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# Dynamics in insulin requirements and treatment safety

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ABSTRACT

*Aims:* The majority of insulin users have elevated HbA1c. There is growing recognition that the low success rates are due to variations in insulin requirements. Thus, frequent dosage adjustments are needed. In practice, adjustments occur sporadically due to limited provider availability. We investigated intra-individual dynamics of insulin requirements using data from a service evaluation of the d-Nav® Insulin Guidance Service. This service facilitates automated insulin dosage adjustments, as often as needed, to achieve and maintain optimal glycemic balance.

*Methods:* Data were collected from subjects who have been using the service for more than a year. Events of considerable and persistent decrease in insulin requirements were identified by drops in total daily insulin ≥25%.

*Results:* Overall, 62 patients were studied over an average period of 2.1 ± 0.5 (mean ± standard deviation) years. Stability in HbA1c was attained after ~3 quarters at 7.4% ± 0.2% (57.4 mmol/mol ± 1 mmol/mol). Events were identified in 56.5% of the patients. On average, each affected patient had 0.8 ± 0.4 events per year, lasting 9.7 ± 6.6 weeks, while total daily insulin dosage decreased by 41.4 ± 13.4%.

*Conclusions:* Our findings may call attention to a major contributing factor to hypoglycemia among insulin users. In reality, insulin dosage is seldom adjusted and thus transient periods of decrease in insulin requirements and overtreatment are usually overlooked.



## 1. Introduction

Insulin is one of the most commonly prescribed classes of medications worldwide. Its main users are patients with advanced type 2 diabetes who have become insulin deficient. Despite the long-term availability and potential advantages of insulin therapy, in practice, its effectiveness has been disappointing. This discrepancy between potential and practice has been called the "insulin paradox" (Hodish, 2015). Compared to other agents used for the management of diabetes, insulin formulations do not have upper dosage limits, they offer diverse pharmacodynamics profiles and have only one source of toxicity, namely hypoglycemia. Yet, average glycated hemoglobin (HbA1c) among patients treated with insulin has not improved for decades (Hoerger, Segel, Gregg, & Saaddine, 2008; Selvin, Parrinello, Daya, & Bergenstal, 2015). Among insulin users in the USA, the average HbA1c is 8.5% (69.4 mmol/mol) while a third of users continue to experience HbA1c at 9% (75 mmol/mol) or higher (Chen, Abbott, Nguyen, Grabner, & Quimbo, 2013).

There is a growing recognition that the "insulin paradox" results from intra-individual and inter-individual variations in insulin requirements. Frequent insulin dosage adjustments can overcome those dynamics and enable maintenance of optimal glycemic control while minimizing occurrences of hypoglycemia (Bashan, Herman, & Hodish, 2011; Davidson, 2009; Hodish, 2015; Riddle et al., 2015; Rosenthal, Herman, WH, & Hodish, 2011). But in practice, insulin adjustments are done sporadically during outpatient clinic visits every 3–6 months.

Intra-individual variations in insulin requirements may potentially explain deterioration in glycemia once frequent insulin adjustments are no longer available. If drops in insulin needs are indeed considerable and expose patients to bouts of hypoglycemia, then the therapy's safety is undermined. This may drive patients and providers to lower insulin dosage, eventually causing prolonged hyperglycemia when future insulin needs increase.

To date, HbA1c goals have been achieved and maintained primarily in clinical trials that implement insulin dosage adjustment every few days–weeks (Bastyr et al., 2015; Bergenstal et al., 2008; Buse et al., 2009; Group TDCaCTR, 1993; Herman et al., 2005; Holman

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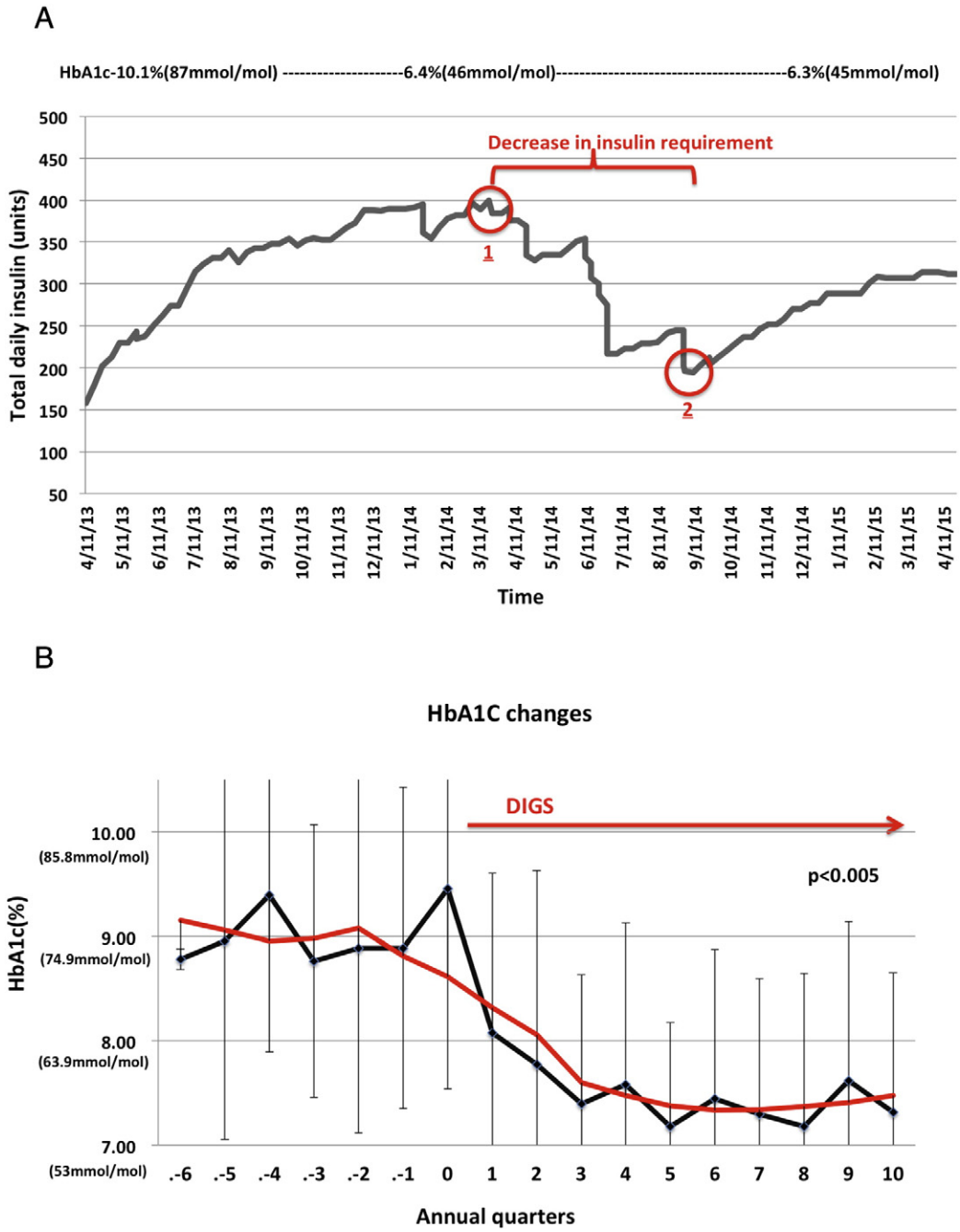


**Fig. 1.** Changes in insulin dosage and HbA1c. A) Example of a patient using basal–bolus insulin therapy for type 2 diabetes. Until 12/2013 total daily insulin was gradually increased by d-Nav up to about 400 units per day when it plateaued for about 4 months. On 03/10/2014, insulin requirements started to decline (red cycle number 1) until reaching a nadir on 9/10/14 (red cycle number 2), at about 200 units per day. In 09/2014, insulin requirements started to rise again. HbA1c levels have remained stable from 12/2013. B) Average changes in HbA1c before and during the d-Nav service. HbA1c stability was attained after 3 annual quarters on the d-Nav Insulin Guidance Service (DIGS). Red line denotes a moving average with a filter of 5 quarters.

et al., 2007; Janka et al., 2005; Riddle et al., 2015; Strange, 2007). This beneficial effect lasts only as long as periodic adjustments are made by the medical staff, evidenced by deterioration of glycemic control within a few months after the studies end and insulin titrations became more sporadic (Hayward et al., 2015; The_writing_team_of_the_DCCT, 2002).

The goal of this study was to determine the magnitude of intra-individual variability in insulin requirements. We have used data from a service evaluation of the d-Nav® Insulin Guidance Service. This service facilitates automated insulin dosage adjustments, as often as needed, to achieve and maintain optimal glycemic balance (Bashan, Harper, Bi, & Hodish, 2015; Donnelly & Harper, 2015). Based on continuous analysis of glucose data, a handheld device called d-Nav provides adjustments to insulin dosage at least on a weekly basis to achieve a consistent balance between hyperglycemia and hypoglycemia. Drops in insulin requirements are recognized in real time and dosage is reduced accordingly. This automated process enables identification of significant decline in insulin requirements in each individual over time.

## 2. Materials and methods

### *2.1. The d-Nav insulin guidance service*

The service includes a combination of diabetes nurses and technology to improve glycemic control in patients. The service relies

**Table 1**
Baseline demographics and clinical characteristics.

| N = 62 SD = standard deviation | | | |
|---|---|---|---|
| Gender (number): | | Diabetes complications (%): | |
| Male | 33 | Retinopathy | 11.3 |
| Age (years; mean ± SD): | 58.1 ± 9.1 | Chronic kidney disease | 11.3 |
| Race (%): | | Proteinuria | 14.5 |
| Caucasian | 54.1 | Neuropathy | 17.7 |
| Afro-Caribbean | 1.6 | Lower limb amputation | 3.2 |
| Not reported | 43.5 | Comorbidities (%): | |
| Diabetes type; number of patients (%): | | Hypertension | 79.0 |
| Type 2 | 56 (90.3%) | Dyslipidemia | 82.2 |
| Secondary | 1 (1.6%) | Coronary artery disease | 37.1 |
| Not reported | 5 (8.1%) | Cerebral vascular disease | 9.7 |
| Duration of diabetes (years; mean ± SD): | 12.1 ± 5.8 | Smoking (current) | 9.7 |
| Duration on Insulin (years; mean ± SD): | 4.7 ± 4.1 | | |
| Duration on the d-Nav® Insulin Guidance Service (years; mean ± SD): | 2.1 ± 0.5 | | |
| BMI (kg/m$^2$; mean ± SD): | 36.6 ± 6.7 | | |
| HbA1c | 9.2% ± 1.4%; 77 ± 7 mmol/mol | | |

on d-Nav (stands for diabetes navigator), which provides patients with an individualized insulin dose for each injection. Patients use d-Nav to monitor glucose level before each injection. In addition to providing the patient's glucose level, d-Nav provides a recommended insulin dose. By analyzing glucose patterns, d-Nav automatically adjusts insulin dosage. This enables providing patients with dynamic insulin therapy to fit their changing needs while preventing an increase in hypoglycemia. Adjustments are typically made weekly by the device. Yet, if insulin requirements drop or hypoglycemia ensues, the device makes more frequent adjustments as needed. The service nurses, periodically follow up with service subscribers via telephone calls and in-person consultations to bestow user confidence, correct usage errors, and identify uncharacteristic clinical courses. The nurses are not involved in the process of insulin dosage titration, which is handled by d-Nav. More technical information can be found elsewhere (Bashan & Hodish, 2012; Bashan et al., 2011, 2015; Bergenstal, Bashan, McShane, Johnson, & Hodish, 2012; Donnelly & Harper, 2015; Rosenthal et al., 2011).

### 2.2. Subjects

Data were obtained from the South Eastern Health and Social Care Trust's Ulster Hospital, Belfast, United Kingdom (Bashan et al., 2015; Donnelly & Harper, 2015). The center referred patients who were adult insulin users and whose HbA1c had been consistently >7.0% (53 mmol/mol). Patients were excluded from the service if they had experienced more than two episodes of severe hypoglycemia in the past year; if they had a history of hypoglycemia unawareness; if they had been using less than a total of 25 units of insulin daily; or if their individual HbA1c goal was different than 6.5%–7.5% (47.5–58.5 mmol/mol) (American Diabetes A, 2014; National_Institute_for_Health_and_Clinical_Excellence(NHS), 2011).

During the initiation visit, d-Nav was set up for each patient with their current insulin regimen and dosage. Patients were then asked to use d-Nav to measure blood glucose before every insulin injection and label each glucose reading (e.g., "breakfast") based on their routine and insulin regimen, and once a week during the night. Patients were also asked to measure their blood glucose every time they suspected or felt symptoms of hypoglycemia to allow d-Nav to immediately adjust insulin dosage if required, with the aim of preventing further hypoglycemic events. Information from d-Nav on insulin dosage and blood glucose levels was regularly downloaded during visits at the service center and with the Ulster diabetes care team.

### 2.3. Analysis of dynamics in insulin requirements

Data from patients whose insulin therapy was managed by the service for more than a year were used for analysis. Total daily insulin was calculated by adding each dosage component in the current d-Nav regimen. For instance, a patient using 30 units of long-acting insulin per day, plus 12 units of rapid-acting insulin for breakfast, 15 units for lunch and 8 units for dinner would be receiving 65 units of total daily insulin. Correction factors were not incorporated in the calculation.

Events demonstrating considerable and persistent decline in insulin requirements were identified as follows. Every time dosage decreased, we examined insulin dosage four weeks after the initial drop occurred. If total daily insulin dosage was lower than the initial drop, then a period of persistent decline in insulin dosage had started. For instance, if on September 1$^{st}$ total insulin dosage dropped from 100 units/day to 92 units per day, then insulin dosage on September 28 would determine whether this drop was persistent. If 4 weeks later the dosage was 91 units per day or less, then on September 1$^{st}$ a period of dosage reduction had started.

Periods of dosage reduction ended when one of the following two criteria was met: a) total insulin dosage was higher than at the point where insulin began to drop (in our previous example that would be a dosage of 101 or more units per day); or, b) a persistent period of dosage increase had started. Once dosage was no longer declining, a search for the minimal dosage point within the valid interval was executed. The magnitude of the dosage decrease was defined by the ratio of the minimum dosage point to baseline dosage at the beginning of the interval. The length was defined as the total time between the initial drop until the minimum has been reached.

A period of dosage increase was defined by examining total daily insulin dosage 13 weeks forward. If in 13 weeks, insulin dosage was higher than at any given point, then that indicated a change of trend; insulin dosage was now increasing, rather than decreasing. The thirteen-week period was used as a threshold since seasonal changes that last about 13 weeks have been suggested to affect hypoglycemic rate (Ishii, Suzuki, Baba, Nakamura, & Watanabe, 2001).

*Duration of each event of decrease in insulin requirements was determined based on the analysis above.* A cutoff of 25% dosage reduction or higher was deemed clinically significant based on published guidelines (Holman et al., 2007). The analysis focused on dosage decrease rather than increase to offer a safety dimension.

The example in Fig. 1A illustrates attenuations in total daily insulin in a patient using basal–bolus insulin therapy. On 03/10/2014, total daily insulin started to decline (red cycle number 1) until reaching a nadir on 09/10/2014 (red cycle number 2). The entire period lasted for 24.3 weeks with a total dosage reduction of 51.25%.

### 2.4. Statistical analysis

Results are presented as mean ± standard-deviation (SD). Median and 75$^{th}$ quartiles were used to illustrate distribution of event durations, frequency and insulin dosage drop. Normality was determined by the Shapiro–Wilk test. The Spearman Correlation test was used to assess correlation between frequency of insulin decrease events and patients' related parameters. Attenuations in HbA1c were assessed for statistical significance by the Wilcoxon matched-pairs signed rank test. A p-value <0.05 was defined as statistically significant.

## 3. Results

Overall, data for 62 patients treated by the d-Nav Insulin Guidance Service for more than a year were available for this analysis. Table 1

shows basic characteristics. Average age was 58.1 ± 9.1 (mean ± SD) years, 56 (90.3%) had type 2 diabetes, patients had diabetes for 12.1 ± 5.8 years, and had been using insulin for 4.7 ± 4.1 years. Initial BMI was 36.6 ± 6.7 kg/m$^2$. Patients were enrolled in the service for 2.1 ± 0.5 years. In average, stability in HbA1c was attained after the 3$^{rd}$ annual quarters at 7.4% ± 0.2% (57.4 mmol/mol ± 1 mmol/mol), while only 4.8% of patients had HbA1C > 8% (64 mmol/mol) (the lowest HbA1c after the 3$^{rd}$ annual quarter on d-Nav) (Fig. 1B).

Events of considerable and persistent decline in insulin requirements (dosage drops ≥25%), were identified in 56.5% of the patients. In 67.7% of patients, dosage dropped ≥20%. In patients who did have significant drops in insulin requirements, each patient had 0.8 ± 0.4 events per year, of which 78.9% started after average HbA1c dropped below 8% (64 mmol/mol). Periods lasted on average 9.7 ± 6.6 weeks and total daily insulin dosage was decreased by 41.4 ± 13.4%.

In half of the patients with reduction in insulin dosage, duration of events exceeded 8.4 weeks and in the 4$^{th}$ quartile it exceeded 13.6 weeks (Fig. 2A). In half of the patients with the events, dosage decreased by more than 37.8% and in the 4$^{th}$ quartile dosage decreased by more than 51.2% (Fig. 2B). In half of the patients with

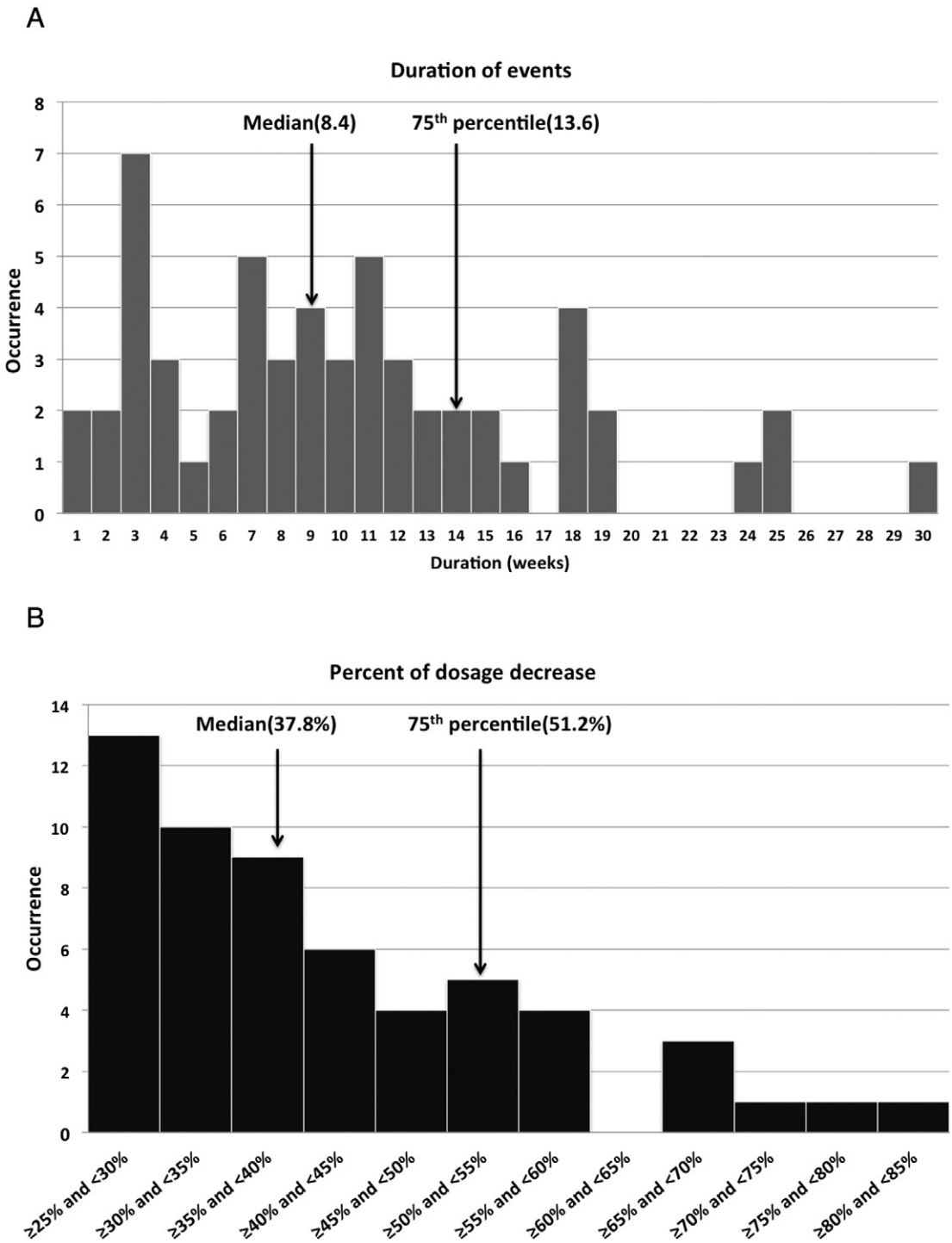


**Fig. 2.** Decline in insulin requirements. A) Histogram depicting duration of decrease in insulin needs. In half of the cases, duration of the period exceeded 8.4 weeks. B) Histogram depicting percentage of dosage reduction in increments of 5%. In half of the cases, total daily insulin dosage decreased by more than 37.8%. C) Histogram depicting frequency of dosage reduction per year. In half of the cases, events occurred more than 0.6 per year. D) Histogram depicting event occurrence as a function of time after d-Nav initiation.

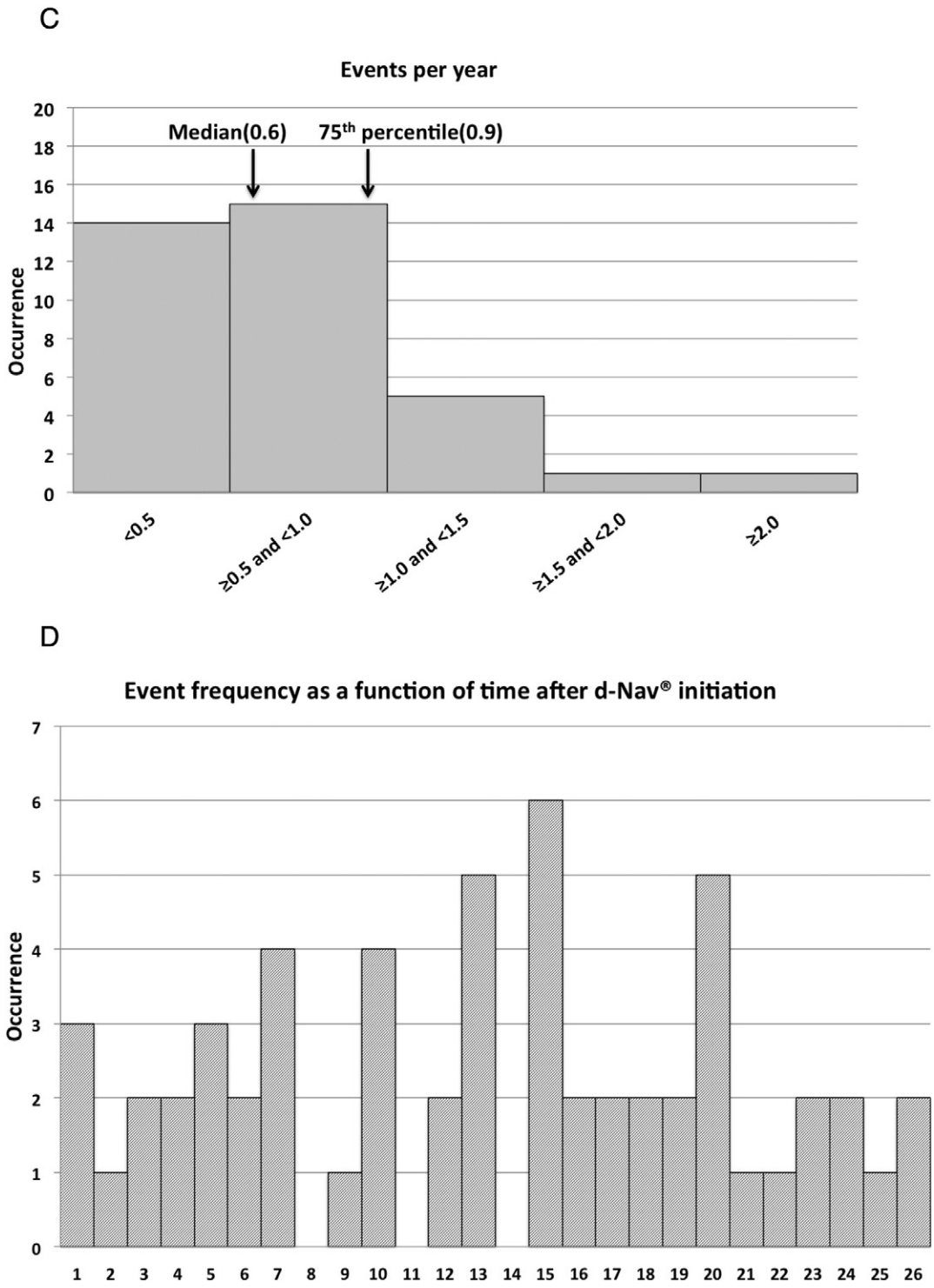


**Fig. 2.** (*continued*).

reduction in insulin dosage, events occurred more than 0.6 times per year and in the 4th quartile it exceeded more then 0.9 (Fig. 2C). Events occurred during all seasons (26% of the events occurred during the winter, 28% during the spring, 18% during the summer and 28% during the fall) and randomly after the initiation of the service (Fig. 2D). Once HbA1c decreased below 8% (64 mmol/mol), there was no further correlation between HbA1c and dosage drops (not shown). No correlation was found between insulin dosage per body-weight per day and dosage drops (not shown).

We examined how many of the events could have been explained by weight loss. Weight data were available for all patients except for 4. We identified weight loss of more than 5% from the highest weight prior to weight loss. Five percent cutoff was used based on its potential impact on the progression of early disease (Knowler et al., 2002). In 4 events the reduction in insulin requirement was associated with weight loss. In the remaining 57 events of significant reduction in insulin requirement, no reduction in weight was observed.

## 4. Discussion

While the concept of frequently adjusted insulin therapy is expanding, more data regarding the physiology/pathophysiology of

insulin requirements is coming to light as we have revealed in this report. When patients are either insulin naïve or overtly undertreated with insulin, the approximate ratio of insulin units required per kg body weight in each patient is unknown and impossible to predict. For instance, when a patient with advanced type 2 diabetes is being considered for insulin therapy, the average requirement can be as high as 2 units per kg of body weight (Bergenstal et al., 2008; Riddle et al., 2015). In addition, inter-individual needs can vary up to 10 fold (e.g., some patients may eventually need 30 units per day or less, while others need 300 units per day or more) (Bergenstal et al., 2008; Riddle et al., 2015). It is clear that the induction of insulin therapy is an intense process, which is best served with frequent dosage titrations. However, what has not been clarified is the dynamic nature of insulin needs, when target HbA1c has already been reached. This is particularly important since hypoglycemia has been a major safety concern in insulin therapy (Pathak et al., 2015).

In a previous work, we reanalyzed data from a clinical trial in which a specialized study team had facilitated frequent insulin dosage adjustment by phone calls in a group of patients with type 2 diabetes over a period of a year. The number of components changed by the team (e.g., breakfast rapid-acting insulin, lunchtime rapid-acting insulin, long-acting insulin, etc.), as well as intensity of changes and the clinical effort needed for those adjustments to maintain HbA1c within the target was similar to the one that was needed to achieve HbA1c goals in the first place (Herman et al., 2005; Rosenthal et al., 2011).

The current report sheds light as to the reason. In a majority of patients, insulin requirements change considerably over time, requiring substantial percentage of dosage change (Fig. 2A and B). Insulin requirements occur in all seasons, unrelated to weight or to HbA1c once decreased below 8% (64 mmol/mol), thus making them difficult to predict.

To our best knowledge, the reasons for these variations have not been elucidated, although they likely include minor changes in physical activity, diet, emotional stressors, etc. Additionally, it is likely that availability in endogenous insulin secretion can change over time and can potentially recover to some extent once glucotoxicity has subsided (Chick & Like, 1970; Flax, Matthews, Levy, Coppack, & Turner, 1991; Harper & Hodish, 2015; Kluth et al., 2011).

As we revealed in our report, events of considerable and persistent decline in insulin needs are common. This may explain why many patients suffer from bouts of hypoglycemia between clinic visits and thus become subject to treatment-related anxiety and risk. It is very likely that such episodes prompt both patients and providers to indiscriminately lower dosage and impair glycemic control while requirements may rise, as suggested in post-clinical trial periods (Hayward et al., 2015; The_writing_team_of_the_DCCT, 2002). *Limitations of the study include limited sample size and lack of multicenter data source.*

Our findings may call attention to a major contributing factor to hypoglycemia among insulin users. Insulin dosage is seldom adjusted, so transient periods of decrease in insulin requirements are often overlooked, leading to overtreatment. Unfortunately, many patients are under-dosed with insulin (Bergenstal et al., 2008; Riddle et al., 2015) and thus changes in insulin requirements are not even apparent.

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