CASE REPORT

A novel approach to optimise glycaemic control in insulin users

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SUMMARY

Insulin therapy has been available for almost a century. However, its success rate is still disappointing where the majority of users sustain harmfully elevated glycated haemoglobin (HbA1c) levels. The key element essential for effective and safe insulin therapy is frequent dosage titration to overcome constant variations in insulin requirements. In reality, dosage titration is done sporadically during clinic visits. A scalable solution to this problem is being reviewed. A diabetes nurses service improves glycaemic control without overburdening the health system. The service relies on a handheld device, which provides patients with an insulin dose recommendation for each injection while using the device to monitor glucose. Similar to the approach providers use during clinical encounters, the device analyses stored glucose trends and constantly titrates insulin dosage without care providers' supervision. In this report, we describe the logic behind the technology by providing examples from users.

BACKGROUND

Insulin is one of the most extensively prescribed classes of medications, and it is mainly prescribed for advanced type 2 diabetes. The latter has become a pandemic and has caused human suffering and immense consumption of public resources.^{1 2} Although insulin has been available as a replacement therapy for almost a century and analogues are now available to overcome pharmacokinetic barriers, the success rate of insulin therapy is disappointing. About two-thirds of patients who use insulin sustain glycated haemoglobin (HbA1c) levels above 53 mmol/mol (above 7%) and likely more than a third sustain levels higher than 75 mmol/mol (above 9%).³

The key element in effective insulin therapy is frequent dosage adjustments.^{4 5} During the first few years of insulin initiation, the dosage increases steadily (up to about 1.5–2 units/kg),^{6 7} and many patients need to switch from simple regimes (eg, once daily long-acting insulin) to basal-bolus regimes.⁸ Furthermore, unpredicted changes in insulin requirements during the day may expose patients to hypoglycaemia or hyperglycaemia.^{4 9} In contradiction to the dynamic nature of insulin therapy, dosage titration is done sporadically during clinic visits typically 2–4 times/year. Evidently, clinical trials that oversee insulin therapy and facilitate frequent dosage adjustments every few weeks by highly skilled study teams achieve predefined HbA1c goals.^{6 10–15} The healthcare system is exhausting its resources with all aspects of diabetes

care, and thus a feasible large-scale insulin titration solution cannot increase the clinician workload burden.

Hygieia Inc has developed a scalable solution to this problem. The Diabetes Insulin Guidance Service (DIGS) comprises a diabetes nurses service that improves glycaemic control in patients without overburdening health systems. The service relies on a handheld device called d-Nav (diabetes navigator), which advises patients what dose of insulin to administer during each injection. Patients use d-Nav to monitor the glucose level before each injection, but in addition to their glucose level, it provides a recommended insulin dose. By analysing glucose patterns, d-Nav automatically adjusts insulin dosage without supervision. This enables dynamic insulin therapy to fit patients' changing needs while preventing an increase in hypoglycaemia. Adjustments are typically made weekly by the device. Yet, if insulin requirements drop or hypoglycaemia ensues, the device makes more frequent adjustments as needed. The service nurses periodically follow up users with 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 the device.

The service was evaluated in the UK by enrolling long-standing insulin users with HbA1c ≥ 53 mmol/mol ($\geq 7.0\%$) and following them for a year. A total of 126 patients were recruited in the service, while 96 completed the evaluation. The mean ($\pm$ SD) HbA1c for the 96 active users decreased from 77 ± 15 mmol/mol ($9.2 \pm 1.4\%$) at baseline to 62 ± 13 mmol/mol ($7.8 \pm 1.2\%$) at the 3–5 month clinic visit and to 58 ± 13 mmol/mol ($7.5 \pm 1.2\%$) at the 6–12 month clinic visit ($p < 0.05$). The frequency of minor hypoglycaemia (glucose ≤ 3.3 mmol/L or ≤ 60 mg/dL) was lower than 0.5 events/week. Thirty patients withdrew (23.8%), of whom only 21 (16.6%) did so due to difficulties in using the device correctly.¹⁶ The service is currently available in Northern Ireland and is used by several hundred patients in primary and secondary care. In this report, we describe the logic behind the technology by providing examples from users.

Technology

d-Nav was developed by Hygieia Inc based on established guidelines for insulin management.¹⁷ The d-Nav insulin guidance system is a simple-to-use handheld device that includes a test strip port

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and an integrated blood glucose sensor. d-Nav is European Conformity (CE)-marked.

It adjusts most types of insulin regimens: (1) once a day basal insulin; (2) two times per day biphasic/premixed long-acting and short-acting insulin and (3) intensive insulin therapy involving long-acting and fast-acting insulin with or without carbohydrate counting.¹⁸ A physician prescribes the initial regimen and dosage that the device adjusts. Following the logic of diabetes specialists and concordant with the gold standard guidelines for insulin management,¹⁷ the device assesses the patient's response to its current insulin dosage by analysing glucose patterns on a weekly basis (glucose readings from the on-board sensor are stored in the device), then automatically adjusts the user's insulin dosage.^{4 9 18 19} d-Nav serves as an extension of the diabetes care team to follow patients and provides simple and safe instructions to modify treatment between clinic visits. The device does not require any behavioural changes from the user. It simplifies diabetes management for the patient and does not increase the burden on the already stressed healthcare system. Since d-Nav provides insulin dose recommendations, it is typically used before every insulin injection, that is, from one to four times a day depending on the regimen, which is sufficient to adjust the dosage. The device adjusts dosage every week or more frequently if glucose levels are trending down during any given time of the day or if a cluster of hypoglycaemia is identified. The service nurses periodically follow up users with telephone calls and in-person consultations. During those encounters, they download the devices using software that helps identify usage errors or uncharacteristic clinical courses. For

illustration, [figure 1](#) denotes a device download from a patient with type 2 diabetes treated with biphasic insulin therapy two times per day (patient 1). For the first several months, his HbA1c remained elevated at 74 mmol/mol (8.9%) with hardly any hypoglycaemia. The d-Nav download showed that the patient was testing his glucose >15 times/week. However, few of those tests were recorded before breakfast or dinner. On average, the patient used d-Nav at breakfast only 1.3 times/week and at dinner only 3.5 times/week. This routine did not enable the device to analyse the glucose pattern and titrate the dosage. However, the patient had measured 9.5 times/week on other occasions before and after meals (labelled as "other" in [figure 1A](#)). The nurse advised the patient to measure glucose predominantly before breakfast, before dinner and whenever he suspected hypoglycaemia. This intervention resulted in proper use of the device and improvement of HbA1c to 58 mmol/mol (7.5%; [figure 1B](#)). More technical information can be found elsewhere.⁴

CASE PRESENTATION

Case 2

Patient number 2 is a 61-year-old woman with a 13-year history of type 2 diabetes, treated with insulin for 2 years. Over the past year prior to starting d-Nav, her HbA1c had become higher than 75 mmol/mol (higher than 9%). On 1 November 2012, she started using d-Nav with a single daily injection of long-acting insulin. The device was set with 50 units of long-acting insulin per day. [Figure 2](#) denotes changes in insulin dosage, weekly mean glucose, hypoglycaemia (glucose ≤ 3.3 mmol/L or

Figure 1 Example of a d-Nav download. (A) The graph showing the average number of glucose readings per week over the past 8 weeks. Detailed are average readings before breakfast, dinner, during nighttime and other (ie, not qualifying for the first 3 categories). (B) d-Nav download; The upper graph denoting the insulin dosage (in insulin units). The lower graph denoting the weekly mean glucose (in mmol/L). Episodes of minor daytime hypoglycaemia are shown in the lower graph as red dots (glucose ≤ 3.3 mmol/L or ≤ 60 mg/dL). The corresponding level of glucose during these events can be inferred from the y-axis. Glycated haemoglobin measurements are shown at the bottom.

Figure 2 d-Nav download in patient 2. (A) 1 November 2012 to 1 May 2013. (B) 1 May 2013 to 10 November 2013. The upper graphs denoting the insulin dosage (in insulin units); the lower graphs denoting the weekly mean glucose (in mmol/L). Episodes of minor daytime hypoglycaemia are shown in the lower graph as red dots (glucose ≤ 3.3 mmol/L or ≤ 60 mg/dL). Episodes of nocturnal hypoglycaemia are shown in the lower graph as blue stars. The corresponding level of glucose during these events can be inferred from the y-axis. Glycated haemoglobin measurements are shown at the bottom.

≤ 60 mg/dL) and attenuations in HbA1c. During the first 6 weeks, d-Nav had gradually up-titrated long-acting insulin to 70 units/day. Yet weekly mean glucose remained elevated at ~ 9 mmol/L (162 mg/dL). On 14 December 2012, the patient was seen in the clinic and the data were downloaded from the device. It was suspected that long-acting insulin alone was inadequate, and thus the regimen was changed to twice daily injections of biphasic insulin at 18 units with breakfast and 30 units with dinner. Throughout a period of 2.5 months, d-Nav gradually increased both breakfast and dinner dosage while the weekly mean glucose improved. In March 2013, the daytime insulin requirement decreased, resulting in several episodes of minor daytime hypoglycaemia. This trend was recognised by the

device that decreased the breakfast dosage (figure 2A). In June 2013, the daytime and nighttime insulin requirements dropped, resulting in several episodes of minor hypoglycaemia, two of which occurred during the night. d-Nav decreased the breakfast and dinner dosage (figure 2B). During this 12-month period, the device made ~ 60 insulin dosage adjustments. The frequency of minor hypoglycaemia during the 2 months ending in October 2013 was 0.25 events/week without nocturnal episodes. Attenuations in HbA1c are shown in figure 2.

Case 3

Patient number 3 is a 58-year-old man with a 22-year history of type 2 diabetes, treated with insulin for 11 years. Lately, he has

Figure 3 d-Nav download in patient 3. The upper graph denoting the insulin dosage (in insulin units); the lower graph denoting the weekly mean glucose (in mmol/L). Episodes of minor daytime hypoglycaemia are shown in the lower graph as red dots (glucose ≤ 3.3 mmol/L or ≤ 60 mg/dL). The corresponding level of glucose during these events can be inferred from the y-axis. Correction factor (insulin to glucose ratio) is not shown. Glycated haemoglobin measurements are shown at the bottom.

been using basal-bolus insulin therapy. Over the past year prior to starting d-Nav, his HbA1c had become higher than 75 mmol/mol (higher than 9%). On 17 January 2013, he started using d-Nav. It was set with 40 units of long-acting insulin per day and 12 units of rapid-acting insulin with breakfast, lunch and dinner. The correction factor was 1 unit for every 5 mmol/L glucose above 6.7 mmol/L (1 unit for every 90 mg/dL glucose above 120 mg/dL). Figure 3 denotes changes in insulin dosage, weekly mean glucose, hypoglycaemia (glucose ≤ 3.3 mmol/L or ≤ 60 mg/dL) and attenuations in HbA1c. During the first 6 months, the device gradually increased long-acting insulin up to ~100 units/day. Whereas rapid-acting insulin dosage for breakfast was changed only slightly, the ones for lunch and dinner saw a greater increase (changes in the correction factor are not shown in the graph). In August 2013, d-Nav reduced long-acting insulin dosage and all boluses due to a decrease in insulin requirements evident through low glucose readings. The frequency of minor hypoglycaemia during the past 2 months of the follow-up ending in September 2013 was 1 event/week without nocturnal episodes. Attenuations in HbA1c are shown in figure 3. During this entire 8-month period, d-Nav adjusted insulin dosage –40 times.

Case 4

Patient number 4 is a 25-year-old woman with type 1 diabetes for 6 years. She has been treated with basal-bolus insulin therapy incorporating carbohydrate counting. Over the past year prior to starting d-Nav, her HbA1c had become higher than 9% (75 mmol/mol). On 28 November 2013, she started using d-Nav, which was set to 46 units of long-acting insulin per day. Initial rapid-acting insulin boluses were based on a ratio of 1 unit of insulin for every 5 g of carbohydrates before each meal, corrected with 1 unit for every 2 mmol/L glucose above 6.7 mmol/L (1 unit for every 36 mg/dL glucose above 120 mg/dL). Figure 4A denotes changes in long-acting insulin dosage, weekly average meal bolus, weekly mean glucose, hypoglycaemia (glucose ≤ 3.3 mmol/L or ≤ 60 mg/dL) and attenuations in HbA1c. Owing to the high frequency of hypoglycaemia, the device rapidly reduced the dosage, particularly long-acting insulin and rapid-acting insulin to carbohydrate ratio for lunch and dinner. By 31 January 2014, she was using 10 units of long-acting insulin per day while rapid-acting insulin boluses were 1 unit for every

11 g of carbohydrates for breakfast, 1:17 for lunch and 1:13 for dinner, with a correction of 1 unit for every 5 mmol/L glucose above 6.7 mmol/L (1 unit for every 90 mg/dL glucose above 120 mg/dL). Since she exhibited consistent patterns of low glucose, the device adjusted dosage 40 times over a period of 2 months, resulting in a considerable decline in the frequency of daytime and nocturnal hypoglycaemia (figure 4B).

Case 5

Patient number 5 is a 68-year-old woman with type 2 diabetes for 13 years, treated with insulin for 4 years. Lately, she has been treated with biphasic insulin therapy two times per day with breakfast and dinner. Her HbA1c was 75 mmol/mol (9%) when she started d-Nav in 2013. Figure 5 denotes changes in insulin dosage, weekly mean glucose, hypoglycaemia (glucose ≤ 3.3 mmol/L or ≤ 60 mg/dL) and attenuations in HbA1c. For 7 months, her insulin dosage and mean weekly glucose levels remained relatively stable until June 2014, when her insulin requirements diminished abruptly by about 50% over a period of 2 weeks and the frequency of hypoglycaemia increased. To compensate for the change in glycaemic trends, d-Nav decreased the breakfast and dinner dosage. In July 2014, she visited the diabetes clinic for a routine follow-up when the device was downloaded and changes in her glycaemic pattern were uncovered. The patient's symptomatology was fairly minor except for progressive fatigue. Investigations identified an antineutrophil cytoplasmic antibodies-positive rapidly progressive glomerulonephritis with deterioration of her plasma creatinine from 1 to 5 mg/dL (93–446 μ mol/L). The patient was subsequently treated with high doses of systemic glucocorticoids and her kidney function improved.

DISCUSSION

The provision of frequent insulin titrations is the single most imperative element in successful insulin therapy. Evidently, most clinical trials supervising insulin therapy provided frequent dosage adjustments by skilled study teams to achieve and maintain predefined HbA1c goals.^{6 10–15} Unfortunately, owing to the growing mismatch between the number of patients and specialised providers who can make dosage titrations, healthcare organisations are short of providing such rigorous chronic care.²⁰

We have mitigated this shortage by supervising automation and empowering patients to make their own frequent dosage

Figure 4 d-Nav download in patient 4. (A) The upper graph denoting the long-acting insulin dosage (in insulin units) and weekly average rapid-acting insulin dose for each meal. Insulin to carbohydrate ratios and correction factor (insulin to glucose ratio) are not shown. The lower graph denoting the weekly mean glucose (in mmol/L). Episodes of minor daytime hypoglycaemia are shown in the lower graph as red dots (glucose ≤ 3.3 mmol/L or ≤ 60 mg/dL). Episodes of nocturnal hypoglycaemia are shown in the lower graph as blue stars. The corresponding level of glucose during these events can be inferred from the y-axis. Glycated haemoglobin measurements are shown at the bottom. (B) Graphic illustration of hypoglycaemia frequency during the first and second months of the period when the device was used (before and after 29 December 2014).

adjustments. The d-Nav process of insulin titration is supervised by a team of nurses to answer patients' questions, correct usage errors (eg, in figure 1), identify atypical clinical courses (eg, in case 5) and above all to extend confidence among users.

The examples shown herein illustrate the rationale behind the service. Without provision of frequent insulin dosage titrations, patient 2 would have her long-acting insulin dosage predominantly adjusted every 3–6 months by her providers during her outpatient clinic visits. At this rate, it would most likely have taken 2 years to uncover the shortcomings of a long-acting insulin regimen and to replace the regimen. Patient number 3 needed about 30 insulin dosage adjustments to achieve the desired glycaemic goal. Accordingly, without frequent dosage adjustments, he would most likely have continued to use less

than half of each of the required long-acting insulin and rapid-acting insulin for lunch and dinner for years. Patient number 4 may have continued to be overdosed with long-acting insulin and rapid-acting insulin for dinner and suffered from recurrent hypoglycaemia. In the case of patient number 5, she may have been exposed to a high frequency of hypoglycaemia owing to the abrupt reduction of insulin requirements. The diagnosis of non-diabetes related kidney disease might have been delayed owing to mild symptomatology.

Potential disadvantages regarding the use of automated insulin dose adjustment could include:

- Dependence on the patient's cooperation. As we described above, only the minority of patients showed challenges in using the device correctly. Our findings are in agreement

Figure 5 d-Nav download in patient 5. The upper graph denoting the insulin dosage (in insulin units); the lower graph denoting the weekly mean glucose (in mmol/L). Episodes of minor daytime hypoglycaemia are shown in the lower graph as red dots (glucose ≤ 3.3 mmol/L or ≤ 60 mg/dL). Episodes of nocturnal hypoglycaemia are shown in the lower graph as blue stars. The corresponding level of glucose during these events can be inferred from the y-axis. Glycated haemoglobin measurements are shown at the bottom.

with the current knowledge related to the magnitude of this phenomenon.^{21 22}

- ▶ The device does not incorporate information about exercise and diet in the process of insulin dosage adjustment. It was previously shown that using glucose readings alone is sufficient to recreate insulin dosage adjustments made by trained providers (who can use additional clinical data), as long as they are done weekly.^{4 19}
- ▶ Lack of comparisons between DIGS and other handheld devices or smartphone applications (ie, positive control).²³ While a variety of smartphone applications and data delivery methods are becoming available, to the best of our knowledge, DIGS is the only system that offers fully automated insulin dosage adjustments without patients entering data or care providers' supervision. Given the growing shortage of care providers in the face of an increasing number of patients, we believe that automation is the only scalable solution for the problem. A comparison of DIGS with the current standard of care (negative control) is not likely to fulfil the equipoise principal, since it is well accepted that frequent insulin dosage titrations is superior, yet it cannot be delivered by the current healthcare model.
- ▶ Cost-effectiveness and reimbursement. Based on our experience, reimbursement of DIGS is well established given the considerable resources saving that it allows.^{24–26}

Preferably, insulin titrations should be performed by care providers experienced in the process of insulin dosage titration. Yet supervision of weekly adjustments by endocrinologists, diabetes nurses or case management specialists is not realistic due to finite resources. For illustration, in the USA, there are about 7 million patients using insulin.³ It takes at least 15 min to talk with a patient over the phone about recent glucose readings, deliberate and convey a dosage recommendation. Accordingly, assuming weekly phone calls for titrations, it would have needed over 1.7 million hours/week or about 50 000 providers fully dedicated to those phone calls. Yet, in the USA, there are less than 5000 endocrinologists and 10 000 diabetes nurses who are already overcommitted.

By coupling the process of capillary glucose monitoring and insulin dosage provision in a single device without the need for constant supervision, the device simplifies the process of insulin management and does not require additional user effort. Medical

staff supervision as part of the service, provides the needed user confidence and medical provision. We believe that DIGS has the potential to transform the standard of care (in the primary and secondary settings) by improving glycaemic balance in the growing population which requires lifelong insulin therapy.

Learning points

- ▶ The majority of insulin users sustain elevated glycated haemoglobin.
- ▶ Frequent dosage titrations are needed to overcome constant variations in insulin requirements.
- ▶ In reality, owing to the high workload, insulin dosage titrations are performed sporadically.

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