥70% were selected for this analysis.

[e]Data available for 566 patients, given that only patients with at least one hypoglycaemic event of more than 15 min of duration were selected (duration of hypoglycaemia is considered 0 min in those with no hypoglyacaemic events).

[f]Data available for 627 patients.

[g]Data available for 628 patients.

[h]Data available for 459 patients, given that only patients with the hypoglycaemia alarm set were selected.

[i]Data available for 338 patients, given that only patients with the hyperglycaemia alarm set were selected.

doses were those most commonly employed by the patients, however, these might vary, especially in the case of rapid-acting insulin, which is often adjusted according to the preprandial blood glucose levels and the amount of ingested carbohydrates (information that was not available in our study). In addition, adherence to insulin injections is not always optimal in people with T1DM, as missed doses of all types of insulin are common.[12] This study included a sample of patients who take three daily doses of rapid insulin (and, therefore, should normally eat three meals a day), although a number of patients might have eaten fewer or additional meals on some of the 14 days on which the CGM data were collected. Similarly, patients' physical activity and health status during the 14-day period could also affect glycaemic control. Future studies are needed to confirm that a high PBI is associated with reduced hypoglycaemic features, a lower GV, and a greater tendency to hyperglycaemia, as well as to examine the influence of the basal/bolus ratio in other populations, such as patients with T1DM treated with closed-loop insulin pumps or patients with type 2 diabetes.

AUTHOR CONTRIBUTIONS

Tomás González-Vidal: Conceptualization (lead), methodology (lead), formal analysis (lead), investigation (equal), data curation (lead), writing—original draft (lead), writing—review (lead), visualization (lead) and supervision (equal). Diego Rivas-Otero, Guillermo Ramos-Ruiz, Pablo Agüeria-Cabal: Investigation (equal), writing—review (equal). Carmen Lambert, Jessica Ares: Writing—review (equal). Elías Delgado, Edelmiro Menéndez-Torre: Supervision (equal) and writing—review (equal). All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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