Journal of Diabetes and Its Complications 30 (2016) 1333–1338

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Dynamics in insulin requirements and treatment safety

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ARTICLE INFO

Article history:
Received 15 April 2016
Received in revised form 17 May 2016
Accepted 17 May 2016
Available online 21 May 2016

Keywords:
Insulin therapy
Dosage
Hypoglycemia
Insulin requirements
Titration

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

Funding source: Hygieia Inc.
Declaration of interests: Eran Bashan is the chief executive officer for Hygieia; Israel Hodish is a co-founder of Hygieia; Raman Minhas is a medical director for Hygieia; Roy Harper, Rosemary Donnelly and Yixi Bi have no financial interest in Hygieia.
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http://dx.doi.org/10.1016/j.jdiacomp.2016.05.017

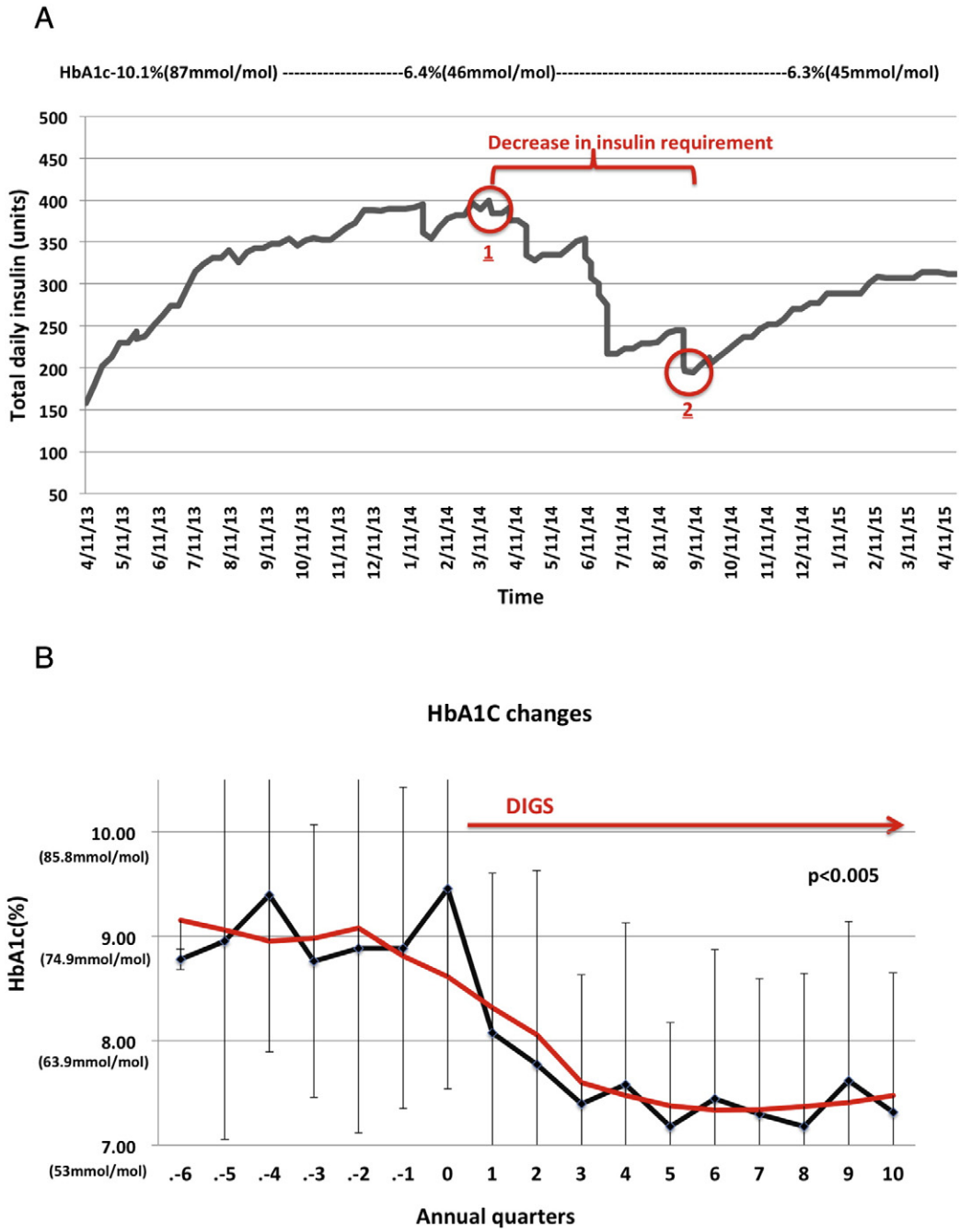

Fig. 1. Changes in insulin dosage and HbA1c. A) Example of a patient using basal–bolus insulin therapy for type 2 diabetes. Until 12/2013 total daily insulin was gradually increased by d-Nav up to about 400 units per day when it plateaued for about 4 months. On 03/10/2014, insulin requirements started 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