Received: 13 July 2023 | Revised: 28 August 2023 | Accepted: 29 August 2023

DOI: 10.1111/dom.15280

RESEARCH LETTER

WILEY

Time in range in patients with type 2 diabetes who are long-term users of d-Nav®, an artificial intelligence-driven technology for autonomous titration of insulin dosing

Kevin J. Williams MD[1] | Eran Bashan PhD[2] | Caitlin Kruse[2] | Sajitha Sritharan[2] | Israel Hodish MD[2,3]

[1]Cardiovascular Research Center, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, USA

[2]Hygieia, Inc., Livonia, Michigan, USA

[3]Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan Medical Center, Ann Arbor, Michigan, USA

Correspondence
Israel Hodish, Hygieia, Inc., 17187 North Laurel Park Drive, Suite 225 Livonia, MI 48152, USA.
Email: ihodish@hygieia.com

Funding information
Hygieia INC.

KEYWORDS: artificial intelligence, continuous glucose monitor, insulin therapy, time in range, type 2 diabetes mellitus

1 | BACKGROUND

Use of artificial intelligence (AI) to titrate insulin therapy frequently has become the mainstay of modern insulin management in diabetes mellitus. There are currently two technology-driven approaches. First, contemporary insulin-pumps combined with continuous glucose monitors (CGM) have been furnished with software packages that autonomously titrate the insulin infusion rate every few minutes, in systems called automated insulin delivery (AID). These systems have been used mainly for patients with type 1 diabetes[1–3] but has also been tested in patients with type 2 diabetes.[4] Second, for patients who use insulin injections mainly for type 2 diabetes, the d-Nav® technology enables autonomous insulin titration at least weekly.[5,6]

It has been suggested that time in range (TIR) for glucose concentrations obtained from CGM devices provides complementary information beyond average glycaemia or levels of glycated haemoglobin (HbA1c).[7]

We have previously reported long-term HbA1c levels in patients who use d-Nav®. Within 6-9 months, the average HbA1c in d-Nav® users reaches a steady state and remains at about 7% for as long as patients use the technology.[6]

In this service evaluation, we report TIR and other standard CGM-acquired parameters in long-term d-Nav® users with type 2 diabetes. Moreover, we compare our findings with published results from AID systems.

2 | METHODS

2.1 | d-Nav® insulin management technology

Descriptions and validations of the d-Nav® technology as a standard of care for hypoglycaemia prevention in patients with type 2 diabetes[7] can be found elsewhere, including data on long-term adherence.[5,6] Briefly, patients referred to the d-Nav® Service are provided with a phone application ('app') called d-Nav®. Patients use their own glucometer or CGM to measure glucose concentrations before each insulin injection, and d-Nav® provides a dose recommendation for that injection. The AI within d-Nav® assesses each patient's responses to his or her current insulin doses by analysing glucose patterns and titrates doses at least weekly. The AI autonomously adjusts each

Reprint requests should be addressed to Dr Israel Hodish.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2023 The Authors. *Diabetes, Obesity and Metabolism* published by John Wiley & Sons Ltd.

patient's insulin doses to reach a clinically achievable balance between preventing hyperglycaemia and preventing hypoglycaemia. If insulin requirements drop or hypoglycaemia ensues, the AI within d-Nav® makes immediate autonomous adjustments as often as needed, following the safety-first approach of prioritizing the avoidance of hypoglycaemia.

Trained health care providers (specifically, registered nurses, licensed practical nurses, medical assistants) are trained to become d-Nav® specialists. They follow-up with patients through telephone calls or in-person meetings at least monthly, to boost user confidence and correct usage errors. Information about the specific roles of frequent d-Nav® autonomous insulin titrations and health care providers support on glycaemia can be found elsewhere.[5] Providers who uses the d-Nav® Service for their patients can review the d-Nav® data for each patient at any given time, allowing them to handle all other medications for diabetes and any comorbid conditions.

2.2 | Population

We obtained de-identified data that had been generated from d-Nav® users within the United States between January 2019 and May 2023. These data were acquired retrospectively and were limited to secondary use of non-identifiable information previously collected during normal clinical care. Thus, the study was exempt from institutional review board approval.

We included patients with type 2 diabetes who have been using d-Nav® >6 months (and thus have reached glycaemic stability), used CGMs, and provided access to their CGM information for ongoing care. Access to patients' CGM information relied on their willingness and ability to share the information.

2.3 | Outcomes

The primary outcome of this service evaluation was the average TIR based on the most recent 14 days of CGM data. The secondary outcome was the correlation between average glucose concentrations and TIR. To assess dynamics over time, we also examined TIR during a 14-day period 6 months before the most recently available data.

Data were compared with standard goals for CGM metrics from the most recent guidelines for glycaemic targets from the American Diabetes Association.[7]

2.4 | Statistical analyses

Unless otherwise specified, continuous variables were displayed as means ± SD. Categorical variables are given as n (%). To allow the attainment of glycaemic stability,[6] our analyses omitted glucose and insulin data from the first 6 months on d-Nav®. To assess the correlation between average glucose concentrations and TIR, we calculated a Pearson's correlation coefficient (r).

TABLE 1 Demographics and key clinical characteristics

Demographics and clinical characteristics	Total (N = 18)
Age, years; mean ± SD	60.3 ± 10.4
Male, %	66.7
Race, %	
American Indian or Alaska Native	5.5
Asian	5.5
African-American	5.5
White	61.1
Other	5.5
Not reported	16.7
Ethnicity, %	
Hispanic	5.5
Non-Hispanic	61.1
Not reported	33.3
Insulin regimen, %	
Basal-bolus insulin therapy	55.5
Premixed insulin	27.8
Basal-only insulin	16.7
Use a Libre® device, %	72.2
Use a Dexcom® device, %	27.8
Duration of diabetes, years; mean ± SD	18.6 ± 7.6
Duration on the d-Nav®-Insulin-Guidance-Service, years; mean ± SD	2.2 ± 1.0
Glucose management indicator or CGM-reported HbA1c, %; mean ± SD	7.0 ± 0.6
Additional antidiabetes medication classes in the beginning of the service, %	
Biguanides	55.6
Sulphonylureas	22.2
Thiazolidinediones	5.5
DPP-4 inhibitors	16.7
GLP-1 receptor agonists	22.2
SGLT2 inhibitors	16.7

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter 2.

3 | RESULTS

We acquired CGM information from 18 patients with type 2 diabetes who had been managed on d-Nav® for 2.2 ± 1.0 years (mean ± SD), corresponding to about 110 autonomous insulin treatment plan (dosage) titrations per patient (i.e. about once per week) and 2500 individual autonomous dose recommendations per patient (i.e. recommendations for one to four insulin doses per day). For example, an insulin treatment plan titration could be a change in base lunch dose from 30 units with a correction factor of 1 extra unit for every 30 mg/dl above 120 mg/dl to 32 units with the same

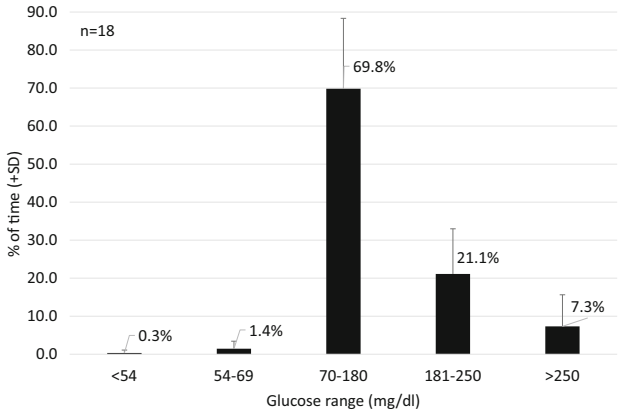

FIGURE 1 Percentage of time spent in different glucose concentration ranges based on the most recent 14 days of continuous glucose monitor data in patients with type 2 diabetes who have been using d-Nav® for more than 6 months (mean ± SD; n = 18 patients). Glucose levels of 70–180 mg/dl are defined as in range, in accordance with recent guidelines for glycaemic targets.[7]

correction. An insulin dose recommendation could be for the administration of 32 units of rapid-acting insulin for lunch on a certain day.

Table 1 shows demographics and key clinical characteristics. Duration of diabetes was 18.6 ± 7.6 years. The average glucose level on d-Nav® was 157.1 ± 29.6 mg/dl, and the glucose management indicator or CGM-reported HbA1c was 7.0% ± 0.6.

Figure 1 shows CGM-reported glucose ranges according to standard reporting. For our primary outcome, the cohort spent 69.8% ± 18.5% of the time in range(TIR), meaning 70-180 mg/dl, nearly achieving the more stringent recommendation of >70% despite long-standing diabetes.[7] The cohort spent 1.8% of the time below range (<70 mg/dl), which was superior to the recommended goal of percentages <4%. Time below 54 mg/dl was 0.3%, also superior to the recommended goal of percentages <1%.[7] More than two-thirds of the time out of range was in near-hyperglycaemia (181-250 mg/dl; Figure 1). These values are consistent with the prioritization within d-Nav® to avoid hypoglycaemia. The coefficient of variation or glycaemic variability was 31.1% ± 6.4%, which met the recommended goal of ≤36%. Sensors were used 76.0% ± 26.6% of the time, which met the recommended >70%.

TIR 6 months earlier, and hence closer to the beginning of the service, was 63.4% ± 24.1% and not statistically different than the value above.

For our secondary outcome, average glucose concentrations over a period of 14 days were highly correlated with TIR (Pearson's $r = 0.97$; $p < .0001$).

We found no correlation between the number of virtual/face-to-face interactions with the d-Nav® specialists over the past 6 months and patients' TIR. Table S1 details TIR and other CGM-acquired parameters in patients separated by their use of different insulin regimens. After initiation of the d-Nav® service, three patients had been transitioned by their physicians from basal-bolus insulin therapy to premixed insulin, all before the initial CGM reports were taken. Figure S1 depicts examples of reports of two CGM devices from two different brands.

4 | DISCUSSION

In this service evaluation, we report TIR and additional standard CGM parameters in patients who use insulin injections for long-standing type 2 diabetes and whose insulin doses have been autonomously titrated by d-Nav®. CGM parameters were favourable, with TIR at 69.8%. Comparing the d-Nav® service to AID systems, recently reported TIRs in patients who use AID systems were 60.6%,[3] 70.1%[1] and 73.9%[2] for patients with type 1 diabetes and 66.3%[4] for patients with type 2 diabetes.

The following are limitations of this service evaluation. First, the study was dependent on patients' willingness and ability to set up sharing of CGM data as part of remote clinical care. This limitation may have biased the results by possibly selecting for more technologically savvy individuals. On the other hand, the average HbA1c of this cohort was similar to the average in the d-Nav® Service in general after about 6-9 months of d-Nav® use,[5,6] suggesting a representative sample of the d-Nav® patient population. Secondly, the current report was not a randomized controlled study, but instead provides real-life retrospective observational data. Finally, another limitation of this study is the unavailability of data regarding the use of non-insulin medications.

In our current cohort, average glucose concentrations and TIR were highly correlated, close to recommended goals for guideline-based care, consistent across insulin regimens and comparable with results from AID systems, which are more complex to use and intrusive. Our findings provide additional metrics of the overall favourable glycaemic profile that d-Nav® users regularly maintain.

AUTHOR CONTRIBUTIONS

KJW, EB and IH designed the study and interpreted the data. KJW and IH wrote the manuscript. SS and CK collected the data and performed the analysis.

ACKNOWLEDGMENTS

Hygieia, Inc. funded the service evaluaton.

CONFLICT OF INTEREST STATEMENT

IH is a cofounder and medical director for Hygieia, Inc.; EB is a cofounder and CEO for Hygieia, Inc.; KJW reports an ownership interest in Hygieia, Inc.; SS and CK are employees of Hygieia, Inc.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15280.

DATA AVAILABILITY STATEMENT

Not applicable.

ORCID

Kevin J. Williams https://orcid.org/0000-0002-0000-2159

Israel Hodish https://orcid.org/0000-0001-8174-384X

REFERENCES

1. Usoh CO, Johnson CP, Speiser JL, Bundy R, Dharod A, Aloi JA. Real-world efficacy of the hybrid closed-loop system. *J Diabetes Sci Technol*. 2022;16:659-662.
2. Brown SA, Forlenza GP, Bode BW, et al. Multicenter trial of a tubeless, on-body automated insulin delivery system with customizable glycemic targets in pediatric and adult participants with type 1 diabetes. *Diabetes Care*. 2021;44:1630-1640.
3. Akturk HK, Snell-Bergeon J, Shah VN. Efficacy and safety of tandem control IQ without user-initiated boluses in adults with uncontrolled type 1 diabetes. *Diabetes Technol Ther*. 2022;24:779-783.
4. Daly AB, Boughton CK, Nwokolo M, et al. Fully automated closed-loop insulin delivery in adults with type 2 diabetes: an open-label, single-center, randomized crossover trial. *Nat Med*. 2023;29:203-208.
5. Bergenstal RM, Johnson M, Passi R, et al. Automated insulin dosing guidance to optimise insulin management in patients with type 2 diabetes: a multicentre, randomised controlled trial. *Lancet*. 2019;393:1138-1148.
6. Harper R, Bashan E, Williams KJ, et al. Challenging the 50-50 rule for the basal-bolus insulin ratio in patients with type 2 diabetes who maintain stable glycaemic control. *Diabetes Obes Metab*. 2023;25:581-585.
7. American Diabetes A. 6. Glycemic targets: standards of medical care in diabetes-2021. *Diabetes Care*. 2021;44:S73-S84.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Williams KJ, Bashan E, Kruse C, Sritharan S, Hodish I. Time in range in patients with type 2 diabetes who are long-term users of d-Nav®, an artificial intelligence-driven technology for autonomous titration of insulin dosing. *Diabetes Obes Metab*. 2023;25(12):3845-3848. doi:10.1111/dom.15280