Exploring the Burden of Mealtime Insulin Dosing in Adults and Children With Type 1 Diabetes

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Timely and accurate mealtime insulin dosing can be an ongoing challenge for people with type 1 diabetes. This multinational, online study aimed to explore attitudes and behaviors around mealtime insulin dosing and the impact of mealtime dose timing, particularly with regard to premeal dosing (15–20 minutes before a meal). Although the majority of surveyed participants (96%) recognized the importance of accurate mealtime bolus insulin dosing, only a small proportion (35%) reported being "very confident" in accurate bolus insulin estimation. Given the choice, the majority of participants would prefer to administer insulin immediately before or after a meal, as this timing would improve their quality of life.

KEY POINTS

- Although the majority of surveyed participants (96%) recognized the importance of accurate mealtime bolus insulin dosing, only a small proportion (35%) reported being "very confident" in accurate bolus insulin estimation.
- Most responding adults with type 1 diabetes (91%) and parents of children with type 1 diabetes (97%) experienced challenge(s) related to premeal insulin dosing.
- Most responding adults with type 1 diabetes (91%) and parents of children with type 1 diabetes (92%) reported worrying about postmeal glucose levels at least occasionally.
- A high proportion of responding adults with type 1 diabetes (67%) and parents of children with type 1 diabetes (72%) said that having the freedom to administer mealtime insulin immediately before or after the start of a meal rather than 15–20 minutes before the meal would have a positive impact on their lives.

A large proportion of people with type 1 diabetes, both adults and children, do not achieve guideline-recommended A1C targets (1,2). Contributing to overall glycemic burden is postprandial glucose (PPG), which, together with fasting plasma glucose, is a target measure that is incorporated into guideline recommendations (3). Elevated PPG levels have been shown to be associated with a significant increase in health care resource utilization, including clinic visits, calls, emails to health care providers, and hospitalizations among adults with diabetes who use a multiple daily injection insulin (MDI) regimen (4). However, managing PPG remains one of the most challenging aspects of diabetes care.

PPG control is multifactorial; contributors include timing, quantity, and composition of the meal and asynchrony between postmeal glucose absorption and maximal exogenous insulin effect, which often lags behind glucose absorption by up to 2 hours. Patient-related causes greatly contribute to suboptimal PPG control and include reduced or skipped mealtime insulin doses and inaccurate estimation of carbohydrate intake (5).

Optimal timing of mealtime insulin dosing is a key factor in controlling PPG levels (6,7). In this article, for clarity, we refer to the administration of insulin 15–20 minutes before a meal as a "premeal bolus." When insulin is administered immediately before a meal (usually

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regarded as 0–2 minutes before the meal), we refer to this as a "mealtime bolus." Administration of insulin after the start of a meal is referred to as a "postmeal bolus."

Multiple studies and clinical practice guidelines have suggested that the optimal time to administer a rapid-acting insulin analog is 15–20 minutes before the start of a meal (6,8). This recommendation follows observations in general practice and studies evaluating the effect on PPG excursions of dose timing of rapid-acting insulin relative to meals in people with type 1 diabetes (Supplementary Table S1) (7,9–13). Premeal bolusing of rapid-acting insulin analogs 15 minutes before mealtime resulted in lower PPG excursions and more time spent in the euglycemic range (3.5–10.0 mmol/L) without increased risk of hypoglycemia (7).

Despite these results and clinical recommendations, real-world studies have demonstrated poor adherence to the recommended injection-to-meal interval, and postmeal bolus dosing is commonly observed (5,14,15). Synchronizing the administration of insulin with its anticipated effect on glucose absorption poses a significant challenge for many people with diabetes, especially children or anyone who struggles to adhere to lifestyle routines. Some of the challenges associated with mealtime insulin dosing include injection pain, embarrassment, and interference with daily activities (5,16).

Quantitative data from studies investigating the challenges of mealtime insulin dosing are scarce. Here, we explore attitudes and behaviors around mealtime insulin dosing and the impact of mealtime dose timing, particularly with regard to premeal dosing, in both adults and children with type 1 diabetes, as well as physicians who treat people with type 1 diabetes.

Research Design and Methods

Study Design and Recruitment

An online closed survey was conducted between 25 November 2019 and 6 February 2020 with adults with type 1 diabetes, parents of children with type 1 diabetes, and physicians who treat people with type 1 diabetes from across the United States, Canada, the United Kingdom, Japan, Spain, and France. Adults with type 1 diabetes and parents of children with type 1 diabetes were recruited online via social networks (e.g., Facebook, Twitter, Instagram, and Snapchat) as well as custom ad networks (Google). Participants were also invited through direct advertising on specific health sites or sourced through collaboration with charities and support groups. Physicians were recruited online from Sermo and its panel partners. Incentives were offered for participation in the form of reward points for participants and money for physicians (see Supplementary Materials). Online pilot interviews were conducted with a small sample of people with type 1 diabetes to ensure that the language, flow, and clarity of the survey was appropriate. An invitation link to the main survey was sent to participants via e-mail. Each participant was assigned a unique survey ID based on their IP address and machine ID. Once accessed, participants could not access the survey again. All participants provided informed consent and chose to take part in the survey, during which no personal identifying information was collected.

The survey was conducted by Ipsos Healthcare in compliance with Market Research Society, European Society for Opinion and Marketing Research, European Pharmaceutical Market Research Association, and British Healthcare Business Intelligence Association guidelines. All data collection/abstraction was conducted according to the Health Insurance Portability and Accountability Act and institutional review board policies and procedures.

Study Participants

Adults (age ≥18 years) and parents of children (age ≤15 years) who had had type 1 diabetes for ≥6 months and were administering insulin with meals (excluding fast-acting insulin aspart) were eligible to take the survey. Physicians were eligible if they fulfilled the following criteria: practicing for 3–40 years, treating at least 15 (United States) or 10 (other countries) people with type 1 diabetes (endocrinologists) or at least 5 people with type 1 diabetes (general practitioners/primary care physicians) in a typical month, responsible for starting or managing treatment for type 1 diabetes and for the prescription of mealtime insulin, and prescribing at least one mealtime insulin that required dosing at least 15–20 minutes before a meal.

Outcomes and Analysis

The survey set out to determine the challenges associated with administration of insulin with meals and to assess the extent to which premeal administration affects daily routines and the emotional well-being of people with type 1 diabetes and their carers. The survey also explored the extent to which physicians believe that premeal insulin dosing presents a challenge to people with type 1 diabetes. The main survey questions used are

provided in the Supplementary Materials. For this survey, premeal insulin administration refers to the administration of insulin 15–20 minutes before a meal.

Results are presented using descriptive statistics; no formal statistical analyses were conducted. Incomplete questionnaires were excluded from the analysis. The analysis provided weighted data, assuming equal sizes for each country, to give an overall indication of results across participating countries. Data analysis was conducted using SPSS statistical software (IBM).

Data Availability

The datasets generated and/or analyzed during this study are available from the corresponding author on reasonable request.

Results

Participants

A flow diagram for study participants is shown in Supplementary Figure S1. Of the 2,711 participants included in the study, 1,401 were adults with type 1 diabetes, and 350 were parents of children (≤15 years old) with type 1 diabetes. The remaining 960 participants were physicians who treated people with type 1 diabetes according to the criteria outlined above.

In adults included in the survey (46% of whom were male), the mean age at baseline was 43 ± 14 years and mean duration of diabetes was 19 ± 15 years. In children (64% of whom were male), the mean age at baseline was 10 ± 4 years, and the mean duration of diabetes was 4 ± 3 years. In both groups, >70% of people were administered insulin using an MDI regimen (pen or syringe), while ∼30% used an insulin pump (continuous subcutaneous insulin infusion). Insulin aspart and insulin lispro were the short-acting insulin analogs most commonly used (in 47 and 32% of adults, and in 38 and 35% of children, respectively), and 73% of adults and 91% of children used continuous glucose monitoring (CGM).

Of the participating physicians, 30.5% (n = 293) were general practitioners or primary care physicians, 39.3% (n = 377) were endocrinologists, 1.6% (n = 15) were pediatric endocrinologists, 23.2% (n = 223) were diabetologists, and 5.5% (n = 53) were pediatricians. Overall, 85.3% of interviewed physicians both initiate and manage insulin therapy for people with type 1 diabetes in their clinics, whereas 14.7% of them help manage their patients' diabetes but do not initiate treatment. Across specialties, the mean number of years in practice was 18.8 years (range 3–40). Of their patients, 72.5% were using MDI (pen or syringe), 26.4% used an insulin pump, and 2.6% used an inhaler; 49.4% of their patients were using CGM. Although survey participants did not have experience administering ultra-fast-acting insulin, 50.8% of participating physicians did have experience prescribing one of these agents, specifically fast-acting insulin aspart.

Attitudes Toward Mealtime Insulin Dosing

The majority of adults with type 1 diabetes (96%, n = 1349) and parents of children with type 1 diabetes (94%, n = 30) surveyed believed it is important (either very or fairly important) to take mealtime insulin accurately (Figure 1*A*). When asked about the level of confidence in accurately estimating the required amount of insulin needed for a meal, only 35% (n = 488) of adults and 47% (n = 164) of parents of children felt very confident, whereas 13% (n = 188) of adults and 10% (n = 35) of parents did not feel very confident or confident at all (Figure 1*B*). Of the surveyed physicians, only 16% (n = 115) felt that their patients were very confident in accurately estimating the amount of insulin required at mealtimes (Figure 1*B*).

Challenges With Mealtime Insulin Dosing

Based on a provided list of challenges associated with mealtime insulin dosing, 91% of adults and 97% of parents of children with type 1 diabetes reportedly experienced at least one of the listed challenges. Accordingly, almost all interviewed physicians (99.6%) believed that their patients faced challenges with mealtime insulin dosing. An overview of these challenges is presented in Supplementary Figures S2 and S3.

Overall, the main challenges reported for adults and children with type 1 diabetes included the need to inject more insulin after a meal because of eating more or different food than anticipated and not knowing how much insulin to take to cover a given amount of carbohydrate (Supplementary Figure S2). Similarly, according to physicians, the main challenge for people with type 1 diabetes regarding mealtime insulin dosing was knowing what and how much food is needed (Supplementary Figure S3). The individual frequencies for respondents who ate more or less than anticipated after mealtime insulin dosing are presented in Figure 2*A* and *B*, respectively. Overall, 70% of adults and 81% of parents of children stated that, at least once a week, they ate more or less food than anticipated after dosing mealtime insulin. Furthermore, at least once a week,

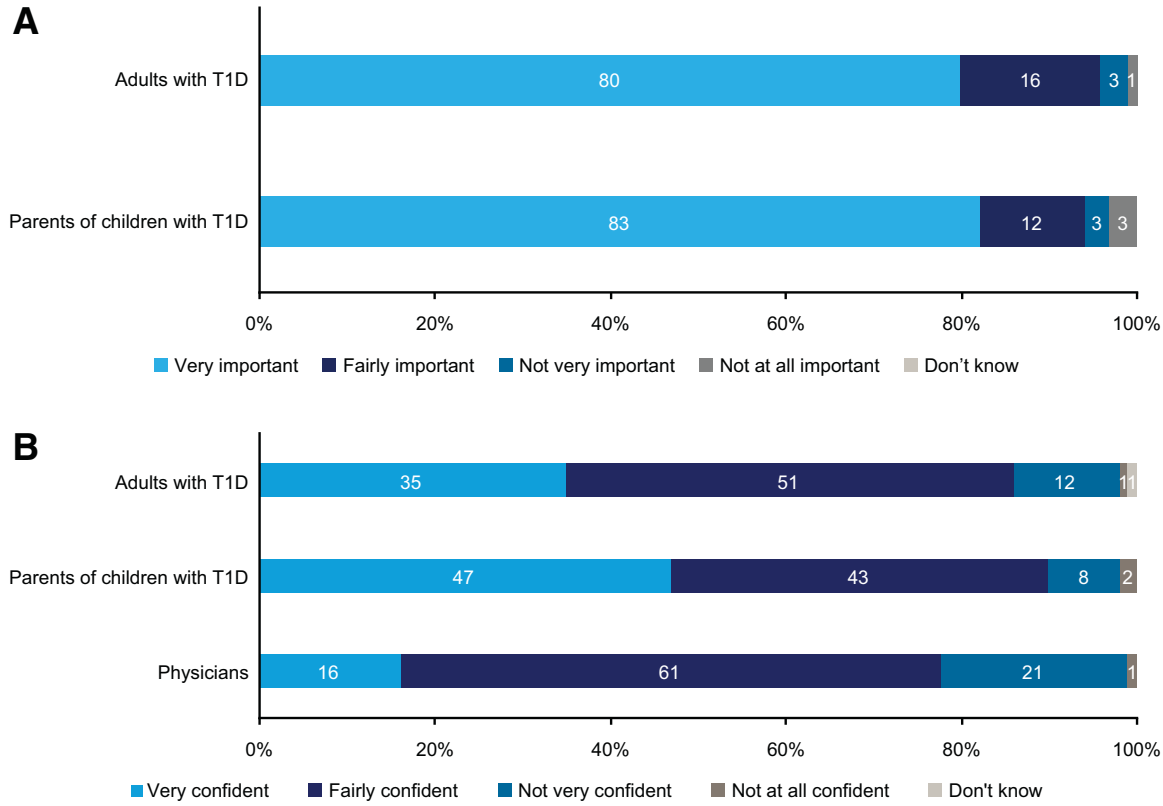

FIGURE 1 Attitudes toward mealtime insulin dosing. *A*) Importance of taking mealtime insulin accurately, as reported by adults and parents of children with type 1 diabetes. *B*) Confidence in estimating the amount of mealtime insulin accurately, as reported by adults with type 1 diabetes, parents of children with type 1 diabetes, and physicians assessing their patients with type 1 diabetes. Corresponding survey questions (A1 and A2 on the patient/parent survey and A1 on the physician survey) are included in the Supplementary Materials. T1D, type 1 diabetes.

58% (n = 720) of adults and 70% (n = 241) of children needed additional food intake as a corrective action to prevent hypoglycemia as a result of eating a meal that had fewer grams of carbohydrates than anticipated (Figure 2*C*). Similarly, corrective insulin after consuming more food than was anticipated was reportedly needed at least once a week by 57% (n = 719) of adults and 65% (n = 219) of children (Figure 2*D*).

Of those surveyed, 25% (n = 348) of adults and 38% (n = 135) of children completely forgot to take their mealtime insulin at least once a week (Figure *2E*). Of the participating physicians, 21% (n = 200) stated that they always discussed mealtime insulin dosing, whereas 68% (n = 650) of physicians reported sometimes and 11% (n = 104) reported hardly ever having this discussion with their patients.

Impact of Premeal Insulin Administration

Overall, 82% of surveyed adults felt that having to administer insulin 15–20 minutes before their meals negatively affected their lifestyle greatly or to some extent. Similarly, 93% of parents felt that this practice had a negative impact to a great or to some extent on their child's day-to-day life. Accordingly, 19% (n = 264) of surveyed adults and 44% (n = 153) of parents chose not to eat out at least once a week because they were unsure about how much bolus insulin might be needed for the meal. The extent of the impact of premeal dosing on life in general, mood, social life, feeling of independence, work, and personal relationships is shown in Figure 3. The majority of physicians (91%, n = 876) agreed that the need for premeal dosing is an extra burden for their patients.

Most adults with type 1 diabetes (91%, n = 1,258) and parents of children with type 1 diabetes (92%, n = 321) worry about PPG levels after a meal to some extent (15 and 21% always, 28 and 31% often, and 48 and 40% occasionally, respectively). Few adults (8%, n = 119) or parents of children (8%, n = 27) reported never worrying about PPG levels.

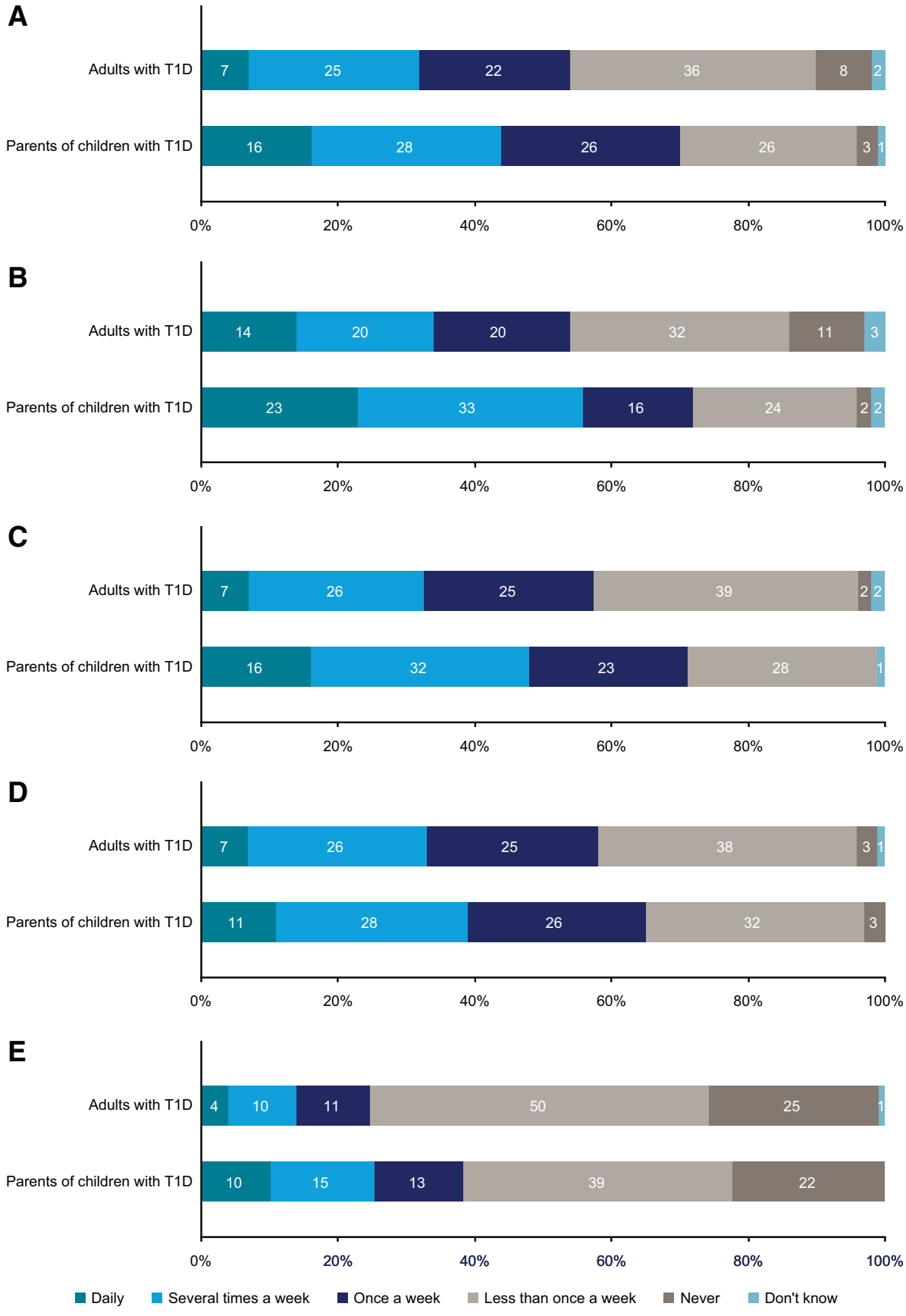

FIGURE 2 Challenges with mealtime insulin dosing as reported by adults and parents of children with type 1 diabetes. *A*) Frequency of eating more than anticipated after dosing insulin according to their physician's guidance. *B*) Frequency of eating less than anticipated after dosing insulin according to their physician's guidance. *C*) Frequency of needing to consume extra food because a meal contained less carbohydrate content than anticipated. *D*) Frequency of needing to take extra insulin to correct additional food intake. *E*) Frequency of completely forgetting to take mealtime insulin. "At least once a week" was calculated by summing the responses for "daily," "several times a week," and "once a week." Corresponding survey questions (A5–A8 and A10 on the patient/parent survey) are included in the Supplementary Materials. T1D, type 1 diabetes.

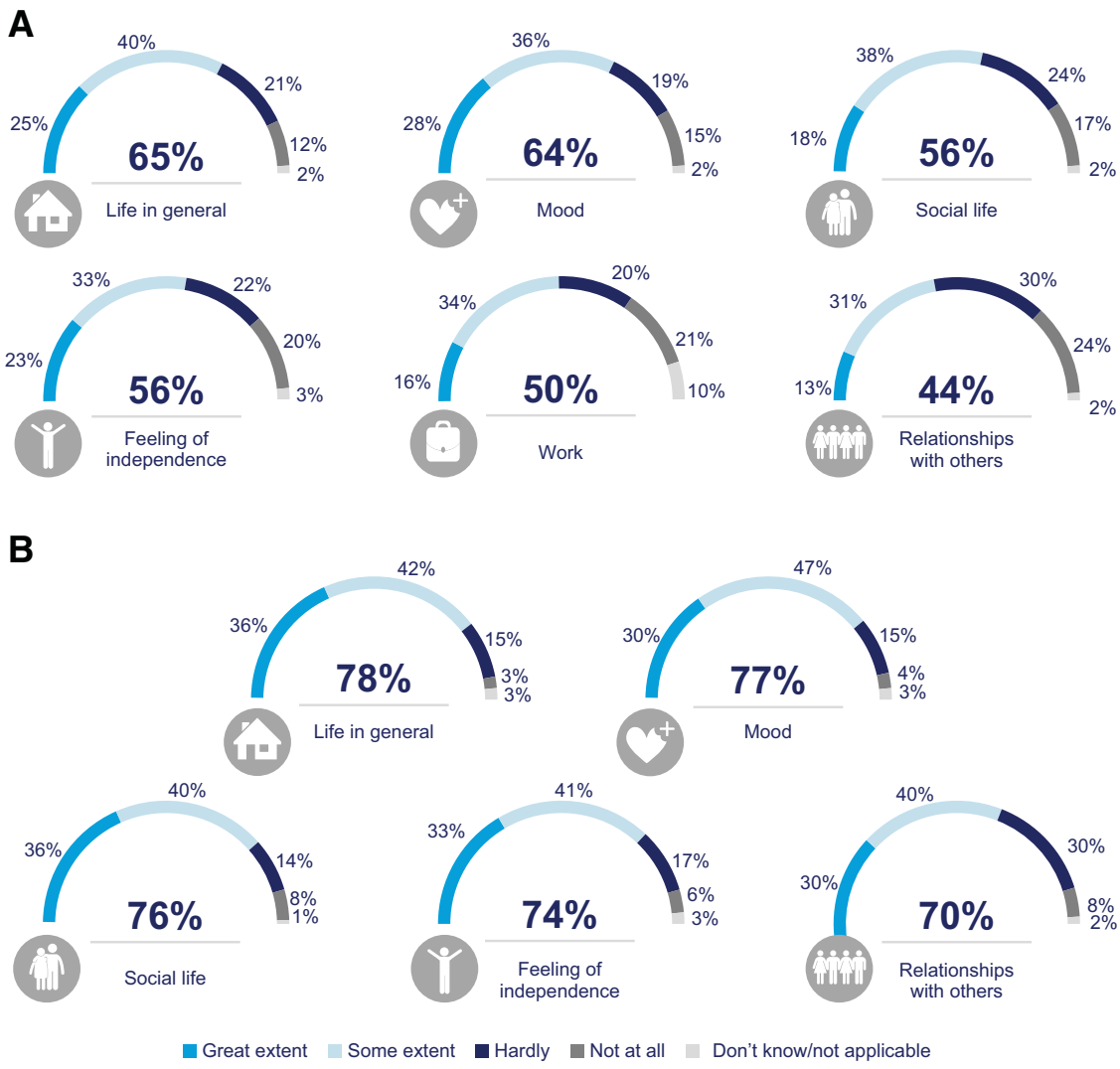

FIGURE 3 The extent of negative impact of premeal insulin dosing on day-to-day life in adults with type 1 diabetes (*A*) and parents of children with type 1 diabetes (*B*). The corresponding survey question (A14 on the patient/parent survey) is included in the Supplementary Materials.

The key emotions associated with mealtime dosing, reported both by adults and parents of children with type 1 diabetes, included acceptance (28 and 31%, respectively), ability to cope (30 and 26%), and being in control (26 and 25%). A feeling of inconvenience was also reported by many adults (34%). Of the interviewed physicians, 85% (n = 819) believed premeal dosing negatively affects the emotional well-being of patients.

Insulin Dosing Preferences

When asked what they would prefer, 73% (n = 1,023) of adults and 67% (n = 231) of parents of children with type 1 diabetes indicated that they would choose bolus

insulin administration either immediately before or after a meal (Figure 4). Furthermore, 55% (n = 772) of adults and 65% (n = 227) of parents of children with type 1 diabetes at least once a week resorted to post-meal insulin administration when they knew exactly what had been eaten.

A large proportion of adults (67%, n = 939) and parents of children (72%, n = 252) with type 1 diabetes claimed that having the freedom to administer insulin at mealtime either immediately before or after the start of a meal would have a positive impact (very positive or fairly positive) on their lives. Likewise, the majority of physicians believed that their patients' quality of life would improve (to a great or some extent) if mealtime insulin administration was feasible immediately before a meal (92% of physicians) or immediately after the start of a meal (89% of physicians).

Discussion

Here, we present the findings of a multinational survey conducted with >1,700 people with type 1 diabetes and >900 physicians with experience treating people with type 1 diabetes to assess perceptions, challenges, and impact of and behaviors associated with mealtime insulin dosing. To our knowledge, this is the first detailed study on understanding the burden associated with pre-meal administration of insulin (15–20 minutes before eating). The insights generated may be useful to clinicians for guiding bolus insulin management and decision-making.

Although nearly all surveyed participants (96%) recognized the importance of accurate mealtime bolus insulin dosing, only a small proportion (35%) reported being "very confident" in accurate bolus insulin estimation.

Moreover, one in four adults with type 1 diabetes and approximately one in three parents of children with type 1 diabetes acknowledged completely forgetting to administer prandial insulin at least once a week. This finding might be driven, in part, by a lack of confidence in accurate mealtime dosing, as reported by both people with type 1 diabetes and physicians in the survey.

Although not all were explored in this survey, it is well recognized that there are multiple barriers to treatment adherence and optimization and that treatment inertia exists (17). Barriers include patient factors (e.g., forgetting to take medications or fear of injections), medication factors (e.g., burdensome regimens and side effects), and system factors (e.g., inadequate follow-up, communication, and support) (17). Importantly, ~70% of surveyed physicians acknowledged only sometimes discussing challenges around mealtime dosing requirements when their patients raised the issue, clearly indicating the need for improved patient-doctor communication on this basic precept of diabetes management.

Not surprisingly, adjusting insulin dose to meals, or vice versa, was a key challenge reported by people with type 1 diabetes and their treating physicians. Accordingly, the need for additional food intake or additional insulin was reported frequently as necessary corrective actions occurring on at least a weekly basis. Parents of children with type 1 diabetes were more likely than adults with diabetes to report these challenges, as it is more difficult to predict the amount of food a child will eat. Consequently, at least half of surveyed participants resorted to postmeal insulin administration at least once a week.

It follows that the majority of surveyed people with type 1 diabetes and physicians felt that the need for premeal

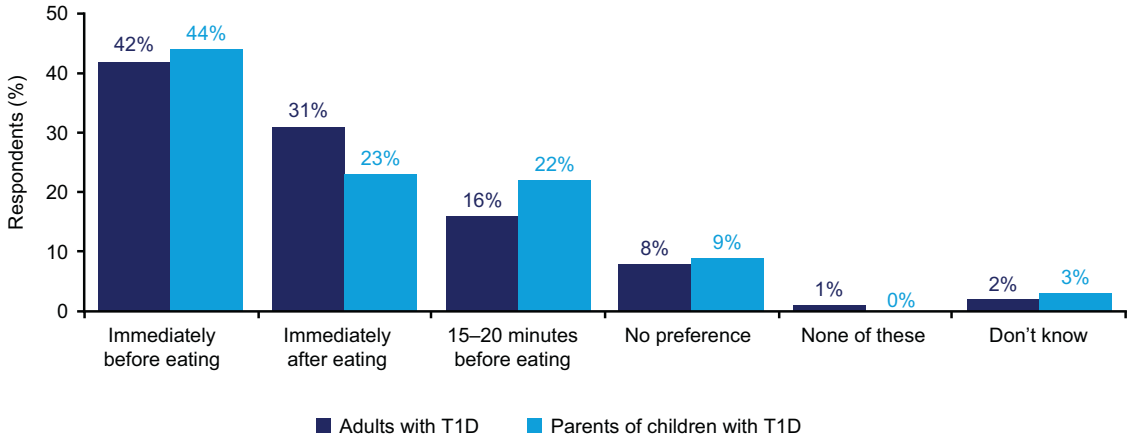

FIGURE 4 Preferred time for taking mealtime insulin given a choice, as reported by adults and parents of children with type 1 diabetes. The corresponding survey question (A18 on the patient/parent survey) is included in the Supplementary Materials. T1D, type 1 diabetes.

insulin administration has a negative impact on lifestyle and that an option to administer mealtime insulin immediately before or immediately after a meal would improve quality of life. This finding highlights the need for better education of people with type 1 diabetes around the correct adjustment of bolus insulin doses before meals. Additional food intake or insulin dosing should not be required as a postmeal corrective action.

Rapid-acting insulin analogs (i.e., insulin lispro, insulin glulisine, and insulin aspart) are generally recommended for use before a meal (18–20), and clinical guidelines recommend premeal insulin administration (21,22). When initially introduced, however, this first generation of mealtime insulin was also approved for postmeal administration, but this practice is now generally recognized as suboptimal, as it can result in higher A1C levels (compared with premeal administration of bolus insulin), postprandial hyper- and hypoglycemia, and ensuing complications (6,15). The importance of PPG is now widely accepted and is reflected in new guidelines (3,23,24).

This PPG emphasis was shown in our surveyed population, in which >90% of adults and parents of children with type 1 diabetes reported worrying about PPG levels to some degree, and ∼70% indicated that they would prefer to administer insulin either at mealtimes or postmeal. Overall, there is an unmet need for safe and effective mealtime insulin alternatives that provide people with type 1 diabetes with the desired flexibility to dose closer to their meals. This need, at least in part, might be addressed by the advent of ultra-fast-acting insulins (25–28).

Fast-acting insulin aspart, one of the first ultra-fast-acting insulin analogs, approved in 2017 (29), has a quicker onset and offset of action and a greater early glucose-lowering effect than insulin aspart (25,30). Mealtime administration (specifically defined here as 0–2 minutes before a meal) of fast-acting insulin aspart showed noninferiority in A1C reduction and improved PPG control compared with insulin aspart in both adults with type 1 or type 2 diabetes (with or without an insulin pump) and children with type 1 diabetes (25,29,31). In a phase 3 treat-to-target trial in adults with type 1 diabetes, subjects randomized to postmeal faster aspart (20 minutes after the start of a meal) for all meals maintained A1C noninferior to that obtained with mealtime insulin aspart (31).

Improvements in PPG control have also been shown with the mealtime administration of ultra-rapid lispro (URLi), indicated for the treatment of type 1 or type 2 diabetes (32–34) and inhaled Technosphere insulin (35) in adults with type 1 diabetes (26–28). In a phase 3 treat-to-target trial in adults with type 1 diabetes, both mealtime and postmeal URLi demonstrated noninferiority to insulin lispro for change in A1C, and mealtime URLi was superior to insulin lispro in reducing PPG excursions (26).

The improved time-action profile, more rapid onset of action, and demonstrated efficacy of ultra-fast-acting compared with rapid-acting insulin analogs might indeed help to alleviate the need for corrective actions after meals and facilitate more flexible insulin dosing around meals while mitigating concerns about PPG excursions. At the time of writing, fast-acting insulin aspart and Technosphere insulin are available in several markets, and URLi was approved in the United States, the European Union, and Japan (32–34).

Patients on intensive insulin regimens should assess glucose levels regularly by either self-monitoring of blood glucose or CGM (36). The fact that 73% of adults and 91% of parents of children with type 1 diabetes in our survey were using CGM is reassuring, as close glucose monitoring is needed to monitor and optimize the use of ultra-fast-acting insulin.

Recent advances in the technology used to manage diabetes have led to the introduction of devices that can both monitor glucose and deliver insulin, some automatically (3), and even provide dosing reminders. Such tools will inevitably reduce the number of missed bolus doses in people with diabetes. “Smart” insulin pens can be programmed to calculate insulin doses to assist patients in real time and provide downloadable data reports allowing treating physicians to retrospectively review doses and make adjustments as needed (37). Sensor-augmented pumps, now approved by the U.S. Food and Drug Administration, are designed to suspend insulin dosing when they either detect low glucose or predict a fall in glucose within the next 30 minutes (3). Automated insulin delivery systems that include an insulin pump, a continuous glucose sensor, and an algorithm that determines insulin delivery, can regulate insulin dosing based on sensor-derived glucose levels. Users of these first-generation “hybrid closed-loop” systems must enter information about meals and deliver bolus insulin doses for meals and snacks. Numerous studies using a variety of systems with different algorithms, pumps, and sensors have been carried out to date in adults and children (3).

The limitations of our study, common to studies with online research designs, include the potential of inaccurate recall, false reporting, and restricted generalizability. Because of the modes of recruitment, our sample does not include people who have no access to a device connected to the Internet or who are inactive on social media platforms, those who are institutionalized, or those with the most severe comorbidities and disabilities. The former exclusion may lead to bias toward individuals with higher socioeconomic status. Nevertheless, the survey included a large number of participants from several countries to help increase the generalizability of its findings. It is also worth noting that the sample was limited to treating physicians and, as such, did not consider the views of other health care professionals involved in the care of people with type 1 diabetes. The survey did not exhaustively cover all potential challenges associated with mealtime dosing, as the impact on postprandial hypoglycemia was not explored. Although not a study limitation per se, it is acknowledged that this survey focused only on type 1 diabetes and that these findings may also be relevant to people with type 2 diabetes receiving insulin with an MDI regimen. Finally, our results might underestimate real-world dosing expectations given the potential of responder embarrassment regarding actual dosing habits.

The increasing availability and use of ultra-fast-acting insulins and their potential for greater flexibility in the timing of insulin administration will warrant further real-world studies to monitor people's attitudes toward the timing of insulin dosing and its potential impact on quality of life.

In summary, this study provides real-world insight into the challenges and behaviors associated with premeal insulin dosing in people with type 1 diabetes. The importance of injection timing is not always discussed by physicians, even though it is critical to achieving PPG control. Although the importance of accurate and timely dosing was recognized, premeal insulin administration poses a clear challenge to people with type 1 diabetes. Given the choice, participants said they would prefer mealtime or even postmeal administration as being clearly advantageous and beneficial to quality of life. Given the high proportion of people with type 1 diabetes with missed insulin boluses, more convenient timing may also aid therapeutic adherence. The advent of ultra-rapid insulin analogs now presents a possible solution to some of these issues. Physicians should aim to explore the issues around administration of insulin with meals and address their patients' needs through support, education, and, where clinically appropriate, consideration of ultra-rapid insulin therapy.

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DUALITY OF INTEREST

W.L. has served on advisory boards and received research grant support from Novo Nordisk and has received honoraria for serving on speakers' bureaus for Dexcom, Insulet, Novo Nordisk, and Xeris. E.L. is an employee of Ipsos MORI, which was commissioned to conduct this research. J.G. and N.R. are employees of Novo Nordisk. N.T. has received fees for speaking and consulting from Novo Nordisk A/S. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

All authors contributed to data interpretation, reviewed and contributed to the content of the manuscript, and approved the manuscript for publication. E.L. was part of the team who collected and analyzed the data. W.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PRIOR PRESENTATION

Parts of this article were presented in abstract form at the virtual 56th Annual Meeting of the European Association for the Study of Diabetes, 21–25 September 2020.

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