Traveling Across Time Zones With Type 1 Diabetes: A Pilot Study Comparing Insulin Degludec With Insulin Glargine U100

Wendy C. Bevier,[1] Kristin N. Castorino,[1] Ceara Axelrod,[1] Gal Haroush,[1] Christian C. Farfan,[1] Nina Shelton,[1] Kristen Nelson,[1] Lisa A. Spink,[1] Hanqing Liu,[2] and David Kerr[1]

Diabetes Care 2022;45:67–73 | https://doi.org/10.2337/dc21-1524

OBJECTIVE

For people with type 1 diabetes, there are limited evidence-based resources to support self-management when traveling across multiple time zones. Here, we compared glycemic control on insulin degludec versus glargine U100 as the basal insulin for adults using multiple daily injections (MDI) while traveling across multiple time zones.

RESEARCH DESIGN AND METHODS

This randomized crossover pilot study compared insulin degludec versus glargine U100 for adults with type 1 diabetes using MDI insulin during long-haul travel to and from Hawaii to New York. Insulin degludec was administered daily at the same time regardless of time zone, and glargine was administered per travel algorithm. Primary end point was the percentage of time in range (TIR) between 70 and 140 mg/dL during the initial 24 h after each direction of travel. Secondary end points included standard continuous glucose monitoring metrics, jet lag, fatigue, and sleep.

RESULTS

The study enrolled 25 participants (56% women, mean ± SD age of 35 ± 14.5 years, HbA_{1c} of 7.4 ± 1.2% [57 ± 13.1 mmol/mol], and diabetes duration of 20.6 ± 15 years). There was no significant difference in glycemic outcomes between the two arms of the study, including TIR, hypoglycemia, or hyperglycemia. Neither group achieved >70% TIR 70–180 mg/dL during travel. Jet lag was greater on glargine U100 in eastward travel but not westward. Fatigue was greater after westward travel on glargine. Sleep was not significantly different between basal insulins.

CONCLUSIONS

In adults with type 1 diabetes using MDI of insulin and traveling across multiple time zones, glycemic outcomes were similar comparing insulin degludec and glargine U100.

Prior to the severe acute respiratory syndrome coronavirus 2 pandemic, airlines serving the U.S. carried an all-time high of 1.1 billion passengers, of which 241 million flew internationally (1). Given there are ∼7.4 million Americans with diabetes

[1]Sansum Diabetes Research Institute, Santa Barbara, CA
[2]Abbott Diabetes Care, Alameda, CA

Corresponding author: Wendy Bevier, wbevier@sansum.org

Received 21 July 2021 and accepted 7 October 2021

Clinical trial reg. no. NCT03668808, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.16776259.

W.C.B. and K.N.C. contributed equally to this study.

using insulin, this makes it likely that a good proportion of the people who board flights each day are flying with insulin-treated diabetes (2). Although the longer-term impact of the pandemic on airline travel is unclear, there is evidence from the 2003 severe acute respiratory syndrome outbreak that once travel bans are removed, the number of visitors to a destinations with high rates of infection quickly returns toward normal (3).

For insulin-treated individuals planning long-haul travel (defined as a flight lasting >6 h), consideration needs to be given to every stage of a journey, including factoring in the impact of crossing multiple times zones and jet lag on choosing a safe and effective insulin (4). In one survey, more than half of travelers with diabetes reported difficulties in glucose management during their journey compared with the month prior to leaving (5). For insulin-treated individuals ~10% of travelers on short- as well as long-haul journeys experienced problems, most commonly hypoglycemia during the journey or in the first 24 h after arriving at their destination (6).

For long-haul travel, there is evidence that many physicians, including endocrinologists, are uncertain how to adjust insulin for travel across several time zones, and some of the existing information provided has been described as "potentially harmful"(6). Currently, there are few resources to offer evidence-based travel guidance to individuals with type 1 diabetes. A common challenge is to plan making adjustments in the dose, timing, and frequency of long-acting basal insulin as long-haul travelers cross multiple time zones and deal with changes in sleep and wakefulness at their destination. It is unclear whether alterations in insulin pharmacology can provide practical benefits to people with diabetes traveling long distances.

Because of its favorable pharmacokinetic and pharmacodynamics properties, insulin degludec has been shown to improve glycemic control (by improvements in hemoglobin A_{1c}), have a lower risk of hypoglycemia, and show less glycemic variability compared with insulin glargine U100 (7,8). In this pilot study, the aim was to compare degludec versus glargine U100 as the basal insulin for adults with type 1 diabetes using multiple daily injections (MDI) of insulin and flying long-haul using profiles from continuous glucose monitoring (CGM) devices worn before, during, and after travel.

RESEARCH DESIGN AND METHODS

Study Design

This study was an open-label, single-center, pilot study with participants randomized to glargine U100 or insulin degludec as the basal insulin, and then after a 2-week break, they crossed over to the alternative insulin for a repeat long-haul journey (Fig. 1). The journey began in Honolulu, HI (HNL, Coordinated Universal Time −10 h) with a nonstop flight to New York, NY (NYC, Coordinated Universal Time −4 h) lasting ~10 h with a 6-h time difference between destinations. After up to 72 h in NYC, they returned to HNL and spent up to 72 h at that destination. Participants continued to use their usual mealtime fast-acting insulin, and they did not adjust their insulin-to-carbohydrate ratio during travel or at each destination. Before each journey, participants had their basal insulin optimized using CGM profiles for 4 weeks (9).

Procedures were approved by Advarra Institutional Review Board, Columbia, MD (UTN U1111-1210-7350) and registered with ClinicalTrials.gov (NCT03668808).

Participants

All participants gave written consent before any study procedures were performed, and eligibility was confirmed by study staff during a screening visit. The participants had a diagnosis of type 1 diabetes for at least 1 year and were under treatment with MDI of any basal and rapid-acting insulin analogs. Participants were adults between 18 and 65 years of age, HbA_{1c} was <10% (86 mmol/mol) within 30 days of being enrolled, and there were no contraindications to long-haul travel. They had to be willing and able to use a CGM device, have the ability to self-manage insulin therapy, and perform all self-monitored blood glucose (SMBG) readings with self-adjustment of insulin doses according to the protocol.

Exclusion criteria included recurrent severe hypoglycemia (more than one severe hypoglycemic event requiring hospitalization during the last 12 months), hypoglycemia unawareness, as judged by a score of >4 on the Gold score (10), or hospitalization for diabetic ketoacidosis during the previous 6 months. Participants were excluded if they currently used an insulin pump, were prescribed any glucose-lowering drug other than insulin, initiated or changed any systemic treatment that could interfere with glucose metabolism (such as systemic corticosteroids, β-blockers, or monoamine oxidase inhibitors), had proliferative retinopathy or maculopathy requiring treatment, or were pregnant or had the intention of becoming pregnant.

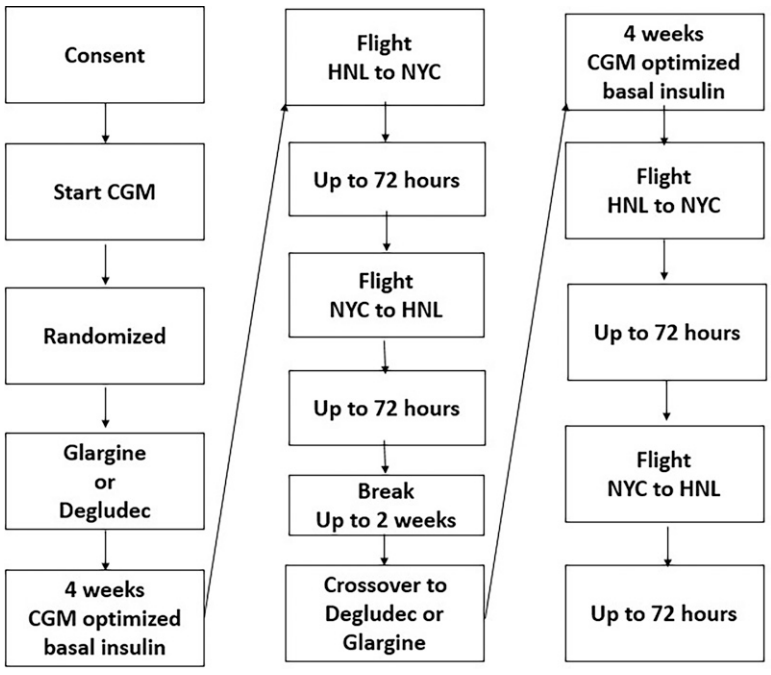

Figure 1—Study design, including timelines and directions of travel.

Study Procedures

Participants who met the eligibility criteria and signed the informed consent continued to the screening visit. The following standard screening assessments were completed at baseline (prerandomization): HbA_{1c} assessment via fingerstick and Siemens DCA Vantage 2000 (Siemens Medical Solutions USA, Malvern, PA), equivalent NGSP-certified point-of-care method, or by a local laboratory, demographics (date of birth, sex, and race and ethnicity), medical history, substance use history (drinking, smoking, and drug habits), concomitant medications, and physical examination to include weight, height, blood pressure, heart rate, and urine pregnancy test. In addition, these scales were administered: hypoglycemia unawareness on the Gold Score Hypoglycemia Questionnaire (10), Hypoglycemia Fear Survey (11), and Hypoglycemic Confidence Scale (12).

At the randomization visit, participants were randomized to starting insulin degludec or glargine U100 insulin according to the label insert and full prescribing information (13,14). A CGM (Abbott Freestyle Libre Pro; Abbott Diabetes Care, Alameda, CA) was inserted per the manufacturer's instructions for use. Clinical study staff trained participants on inserting and using the study CGM device. CGM data collection was ongoing over the next 2–4 weeks for the purpose of basal and mealtime insulin optimization. The clinical staff reviewed the dose of basal insulin and made necessary adjustments based on the CGM values at least once a week. The investigator used clinical judgment to adjust the basal insulin dose, insulin-to-carbohydrate ratio, and correction factor to ensure participant safety prior to continuing the study. These values once set were not changed during travel.

Travel

Participants were recruited in Santa Barbara, CA, and traveled to Honolulu, HI, where they spent 2 days adjusting to that time zone. After this, they flew to New York, NY, where they spent 72 h before returning to Honolulu, HI, to spend 72 h there and then returned to Santa Barbara, CA. The return to Santa Barbara was followed by a 2-week period where the participants returned to their original insulin regimen. After 2 weeks, the alternative basal insulin was started (glargine U100 to insulin degludec or insulin degludec to glargine U100), and the optimization protocol outlined above was repeated. Participants traveled in the same direction of travel as for the first trip but on the new basal insulin. All participants and study staff traveled in the economy or coach section of the plane for all flights, and all flights were nonstop. Most traveling was done in the winter and spring, and one group traveled in the fall. No group traveled in the summer, and we avoided any changes in time due to daylight savings time.

During travel, glargine U100, insulin degludec, and rapid-acting insulin were maintained in cool storage (36°–46°F [2°–8°C]) until first use using a proprietary travel storage pack (e.g., Frio Cooling Pack). During each flight, blood glucose meters and strips and CGM devices were taken in hand luggage. All doses of basil and rapid-acting insulin and time of insulin injections were recorded.

For each flight, the relevant basal insulin was adjusted as described below, and interstitial blood glucose was measured with blinded CGM (Freestyle Libre Pro, Abbott Diabetes Care). The Liverpool Jet-Lag Questionnaire (15) was administered after 24 and 48 h at the destination. Sleep was monitored during each flight and for 24 h at the destination with an ActiGraph wGT3X-BT activity monitor (ActiGraph, Pensacola, FL) worn on the nondominant wrist. The following variables were analyzed:

- Total sleep time—The total number of minutes scored as "asleep."
- Sleep efficiency (%)—Number of sleep minutes divided by the total number of minutes the subject was in bed.
- Wake after sleep onset—The total number of minutes the subject was awake after sleep onset occurred.
- Sleep Fragmentation Index—Sleep Fragmentation is an index of restlessness during the sleep period expressed as a percentage. The higher the index, the more sleep is disrupted.
- Number of awakenings and the average length (min) of the awakening.

Safety During Travel

As both insulin degludec and glargine U100 are approved for use for type 1 diabetes in the U.S., no additional safety requirements are required beyond usual clinical care. All participants were provided with oral glucose for the prevention of hypoglycemia. In addition, participants had with them at all times an experienced member of the research team who was in contact with Sansum Diabetes Research Institute (SDRI) physicians for any advice or problems that might arise.

Insulin Degludec and Glargine U100 Basal Insulin Adjustments for Travel

As shown in clinical trials for adults with type 1 and type 2 diabetes, insulin degludec allows for flexibility in the timing of dose administration, provided a minimum of 8 h and a maximum of 40 h between injections is ensured (16,17). For this reason, when participants were using insulin degludec, they could administer their basal insulin at the same time, regardless of time zone and without adjustments or calculations. With glargine U100 as the basal insulin, participants adjusted their basal insulin based on discussion with their specialist diabetes team using the basal insulin adjustment algorithm for long-haul travel (18) shown in Supplementary Figs. 1 and 2, and they took this dose once per day. The basal insulin adjustment algorithm for glargine U100 is based on expert opinion and on knowledge of insulin pharmacokinetics and extensive clinical experience. The algorithm also assumes linear absorption, which may not be the case.

Statistical Methods

The study had an open-label, randomized crossover design. Randomization was for basal insulin alone. This is a pilot study, as no previous studies have been performed comparing basal insulins during long-haul travel. The aim was to compare the impact of long-haul travel on glycemic control assessed by CGM-derived data for percentage of time in range (TIR) 70–140 mg/dL as the primary end point, and TIR 70–180 mg/dL as a secondary end point, with the assessment during the initial 24 h after arriving at NYC and HNL (starting within 2 h after arrival) comparing glargine U100 versus insulin degludec as the basal insulin. Comparisons were made for:

- 24 and 72 h after each flight at each destination

- During each flight (total time, from take-off to meal and from meal to landing)
- During sleep at each destination

Clinical targets for continuous glucose monitoring have been published, including an international consensus on time in range, and these metrics were also included in our secondary end points (19). Below are the methods used here for the TIR calculation:

- TIR was defined as percentage of time glucose values were between 70 and 140 mg/dL and the percentage of time glucose values were between 70 and 180 mg/dL. Hypoglycemia was defined as excursions of at least 15 min with glucose values <70 mg/dL (i.e., for 15-min data at least two observations of the sensor data outside the boundary 70–140 mg/dL). Hyperglycemia was defined as excursions of at least 15 min with glucose values >140 mg/dL (i.e., for 15-min data at least two observations of the sensor data outside the boundary 70–140 mg/dL).
- The duration of a hypo- or hyperglycemic excursion was defined as the time elapsed from the first excursion to the first reading outside of the excursion.
- The duration of TIR was defined as all the remaining time not allocated to hypo- or hyperglycemia except where data "gaps" occurred: *1*) if only one glucose reading was below or above the TIR boundary of either 70-140 mg/dL or 70-180 mg/dL, then the duration was not affected and the participant was still considered to be in range; *2*) when there were more than one glucose reading missing, then the last glucose reading could be held as long as 3,600 s. If there were >3,600 s between consecutive glucose readings, then the time elapsed between the consecutive glucose readings was not counted toward duration of TIR.
- Percentage of total time spent in each range was calculated as:

$$\frac{\text{Total time}_{\text{time in range/hypoglycemia/hyperglycemia}}}{\text{Total time}} \times 100$$

where total time = TIR + total time in hypoglycemia + total time in hyperglycemia. Total time does not include gaps.

- Comparisons were made using Student paired *t* tests (two-sided) for normative and log-transformed data and Wilcoxon signed rank testing for nonparametric data. Data were expressed wherever possible as mean difference with 95% confidence limits for the difference or as mean ± SD for the difference. Nonparametric data are presented as median differences with interquartile ranges. Furthermore, to gain as much information as possible from this pilot study, all hypotheses were tested at 0.05, and no adjustments for multiplicity were made. Statistical analyses were performed with SAS 9.4 software and with Microsoft Office Excel 2013.

RESULTS

In this pilot study, 25 participants provided informed consent, and 21 completed the study. Two participants withdrew consent after completing part of the travel, one due to the stress of jet lag and long-haul travel and the other due to work conflicts. One participant had diabetic ketoacidosis during the washout period and was no longer eligible for study participation, and the fourth participant withdrew consent prior to travel due to unforeseen conflicts with travel dates. All participants who completed at least one arm of the study were included in the data analysis.

Overall, participants were an average age of 35 ± 14.5 (mean ± SD) years, had HbA_{1c} of 7.4 ± 1.2% (57 ± 13.1 mmol/mol), and diabetes duration of 20.6 ± 15 years. Fourteen identified as female, and the majority (*n* = 23) were White. Three identified as Hispanic/Latino, one as American Indian or Alaska Native, and one as Asian. Prior to enrollment, 40% of participants were taking a formulation of glargine U100 at baseline; 32% were taking insulin degludec, and the rest were on insulin detemir or glargine U300. During travel, the average dose of basal insulin was similar comparing both insulins (21.7 ± 11.3 units on insulin degludec and 23.2 ± 10.8 units on glargine U100, *P* = NS). The regimen advised for insulin degludec used a simplified dosing regimen (see above). For glargine U100, the suggested regimen was based on the travel algorithm from Pinsker et al (20). People with type 1 diabetes on oral antidiabetic agents or inhaled insulin were excluded from the study. Bolus doses of rapid-acting insulin and correction factors were determined before travel started and did not change during travel.

Overall, participants had generally healthy behaviors, attitudes, and beliefs about hypoglycemia, with a Gold (10) score of 2.0 ± 1.2, a score of 36.6 ± 18.1 on the Fear of Hypoglycemia scale (11), and scored between "moderate" and "very confident" at managing hypoglycemia on the Behavioral Health Institute's Hypoglycemic Confidence Scale (12).

Table 1 shows the primary end point, defined as percentage TIR of 70–140 mg/dL during the initial 24 h local time (starting within 2 h after arriving) in New York after flying 9–10 h eastward (from Honolulu, HI), and after the return journey from New York to Honolulu (flying westward). The secondary end points are percentage TIR 70–180 mg/dL, percentage time <70 mg/dL, percentage time >180 mg/dL, glycemic variability by coefficient of variation (CV, %), and mean glucose (mg/dL). Table 2 shows CGM outcomes during flight. Overall, neither group achieved the default recommended time in target of >70% TIR 70–180 mg/dL while flying. Table 3 gives the TIR metrics after each long-haul flight and during 72 h at each destination.

The CGM value at 6 A.M. (± 10 min) on the day after arrival at each destination was used as a surrogate for fasting glucose. The mean 6 A.M. glucose in the insulin degludec arm was 143 ± 80 mg/dL after eastward travel and 137 ± 60 mg/dL after westward travel. In the glargine U100 arm, the mean 6 A.M. glucose value was 137 ± 60 mg/dL after eastward travel and 140 ± 79 mg/dL after westward travel. There were no statistically significant differences between fasting glucose levels.

Jet Lag and Fatigue

Participants completed the Liverpool Jet-Lag questionnaire (15) at specified time points per the questionnaire instructions. Jet lag was rated on a 0–10 scale (insignificant jet lag to very bad jet lag), and fatigue was rated on a scale of −5 to +5 (more fatigue to less fatigue).

Table 1—Primary and secondary end points—TIR during the initial 24 h

	Initial 24 h after eastward long-haul travel			Initial 24 h after westward long-haul travel		
Glycemic targets for CGM	Degludec (n = 21)	Glargine (n = 20)	P	Degludec (n = 20)	Glargine (n = 20)	P
TIR 70–140 mg/dL (%)	36.3 ± 22.2	45.6 ± 21.1	NS	37.2 ± 22.2	43.9 ± 20.0	NS
TIR 70–180 mg/dL (%)	55.0 ± 21.7	62.3 ± 19.3	NS	54.5 ± 24.7	61.2 ± 24.7	NS
Time below range <70 mg/dL (%)	8.4 ± 8.5	11.1 ± 12.3	NS	9.2 ± 8.8	7.9 ± 9.4	NS
Time above range >180 mg/dL (%)	36.6 ± 25.2	26.7 ± 17.7	NS	31.9 ± 23.8	30.8 ± 25.2	NS
Glycemic variability (CV, %)	36.4 ± 9.4	41.4 ± 14.7	NS	36.3 ± 13.6	38.8 ± 10.4	NS
Glucose (mg/dL)	160.8 ± 47.8	145.5 ± 36.0	NS	151.4 ± 43.7	154.8 ± 41.3	NS

Data are mean ± SD.

Eastward

After 24 h at the destination, jet lag in NYC was significantly different (2.5 ± 2.6 on insulin degludec vs. 4.1 ± 2.8 on glargine U100, P = 0.002). In contrast, scores for fatigue were similar. After 48 h at the destination, jet lag was still significantly different comparing insulin degludec with glargine U100 (1.6 ± 2.7 on insulin degludec vs. 3.8 ± 3.4 on glargine U100, P = 0.003). Fatigue was not different comparing insulins.

Westward

Comparing basal insulins, there were no significant differences for jet lag or fatigue on the postwestward travel period after 24 h at the destination. After 48 h at the destination, jet lag was not significantly different, whereas participants reported more fatigue using glargine U100 compared with insulin degludec, (−0.7 ± 2.4 vs. 3.5 ± 2.9, respectively; $P \leq 0.001$).

Comparing direction of travel (eastward vs. westward), there was no difference for jet lag at 24 h or 48 h. Fatigue was significantly greater for westward travel at 24 h (0.2 ± 2.2 vs. −1.5 ± 2.1, $P \leq 0.001$) but not after 48 h.

Sleep

No difference between basal insulins was found for any objective sleep variable in NYC or in HNL (Supplementary Table 1). Total sleep time and sleep efficiency were significantly different between NYC and HNL, with longer sleep (median [IQR] 489 [390, 572] vs. 398 [337, 422] minutes, $P < 0.001$) and more efficient sleep (92% [90, 95] vs. 89% [86, 94], $P < 0.05$) after west to east travel.

CONCLUSIONS

For people with type 1 diabetes planning travel, recommendations for diabetes management during air travel are based mostly on expert opinion with limited consensus on insulin adjustment protocols (21). As use of CGM systems for type 1 diabetes expands, a number of metrics have been suggested for interpreting the glucose profiles provided by CGM systems. These include TIR between 70 and 180 mg/dL with the target of at least 70% of the time each day within this range (19). However, there are no data to determine whether these remain realistic in certain situations such as long-distance travel. In this study of adults with type 1 diabetes using MDIs of insulin and flying across multiple time zones, achieving this metric proved to be elusive. Furthermore, other established metrics, including average glucose, glucose variability, and time above or below this range, were also very difficult to achieve at all stages of the journey. In addition, we found no significant differences in these glycemic outcomes comparing insulin degludec with glargine U100 as the basal insulin for long-haul travel.

This pilot study provides further evidence that long-distance flying while taking multiple injections of insulin can be challenging. In this study, in addition to not meeting recommended guidelines for achieving a percentage of TIR between 70 and 140 or 70–180 mg/dL during a long-haul flight and at each destination, participants also spent up to a third of their travel with glucose levels >180 mg/dL and 8–10% of the time in hypoglycemia (<70 mg/dL). Jet-lag was significantly greater on glargine U100 compared with degludec after flying west to east after 24 h and after 48 h at the destination. Fatigue was greater

Table 2—In-flight glycemic control by direction of travel and basal insulin type

	In-flight glycemic control during eastward travel*			In-flight glycemic control during westward travel*		
Glycemic targets for CGM	Degludec (n = 20)	Glargine (n = 20)	P	Degludec (n = 21)	Glargine (n = 20)	P
TIR 70–140 mg/dL (%)	27.3 ± 22.2	41.1 ± 28.9	NS	40.7 ± 27.4	44.1 ± 27.0	NS
TIR 70–180 mg/dL (%)	50.5 ± 24.0	58.9 ± 30.8	NS	65.1 ± 23.6	64.0 ± 21.0	NS
Time below range <70 mg/dL (%)	9.9 ± 21.5	8.9 ± 13.5	NS	4.1 ± 7.3	9.9 ± 12.9	NS
Time above range >180 mg/dL (%)	39.5 ± 27.9	32.3 ± 31.5	NS	30.8 ± 25.4	26.0 ± 23.5	NS
Glycemic variability (CV, %)	30.6 ± 15.9	31.0 ± 14.0	NS	28.2 ± 8.4	33.7 ± 10.1	NS
Glucose (mg/dL)	166.3 ± 55.2	158.8 ± 58.9	NS	157.0 ± 37.5	146.1 ± 52.3	NS

Data are mean ± SD. *Flight time eastward was ∼9.5 h and westward was ∼11 h, calculated from gate to gate times.

Table 3—TIR during 72 h at each destination

	72 h after eastward long-haul travel			72 h after westward long-haul travel		
Glycemic targets for CGM	Degludec (n = 21)	Glargine (n = 20)	P	Degludec (n = 21)	Glargine (n = 21)	P
TIR 70–140 mg/dL (%)	40.1 ± 19.0	44.2 ± 18.9	NS	35.7 ± 19.0	40.8 ± 18.5	NS
TIR 70–180 mg/dL (%)	58.3 ± 18.8	62.0 ± 16.2	NS	56.7 ± 18.8	59.2 ± 23.0	NS
Time below range <70 mg/dL (%)	10.0 ± 9.6	10.5 ± 8.6	NS	8.4 ± 6.8	8.2 ± 6.9	NS
Time above range >180 mg/dL (%)	31.7 ± 21.3	27.6 ± 17.2	NS	34.9 ± 21.9	32.7 ± 23.1	NS
Glycemic variability (CV, %)	39.9 ± 9.3	41.0 ± 10.8	NS	38.6 ± 7.4	39.5 ± 9.3	NS
Glucose (mg/dL)	154.3 ± 43.8	147.6 ± 34.0	NS	160.4 ± 35.4	156.3 ± 34.6	NS

Data are mean ± SD.

after flying in the opposite direction with glargine U100.

With the introduction of insulin degludec as a basal insulin for type 1 diabetes and the opportunity to vary time of injection between 8 and 40 h, theoretically, insulin degludec as a basal insulin could make it easier for both people living with type 1 diabetes and clinicians to plan long-haul travel compared with the use of existing basal insulins when crossing multiple time zones as the latter requires complex adjustments to dose and timing based on the direction of travel. Although algorithms are available to help, this process can be time consuming for both the clinician and the person with diabetes.

Travelers, clinicians, and diabetes educators have few resources for evidence-based recommendations for insulin administration across multiple time zones. Available sources of information include publications targeting physicians and scientific researchers, online articles providing generalized tips (transportation and storage of supplies, suggested immunizations, diet regimens to follow, optimizing insulin dose modification across time zones) and free electronic dosage calculators (22–24). For the most part, these guidelines are overly complicated with medical jargon and complex tables describing insulin dosing adjustments. Previously, we reported the real-life experiences of individuals traveling long-haul with type 1 diabetes (20). In an on-line survey of 503 members of the T1D Exchange, 71% of participants had flown long-haul over the previous 5 years. When asked about their perceived "fear of flying," respondents using continuous subcutaneous infusions of insulin, with and without a CGM, reported their primary anxiety was "losing supplies," while those who did not use continuous subcutaneous infusions of insulin described concerns over "unstable blood glucose (highs and lows)." In addition, almost three-quarters of participants reported more hypoglycemia and/or hyperglycemia while traveling overseas, and 9% had avoided international travel altogether because of problems related to diabetes management. Furthermore, 37% reported inadequate attention in current sources of information to the unpredictability of self-management needs while traveling (20). It remains to be determined whether glycemic control can be improved and jet lag attenuated during long-haul travel using a hybrid or fully automated closed-loop system.

There have been no formal comparisons of different insulin delivery systems to support travel and type 1 diabetes. Similarly, comparisons between different glucose monitoring systems at altitude and across multiple time zones have also not been performed. In this study, we assumed that the CGM device performance would be similar in a pressurized aircraft cabin compared with a lower altitude; this is based on previous research with blood glucose meters using glucose oxidase- and glucose dehydrogenase-based systems (25). Here, participants were given free range to adjust the dose of mealtime rapid-acting insulin given by injection. Changes in pressure experienced during a flight have been reported to impact insulin delivery during takeoff and landing (26). With the introduction of smart insulin pens providing data on the dose and timing of an insulin injection, it is unclear whether this technology can also be used to reduce the burden of travel for individuals with type 1 diabetes.

Jet lag and fatigue during travel across multiple time zones are thought to arise due to a disruption between the local time and the body's endogenous time clock. Determinants of the degree of jet lag and fatigue during travel may depend on several factors, such as sex, age, and chronotype (morning vs. evening types) (15). For our travelers, jet lag was worse after eastward travel using glargine U100, which may have been due to the time intensiveness and concentration needed for calculations and timing of insulin injections. The difficulty of using the insulins was not measured and would have contributed to a better understanding of jet lag and fatigue. Overall, fatigue was much worse traveling east to west regardless of insulin.

There are a number of limitations to be considered. As this was a pilot study with a small sample size, the likelihood of a type II statistical error increases when comparing basal insulins. We also did not measure changes in circadian rhythms, including the effect of time zone changes on food preferences and physical activity levels, which could influence CGM profiles. In addition, subjects did spend limited time in HI. It is possible that as more time at that destination would have been needed to reset circadian rhythms, jet lag and other travel effects with eastward travel reported here may have been smaller than expected. Fear of hypoglycemia was only measured at baseline, and whether travel and in-flight experience could impact this is unclear. Also unclear is whether the negative effects of travel on CGM profiles were a consequence of the flight time, direction, and duration of travel independent from the number of time zones crossed. Another limitation is the stopping of the study due to the coronavirus disease 2019

pandemic, and we could not replace participants who did not complete all travel.

Nevertheless, traveling with insulin has been a neglected topic among the research community but is an important real-world consideration for people with diabetes and their families. There is clearly a need to investigate further the potential for developing evidence-based recommendations using existing glucose monitoring systems and insulin delivery devices and to examine the potential for added value with the introduction of new technologies and therapies. Even more importantly, there is a need to better understand the personal burdens associated with travel and insulin and to develop novel approaches to reduce these burdens.

Acknowledgments. The authors thank the participants for their dedication and time and Novo Nordisk for their generous support.

Duality of Interest. This research was funded by an Investigator Initiated Study award from Novo Nordisk (ISS-001227). D.K. reports nonfinancial support from Abbott Diabetes Care, grants from Eli Lilly and Novo Nordisk, and personal fees from Novo Nordisk and Sanofi unrelated to this study. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. W.C.B. and K.N.C. cowrote the manuscript and co-led data collection and analysis. C.A. performed the initial data analysis. G.H., C.C.F., N.S., K.N., and L.A.S. coordinated study and data collection. H.L. provided analytic expertise and data analysis. D.K. was responsible for conceptualization, funding acquisition, and writing of the original draft manuscript. All authors contributed to the writing, review, and editing of the manuscript. D.K. is the guarantor of this work and, as such, had full access to all of 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 study were presented in abstract form at the 80th Scientific Sessions of the American Diabetes Association, 12–16 June 2020.

References

1. 2019 Traffic Data for U.S. Airlines and Foreign Airlines U.S. Flights - Final, Full-Year, 11 June 2020. Accessed 25 September 2020. Available from https://www.bts.gov/newsroom/2019-traffic-data-us-airlines-and-foreign-airlines-us-flights-final-full-year
2. Cefalu WT, Dawes DE, Gavlak G, et al.; Insulin Access and Affordability Working Group. Insulin Access and Affordability Working Group: conclusions and recommendations. Diabetes Care 2018;41:1299–1311
3. Mao C-K, Ding CG, Lee H-Y. Post-SARS tourist arrival recovery patterns: an analysis based on a catastrophe theory. Tour Manage 2010;31:855–861
4. 35 Top Tips for Travel With Diabetes, 2017. Accessed 25 September 2020 Available from https://transcendfoods.com/blog/35-top-tips-for-travel-with-diabetes
5. Driessen SO, Cobelens FG, Ligthelm RJ. Travel-related morbidity in travelers with insulin-dependent diabetes mellitus. J Travel Med 1999;6:12–15
6. Burnett JC. Long- and short-haul travel by air: issues for people with diabetes on insulin. J Travel Med 2006;13:255–260
7. Bode BW, Buse JB, Fisher M, et al.; BEGIN® Basal-Bolus Type 1 trial investigators. Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal-bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN (®) Basal-Bolus Type 1): 2-year results of a randomized clinical trial. Diabet Med 2013;30:1293–1297
8. Ratner RE, Gough SC, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. Diabetes Obes Metab 2013;15:175–184
9. Pinsker JE, Lee JB, Dassau E, et al. Randomized crossover comparison of personalized MPC and PID control algorithms for the artificial pancreas. Diabetes Care 2016;39:1135–1142
10. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care 1994;17:697–703
11. Gonder-Frederick LA, Schmidt KM, Vajda KA, et al. Psychometric properties of the Hypoglycemia Fear Survey-II for adults with type 1 diabetes. Diabetes Care 2011;34:801–806
12. Polonsky WH, Fisher L, Hessler D, Edelman SV. Investigating hypoglycemic confidence in type 1 and type 2 diabetes. Diabetes Technol Ther 2017;19:131–136
13. Tresiba [package insert]. Plainsboro, NJ, Novo Nordisk Inc., 2019
14. Lantus (insulin glargine injection) for subcutaneous injection [package insert]. Bridgewater, NJ, A Sanofi Company, 2020
15. Waterhouse J, Edwards B, Nevill A, et al. Identifying some determinants of "jet lag" and its symptoms: a study of athletes and other travellers. Br J Sports Med 2002;36:54–60
16. Mathieu C, Hollander P, Miranda-Palma B, et al.; NN1250-3770 (BEGIN: Flex T1) Trial Investigators. Efficacy and safety of insulin degludec in a flexible dosing regimen vs. insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. J Clin Endocrinol Metab 2013;98:1154–1162
17. Zhou W, Tao J, Zhou X, Chen H. Insulin degludec, a novel ultra-long-acting basal insulin versus insulin glargine for the management of type 2 diabetes: a systematic review and meta-analysis. Diabetes Ther 2019;10:835–852
18. Pinsker JE, Becker E, Mahnke CB, Ching M, Larson NS, Roy D. Extensive clinical experience: a simple guide to basal insulin adjustments for long-distance travel. J Diabetes Metab Disord 2013;12:59
19. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. Diabetes Care 2019;42:1593–1603
20. Pinsker JE, Schoenberg BE, Garey C, Runion A, Larez A, Kerr D. Perspectives on long-distance air travel with type 1 diabetes. Diabetes Technol Ther 2017;19:744–748
21. Pavela J, Suresh R, Blue RS, Mathers CH, Belalcazar LM. Management of diabetes during air travel: a systematic literature review of current recommendations and their supporting evidence. Endocr Pract 2018;24:205–219
22. Boerner H. Tips to trip by. The art and science of traveling with diabetes. Diabetes Forecast 2008;61:42–45
23. Nassar AA, Cook CB, Edelman SV. Diabetes management during travel. Diabetes Management 2012;2:205–212
24. Chandran M, Edelman SV. Have insulin, will fly: diabetes management during air travel and time zone adjustment strategies. Clin Diabetes 2003;21:82–85
25. Olateju T, Begley J, Flanagan D, Kerr D. Effects of simulated altitude on blood glucose meter performance: implications for in-flight blood glucose monitoring. J Diabetes Sci Technol 2012;6:867–874
26. Brubaker PL. Adventure travel and type 1 diabetes: the complicating effects of high altitude. Diabetes Care 2005;28:2563–2572