Automated insulin dosing guidance to optimise insulin management in patients with type 2 diabetes: a multicentre, randomised controlled trial

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Summary

Background Insulin therapy is most effective if dosage titrations are done regularly and frequently, which is seldom practical for most clinicians, resulting in an insulin titration gap. The d-Nav Insulin Guidance System (Hygieia, Livonia, MI, USA) is a handheld device that is used to measure glucose, determine glucose patterns, and automatically determine the appropriate next insulin dose. We aimed to determine whether the combination of the d-Nav device and health-care professional support is superior to health-care professional support alone.

Methods In this multicentre, randomised, controlled study, we recruited patients from three diabetes centres in the USA (in Detroit MI; Minneapolis, MN; and Des Moines IA). Patients were eligible if they were aged 21–70 years, diagnosed with type 2 diabetes with a glycated haemoglobin (HbA_{1c}) concentration of 7·5% or higher (≥58 mmol/mol) and 11% or lower (≤97 mmol/mol), and had been using the same insulin regimen for the previous 3 months. Exclusion criteria included body-mass index of 45 kg/m² or higher; severe cardiac, hepatic, or renal impairment; and more than two severe hypoglycaemic events in the past year. Eligible participants were randomly assigned (1:1), with randomisation blocked within each site, to either d-Nav and health-care professional support (intervention group) or health-care professional support alone (control group). Both groups were contacted seven times (three face-to-face and four phone visits) during 6 months of follow-up. The primary objective was to compare average change in HbA_{1c} from baseline to 6 months. Safety was assessed by the frequency of hypoglycaemic events. The primary objective and safety were assessed in the intention-to-treat population. We used Student's *t* test to assess the primary outcome for statistical significance. This study was registered with ClinicalTrials.gov, number NCT02424500.

Findings Between Feb 2, 2015, and March 17, 2017, 236 patients were screened for eligibility, of whom 181 (77%) were enrolled and randomly assigned to the intervention (n=93) and control (n=88) groups. At baseline, mean HbA_{1c} was 8·7% (SD 0·8; 72 mmol/mol [SD 8·8]) in the intervention group and 8·5% (SD 0·8; 69 mmol/mol [SD 8·8]) in the control group. The mean decrease in HbA_{1c} from baseline to 6 months was 1·0% (SD 1·0; 11 mmol/mol [SD 11]) in the intervention group, and 0·3% (SD 0·9; 3·3 mmol/mol [9·9]) in the control group (p<0·0001). The frequency of hypoglycaemic events per month was similar between the groups (0·29 events per month [SD 0·48] in the intervention group *vs* 0·29 [SD 1·12] in the control group; p=0·96).

Interpretation The combination of automated insulin titration guidance with support from health-care professionals offers superior glycaemic control compared with support from health-care professionals alone. Such a solution facilitated safe and effective insulin titration in a large group of patients with type 2 diabetes, and now needs to be evaluated across large health-care systems to confirm these findings and study cost-effectiveness.

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Introduction

More than a quarter of all patients with diabetes use insulin therapy (all types of diabetes), but its effectiveness has been unsatisfactory. Despite advancements in technology and pharmacotherapy, average concentrations of glycated haemoglobin (HbA_{1c}) in insulin users in high-income countries have been approximated to be 8·5% (69 mmol/mol). Only a third of patients reach the recommended HbA_{1c} goal of less than 7% (53 mmol/mol), and a third of patients remain at concentrations of 9% (75 mmol/mol) or higher.[1,2]

Awareness is increasing that insulin therapy can be effective if titrations are done regularly and frequently to overcome intraindividual and interindividual variations in insulin requirements.[3–10] But in practice, because of restricted time and medical expertise, adjustments in insulin dosages are done sporadically during outpatient clinic visits every 3–6 months. Moreover, based on the units of insulin per kg bodyweight used in previous clinical trials assessing effective insulin therapy in type 2 diabetes management, most patients using insulin are underdosed.[11]

Research in context

Evidence before this study

The National Health and Nutrition Examination Survey (NHANES) collects cross-sectional, complex probability samples of the US population on a regular basis. In a 2015 study, nearly 5000 adults who were diagnosed with diabetes in 1988–94 and 2005–12 NHANES cycles were compared and assessed for trends in insulin use and diabetes control. Both the proportion of people using any insulin (30% in 1988–94, 29% in 2005–12) and the proportion achieving a glycated haemoglobin (HbA_{1c}) concentration below 7% (34% in 1988–94, 32% in 2005–12) were remarkably constant over this approximately 20 year period. Despite advancements in technology and pharmacotherapy, most patients who use insulin do not achieve their therapy goals, increasing the risk of debilitating and costly complications. We did a literature review using PubMed for articles published in English until the end of 2018, without date restrictions using the search terms "insulin", "adjustments", "dose", "dosage", "healthcare professionals", "providers", and "HbA_{1c}". Our findings from this review indicate that health-care support and frequent and ongoing insulin dose adjustments are two key elements associated with improved glycaemic control. Despite this evidence, timely and effective insulin dose titrations are rarely made on a regular basis, in part because of restricted time and medical expertise. We aimed to assess whether technology for insulin-dosing guidance in combination with support from a health-care professional would result in improved concentrations of HbA_{1c} in patients with type 2 diabetes who use insulin, while minimising hypoglycaemia compared with health-care professional support alone.

Added value of this study

In this multicentre, randomised, controlled study, we tested whether the d-Nav insulin guidance system (Hygieia, Livonia, MI, USA), a handheld device that contains a glucose meter and software that adjusts insulin dose that provides its user with a dose-by-dose insulin recommendation, together with health-care professional support, is superior to a health-care professional support model alone. Over a period of 6 months, the combination of d-Nav and health-care professional support resulted in lower HbA_{1c} concentrations in patients with type 2 diabetes than health-care professional support alone, with a similar safety profile.

Implications of all the available evidence

Insulin can be used effectively to achieve improved glycaemic control if technology to provide automated insulin titration guidance is combined with health-care professional support. Such an approach now needs to be evaluated across large health-care systems to confirm these findings and study its cost-effectiveness.

For patients with type 1 diabetes, this gap in insulin titrations is addressed by use of hybrid closed-loop insulin delivery systems. The system includes an insulin pump, a linked continuous glucose monitor, and an algorithm in the pump or a hand-held unit that adjusts insulin doses every 5 min. In a randomised controlled study by Thabit and colleagues,[12] children and adults decreased their HbA_{1c} from an average of approximately 8·5% (69 mmol/mol) to approximately 7·5% (58 mmol/mol) in 12 weeks.

Because of the cost and complexity of hybrid closed-loop therapy,[13,14] implementation of such systems is mostly too complex and cost-prohibitive for a large population of patients with type 2 diabetes. For each individual with type 1 diabetes who uses insulin, five individuals use insulin to manage their type 2 diabetes.[1,15]

Hygieia (Livonia, MI, USA) has developed a scalable system to improve the effectiveness of insulin therapy. The system automates the guidance of insulin titration and can be used by patients with type 2 diabetes who use insulin.[9,16–20] The system relies on d-Nav, a handheld device that automatically titrates a dose of insulin on the basis of the glucose readings the patient is already scheduled to take with d-Nav. Patients use the device to check their glucose concentration before each injection and obtain a recommended insulin dose. By analysing glucose patterns, d-Nav automatically adjusts the insulin dosage over time without supervision to fit patients' changing needs while working to prevent hypoglycaemia. Additional software tools are available to provide further insight regarding insulin dynamics.[16]

The d-Nav device has been shown to be effective when coupled with the support of dedicated health-care professionals. The support specialists initiate periodic telephone calls and in-person consultations several times a year to impart user confidence, correct errors of use, and identify uncharacteristic clinical courses. The support specialists are not involved in the process of insulin dose titrations, which is handled by the device and therefore enables scalability to the growing population of patients with type 2 diabetes who use insulin. This system has been in use in the UK since 2012.[21]

This multicentre randomised controlled study aimed to assess whether use of d-Nav plus health-care professional support for the management of type 2 diabetes that is treated with insulin is superior to management of insulin therapy with support from a health-care professional alone.

Methods

Study design and participants

In this prospective, open-label, multicentre, randomised controlled study, we recruited patients with type 2 diabetes from three diabetes centres in the USA: the International Diabetes Center at Minneapolis, MN; Henry Ford Medical Center Endocrinology, Detroit, MI; and the Iowa Diabetes

and Endocrinology Research Center, Des Moines, IA; all study sites were accredited specialty diabetes clinics, led by experienced diabetologists. Patients were eligible for inclusion if they were aged 21–70 years at screening, diagnosed with type 2 diabetes with HbA_{1c} of 7·5% or higher (≥58 mmol/mol) and 11% or lower (≤97 mmol/mol), and had been using the same insulin regimen for the previous 3 months, with or without other anti-diabetes drugs at a stable dosage for the past 3 months. Exclusion criteria included body-mass index (BMI) of 45 kg/m² or more; severe impairment of cardiac, hepatic, or renal functions; psychological or cognitive impairment; more than two episodes of severe hypoglycaemic events in the past year; a history of hypoglycaemia unawareness; and a lack of regularly monitored blood glucose. Full inclusion and exclusion criteria are in the protocol (appendix).

See Online for appendix

The study protocol was approved by the appropriate local ethics committees or institutional review boards of each study centre, and the study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. All participants provided written informed consent.

Randomisation and masking

Upon enrolment, participants were randomly assigned (1:1) either to d-Nav plus health-care professional support (intervention group) or to health-care professional support alone (control group). Randomisation by use of randomisation envelopes was blocked within each site to ensure approximately equal distributions of treatment groups within the sites. The randomisation sequence was generated by the International Diabetes Center, affiliated with RMB. The trial was designed as open-label since the difference in equipment between the groups could not be masked.

Procedures

During the initial visit at baseline, participants who were randomly assigned to the intervention group were provided with and trained on the use of the d-Nav device. The d-Nav device was then set up with the participant's current insulin regimen and dosage. Participants in both groups received free testing supplies either for d-Nav (intervention group) or for their glucose meters' consumables (control group). All participants were encouraged to measure their blood glucose before each insulin injection and any time they felt symptoms of hypoglycaemia.

Participants were on one of the following four insulin regimens at baseline: a single injection of long-acting insulin analogue per day (required one glucose measurement per day); twice daily biphasic or premixed insulin (required two glucose measurements per day); a basal-bolus regimen with fixed meal doses and a correction factor (required four glucose measurements per day); and a basal-bolus regimen with carbohydrate counting and a correction factor (required four glucose measurements per day). Participants could change insulin regimens during the study if their clinician recommended to do so.

Participants were followed up for 6 months, during which participants in both groups had seven health-care professional–patient interactions (three face-to-face and four phone visits) with the study team who inquired about participants' wellbeing, health changes, challenges in management, and any side-effects; no specific questionnaire was followed. Participants assigned to the intervention group were also asked about details pertaining to the use of the device by use of a pre-prepared follow-up form, which was filled in by the health-care professional. The study team included endocrinologists (RMB, AB), diabetes educators (DFK, MJ), and study coordinators (RP, NY) who could make changes in the insulin dosage if deemed necessary. Face-to-face visits were done at study centres at baseline, 3 months, and 6 months (ie, visit 1, 2, and 3) during which data from their d-Nav devices (intervention group) or glucose meters (control group) were downloaded. HbA_{1c} data collected at each visit were assessed at a central reference laboratory (Advanced Research and Diagnostic Laboratory, University of Minnesota, MN, USA) using high-performance liquid chromatography. Phone visits were initiated by the study centre at weeks 1, 2, 4, and 20.

Some patients are particularly susceptible to hypoglycaemia,[22] which could preclude the safe decrease of average glucose and HbA_{1c} concentrations. Accordingly, we planned to divide the patients enrolled in the study into two predefined cohorts: the primary cohort, the group that does not have frequent hypoglycaemia—we estimated that 90% of patients would be in this cohort; and the secondary cohort, the group that has frequent hypoglycaemia. Frequent hypoglycaemia was defined a priori as more than 42 glucose readings of less than 65 mg/dL (3·6 mmol/L) during the 6 month study (ie, >85 hypoglycaemic events per year) as described previously.[23] By the end of the study period only two participants in the intervention group and one in the control group were found to qualify for the secondary cohort, so we decided to include all participants in the primary cohort without segregating patients.

Outcomes

The primary objective was to assess whether d-Nav users who also had health-care professional support (intervention group) and patients with only health-care professional support (control group) had different average change (difference in difference) in HbA_{1c} between baseline and 6 months. The secondary objectives were to determine the difference between the intervention and control groups in the proportion of participants who achieved HbA_{1c} of less than 7% (53 mmol/mol), less than 8% (64 mmol/mol), and more than 9·0% (75 mmol/mol) at 6 months. Additional analyses included determining the difference in the

proportion of participants between the intervention and control groups who achieve HbA_{1c} less than 7% (<53 mmol/mol) and less than 8% (<64 mmol/mol) without a severe hypoglycaemic event by 6 months; the difference between the groups in the frequency of glucose readings below 50 mg/dL (<2·8 mmol/L), below 60 mg/dL (<3·3 mmol/L), and below 70 mg/dL (<3·9 mmol/L), symptomatic or asymptomatic; the difference between the groups in the mean fasting glucose concentration; and the difference between the groups in the SD and coefficient of variation of the mean fasting glucose concentration. All differences in glucose were determined using the documented downloaded glucose values at 3 months and 6 months. Furthermore, the difference between the groups in the number of blood glucose test strips (ie, number of glucose measurements) used at 3 months and 6 months was reported. Safety was assessed by use of the frequency and severity of hypoglycaemic events, reporting of glycemia-related adverse events, and any changes in the health of the participants. Severity of adverse events was measured using a predetermined scale.

Statistical analysis

The study was powered to detect a mean difference in HbA_{1c} of 0·5% (5·5 mmol/mol) between treatment groups with an estimated SD of 1·0. On the basis of a 0·05 level two-sample Student's *t* test, 77 patients per group would give 80% power. The HbA_{1c} difference outcome in each patient was used to account for baseline differences including baseline HbA_{1c}. To allow for potential attrition, 100 patients were to be recruited per group. Because the attrition rate was lower than expected, recruitment was completed after 181 participants had been enrolled.

Of the participants who did not complete follow-up, three (23% of observations and 1·6% of recruited participants) had partial data. An analysis using last observation carried forward did not change the result of the primary objective and thus for outcomes with continuous variables we report the participants with available data at 6 months, and report all available data for descriptive statistics reported at baseline. For binary outcomes, such as frequency of hypoglycaemic events, which offered no opportunity for a carry-forward approach, we conservatively used the total number of participants in each group as the denominator regardless of attrition. Although the protocol prespecified regression for analyses, in a linear regression analyses the effects of clinical site and treatment regimen were not significant. Thus, we report results pooled over site and regimen. No interim analysis was planned or performed.

We used descriptive statistics for each variable, including measures of central tendency and variation. We used Student's *t* test to assess continuous variables. When the distribution of a variable did not support the use of parametric statistics, we used non-parametric approaches or data transformations; we used the Mann-Whitney *U* test for non-parametric variables. We used the χ^2 test to assess differences between categorical variables, and the Wilcoxon signed-rank test to assess differences between repeated observations. We used an intention-to-treat analysis approach for all objectives and safety. Unless stated otherwise, results are presented as mean (SD). SEM was used in graphs for clearer illustration of the results. We determined statistical significance on the basis of an α value of 0·05.

We did analysis using R version 3.4.4. The trial was registered with ClinicalTrials.gov, number NCT 02424500.

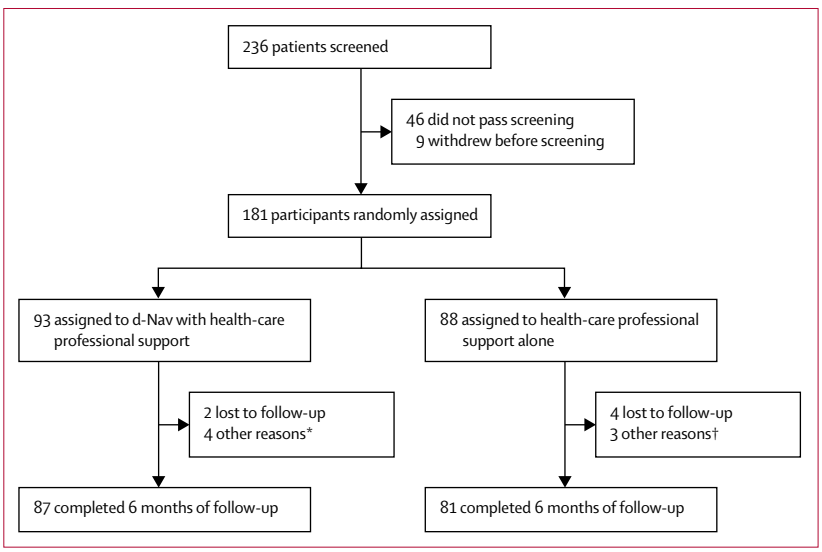

Figure 1: **Trial profile**
Intervention group used d-Nav (Hygieia, Livonia, MI, USA) device and health-care professional support; control group used health-care professional support alone. *One because they were overwhelmed by the information they were given on d-Nav, one because of resistance to changing their insulin regimen, one due to an unrelated medical concern (foot fracture), and one lost their d-Nav device and decided not to continue. †One because they did not see any benefit in participating, and two because they did not respond to phone calls from the study team.

Role of the funding source

The funder of the study had no role in study design, data collection, analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 2, 2015, and March 17, 2017, of 236 patients with type 2 diabetes screened, 181 (77%) were enrolled in the study. 93 (51%) of 181 were randomly assigned to the intervention group and 88 (49%) to the control group, comprising the intention-to-treat population. 87 (94%) participants in the intervention group and 81 (92%) of those in the control group completed the study (figure 1). 13 participants discontinued the study before completion: six from the intervention group discontinued the study (n=2 lost to follow up, n=4 other reasons) and seven from the control group (n=4 lost to follow-up, n=3 other reasons; figure 1). Of these participants who discontinued

	Intervention group (n=93)	Control group (n=88)
Sex		
Female	48 (52%)	40 (45%)
Male	45 (48%)	48 (55%)
Age, years	61·7 (6·9)	58·8 (8·5)
Race		
American Indian or Alaska Native	2 (2%)	2 (2%)
Asian	2 (2%)	5 (6%)
African American	19 (20%)	19 (22%)
Native Hawaiian or other Pacific Islander	0	0
White	68 (73%)	57 (65%)
More than one	0	2 (2%)
Unknown	2 (2%)	3 (3%)
Ethnicity		
Hispanic	3 (3%)	5 (6%)
Non-Hispanic	76 (82%)	69 (78%)
Unknown	14 (15%)	14 (16%)
Weight, kg	100·2 (17·1)	101·1 (17·2)
Body-mass index, kg/m²	34·7 (5.1)	34·9 (5·0)
Duration of diabetes, years	16·1 (7·3)	15·3 (6·0)
Duration of insulin therapy, years	4·6 (3·4)	5·2 (4·0)
Baseline HbA_{1c}, % (mmol/mol)	8·7% (0·8; 72 [8·8])	8·5% (0·8; 69 [8·8]
Complications		
Retinopathy	14 (15%)	10 (11%)
Nephropathy or albuminuria	12 (13%)	8 (9%)
Neuropathy	26 (28%)	19 (22%)
Coronary artery disease or congestive heart failure	6 (6%)	7 (8%)
Peripheral vascular disease	2 (2%)	2 (2%)
Comorbidities		
Hypertension	72 (77%)	70 (80%)
Dyslipidaemia	85 (91%)	71 (81%)
Tobacco smoking	42 (45%)	43 (49%)
(Table 1 continues in next column)		
(Continued from previous column)		
Education		
Junior high	0	0
Some high school	2 (2%)	3 (3%)
Graduated high school	10 (11%)	9 (10%)
Some college	31 (33%)	26 (30%)
Associate's degree	18 (19%)	15 (17%)
Bachelor's degree	19 (20%)	21 (24%)
Postgraduate degree	13 (14%)	11 (13%)
Not reported	0	3 (3%)
Initial insulin regimen		
Long-acting insulin only	31 (33%)	35 (40%)
Biphasic or premixed insulin	12 (13%)	9 (10%)
Basal bolus therapy	42 (45%)	27 (31%)
Basal bolus therapy with carbohydrate counting	8 (9%)	17 (19%)
Other medications		
Biguanides	29 (31%)	32 (36%)
Sulfonylureas	6 (7%)	9 (10%)
Thiazolidinediones	1 (1%)	0
Meglitinides	0	0
DPP-4 inhibitors	2 (2%)	3 (3%)
SGLT2 inhibitors	2 (2%)	5 (6%)
GLP-1 agonists	3 (3%)	9 (10%)

Data are n (%) or mean (SD). Intervention group used d-Nav (Hygieia, Livonia, MI, USA) device and health-care professional support; control group used health-care professional support alone. HbA_{1c}=glycated haemoglobin. DPP-4=dipeptidyl peptidase-4. SGLT2=sodium-glucose co-transporter-2. GLP-1=glucagon-like peptide-1.

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

the study, three provided partial data. All randomly assigned participants were included in the analysis whether they completed the follow-up period or not; therefore, data obtained from participants before discontinuation of their participation were included in analysis. The entire study population was cumulatively followed for 83·2 patient-years.

Baseline characteristics were similar in both treatment groups (table 1). Characteristics of the entire study population were mean age of 60·3 years (SD 7·9); mean duration of diabetes 15·7 years (SD 6·7); mean HbA_{1c} 8·6% (SD 0·8; 70 mmol/mol [SD 9]); and initial total daily dose of insulin 0·7 units per kg per day (SD 0·4). Insulin regimens were similar between the groups (table 1). Six (3%) of 181 participants changed insulin regimen during the study (n=3 intervention group, n=3 control group). In the intervention group, two participants changed from long-acting insulin only to basal-bolus without carbohydrate counting, and one from biphasic insulin to basal-bolus without carbohydrate counting. In the control group, two participants changed from long-acting insulin only regimens to basal-bolus without carbohydrate counting, and one from basal-bolus without carbohydrate counting to the same with carbohydrate counting. For classification in tests for regimen differences, they were counted on the basis of the latest regimen. Information about additional anti-diabetes drug classes can be found in table 1.

At baseline, mean HbA_{1c} concentrations were similar between the groups (intervention group 8·7% [SD 0·8] or 72 mmol/mol [SD 8·8]; control group 8·5% [SD 0·8%] or 69 mmol/mol [SD 8·8]; p=0·24). The mean decrease in HbA_{1c} from baseline to 6 months was 1·0% (SD 1·0; 11 mmol/mol [SD 11]) in the intervention group, and 0·3% (SD 0·9; 3·3 mmol/mol [9·9]) in the control group (p<0·0001 between groups; effect size 0·7%, 95% CI 0·4 to 1·0; or 7·7 mmol/mol, 95% CI 4·7 to 10·8). In both groups, changes in HbA_{1c} during the study were significant (figure 2). In a linear regression analysis, clinical site was not found to affect the differences in change in HbA_{1c} between the groups: mean differences

were –0·688 (95% CI –0·977 to –0·400) unadjusted for clinical site, and –0·689 (–0·978 to –0·399) when adjusted for clinical site.

At baseline, 21 (23%) of 93 participants in the intervention group and 28 (32%) of 88 in the control group had a HbA_{1c} concentration of less than 8% (64 mmol/mol; table 2; appendix). By 6 months, 58 (62%) of participants in the intervention group had an HbA_{1c} concentration of less than 8% (64 mmol/mol), compared with 29 (33%) in the control group (effect size 29·4%, 95% CI 13·9–42·2; p=0·0001; table 2, appendix). Interestingly, 38 (43%) participants in the control group had a deterioration in or lack of improvement in glycaemia,compared with 14 (15%) participants in the intervention group (appendix).

Mean weekly glucose and mean fasting weekly glucose concentrations decreased significantly during the study in the intervention group (p<0·0001; appendix). In the control group, mean weekly glucose (p=0·73) and mean fasting weekly glucose (p=0·34) concentrations remained stable (appendix).

Throughout the 6 month study period, the average frequency of confirmed hypoglycaemia (glucose readings <54 mg/dL or <3 mmol/L),[24] as recorded by d-Nav or glucose meters, was similar in both groups at 0·29 per month (SD 0·48) in the intervention group, and 0·29 per month (SD 1·12) in the control group (p=0·96; effect size 0, 95% CI –0·25 to 0·25; table 3). When a non-parametric analysis using the Mann-Whitney test was applied, the two groups had different distributions (intervention group, median 0·085 per month [IQR 0–0·35], maximum 2·1; control group, median 0 per month [IQR 0–0·12], maximum 8·7; p=0·0031). Although more patients in the intervention group had at least one hypoglycaemic event (45 [48%] *vs* 19 [22%]), the values of glucose readings during a hypoglycaemic event were lower in the control group than in the intervention group. As shown in table 2, the frequency of glucose readings below 50 mg/dL (2·8 mmol/L) in the control group was higher than in the intervention group (p=0·022), whereas more readings were seen in the upper ranges in the intervention group than in the control group (between ≥50 mg/dL [2·8 mmol/L] and <60 mg/dL [3·3 mmol/L], p=0·0077; and between ≥60 mg/dL [3·3 mmol/L] and <70 mg/dL [3·9 mmol/L], p=0·0013).

Three severe hypoglycaemic events (ie, requiring the assistance of another person) were reported in the intervention group and two in the control group (p=0·69; table 3). No fatal or near-fatal events were reported. 20 (22%) participants in the intervention group and three (3%) in the control group had an HbA_{1c} concentration below 7% (53 mmol/mol) without severe hypoglycaemia by 6 months (effect size 18·1%, 95% CI 8·7–27·8; p=0·0003). 56 (60%) participants in the intervention group and 28 (32%) in the control group had an HbA_{1c} concentration below 8% (64 mmol/mol) without severe hypoglycaemia by 6 months (effect size 28·4%, 95% CI 13·9–41·2; p=0·0001; table 2). No other study-related severe adverse events were reported.

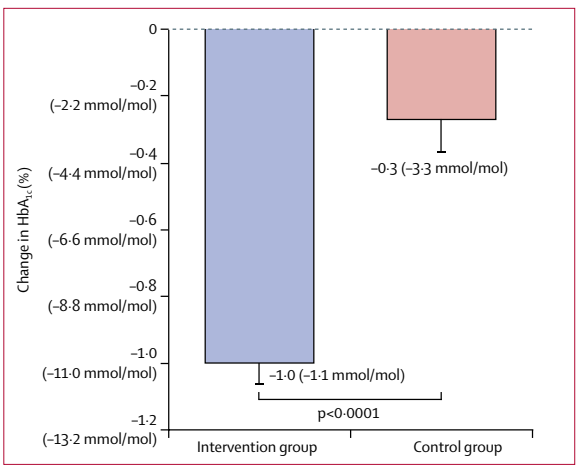

Figure 2: **Average change in HbA_{1c} by 6 months, by group**
Data are mean (SEM) for the d-Nav (Hygieia, Livonia, MI, USA) plus health-care provider support (intervention) group versus health-care provider support only (control) group. HbA_{1c}=glycated haemoglobin.

On average, for participants in the intervention group, insulin dose adjustments were done 1·1 times per week (SD 0·2), whereas 0·2 adjustments per week (SD 0·3) resulted in a decrease in dose. In other words, 1 (15·4%) of every 6·5 dose adjustments decreased the insulin dose. Data on the titration frequency of the control group were not available.

The baseline average weight in the intervention group was 100·2 kg (SD 17·1) with a BMI of 34·7 kg/m² (SD 5·1). The baseline average weight in the control group was 101·1 kg (SD 17·2) with a BMI of 34·9 kg/m² (SD 5·0; p=0·73). Small weight gain was seen in both groups during the study—to 101·6 kg (SD 18·0) in the intervention group and to 101·8 kg (SD 17·4) in the control group. Average proportional increase in weight from baseline was 2·3% in the intervention group and 0·7% in the control group (p=0·0001 between groups; figure 3).

Total daily dose of insulin normalised to bodyweight increased in both groups (figure 4). In the intervention group, total daily dose of insulin increased from 0·77 units per kg per day (SD 0·4) at baseline to 1·24 units per kg per day (SD 0·8) at 6 months. By contrast, in the control group total daily dose of insulin increased from 0·71 units per kg per day (SD 0·4) at baseline to 0·76 units per kg per day (SD 0·4) at 6 months. The final total daily dose (normalised to bodyweight) was 63·8% higher in the intervention group than in the control group (p=0·0001; figure 4).

Frequency of glucose measurements per week (ie, number of test strips used) before the study was self-reported in the screening questionnaire. Frequency of glucose measurements during the study was calculated on the basis of data downloaded from d-Nav or glucose

	Intervention group (n=93)	Control group (n=88)	Effect size (95% CI)	p value
Primary objective				
Reduction in HbA_{1c} at 6 months, % (mmol/mol)	1·0% (1·0; 11 [11])	0·3% (0·9; 3·3 [9·9])	0·7% (0·4 to 1·0; 7·7 [4·7 to 10·8])	<0·0001
Secondary objectives				
HbA_{1c} <7% (53 mmol/mol)				
Baseline	0	0		
6 months	20 (22%)	4 (5%)	17·0% (7·3 to 26·8)	0·0008
HbA_{1c} <8% (64 mmol/mol)				
Baseline	21 (23%)	28 (32%)	9·2% (–3·7 to 21·8)	0·16
6 months	58 (62%)	29 (33%)	29·4% (13·9 to 42·2)	<0·0001
HbA_{1c} >9% (75 mmol/mol)				
Baseline	24 (26%)	20 (23%)	3·1% (–9·4 to 15·4)	0·62
6 months	10 (11%)	7 (8%)	2·8% (–6·2 to 11·7)	0·51
Additional objectives				
HbA_{1c} <7% (53 mmol/mol) without severe hypoglycaemia by 6 months	20 (22%)	3 (3%)	18·1% (8·7 to 27·8)	0·0003
HbA_{1c} <8% (64 mmol/mol) without severe hypoglycaemia by 6 months	56 (60%)	28 (32%)	28·4% (13·9 to 41·2)	0·0001
Frequency of glucose readings				
<50 mg/dL (2·8 mmol/L)				
Per month	0·1 (0·2)	0·2 (0·9)	0·1 (–0·1 to 0·3)	0·022
Per week	0·03 (0·05)	0·05 (0·24)	..	..
Proportion of total hypoglycaemic readings	64/996 (6·4%)	87/379 (23·0%)	..	..
Proportion of total readings	64/37 954 (0·2%)	87/22 350 (0·4%)	..	..
≥50 mg/dL (2·8 mmol/L) and <60 mg/dL (3·3 mmol/L)				
Per month	0·6 (0·9)	0·2 (0·6)	0·4 (0·2 to 0·6)	0·0077
Per week	0·14 (0·24)	0·06 (0·14)	..	..
Proportion of total hypoglycaemic readings	289/996 (29·0%)	101/379 (26·6%)	..	..
Proportion of total readings	289/37 954 (0·8%)	101/22 350 (0·5%)	..	..
≥60 mg/dL (3·3 mmol/L) and <70 mg/dL (3·9 mmol/L)				
Per month	1·2 (1.6)	0·5 (0·7)	0·7 (0·3 to 1·1)	0·0013
Per week	0·31 (0·4)	0·11 (0·17)	..	..
Proportion of total hypoglycaemic readings	643/996 (64·6%)	191/379 (50·4%)	..	..
Proportion of total readings	643/37 954 (1·7%)	191/22 350 (0·9%)	..	..
≥54 mg/dL(3·0 mmol/L) and <70 mg/dL (3·9 mmol/L)				
Per month	1·6 (2·2)	0·6 (1·0)	1·0 (0·5 to 1·5)	0·0015
Per week	0·41 (0·54)	0·15 (0·25)	..	..
Proportion of total hypoglycaemic readings	851/996 (85·4%)	260/379 (68·6%)	..	...
Proportion of total readings	851/37 954 (2·2%)	260/22 350 (1·2%)	..	..
Difference in fasting glucose concentration between 0 and 6 months, mg/dL (mmol/L)	–28·0 (56·4; –1·6 [3·1])	–9·8 (45·9; –0·5 [2·6])	18·2 (3·1 to 33·3)	0·00005
CV of mean fasting glucose				
At baseline (first week on the study)	29·8%	27·6%	..	..
At 3 months (last week before visit 2)	35·7%	25·1%	..	..
At 6 months (last week before visit 3)	26·6%	31·2%	..	..

Data are n (%), mean (SD), or effect size, with 95% CI in parentheses, unless otherwise indicated. Intervention group used d-Nav (Hygieia, Livonia, MI, USA) device and health-care professional support; control group used health-care professional support alone. CV=coefficient of variation. HbA_{1c}=glycated haemoglobin.

***Table 2*: Primary and secondary outcomes**

meters. The average expected frequency of glucose measurements per week was calculated on the basis of seven readings for a patient using a long-acting insulin regimen, 14 readings for a patient on a biphasic or premixed regimen, and 28 readings for a patient on a basal-bolus regimen with or without carbohydrate counting. Before the study, the self-reported frequency of glucose measurements was higher than 100% of the expected frequency in both groups, whereas, during the study, patients in the intervention group measured their glucose concentration more often than those in the control group (appendix). In the intervention group, the

	Intervention group		Control group		Effect size (95% CI)	p value
	n	Severity (relation to intervention)	n	Severity (relation to intervention)		
Frequency of glucose reading <54 mg/dL (3 mmol/L)						
Per month	0·29 (0·48)	Not defined	0·29 (1·12)	Not defined	0 (–0·25 to 0·25) per month	0·96
Per week	0·07 (0·12)	Not defined	0·07 (0·28)	Not defined	..	
Severe hypoglycaemia (event per 6 months)	3	Severe (unrelated to intervention; n=1); moderate (reasonable possibility of relation to intervention; n=1); undefined (undefined relation to intervention; n=1)	2	Severe (unrelated to intervention; n=2)	..	0·69

Data are n (SD) and effect size with 95% CI in parentheses. Intervention group used d-Nav (Hygieia, Livonia, MI, USA) device and health-care professional support; control group used health-care professional support alone. Severe hypoglycaemia is defined as a hypoglycaemic event requiring assistance of another person to actively administer carbohydrates, glucagon, or other resuscitative action.

Table 3: **Occurrence of hypoglycaemia**

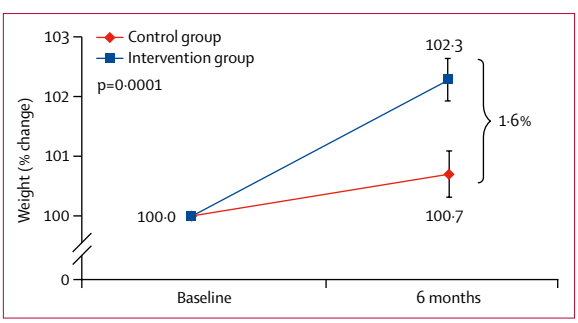

Figure 3: **Average change in bodyweight from baseline to 6 months, by study group**
Data are mean (SEM) for the d-Nav (Hygieia, Livonia, MI, USA) plus health-care professional support (intervention) group versus health-care provider support only (control) group. Average percentage change in weight was calculated by averaging individual percent weight change.

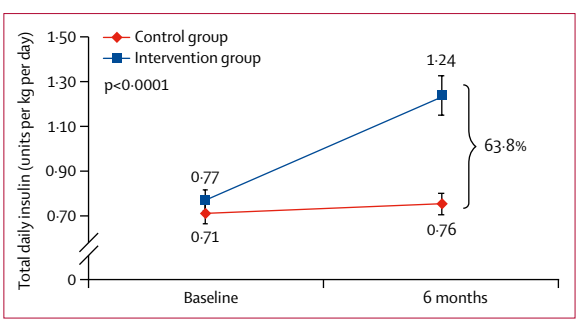

Figure 4: **Average total daily dose of insulin normalised to bodyweight from baseline to 6 months, by study group**
Data are mean (SEM) for for the d-Nav (Hygieia, Livonia, MI, USA) plus health-care professional support (intervention) group versus health-care provider support only (control) group.

lowest frequency of measurements did not fall below the recommended frequency and the number of overall glucose measurements in the control group was 30–40% lower than the number in the intervention group (appendix). Notably, this difference between the groups was also seen during the second face-to-face visit, during which superior average HbA_{1c} concentrations in the intervention group were already being seen (data not shown).

Baseline questionnaires showed that diabetes was managed by primary care physicians for about half of participants (41 [44%] from the intervention group, and 44 [50%] from the control group), and by endocrinologists for the other half (appendix). In both groups, during the year before the study, three-quarters of the participants' insulin dose was titrated two or fewer times. By the end of the study, 75% (70 of 93) of the intervention group and 68% (59 of 88) of the standard of care group were either satisfied or very satisfied with their diabetes management during the study. 82% (76) of the intervention group and 76% (67) of the standard of care group reported that they would probably or definitely agree to continue to monitor their glucose as often as needed, as dictated by their insulin regimen. In the intervention group, 37 (39%) of 93 were very comfortable having their insulin titrated by the d-Nav device rather than their health-care professional, 29 (31%) were comfortable, and 19 (20%) were somewhat comfortable.

Discussion

In this Article, we provide evidence to support the superiority of automated titration guidance technology with health-care professional support over health-care professional support alone. The d-Nav system streamlines the insulin titration process in what appears to be a scalable way. Frequent insulin titration is a key part of effective insulin therapy.[3–10] Yet, the frequent titrations needed to adjust to dynamic insulin needs and high volumes of patients prohibit clinicians from fulfilling this need. The evolving technology of closed-loop delivery systems is aiding in closing the titration gap in patients with type 1 diabetes. However, because of the cost and complexity of such systems, most insulin users with type 2 diabetes are unlikely to use closed-loop delivery systems.[13,14]

The population recruited for the study was ethnically and geographically diverse. Compared with the control group, the glycaemic outcomes in the intervention group were superior as measured by several endpoints. Improvements in HbA_{1c} were three times greater in the

intervention group than in the control group. Patients in the intervention group were three times more likely to show any glycaemic improvement than those in the control group, with twice as many patients decreasing their HbA_{1c} concentration to below 8% (64 mmol/mol) and five times as many decreasing it below 7% (53 mmol/mol). The restricted number of self-measured glucose readings per day is the most probable reason why HbA_{1c} did not precisely match the average glucose and average fasting glucose concentrations.

The average frequency of hypoglycaemic events (ie, glucose concentration <54 mg/dL [3·0 mmol/L]) was similar in both groups. By contrast, although more patients in the intervention group had at least one hypoglycaemic event than those in the control group did, the values of the low glucose readings were lower in the control group than in the intervention group. This result corresponds with the current consensus in the scientific literature regarding risk stratification and reporting of hypoglycaemia.[24] The frequency of severe hypoglycaemic events was low and similar between groups. However, the number of patients who achieved the glycaemic goal (HbA_{1c} <7% [53 mmol/mol]) without severe hypoglycaemia was more than six times higher in the intervention group than in the control group. The number of overall glucose measurements in the control group was 30–40% lower than the number in the intervention group. Therefore, the reported frequency of hypoglycaemic events in the control group could have underestimated the actual frequency.

Preservation of adequate treatment safety while achieving superior glycaemic control, as suggested by our results, is expected when insulin titrations are done frequently. Insulin requirements do not have a steady state. Previous studies have shown that most patients have a cycle of 1·3 years, and every 1·3 years they will undergo a period of 10 weeks (SD 7·7) during which their insulin requirements decrease by an average of 39% (SD 12·6).[9,25] Therefore, capacity to promptly down titrate insulin is fundamental. This feature (decrease in insulin dose as needed) was used by the d-Nav device in 15·4% of the titrations during the study in the intervention group.

By the end of the 6 month follow-up period, total daily insulin normalised to bodyweight was more than 60% higher in the intervention group compared with the control group. Since the proportion of weight gain was only 1·6% higher in the intervention group, weight changes in our study did not explain changes in insulin needs, as has been shown by others.[26] Weight gain is an inherent and well known phenomenon associated with insulin intensification. Also, average insulin requirements in patients with long-standing type 2 diabetes are known to be about 1·7 units per kg bodyweight per day.[5] Reassuringly, both phenomena have not been shown to compromise the benefit of insulin replacement.[27,28]

The final total daily dose of 1·24 units per kg per day in the intervention group is, in fact, lower than the expected dose for age-matched and BMI-matched US patients.[5,29] As we have shown, because of the small but steady nature of the d-Nav device's dose increments, more than 6 months of use is needed to allow HbA_{1c} and insulin requirements to stabilise, but longer follow-up would be needed to show this stabilisation.[26] Many patients with type 2 diabetes are underdosed with insulin and a wide gap exists between their prescribed dose and their approximate requirements.[5,11,29] For most patients, insulin titrations in real-world settings are incapable of closing this gap in a reasonable timeframe.

In this study, most patients in each group were treated with regimens that could be used for the long-term—namely, basal-bolus or biphasic insulin therapy.[30] Thus the use of a long-acting insulin regimen was unlikely to affect the average total daily dose of insulin.

The high frequency of health-care professional–patient communication in both groups exceeded the typical standard of care. Yet, glycaemic improvement was modest in the control group with health-care professional support alone. The titrations made by the d-Nav device in the intervention group were well accepted by patients. Also, participants in the intervention group tended to measure their glucose concentrations more frequently than those in the control group did, and had superior average HbA_{1c}, as was already observed from the data collected at the second face-to-face visit. However, at this timepoint, participants in both groups measured their glucose levels more than expected. These data imply that the difference in the frequency of glucose measurements was unlikely to be the cause of the difference in glycaemia between the groups; instead witnessing their improved glycaemia might have been the driving force for the patients in the intervention group to measure more often than those in the control group did, an observation that has been noted previously.[31]

Several alternative approaches to optimising insulin therapy exist. As digital communication technology advances, many data delivery systems enable real-time delivery of patients' glucose readings from their monitoring devices to their providers.[32] Many titration guidelines have been transformed into decision support systems that are used by providers. Telemedicine platforms allow providers to have video calls with patients and to make medication adjustments.[33] However, such solutions still require health-care professionals—whose time is already overstretched—to adjust and convey the new insulin dosages to patients. Many titration guidelines have been transformed into mobile phone apps that can be used by patients to titrate their insulin dose, although such US Food and Drug Administration cleared apps are prescription-only devices.[34] However, despite the long-term availability of insulin self-titration instructions, glycaemic control in patients who are treated with insulin has not improved for decades.[1,2]

The main limitation of our study was its relatively short duration and its restriction of recruitment from one

continent. The main strengths of the study were the large number of participants, and the diverse ethnic background of the participants. Furthermore, all study sites were accredited specialty diabetes clinics, led by experienced diabetologists; hence, the teams at each centre were unlikely to be biased against adjusting insulin dosage in the group of participants who were supported by a health-care professional alone.

In summary, health-care professional support without self-titration technology did not substantially improve the care of patients with type 2 diabetes who use insulin, whereas combination of an automated guidance system for insulin titration with health-care professional support closes the titration gap in a way that facilitates significant improvement in glycaemic control while maintaining adequate treatment safety.

Contributors

RMB contributed to study design, data interpretation, and writing and editing of the manuscript. MJ contributed to study design and data collection. RP, AB, and NY contributed to data collection. DFK contributed to data collection. EB contributed to the study design, data analysis, and data interpretation. SGB contributed to drawing of figures and data analysis. DJMI contributed to data analysis and interpretation. IH contributed to the literature search, drawing of figures, study design, data analysis, data interpretation, and writing and editing of the manuscript.

Declaration of interests

EB is the chief executive officer for Hygieia (Livonia, MI, USA). IH is a co-founder of Hygieia. SGB is an employee of Hygieia. DFK holds stocks in Hygieia. DJMI is a paid consultant for Hygieia. RMB, MJ, RP, AB, and NY have no financial interest in Hygieia and declare no other competing interests.

Data sharing

Data collected for the study is currently not available to others.

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