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Delayed prandial insulin boluses are an important determinant of blood glucose control and relate to fear of hypoglycemia in people with type 1 diabetes on advanced technologies

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ABSTRACT

Aims: Automated insulin delivery systems improve blood glucose control in patients with type 1 diabetes (T1D). However, optimizing their performance requires patient's proper compliance to meal insulin bolus administration. We explored real-life prevalence of delayed prandial boluses (DBs) in adults with T1D on advanced technologies, and their association with glycemic control and fear of hypoglycemia (FH).

Methods: In the last two-week web-based reports of 152 adults with T1D on Hybrid Closed Loop Systems (HCLS) or Sensor Augmented Pump (SAP), DBs were identified when a steep increase in blood glucose occurred at CGM before the prandial bolus, and CGM metrics were evaluated. All participants completed an online questionnaire on FH.

Results: Mean DBs over two weeks were 10.2 ± 4.7 (M ± SD, range 1–23) and more frequent in women than men (11.0 ± 4.6 vs. 9.4 ± 4.7, $p = 0.036$). Participants with more DBs (>12) showed significantly lower Time-In-Range (62.4 ± 13.8 vs. 76.6 ± 9.0 %) than those with less DBs (<7.7), along with higher Time-Above-Range, GMI, and Coefficient-of-Variation (ANOVA, $p < 0.001$ for all). Participants with higher FH score showed more DBs (11.6 ± 5.0) than those in lower tertiles (9.57 ± 4.59 and 9.47 ± 4.45, ANOVA $p = 0.045$).

Conclusions: In patients on advanced technologies, delayed boluses are extremely common, and associate with significantly worse glycemic control. Utmost attention is needed to bolus timing, mainly tackling fear of hypoglycemia.

1. Introduction

Automatic insulin delivery systems improve overall blood glucose control in individuals with type 1 diabetes (T1D).[1] However, optimal postprandial blood glucose control remains challenging.[2] Many factors may determine an inadequate postprandial glucose response, including the limitations of carbohydrate counting technique, mainly related to the effects of other dietary components, i.e., carbohydrate quality, protein, and fat.[3,4] Focusing on these factors may drive professionals and patients to neglect other relevant issues, like mistimed boluses, not as rare as previously thought, as shown by data on the extensive use of integrated CGM and insulin pumps. Questionnaire data indicate that over 30 % of adult patients report giving insulin boluses during or after meal.[5]

Mistimed doses are associated with clinical outcomes.[6] In T1D patients, a better postprandial glucose control was observed with an insulin bolus given 20 min prior to the meal than just prior to the meal or 20 min after meal initiation.[7] With hybrid closed-loop systems (HCLS), the delayed insulin bolus adds to the algorithm-driven over-delivery of insulin and frequently induces hypoglycemia.[8]

Correct timing of insulin dose may be challenged by many factors related to disrupted daily routines and social situations, but also by intentional avoidance due to fear of hypoglycemia. Fear of hypoglycemia strongly affects patients' metabolic control and quality of life, promoting deleterious behaviors, including overfeeding, underdosing of insulin, undertreatment of hyperglycemia, excess correction of light hypoglycemia, but also delayed prandial boluses.[9,10]

In this study, we explored in people with T1D on advanced technologies in real-life conditions, the prevalence of delayed prandial boluses (DBs), identified through integrated CGM and insulin pump

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reports, testing the hypothesis that the frequency of DBs may associate with blood glucose control and fear of hypoglycemia evaluated by a self-administered questionnaire.

2. Subjects, materials and methods

2.1. Participants

The study participants were consecutively recruited at the outpatient diabetes clinic of the Federico II University Hospital, Naples, Italy. The characteristics of the 152 adult participants with T1D are shown in Table 1. Sexes were equally represented, 74 men (48 %) and 78 women (52 %), and they had mean age 42 ± 14 (range 19–72) years, body mass index 25 ± 4 (17–36) kg/m^2, diabetes duration 25 ± 11 (3–52) years, and CSII duration 10 ± 6 (1–19) years. Participants were on HCLS (n = 121, 80 %) or Sensory-Augmented-Pump (SAP) (n = 31, 20 %). All patients had started insulin pump therapy after a structured training period with an experienced team consisting of diabetes nurses, dietitians, and physicians. Over the two-week study observation, sensor use was 89.6 ± 7.3 (72–99) %, and Glucose Management Indicator 6.99 ± 0.47 (5.4–8.3) %. A written informed consent for participation in the study was obtained from all patients.

2.2. Procedures

2.2.1. Identification of bolus delay

Two diabetologists (RT, RDA) independently reviewed the CGM and pump reports of all participants related to the last two-week period available on the web-based platforms, while participants were under their normal living conditions. The mean of the two readings, after correction for the individual percent use of sensor during the two-week period ("number of DBs identified in the two-week CGM" divided by "percent sensor use during the two-week period" multiplied by 100), is reported and used for analysis in this study. DBs were assigned when at mealtime (only at the main meals: breakfast, lunch, and dinner) an increase in blood glucose >50 mg/dl on CGM preceded an insulin bolus. To minimize possible mis-classification due to treatment of hypoglycemia, glucose excursions starting with baseline glucose <70 mg/dL were not evaluated. Missed meal boluses (i.e. glucose excursions that were not accompanied by a bolus) were very few and were included in the analysis as DBs.

2.2.2. Fear of hypoglycemia scale FH-15

The Italian translation of the self-administered online questionnaire on Fear of Hypoglycemia[11,12] was completed by all participants except one female patient. The questionnaire was composed of 15 items concerning three main factors, fear, avoidance, and interference. The response options were: 1 (Never), 2 (Almost never), 3 (Sometimes), 4 (Almost always), 5 (Every day), which yields a maximal total score of 75.

Table 1
Characteristics of the Type 1 Diabetes patients participating in the study (n = 152).

Sex n (%)	Female	78 (52)
	Male	74 (48)
Age (years)		41.9 ± 14.2 (19–72)
Body mass index (kg/m^2)		25.4 ± 3.7 (17–36)
Duration of diabetes (years)		25.0 ± 11.0 (3–52)
CSII n (%)	HCLS	121 (80)
	SAP	31 (20)
Duration of CSII (years)		10.0 ± 5.6 (1–19)
Use of sensor (%)		89.6 ± 7.3 (72–99)
Glucose Management Indicator (%)		6.99 ± 0.47 (5.4–8.3)
Number of delayed boluses		9.2 ± 4.4 (1–21)

CSII, continuous subcutaneous insulin infusion; HCLS, hybrid closed loop system; SAP, sensory augmented pump.
Data are n (%) or M ± SD (range).

2.3. Statistical analysis

Data are expressed as mean ± SD unless otherwise stated. Differences between tertiles of DBs and FH-15 scores were evaluated by ANOVA and LSD post-hoc comparisons. Associations were analyzed by Pearson's correlation. A two-sided p-value <0.05 was considered statistically significant. The statistical analysis was performed according to standard methods using the Statistical Package for Social Sciences software, v27 (SPSS/PC; Chicago, USA).

3. Results

At least one delayed bolus was identified in all participants (Table 1). The mean total number of DBs over two weeks was 10.2 ± 4.7 (range 1–23). DBs were more frequent in women than men (11.0 ± 4.6 vs. 9.4 ± 4.7, p = 0.036), and in patients on SAP than HCLS (12.3 ± 5.2 vs. 9.7 ± 4.5, p = 0.006). Compared with participants showing less DBs (low-tertile, <7.7 DBs), participants showing more DBs (high-tertile, >12 DBs) were on average significantly younger (41.0 ± 13.9 vs. 47.8 ± 15.5 years, p < 0.001), had a shorter duration of diabetes (24.9 ± 11.4 vs. 28.0 ± 12.5 years, p = 0.039), but a similar BMI (25.8 ± 3.7 vs. 24.9 ± 3.5 kg/m^2, p = 0.263) and CSII duration (10.2 ± 5.6 vs. 9.3 ± 6.0 years, p = 0.447). The number of DBs directly correlated with total daily insulin doses (p = 0.036).

A clear dose-response relationship was evident between the sum of DBs and CGM metrics during the two-week observation period (Fig. 1). Participants in the high DBs tertile showed a significantly lower Time-In-Range (TIR) 70-180 mg/dl (62.4 ± 13.8 %) compared to those in the medium (73.3 ± 9.2 %, p < 0.001) and low (76.6 ± 9.0 %, p < 0.001) tertiles (ANOVA F = 23.55, p < 0.001). Additionally, Time-Above-Range (TAR) 180-250 mg/dl and TAR >250 mg/dl were significantly higher in the high DBs tertile (24.6 ± 9.1 % and 9.76 ± 8.36 %, respectively) than in the medium (18.9 ± 6.2 %, p < 0.001, and 5.56 ± 5,37 %, p < 0.001) and low (18.1 ± 6.9 %, p < 0.001, and 3.61 ± 2.99 %, p < 0.001) tertiles (ANOVA F = 14.03, p < 0.001, and F = 11.29, p < 0.001, respectively). Time-Below-Range (TBR) 54-70 mg/dl showed no significant differences between the tertiles (2.22 ± 2.89 %, 1.76 ± 1.57 %, 1.63 ± 1.74 %, n.s.) (ANOVA F = 1.04, p = 0.354). TBR <54 mg/dl in the high DBs tertile (1.00 ± 2.72 %) was not significantly higher than in the medium tertile (0.50 ± 0.99 %, p = 0.144) but was significantly higher than in the low tertile (0.27 ± 0.60 %, p = 0.034) (ANOVA F = 2.71, p = 0.70). Moreover, Glucose Management Indicator and Coefficient of Variation in the high DBs tertile (7.22 ± 0.60 % and 35.4 ± 4.9 %, respectively) were significantly higher than in the medium (6.91 ± 0.38 %, p < 0.001, and 33.7 ± 5.2 %, p = 0.079) and low (6.83 ± 0.28 %, p < 0.001, and 31.1 ± 4.1 %, p < 0.001) tertiles (ANOVA F = 10.83, p < 0.001, and F = 10.64, p < 0.001, respectively).

The significant differences in TIR, TAR 180-250 mg/dl, TAR >250 mg/dl, Glucose Management Indicator, and Coefficient of Variation between participants with more or less DBs were also observed when the analysis was restricted to the patients on HCLS (n = 121).

The mean total score for the Fear of hypoglycemia questionnaire was 32.2 ± 9.9, ranging from 15 to 72. FH score was significantly higher in women than men (34.3 ± 10.3 vs. 30.5 ± 9.0, p = 0.008). Participants with higher FH score (high tertile, >35) showed a significantly higher number of DBs (11.6 ± 5.0) than the medium and low tertile (9.57 ± 4.59 and 9.47 ± 4.45, respectively, ANOVA p = 0.045) (Fig. 2). According to the main domains, the number of DBs correlated significantly with Fear (r = 0.217, p = 0.008) and Interference (r = 0.179, p = 0.029), but not with Avoidance (r = 0.042, p = 0.608). The number of DBs directly correlated significantly with specific items concerning the fear of having hypoglycemia: a) while alone, b) at night, c) while working, d) with loss of consciousness (p < 0.05 for all) (Fig. 3).

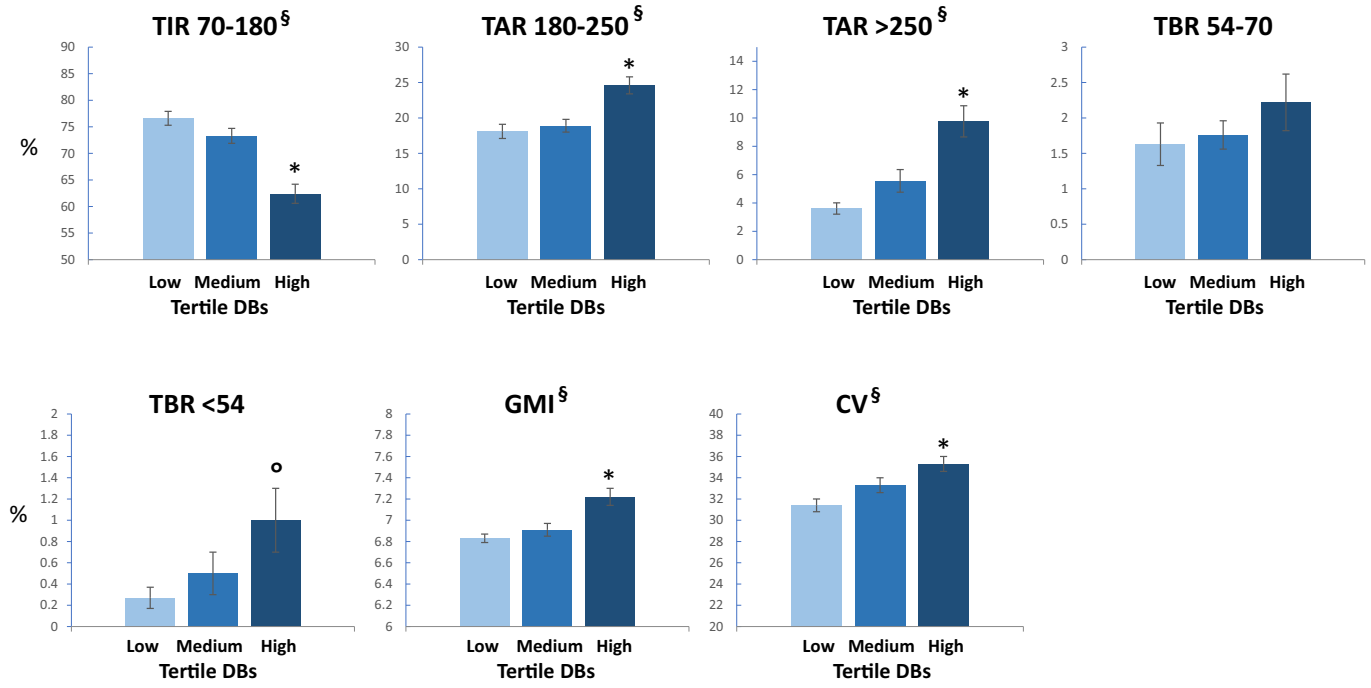

Fig. 1. CGM metrics by tertiles of number of delayed boluses (DBs) over 2 weeks.
Low tertile (<7.7 DBs, n = 51), Medium tertile (7.7–12 DBs, n = 50), High tertile (>12 DBs, n = 51).
TIR 70–180, time-in-range (70–180 mg/dl); TAR 180–250, time-above-range (180–250 mg/dl); TAR >250, time-above-range (>250 mg/dl); TBR 54–70, time-below-range (54–70 mg/dl), TBR <54, time-below-range (<54 mg/dl); GMI, Glucose Management Indicator; CV, Coefficient of variation. M ± SE. §p < 0.001 for overall differences between groups (ANOVA), *p < 0.001 vs. Low and Medium tertiles, °p = 0.034 vs. Low tertile.

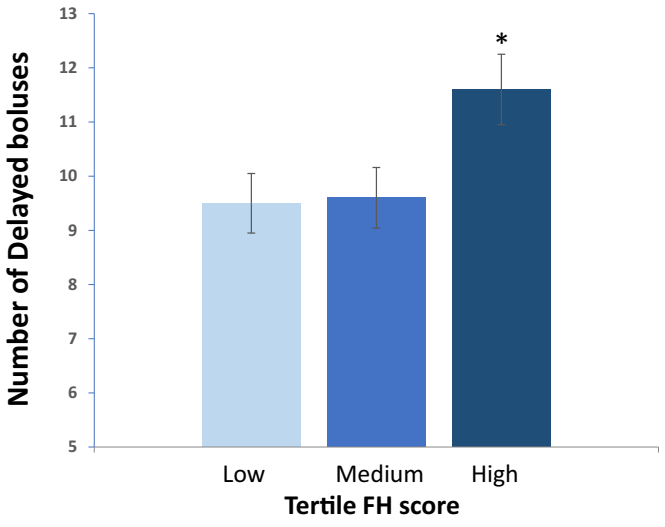

Fig. 2. Number of delayed boluses by tertiles of Fear-of-Hypoglycemia (FH) total score. M ± SE. p = 0.045 for overall differences between groups (ANOVA), *p < 0.05 vs. Low and Medium tertiles.

4. Discussion

This study shows that delayed insulin boluses are extremely common (on average 1 out of 4 meals) also in patients on advanced technologies. At difference with previous self-report surveys based on questionnaires and interviews, this study confirms the high prevalence of DBs through an objective measurement, i.e., the CGM and insulin pump data, obtained in real-life conditions. The proportion of patients reporting mistiming of insulin has previously been reported in the range of 20–45 %, depending on the study; this has been associated with higher rates of hypoglycemia and higher HbA1c.[6] Data from The T1D Exchange Registry show that adults who dosed postprandially were characterized by higher HbA1c, younger age, and larger insulin doses than patients who dosed preprandially.[5]

Real life clinical care highlights the importance of prandial insulin bolus timing also with HCLS. Delaying mealtime insulin bolus may cause over-delivery of insulin and subsequent hypoglycemia as this adds to the closed-loop directed insulin.[8] Very often, insulin mistiming represents long-lasting established habits that continue while using the new advanced technologies. To this regard, in our study, the frequency of DBs was lower among participants on HCLS than SAP, suggesting a favorable influence of using a more protective closed-loop system, although a reverse causality cannot be excluded with individuals who tend to miss fewer prandial boluses more likely to choose to use a closed-loop system.

The second finding of this study is that DBs associate with a significantly worse blood glucose control. The participants with more mistimed boluses showed a striking 13 % lower TIR and similar clinically relevant differences were observed also for TAR and glucose variability. The association of reported mistimed dosing with clinical outcomes has been shown in previous studies where hypoglycemia was more frequent among patients who dosed insulin bolus after meal compared with those who dosed during or pre-meal.[6] In addition, glycemic control was reported to be better among patients who administered their insulin dose premeal.[6]

Reasons for mistimed insulin boluses are multifactorial and include forgetfulness, disruption of usual routines that interfere with usual daily activities, but also intentional non-adherence in case patients are not sure when they will be able to eat, what the carbohydrate content is likely to be, whether they will eat the full portion, or because of the unpredictable response due to gastroparesis.[5] In our study, an association was found between the number of DBs and fear of hypoglycemia, i.e., patients with a higher score for fear of hypoglycemia showed a higher number of DBs. This may suggest that fear of hypoglycemia causes a

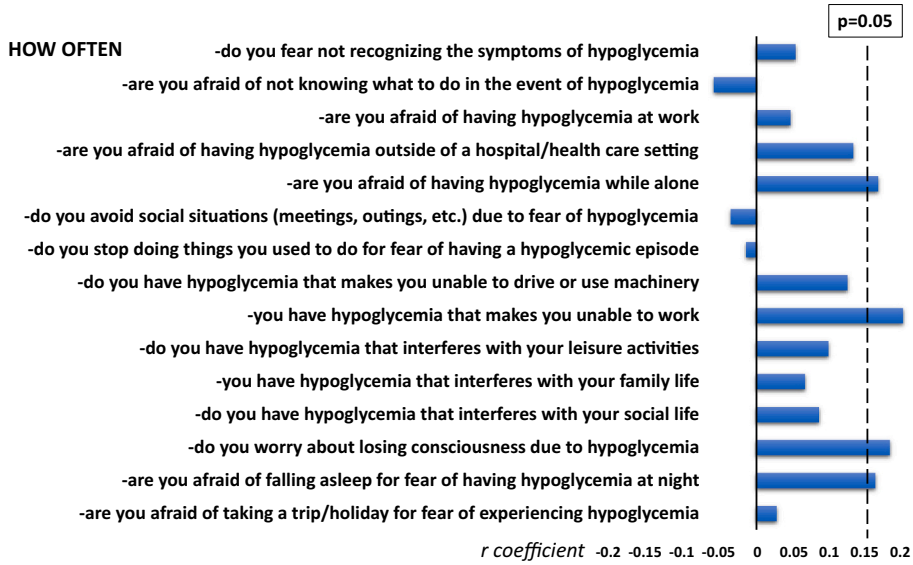

Fig. 3. Pearson correlations between number of delayed boluses and different items of the Fear-of-Hypoglycemia questionnaire.

higher frequency of delayed boluses, although it is possible that delayed insulin administration contributes to an elevated fear of hypoglycemia by increasing the likelihood of hypoglycemic episodes. Different items of the FH questionnaire correlated with the number of delayed boluses. This is in line with the patients' belief that administering mealtime insulin immediately before or after the start of a meal rather than 15–20 min before the meal would have a positive impact on their lives[13] and may be the tentative action to avoid the aversive symptoms of past hypoglycemic episodes.[9] It is of note that women exhibited higher scores in FH than men and it would be worthy investigating the factors behind this association.

The main strength of this study is that for the first time delayed insulin boluses (previously shown in self-report surveys) were measured objectively on integrated CGM/pump reports, under real-life conditions in patients on novel technologies.

Limitations of the study are that only adults were studied, and, therefore, data may differ in children and adolescents, and the 2-week observation period may not be representative of the overall blood glucose and insulin administration patterns. Moreover, the definition of DB was arbitrary; however, during everyday visits, we consistently have confirmation by the patients that, with that type of response pattern in the CGM/pump reports, starting meal precedes insulin bolus. In addition, the constancy of mealtimes in the individual patient greatly increases the likelihood of correctly identifying the meal.

In conclusion, in adults with T1D on advanced technologies, delayed boluses are extremely common and are associated with a significantly worse blood glucose control. Therefore, adequate attention should be given to bolus timing also in these patients, for whom the new techniques favor independent management of their diabetes. Tackling mistimed bolus may be the main factor to be addressed, as focusing only on carbohydrate counting may drive diabetes professionals to neglect this clinically relevant issue.

While waiting for closed-loop systems able to detect unannounced meals and automatically deliver proper insulin boluses, changing incorrect habits is required. As fear of hypoglycemia is one driving factor to delaying insulin boluses, this should be dealt with through structured education programs, sharing with patients the vision of CGM and insulin pump data focusing on the correspondence between insulin action and blood glucose levels.

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Prior presentation

Parts of this study were presented as poster presentation at the ATTD 2022 Meeting, Barcelona, Spain, April 2022, and oral presentation at the 58th Annual Meeting of the European Association for the Study of Diabetes, Stockholm, Sweden, September 2022.

CRediT authorship contribution statement

Giovanni Annuzzi: Conceptualization, Writing – review & editing. **Raffaella Triggiani:** Investigation. **Raffaele De Angelis:** Investigation. **Carmen Rainone:** Investigation. **Alessandra Corrado:** Data curation. **Giuseppe Scidà:** Data curation. **Roberta Lupoli:** Validation. **Lutgarda Bozzetto:** Supervision.

Declaration of competing interest

No potential conflicts of interest relevant to this article were reported.

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