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ORIGINAL ARTICLE

Temporary Reductions in Insulin Requirements Are Associated with Hypoglycemia in Type 2 Diabetes

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Abstract

Background: In patients with type 2 diabetes, insulin therapy necessitates regular and frequent dosage titration to overcome variations in insulin requirements. The goal of this study was to evaluate changes in insulin requirements, using data from a technology-based insulin-titration service.
Methods: To keep glycemia stable, the service adjusts and records insulin dosage at least weekly. Therefore, insulin dosage closely tracks insulin requirement. Events of considerable and persistent decrease in insulin requirements were identified by reductions in total daily dose (TDD) of insulin ≥25%. Periods ended when a persistent increase in TDD of insulin has started. The average frequency of hypoglycemia was expressed as any glucose reading <54 mg/dL (both inside or outside periods of decrease in insulin dosage) divided by the total number of months for each patient.
Results: Patients ($n = 246$) were followed for 2.8 ± 0.9 years. Reductions of TDD of insulin were experienced by 70.3% of the patients, occurred 0.8 ± 0.5 times per year, lasted 10.0 ± 7.7 weeks, and insulin requirements declined by $39.9\% \pm 12.6\%$. The frequency of hypoglycemia (<54 mg/dL) was low, at 0.5 ± 0.6 per month, and the difference in frequencies in biphasic/premixed and basal-bolus insulin regimens was not statistically significant. Hypoglycemia was 6.5 times more prevalent during reductions in TDD of insulin.
Conclusions: Sizeable changes in insulin requirements occur over time, which demand persistent and frequent titration to preserve treatment safety.

Keywords: Dosage, Hypoglycemia, Insulin, Titration.

Introduction

Insulin is mainly prescribed for patients with advanced type 2 diabetes. There is a growing recognition that effective insulin therapy requires regular and frequent titration of dosage to overcome intraindividual and interindividual variations in requirements.[1–3] Dosage titration is referred to as modification of insulin prescription or provider instructions (modification of biphasic insulin regimen by increasing the breakfast dose component and reducing the evening dose component; increase in long acting insulin dosage; reduction of rapid acting insulin dosage for a meal; intensification of insulin to glucose ratio, etc.). Calculation of bolus based on the provider instructions (i.e., bolus calculation) was not considered titration.[4] Owing to deficient availability in medical expertise, technology solutions are needed to facilitate frequent insulin titrations to maintain glycemic goals while avoiding excessive hypoglycemia. Understanding variations in insulin requirements is paramount, since most patients who use insulin are not able to maintain the recommended treatment objectives.[5]

The d-Nav® Insulin Guidance Service was designed to overcome this limitation of insulin therapy. This service provides patients with automated insulin dosage adjustments under the supervision of dedicated providers. Changes in dosage occur at least weekly and are tracked over time.[6–9] Therefore, changes to insulin dosage closely track the patient's insulin requirement, which offers a unique opportunity

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to investigate the physiology/pathophysiology of insulin requirements over time.

The overall goal of our inquiry is to understand how insulin requirements change over time and to determine whether these changes have implications for patient safety. The scope of this article is limited to periods of dosage reductions, because these periods may cause hypoglycemia if not appropriately titrated. We used the data to achieve three objectives: (1) examine the proportion of patients who experienced clinically significant dosage reduction among three different treatment regimens, (2) determine the frequency of hypoglycemia among patients with three treatment regimens, and (3) identify variables that are associated with reduction in insulin dosage requirements.

Methods

The d-Nav Insulin Guidance Service

The particulars of the service have been described elsewhere.[6,10] In brief, patients referred to the service are provided with a handheld device called d-Nav (stands for diabetes navigator). Patients use d-Nav to measure glucose before each insulin injection. In turn, d-Nav provides a recommended insulin dose. The device assesses the patient's response to its current insulin dosage by analyzing glucose patterns, then automatically adjusts the user's insulin dosage. Adjustments are typically made weekly. Yet, if insulin requirements drop or hypoglycemia ensues, d-Nav makes immediate adjustments as often as needed, following the safety-first approach. d-Nav adjusts most types of insulin regimens: (A) once a day basal insulin (requires once daily glucose reading), (B) twice daily biphasic/premixed long- and short-acting insulin (requires two daily glucose reading), and (C) intensive insulin therapy involving long-acting and fast-acting insulin with or without carbohydrate counting (requires four daily glucose reading).

The d-Nav care specialists periodically follow up with users through telephone calls and in-person consultations to bestow user confidence, correct usage errors, triage, and identify uncharacteristic clinical courses. Additional software tools are available to provide further insight regarding insulin dynamics.[8] The care specialists are not involved in the process of insulin dosage titration, which is handled by d-Nav. The service is linked to a wider health care system such that a patient's data are always available to be reviewed by the patient's physicians, who handle all other diabetes and nondiabetes related drugs.

Subjects

Data were obtained from the South Eastern Health and Social Care Trust, Ulster Hospital, Belfast, United Kingdom.[6,8] The data were acquired retrospectively and were limited to secondary use of nonidentifiable information previously collected in the course of normal care. The investigation was approved by the Health and Social Care Trust Research & Development Governance Office. Data from this cohort were described in prior publications.[9] The hospital referred adults using insulin with HbA1c >53 mol/mol (HbA1c >7.0%) to the d-Nav Insulin Guidance Service. Exclusion criteria included >2 episodes of severe hypoglycemia in the past year, hypoglycemia unawareness, using <25 U of insulin daily, or a patient HbA1c goal was other than 48–58 mmol/mol (6.5%–7.5%). For the current analysis, data were limited to patients who have used the service >19.5 months, have not had a gap in insulin dosage information >3 months, and have not changed insulin regimens during that period.

Analysis of dynamics in insulin requirements

To quantify reductions in insulin requirements per our first objective, we used a method specified by our previous study.[9] In brief, total daily dose (TDD) of insulin was calculated by adding each dosage component in the current regimen. A period of reduction in insulin requirements was evaluated for two parameters: length and magnitude. The length of a decrease was defined as the total time between the initial decrease until a valid minimum had been reached. The magnitude of the TDD decrease was defined by the ratio of the minimum TDD point to TDD at the beginning of the interval. Therefore, we had to define the starting point, and the ending point of an interval over which a minimum will be searched.

The starting point was defined as a point in time where a reduction in TDD had occurred and where in the following 4 weeks TDD had not increased to exceed the TDD at baseline (the last TDD before the reduction). This definition was used to assess the consistency of a decrease, whereby consistency meant that the reduction was not random as during at least 4 weeks, TDD was lower than at the beginning of the period. The end point of an interval was defined as the earliest of the following two to occur:

a. a point where TDD was greater than baseline TDD or
b. a point where TDD was higher than TDD 13 weeks earlier, and that was at least 13 weeks after the starting point.[11]

The first point (a) is useful to define a period where after an initial drop, TDD climbed to exceed the starting point. The second point (b) is useful to define a period where TDD is still lower than baseline, for at least 3 months TDD had stopped falling and started increasing. Once an ending point was defined, the interval was searched to find the lowest point of TDD. We then used the lowest point to define length and magnitude of the interval as described previously.

Changes in insulin requirements lie in a continuum, yet a cutoff is needed to enable the analysis. To ensure that the cutoff is clinically meaningful beyond the standard of care and the analysis will not overestimate the changes in insulin requirements, we chose an a priori cutoff of 25% in TDD reduction.[9] The 25% threshold was used since it is 5% higher than published clinical standards for a single titration.[12,13]

Since closed loop insulin delivery systems were not implemented, we could not evaluate dynamics in insulin requirements during the day.[14]

For our second objective (i.e., determine the frequency of hypoglycemia), frequency of hypoglycemia was expressed as the total number of any reading <54 mg/dL or <3 mmol/L (both inside or outside periods of decrease in insulin dosage) divided by the total number of months for each patient.

Exploratory statistical analysis

Results are presented as mean ± standard deviation (SD). A P-value <0.05 was defined as statistically significant.

Table 1. Baseline Demographics and Clinical Characteristics ($N=246$)

	Total	*Basal insulin only*	*Biphasic insulin*	*Basal-bolus insulin*
Gender				
Male (%)	62.6	72.1	66.7	57.3
Age (years; mean ± SD)[a]	62.2 ± 8.7	61.4 ± 8.2	66.8 ± 7.7	61.3 ± 8.9
Race (%)				
Caucasian	97.2	96.7	100	96.5
Afro-Caribbean	0.4	0	0	0.7
Asian	2.0	3.3	0	2.1
Other	0.4	0	0	0.7
Duration of diabetes (years; mean ± SD)[a]	15.3 ± 6.7	13.7 ± 5.5	14.1 ± 6.3	16.4 ± 7.1
Duration on insulin (years; mean ± SD)[a]	8.4 ± 6.3	5.4 ± 5.1	7.6 ± 5.4	10.0 ± 6.5
Duration on the d-Nav® Insulin Guidance Service (years; mean ± SD)[a]	2.8 ± 0.9	2.5 ± 0.8	2.6 ± 0.7	2.9 ± 1.0
Baseline HbA1c	9.4% ± 1.6%; 79 mmol/mol	9.5% ± 1.6%; 80 mmol/mol	9.1% ± 1.3%; 76 mmol/mol	9.5% ± 1.6%; 80 mmol/mol
Latest HbA1c[a]	7.6% ± 0.9%; 60 mmol/mol	7.3% ± 0.9%; 56 mmol/mol	6.7% ± 0.8%; 50 mmol/mol	7.2% ± 1.0%; 55 mmol/mol

[a]$P < 0.05$ between groups.
SD, standard deviation.

Baseline demographics and clinical characteristics were compared with the Kruskal–Wallis test. Descriptive correlations between continuous variables were assessed with the Spearman correlation test.

To achieve our third objective (i.e., identify variables that are associated with reduction in insulin dosage requirements), we defined our outcome variable as a binary (yes/no) indication of a decrease in TDD of insulin. We categorized this variable a priori due to our concerns about the nonnormality of reductions in TDD of insulin. We developed a multivariable logistic regression model to identify clinical predictors for the occurrence of any reductions in insulin requirements (listed in Table 2). Owing to sparsity of hypoglycemic events in patients without dosage reductions and resulting instability of estimates, we rendered hypoglycemia to a categorical variable (i.e., average frequencies of hypoglycemia: >0 and ≤0.5 per month; >0.5 and ≤1.0; or >1.0). Owing to concerns about collinearity between predictors, we first examined univariate models. Then, we used stepwise variable selection with an $\alpha < 0.05$ to include and $\alpha \geq 0.05$ to exclude, to identify which variables were independent predictors of a decrease in TDD of insulin. We examined the difference in *P*-values between the multivariable and univariate models to evaluate redundancies between candidate predictor variables.

Analyses were performed in R3.4.4 (www.r-project.org). The software was developed in Bell Laboratories by John Chambers and colleagues and currently offered free of charge.

Results

Data for 246 patients treated by the d-Nav Insulin Guidance Service for >19.5 months were available. On average, patients were followed for 33.0 ± 10.7 months. Regimens were basal insulin only in 24.8% of the patients, biphasic/premixed in 17.1%, and basal bolus in 58.1%. Table 1 shows baseline demographics and characteristics with minor differences between groups. Insulin titrations occurred on average 1.1 ± 0.3 times per week. Stability in average HbA1c for the entire cohort after the ninth month is shown in Figure 1A. The average SDs of weekly average glucose beyond the ninth month (once average HbA1c stabilizes; see Fig. 1A) was 23.0 mg/dL with a confidence interval of 21.6–24.4 mg/dL (basal insulin only regimen 23.5 mg/dL 20.7–26.3; biphasic/premixed regimen 21.6 mg/dL 18.2–25.0; basal-bolus regimen 23.2 21.3–25.1), indicating limited glycemic variability. Clinically similar HbA1c was achieved in all regimens.

Average TDD of insulin increased from ~0.75 U/kg at baseline to ~1.5 U/kg at the 15th month as previously reported[15] from which point it plateaued (Fig. 1B). The coefficient of variation of TDD of insulin beyond the 15th month was ~75%.

Considerable and persistent declines in insulin requirements were identified in 70.3% of the patients (details for each regimen shown in Fig. 1C). Among patients who did have significant reductions, patients averaged 0.8 ± 0.5 events per year (details for each regimen shown in Fig. 1D), with the average decline lasting 10.2 ± 7.1 weeks (details for each regimen shown in Fig. 1E), and TDD of insulin decreasing by 40.09% ± 10.5% (details for each regimen shown in Fig. 1F). The frequency of reductions of insulin requirements per patient during the first year was similar to that during the second year (0.6 vs. 0.7 per year).

The average frequency of hypoglycemia (events <54 mg/dL or <3 mmol/L per month) was low, at 0.5 ± 0.6 per month (0.6 ± 0.7 for glucose <56 mg/dL).[16,17] We did not find a statistically significant difference in the frequency of hypoglycemia between biphasic/premixed and basal-bolus regimens (Fig. 1G). Also, we did not find a meaningful correlation

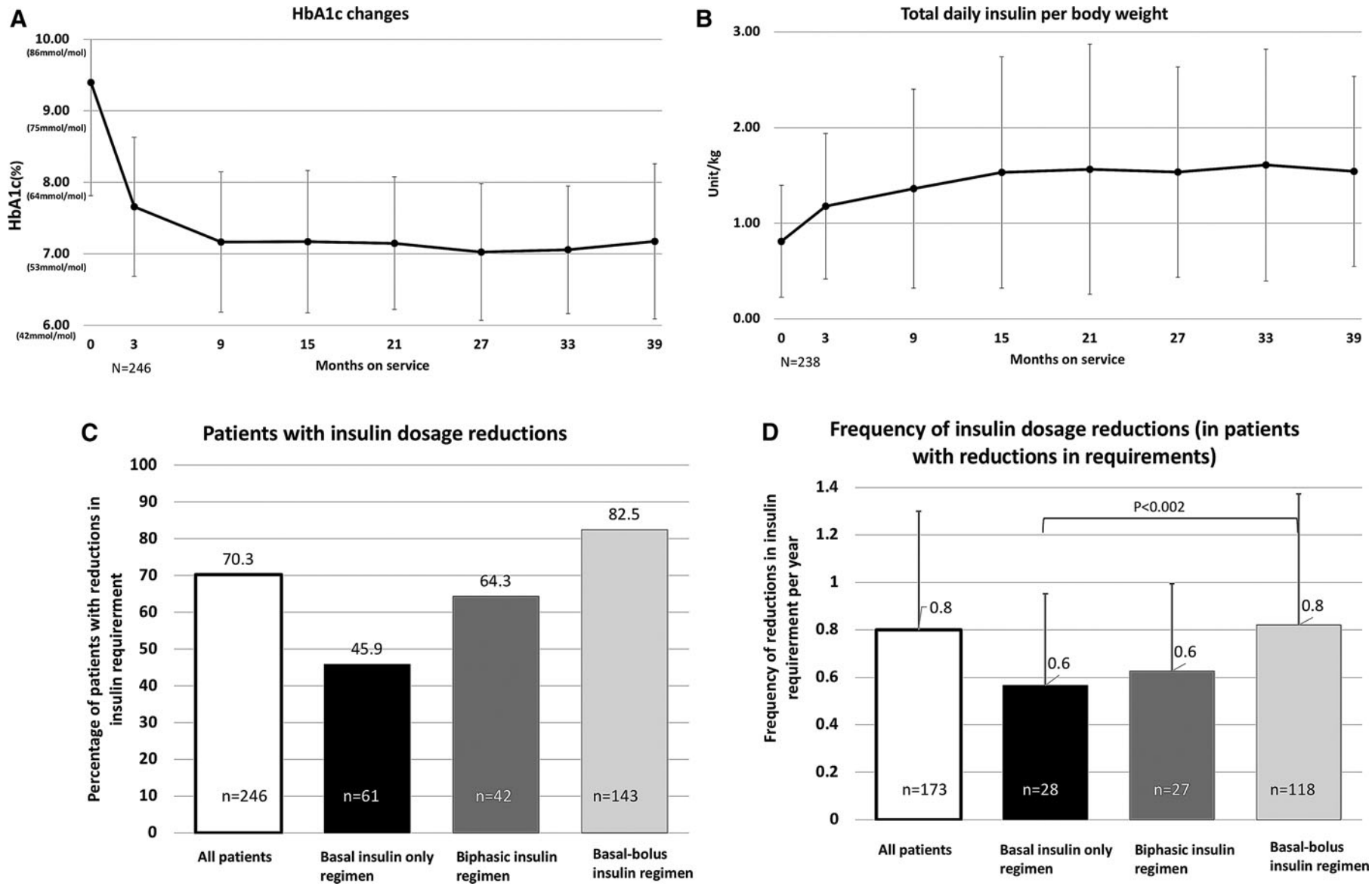
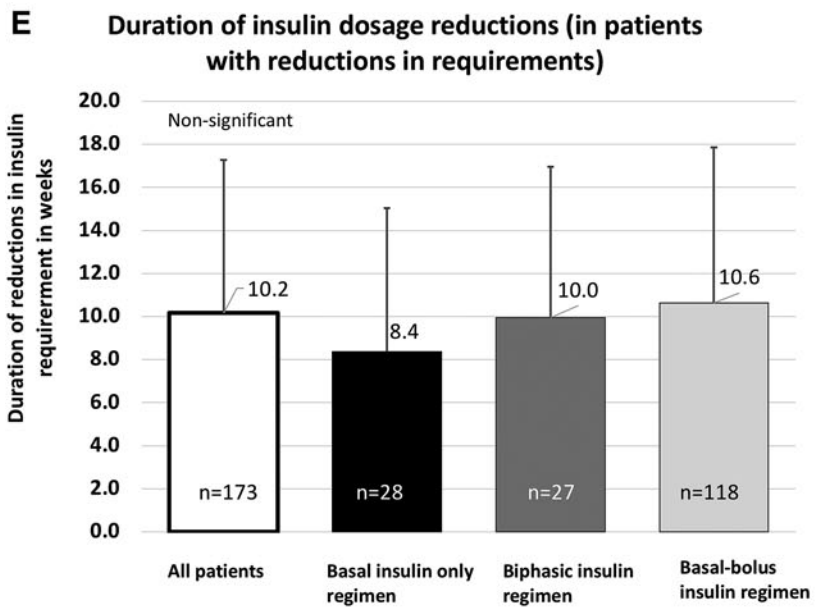
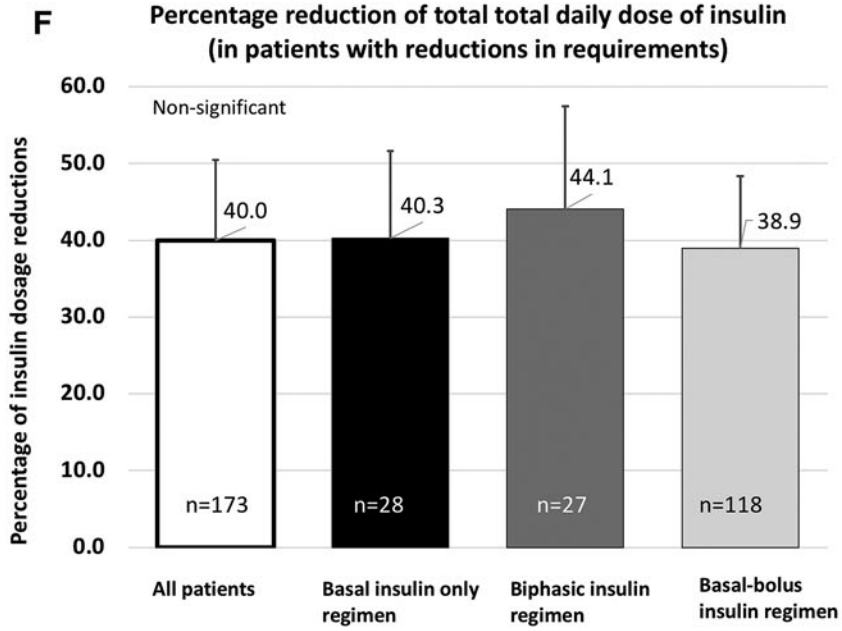
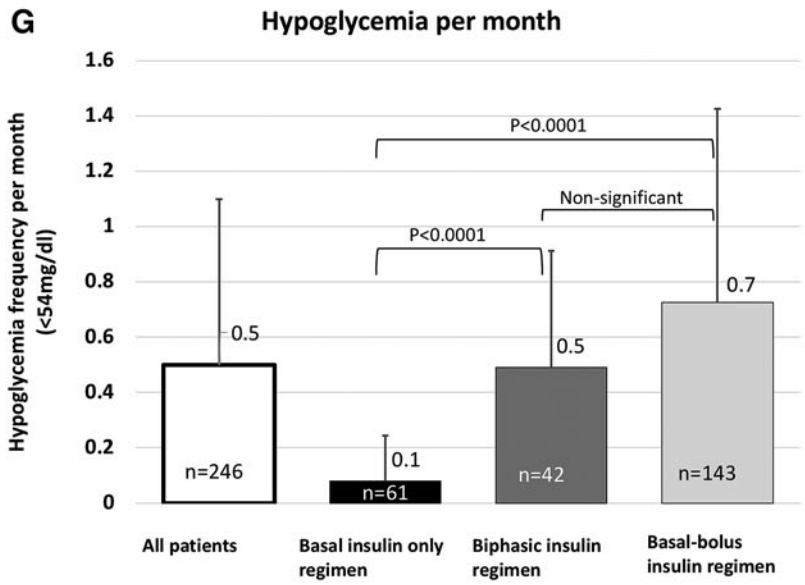


FIG. 1. **(A)** Average in HbA1c for patients in the observed cohort during the d-Nav® service. **(B)** Average TDD of insulin for patients in the observed cohort during the d-Nav service. **(C)** Percentage of patients experiencing reductions in TDD of insulin in different regimens. **(D)** Frequency of insulin dosage reductions in different regimens, in patients who had reductions in insulin requirements. **(E)** Duration of insulin dosage reductions in different regimens, in patients who had reductions in insulin requirements. **(F)** Percentage of TDD of insulin reduction, in patients who had reductions in insulin requirements. **(G)** Frequency of hypoglycemia (<54 mg/dL or <3 mmol/L) in different regimens. **(H)** Relationship between the frequency of reductions in TDD of insulin and updated TDD (normalized to body weight). TDD, total daily dose.







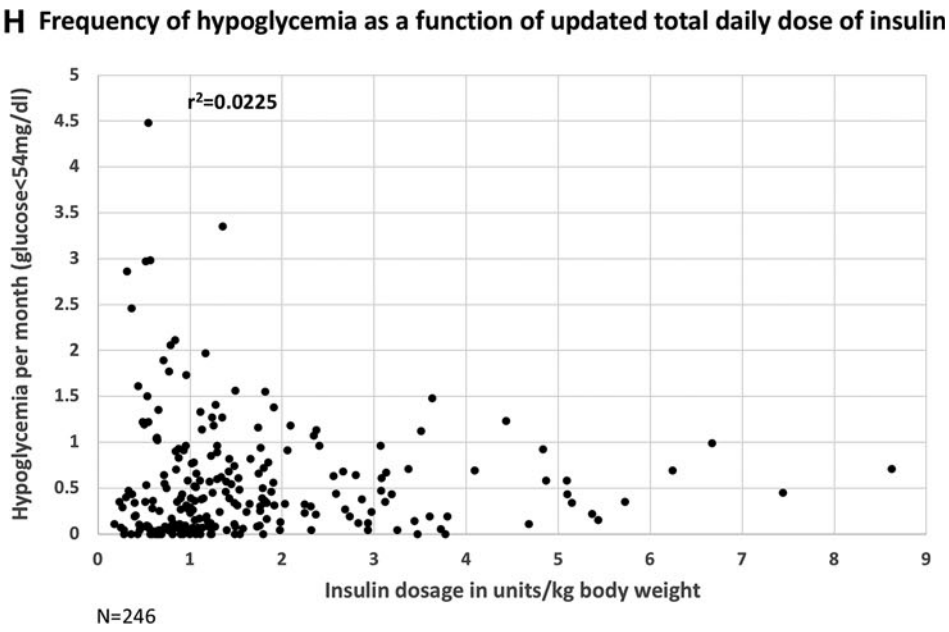


FIG. 1. (Continued)

between the frequency of hypoglycemia and updated TDD of insulin per kilogram body weight (Fig. 1H). Updated TDD of insulin denotes average of the same for the past 3 months. As expected, patients using basal insulin only experienced less hypoglycemia.[12,18] The average frequency of hypoglycemia during periods of reductions in TDD of insulin was 6.5 times as high as outside such periods ($P<0.0001$). On average, the frequency of hypoglycemia during periods of reductions in TDD of insulin was 2.4 ± 4.4 per month (basal insulin only regimen 0.5 ± 0.8; biphasic/premixed regimen 3.4 ± 4.7; basal-bolus regimen 2.7 ± 4.7), whereas outside these periods it was 0.5 ± 0.5 per month (basal insulin only regimen 0.1 ± 0.1; biphasic/premixed regimen 0.4 ± 0.3; basal-bolus regimen 0.6 ± 0.5). In total, 39.9% of hypoglycemic events occurred during the 10.5% of time when patients' insulin requirements were declining.

In univariate analysis, many covariates were statistically significant predictors of reductions in TDD of insulin ($\alpha < 0.05$). However, when all candidate predictors were included in the multivariable model, four covariates were found to be significant predictors (Table 2). The frequency of hypoglycemia was found to be a highly significant predictor ($P<0.005$). In fact, the frequency of reduction in insulin requirement was highly correlated with the frequency of hypoglycemia in a linear manner ($r^2=0.449$; $P<0.0001$). Updated TDD of insulin was inversely correlated with dose reduction ($P=0.01$). For each 1 U per kilogram of body weight increase in updated TDD of insulin, the odds of developing significant reductions in insulin requirement were ~30% lower. The time on the d-Nav Insulin Guidance Service was found to be a predictor for decrease in TDD of insulin ($P<0.005$). Basal only insulin regimen was associated with a lower chance of experiencing a reduction in TDD of insulin ($P=0.02$). Using biphasic/premixed versus basal-bolus insulin regimens was not found to be a predictor. Seasons of the year, gender, age, BMI, duration of diabetes and insulin therapy, kidney function, and HbA1c were not found to be predictors of reductions in insulin requirements.

Discussion

In the presented study, a technology-assisted titration service adjusted insulin dosage to accommodate changes in insulin requirements while keeping glycemia stable (i.e., HbA1c). As recommended by clinical guidelines,[13] d-Nav responds to hypoglycemia by reducing insulin dosage and stops reducing it once hypoglycemia subsides. Therefore, a hypoglycemia-driven d-Nav dosage decrease indicates a reduction in insulin requirements. This allows for the study of physiology and pathophysiology as they relate to insulin.

In most patients, insulin requirements decreased considerably on average every 1.3 years for a period of weeks. Events of reductions in TDD of insulin occurred in all

Table 2. Multivariable Logistic Regression Analysis for Any Dosage Reduction

	Univariate				*Multivariable*			
	Odds ratio	*95% confidence interval*		P	*Odds ratio*	*95% confidence interval*		P
Gender (male)	0.824	0.461	1.451	0.5	—	—	—	—
Age (per year)	1.001	0.970	1.033	0.9	—	—	—	—
Baseline BMI (per kg/m^2)	0.992	0.954	1.033	0.7	—	—	—	—
Duration of diabetes (per year)	1.086	1.037	1.143	0.0008	—	—	—	—
Duration of insulin therapy (per year)	1.133	1.066	1.213	0.0001	—	—	—	—
Duration on the d-Nav® Insulin Guidance Service (per month)	1.074	1.039	1.114	0.0001	1.069	1.030	1.114	0.0009
Hypoglycemia								
>0 and ≤0.5 per month	2.833	1.198	7.106	0.02	1.895	0.690	5.427	0.221
>0.5 and ≤1.0 per month	31.481	8.582	156.815	0.0001	19.882	4.111	126.445	0.0005
>1.0 per month	67.999	11.680	1310.091	0.0001	31.536	4.572	648.927	0.003
Regimen								
Long-acting vs. basal bolus	0.180	0.091	0.346	<0.0001	0.321	0.125	0.803	0.02
Biphasic vs. basal bolus	0.381	0.178	0.828	0.01	0.402	0.154	1.033	0.06
Baseline HbA1c (per unit %)	1.030	0.858	1.247	0.8	—	—	—	—
Latest HbA1c (per unit % or 11 mmol/mol)	1.157	0.867	1.573	0.3	—	—	—	—
Updated total daily dose of insulin per body weight (per U/kg)	0.924	0.759	1.136	0.4	0.693	0.520	0.909	0.01
Season								
Spring (vs. Fall)	0.962	0.420	2.293	0.9	—	—	—	—
Summer (vs. Fall)	1.480	0.712	3.178	0.3	—	—	—	—
Winter (vs. Fall)	1.018	0.508	2.064	1.0	—	—	—	—
Baseline creatinine (per μmol/L)	1.005	0.996	1.015	0.3	—	—	—	—

"—," these variables were excluded from the final model based on stepwise selection using $\alpha < 0.05$.

seasons, unrelated to demographics, duration of the disease, kidney function, use of biphasic/premixed insulin, or initial glycemia, as previously reported,[9] and were not preceded by any clinical indication.

Looking at potential covariates, the individual frequency of hypoglycemia was a major predictor of reductions in insulin requirements. The patients with more frequent hypoglycemia typically had more frequent reductions. Updated TDD of insulin (normalized to body weight) was found to be an independent predictor that was inversely associated with reduction in TDD of insulin. The patients who used more insulin were less likely to have reductions in insulin requirements. Our results are consistent with previous reports showing that higher frequency of hypoglycemia and lower TDD of insulin are markers for more labile disease.[18] As expected, given an earlier stage of disease and residual endogenous insulin secretion,[12,18] patients using basal insulin only regimen were less likely to have experienced significant reductions in insulin requirements, had lower frequency of dosage reductions, and were less likely to develop hypoglycemia. As anticipated, patients who used the d-Nav Insulin Guidance Service longer were more likely to exhibit reductions in insulin requirements than those who used the service for a shorter period of time.

During the first year, TDD of insulin (normalized to body weight) was lower than that during the second year, and average HbA1c during the first year was higher than that during the second year. Yet, the frequency of significant insulin dosage reductions was similar in the first 2 years.

The frequency of hypoglycemia (<54 mg/dL) was low, at 0.5 ± 0.6 per month, and the difference in frequencies in biphasic/premixed and basal-bolus insulin regimens was not statistically significant. Similarly to previous reports,[19] we did not find a meaningful correlation between updated TDD of insulin (normalized to body weight) and hypoglycemia.

As much as $\sim$40% of hypoglycemic events occurred during only $\sim$10% of the time when insulin requirements decreased. When automatic insulin titration is not available and rapid reduction of insulin dosage does not transpire, hypoglycemic burden is expected to be higher,[16] which can prevent achievement and maintenance of HbA1c goals.[5] Evidently, in real life when insulin titrations occur infrequently, the reported rate of hypoglycemia is approximately three times higher.[16,17] Of interest, insulin requirements have also shown to be dynamic in patients with type 1 diabetes.[14]

The study limitations include its observational design, limited ethnic diversity, lack of information on additional antidiabetes medications, and lack of a negative control group. However, these data present a unique opportunity to investigate dynamics in insulin requirements in a real-life setting, when insulin is constantly titrated to maintain and preserve the therapy goals.

In summary, we found considerable dynamics in insulin requirements among patients with type 2 diabetes over time. Lack of insulin titration to accommodate reductions in insulin requirements is potentially a major cause of hypoglycemia. As technology-augmented frequent insulin titration becomes more accessible, we believe that a variety of insulin regimens can be used to improve outcomes and enhance treatment safety.

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Author Disclosure Statement

E.B. is the chief executive officer for Hygieia, I.H. is a cofounder of Hygieia, S.G.B. and M.W. are employees of Hygieia, and D.J.M.I. is a paid consultant of Hygieia. R.H. has no financial interest in Hygieia.

References

1. Riddle MC, Yki-Jarvinen H, Bolli GB, et al.: One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. Diabetes Obes Metab 2015;17:835–842.
2. Davidson MB: How our current medical care system fails people with diabetes: lack of timely, appropriate clinical decisions. Diabetes Care 2009;32:370–372.
3. Bastyr EJ, 3rd, Zhang S, Mou J, et al.: Performance of an electronic diary system for intensive insulin management in global diabetes clinical trials. Diabetes Technol Ther 2015;17:571–579.
4. Hirsch IB, Bergenstal RM, Parkin CG, et al.: A real-world approach to insulin therapy in primary care practice. Clin Diabetes 2005;23:78–86.
5. Selvin E, Parrinello CM, Daya N, Bergenstal RM: Trends in insulin use and diabetes control in the U.S.: 1988–1994 and 1999–2012. Diabetes Care 2016;39:e33–e35.
6. Donnelly RC, Carr S, Harper R: Diabetes insulin guidance system: a real-world evaluation of new technology (d-Nav) to achieve glycaemic control in insulin-treated type 2 diabetes. Practical Diabetes 2015;32:247–252.
7. Bergenstal RM, Bashan E, McShane M, et al.: Can a tool that automates insulin titration be a key to diabetes management? Diabetes Technol Ther 2012;14:675–682.
8. Bashan E, Harper R, Bi Y, Hodish I: A novel approach to optimise glycaemic control in insulin users. BMJ Case Rep 2015;2015.
9. Harper R, Donnelly R, Bi Y, et al.: Dynamics in insulin requirements and treatment safety. J Diabetes Complications 2016;30:1333–1338.
10. Hodish I: Insulin therapy for type 2 diabetes—are we there yet? The d-Nav(R) story. Clin Diabetes Endocrinol 2018;4:8.
11. Ishii H, Suzuki H, Baba T, et al.: Seasonal variation of glycemic control in type 2 diabetic patients. Diabetes Care 2001;24:1503.
12. Holman RR, Thorne KI, Farmer AJ, et al.: Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med 2007;357:1716–1730.
13. American Diabetes Association: 8. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2018. Diabetes Care 2018;41:S73–S85.
14. Ruan Y, Thabit H, Leelarathna L, et al.: Variability of insulin requirements over 12 weeks of closed-loop insulin delivery in adults with type 1 diabetes. Diabetes Care 2016;39:830–832.
15. Bergenstal RM, Johnson M, Powers MA, et al. (2008) Adjust to target in type 2 diabetes: comparison of a simple

algorithm with carbohydrate counting for adjustment of mealtime insulin glulisine. Diabetes Care 31:1305–1310.
16. Khunti K, Alsifri S, Aronson R, et al.: Rates and predictors of hypoglycaemia in 27 585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study. Diabetes Obes Metab 2016;18:907–915.
17. Khunti K, Alsifri S, Aronson R, et al.: Impact of hypoglycaemia on patient-reported outcomes from a global, 24-country study of 27,585 people with type 1 and insulin-treated type 2 diabetes. Diabetes Res Clin Pract 2017;130: 121–129.
18. UK Hypoglycaemia Study Group: Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 2007;50:1140–1147.
19. Akram K, Pedersen-Bjergaard U, Borch-Johnsen K, Thorsteinsson B: Frequency and risk factors of severe hypoglycemia in insulin-treated type 2 diabetes: a literature survey. J Diabetes Complications 2006;20:402–408.

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