Diabetes Knowledge and Metabolic Control in Type 1 Diabetes Starting with Continuous Glucose Monitoring: FUTURE-PEAK.

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ABSTRACT

Purpose: To investigate whether diabetes knowledge and health literacy impact glycemic control after one year of intermittently scanned continuous glucose monitoring (isCGM) in people with type 1 diabetes (PWD1) ≥ 16 years.

Methods: In this prospective real-world cohort study we assessed diabetes knowledge using a new 10-item questionnaire (Patient Education And Knowledge [PEAK]), and health literacy using the validated 6-item Newest-Vital Sign-D (NVS-D) questionnaire. Primary endpoint was association between PEAK score and change in HbA1c. Secondary endpoints were link between NVS-D score and change in HbA1c, and that between time spent in/above/below range and PEAK/NVS-D scores.

Results: 851 subjects were consecutively recruited between 07/2016 and 07/2018. Median PEAK score was 8 (range:0-10) and median NVS-D score was 6 (range 0-6). HbA1c evolved from 7.9 [7.8-8.0]%, 63 [62-64] mmol/mol at start to 7.7 [7.6-7.7]%, 61 [60-61] mmol/mol ($p < 0.001$) at 6 months and to 7.8 [7.7-7.9]%, 62 [61-63] at 12 months ($p < 0.001$). HbA1c only improved in subgroups with higher scores (PEAK subgroups with score 7-8 [$p = 0.005$] and 9-10 [$p < 0.001$] and NVS-D score 4-6 [$p < 0.001$]). At 12 months, time spent below 70 mg/dl was reduced by 15 % ($p < 0.001$) and time spent below 54 mg/dl was reduced by 14% ($p < 0.001$), irrespective of PEAK/NVS-D score. Multiple linear regression analysis demonstrated an association of PEAK score, scan frequency and baseline HbA1c with evolutions in time in range and time in hyperglycemia.

Conclusions: isCGM reduced time in hypoglycemia and HbA1c evolved favourably. Our findings suggest that diabetes and health literacy affect glucometrics emphasizing the importance of education.

Key Words: type 1 diabetes, intermittently scanned continuous glucose monitoring (isCGM), education, time in range

INTRODUCTION

Obtaining good glycemic control is essential to avoid acute (hypo- and hyperglycemic events) and chronic complications in people with type 1 diabetes (PWD1). However, strict glycemic control is associated with an increased risk of hypoglycemia (1-3). Hypoglycemia is the main barrier in achieving tight glycemic control and also affects quality of life (4-5). To achieve good glycemic control frequent glucose monitoring, intensive insulin titration and a good insight into aspects of healthy living (health literacy) are required. PWD1 should be educated on how food (particularly carbohydrates), physical activity, stress, alcohol intake, and illness can affect glucose profiles, and how to prevent and correct hypo- and hyperglycemic episodes.

The advent of continuous glucose monitoring (CGM) systems has changed the way patients, doctors and diabetes nurses manage diabetes nowadays. CGM systems provide a comprehensive picture of glucose profiles allowing patients to make therapeutic adjustments to improve metabolic control. From 2014 onwards, intermittently scanned CGM (isCGM) (Freestyle Libre, Abbott Diabetes Care, Witney, UK) was introduced onto the market. This device differs from other CGM devices by the need for active “scanning” of the sensor, absence of alarms in the first version, and no need for calibration. It is fully reimbursed for PWD1 in Belgium since 2016. isCGM has transformed the daily life of PWD1 because it helps to reduce time in hypoglycemia, increase time in range (3.9-10.0 mmol/L), and improve HbA1c and quality of life (6-9).

The success of these novel technologies might however be critically dependent on the level to which people are educated, capable, and motivated to use them. Education is needed at the start of CGM, not only about technical aspects but also about lag time and the meaning of trend arrows, to be able to adjust rapid-acting insulin doses for correction boluses or for hypo prevention or correction (10). Health literacy is defined as a set of skills which allows an individual to obtain, process, and use health care information to make decisions favoring general health status. Diabetes literacy is an analogue of health literacy, focusing on skills needed for diabetes optimization. Diabetes literacy is closely linked to health literacy (11-13). However, there is conflicting data concerning the relationship between health/diabetes literacy and glycemic control (11-19). To the best of our knowledge we are the first to examine the impact of health literacy and diabetes knowledge on metabolic control in PWD1 starting with isCGM. We also assessed the impact of health literacy and diabetes knowledge on severe hypoglycemia, hypoglycemic coma and days of work/school absenteeism.

MATERIALS AND METHODS

Study design and participants

The present study is part of the FUTURE trial (Flash glucose monitoring study for diabetes, ClinicalTrials.gov: NCT02898714), which is a real-world cohort study in an unselected population of PWD1 (7). Participants aged 16 years or above were consecutively enrolled from 2 tertiary centers (Antwerp University Hospital and

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Data Collection

A self-developed 10-item questionnaire (Patient Education And Knowledge [PEAK] questionnaire) was used to assess diabetes literacy (cfr infra). A multidisciplinary team consisting of diabetologists, diabetes educators and PWD1 developed this PEAK questionnaire because there is a need for a tool that evaluates knowledge about insulin titration skills, correction factor, carbohydrate counting, physical activity, and interpretation of glucose trends. To the best of our knowledge, such a specific questionnaire did not exist. PEAK scores ranged from 0 to 10 with 0 “no diabetes knowledge” and 10 “excellent diabetes knowledge”. The correct answers are 1D, 2B, 3B, 4D, Q5 = 7 units, 6C, 7C, Q8 = 21 units, 9A, 10A.

We aim to evaluate your diabetes knowledge. Please check the box of the correct answer or write the correct answer in the designated area.

1 Before lunch you find out you forgot your morning dose of insulin. What do you do?

- 4

☐ Check glycemia and adjust the lunch bolus according to current glycemia

2 Does an apple contain carbohydrates?

- ☐ No, an apple does not contain carbohydrates.
- ☐ Yes, an apple contains 12.5 g of carbohydrates (1 carbohydrate portion)
- ☐ Yes, an apple contains 25 g of carbohydrates (2 carbohydrate portions)

3 Your glycemia is 90 mg/dl before going to bed. You went for an intensive biking session during 90 minutes. What do you do?

- ☐ Nothing, I plan a control of my glycemia in 60 minutes.
- ☐ I consume an extra snack (slow-acting carbohydrates) and try to plan an additional control of my glycemia in 60 minutes.
- ☐ I drink 30cc of coca cola and plan a control of my glycemia in 60 minutes.

4 Which of following products only consists of fast-acting carbohydrate?

- ☐ An apple
- ☐ A slice of brown bread
- ☐ A banana
- ☐ A glass of apple juice

5 You inject 1U of insulin for 10 g carbohydrates before a meal. Furthermore, you use an insulin correction schedule as follows: > 120 mg/dl: + 2U insulin; > 150 mg/dl: +4U insulin; > 180 mg/dl: +6U insulin. Before lunch your glycemia is 140 mg/dl and you will eat 50 g of carbohydrates. Please write down your administered insulin bolus.

6 You suffer from the flu and have a fever. What do you do?

- ☐ I reduce my insulin doses because my insulin need is decreased.
- ☐ I drink less.
- ☐ I plan extra controls of my glycemia and adjust my doses accordingly.

7 At 5 pm you measure your glycemia and the result is 'HIGH'. Your last meal was 4 hours ago. What do you do?

- ☐ I drink extra water and wait until the next meal (6pm) to administer an insulin correction bolus.
- ☐ I administer insulin as per my insulin correction schedule; I wait and plan a control of my glycemia before the next meal.
- ☐ I drink extra water and administer insulin as per my insulin correction schedule; I plan a control of my glycemia in one hour; If my result is still 'HIGH', I will contact my diabetes team; I will do this especially if I feel unwell and have to vomit.

8 You were instructed to use an insulin correction schedule as follows: >150 mg/dl: +1U; >200 mg/dl: +2U; >250 mg/dl: +3U; >300 mg/dl: +4U; >400 mg/dl: +6U. When scanning the sensor you measure a glycemia of 278 mg/dl. Your normal pre-prandial dose is 18U. How many units do you inject?

9 You notice a fatty deposition on your belly near your usual insulin injection sites. What do you do?

- ☐ I avoid injecting in these deposits as it can influence my glycemia.
- ☐ I carry on as usual. These deposits do not influence my glycemia.

10 Your glycemia on the sensor is 50 mg/dl, but you do not have a feeling of hypoglycemia. What do you do?

- ☐ I control my glycemia with a finger-stick; If I have a hypo I consume rapid-acting carbohydrates and an additional snack (e.g. fruit).
- ☐ I consume rapid-acting carbohydrates and an additional snack without controlling my glycemia.
- ☐ I don't feel like having a hypo, so I don't have to do anything.

The PEAK Questionnaire was analysed for its internal consistency using Cronbach's alpha and for the quality of questions as assessed with the "p" and "rit" values. The "p" value assesses the rate of difficulty, in other words the percentage of people that correctly answered the question. The higher the value, the easier the question. The "rit" value indicates how well a question fits the test; the higher, the better. A value >0.4 is very good, a value <0.2 indicates that reconstruction of the question should be considered. A high "rit" value means that the question has a good power to discriminate well-educated vs less well-educated people. The respective "p" values of the 10 PEAK questions were 0.96, 0.76, 0.76, 0.69, 0.57, 0.96, 0.49, 0.75, 0.93 and 0.83. The respective "rit" values were 0.32, 0.49, 0.38, 0.42, 0.30, 0.48, 0.58, 0.32 and 0.34. So, for instance Question 7 was a difficult question with a p-value of 0.49, but it has an excellent discriminative power with a rit value of 0.58. This means that in general those with a high total score gave a correct answer and those with a low total score answered this question incorrectly. For the purpose of analysis, we

divided the study population in tertiles according to score on the PEAK questionnaire (scores 0-6 vs 7-8 vs 9-10). Health literacy was assessed using a validated questionnaire (Newest Vital Sign-D [NVS-D]) with range 0 to 6 (20). A score of at least 4 (out of 6) discriminates between adequate and inadequate health literacy. Subjects filled out both questionnaires after the training session at the start of the study. Cronbach's alpha for the PEAK score was 0.712 and that of the validated NVS-D score was 0.735.

At baseline, after 6 and 12 months participants were asked to report on how many days of work or school absenteeism and how many diabetes-related events they experienced in the previous 6 months. Patient-reported medical interventions and emergency room admissions were validated using hospital records.

Outcomes

Primary endpoint was defined as the relationship between the change in HbA1c and the score on the PEAK questionnaire. Secondary endpoint was defined as the relationship between the change in HbA1c and the score on the NVS-D questionnaire. Other endpoints were the relationship between the score on the PEAK/NVS-D questionnaires and the change in time spent in different glycemic ranges (Time in Range [TIR: 70-180 mg/dl, 3.9-10.0 mmol/L], time below 54mg/dl [T<54: <54 mg/dL, <3.0 mmol/L], time below 70 mg/dl [T<70: <70 mg/dL, <3.9 mmol/L], time above 180 mg/dl [T>180: >180 mg/dL, >10.0 mmol/L], time above 250mg/dl [T>250: >250 mg/dL, >13.9 mmol/L]), and the impact on severe hypoglycemia, hypoglycemic coma, and days of work/school absenteeism.

Ethics

The protocol was approved by the institutional review board (Ethics Committee number 17/2/12). The study was executed in line with Good Clinical Practice guidelines of the Declaration of Helsinki in its latest form.

Statistics

Statistical analyses were performed using SPSS software for Windows (version 25; Armonk, NY: IBM Corp). Descriptive statistics were used to analyze population characteristics. Distributions of continuous data were tested for normality by the Kolmogorov-Smirnov test. One-way ANOVA was used to determine differences between groups for continuous data. Data are expressed as mean±standard error or mean±95%CI, except for patient characteristics, which are reported as mean±standard deviation. Differences in distributions of categorical data were evaluated by χ^2 (with Cramer's V) or Fisher Exact test. A linear mixed model with an unstructured covariance matrix was used to assess the evolution of HbA1c/time spent in different glycemic ranges in the total population and in the different PEAK/NVS-D subgroups. Cochran's Q-test (and post-hoc McNemar's test) was used to assess evolution of absenteeism, severe hypoglycaemia and hypoglycemic coma. Multiple linear regression was performed to assess whether age, gender, level of education, type of therapy (multiple daily injections/continuous subcutaneous insulin

infusion), HbA1c at start, scan frequency at 12 months, and score on the PEAK or NVS-D questionnaire (separately) were independently associated with either change in HbA1c (at start vs. 12 months) or time spent in the different glycemic ranges. The α -significance level was set at 0.05.

RESULTS

Patient characteristics

Between July 2016 and July 2018, 851 PWD1 were consecutively recruited. A slight majority of the participants were male (53%). Mean age was 45.4 ± 15.8 years with a diabetes duration of 25.1 ± 14.3 years, a BMI of 25.4 ± 4.2 kg/m² and a mean baseline HbA1c of $7.9 \pm 1.4\%$ (63 ± 14 mmol/mol). Most participants were on multiple daily injections (n=662, 79%). Medical records indicated that impaired awareness of hypoglycemia was present in 180 subjects (21.7%).

Level of education, diabetes and health literacy

Approximately half of the subjects (n=398/784, 50.8%) were higher educated than secondary school, 46.3% (n=363/784) were educated at secondary school level, and 2.9% (n=23/784) were educated at primary school level. Scores on both literacy questionnaires were high: 81.5% (n=528/648) of participants had a score of 7 or higher on the PEAK questionnaire (45.1% [n=292/648] had a very high score of 9-10) and 83.4% (n=584/700) had a score of 4 or more on the NVS-D questionnaire. Median PEAK score was 8 and median NVS-D score was 6. The correlation between the PEAK and the NVS-D score was 0.433 ($p < 0.001$). The average scanning frequencies at 6 and 12 months were respectively 9.4 ± 6.6 and 9.9 ± 6.4 scans/day.

Baseline characteristics of the different PEAK subgroups (scoring 0-6 vs. 7-8 vs. 9-10) were analyzed. Individuals with a higher score were younger, had a shorter diabetes duration, were more likely to be female, were more often using continuous subcutaneous insulin infusion and had a higher educational level (Table 1). Scanning frequency at 6 months was higher in the highest scoring PEAK subgroup compared to the lowest scoring PEAK subgroup (10.6 [9.6 ; 11.5] vs. 8.4 [7.4 ; 9.3], $p = 0.021$), however no difference between these two groups was noted after 12 months (10.7 [9.8 ; 11.7] vs 9.3 [8.1 ; 10.6] scan, $p = 0.29$). The percentage of T<70 and T<54 in the first two weeks of isCGM was lower in the group with the highest PEAK score compared to those scoring 7-8 ($p = 0.018$ and 0.022 respectively) (Table 1). No specific interaction between PEAK score and age was observed for glucometrics.

Analysis of baseline characteristics of the population according to the NVS-D questionnaire showed that individuals with a higher NVS-D score (score 4-6) were younger, had a shorter diabetes duration, and a higher level of education. Scanning frequency did not differ between NVS-D subgroups.

We noticed that 23.9% of the data of the PEAK questionnaire and 17.7% of the data of the NVS-D questionnaire were either lacking or invalid. Subjects either did not fill out the questionnaire at all or did not fill out the questionnaire correctly (forgot the backside of the paper). This may either be accidental (e.g. lapse in concentration) or

intentional (e.g. fear of failing the test in people with a lower educational level). Individuals who did not fill out the PEAK questionnaire correctly were older (53.3 ± 1.1 vs. 43.0 ± 0.6 years, $p < 0.001$), had a longer diabetes duration (28.8 ± 1.0 vs. 23.9 ± 0.6 years, $p < 0.001$) and a lower level of education ($p < 0.001$) than those who filled it out. All other parameters including HbA1c were similar between those who did and those who did not fill out the questionnaire. However, we cannot assume lower scores in people who did not fill out the PEAK questionnaire compared to those who did.

Evolution of HbA1c

For the total population, HbA1c slightly improved from 7.9 [7.8; 8.0]% (63 [62; 64] mmol/mol) at baseline to 7.7 [7.6; 7.7]% (61 [60; 61] mmol/mol) ($p < 0.001$) after 6 months and 7.8 [7.7; 7.9]% (62 [61; 63] mmol/mol) ($p < 0.001$) at 12 months (Fig 1A). When analyzing the evolution of HbA1c in relation to diabetes and health literacy, we observed no improvement in HbA1c in the group with the lowest PEAK score nor in the group with the lowest NVS-D score. However, HbA1c did improve in the groups with the higher PEAK scores and in the NVS-D group scoring 4-6 (Fig 1B & C). Linear regression analysis showed the following regression equation: change in HbA1c [HbA1c 12 months – HbA1c at start] = $5.103 - [0.636 \times \text{HbA1c at start}] + [0.252 \times \text{gender}] + [0.006 \times \text{age}] - [0.221 \times \text{level of education}] - [0.04 \times \text{scan frequency at 12 months}]$; $F=100.467$, $p < 0.001$, adjusted $R^2=0.538$). PEAK-score, NVS-D score and type of insulin therapy were no significant predictors of change in HbA1c.

Evolution of time in ranges

For the total population, percentage of $T < 70$ and $T < 54$ decreased respectively from 9.6 [9.1; 10.1]% and 4.2 [3.9; 4.5]% in the first two weeks to 8.4 [8.0; 8.9]% and 3.7 [3.4; 4.0]% at 6 months ($p < 0.001$ and $p = 0.001$ resp.) and 8.2 [7.8; 8.7]% and 3.6 [3.4; 3.9]% at 12 months ($p < 0.001$ for both levels of hypoglycemia) (Fig 2A). In other words, $T < 70$ and $T < 54$ were reduced by 15% and 14% respectively at 12 months, corresponding with an absolute reduction of 20.2 minutes/day and 7.6 minutes/day. The decrease in $T < 70$ and $T < 54$ was similar among the PEAK/NVS-D subgroups, but just failed to reach statistical significance for $T < 54$ for the PEAK subgroup with the highest score and for the NVS-D subgroup scoring 0-3 (Fig 2B & C). Multiple linear regression analysis could not find any parameter predicting change in $T < 54$ and $T < 70$.

TIR did not change during the study period, neither in the total population nor according to PEAK/NVS-D scores. However, a significant regression equation was found with HbA1c at start, scan frequency and PEAK score for change in TIR (change in TIR [TIR 12 months – TIR at start] = $0.088 - [0.917 \times \text{HbA1c at start}] + [0.510 \times \text{PEAK score}] + [0.237 \times \text{scan frequency at 12 months}]$; $F=7.708$; $p < 0.001$; adjusted $R^2=0.042$). NVS-D score was not a significant predictor of evolution of TIR. In the total population, $T > 180$ slightly increased from 37.7 [36.6; 38.9]% in the first two weeks to 39.5 [38.3; 40.7]% at 6 months and 39.9 [38.7; 41.1]% at 12 months ($p < 0.001$ for both time points). $T > 180$ increased in all PEAK subgroups, irrespective

of their score, whereas for NVS-D it only increased in the lowest scoring subgroup. PEAK score and scan frequency were independent predictors of change in T>180 (change in T>180 [T>180 12 months – T>180 at start] = $8.468 - [0.539 \times \text{PEAK score}] - [0.212 \times \text{scan frequency at 12 months}]$; $F=4.564$, $p=0.011$, adjusted $R^2=0.015$).

T>250 showed no evolution from two weeks to 12 months, not in the total group and no differences across the different PEAK/NVS-D subgroups were noted (supplemental material – S4). HbA1c at start, scan frequency and PEAK score were significant predictors of change in T>250 (equation: change in T>250 [T>250 12 months – T>250 at start] = $-4.326 + [1.254 \times \text{HbA1c at start}] - [0.462 \times \text{PEAK score}] - [0.174 \times \text{scan frequency at 12 months}]$; $F=9.243$, $p<0.001$, adjusted $R^2 = 0.052$). NVS-D score was not a significant predictor of evolution of T>180 nor of T>250.

Evolution of severe hypoglycemia and work/school absenteeism

In the total population the number of individuals experiencing severe hypoglycemia and who reported diabetes-related work/school absenteeism decreased over the 12-month follow-up period ($p<0.001$ for both), whereas the number of subjects experiencing hypoglycemic coma remained stable.

The number of subjects experiencing severe hypoglycemia in the last 6 months decreased at 12 months in the PEAK subgroup with a score 0-6 (from 22 [24.0%] to 3 [4.0%], $p<0.001$) and in those with a score 7-8 (from 46 [22.3%] to 13 [7.2%], $p=0.001$). In the subgroup with the highest PEAK score, a significant decrease was noted at 6 months compared to baseline (from 43 [16.7%] to 20 [9.6%], $p=0.031$), but at 12 months there was no difference compared to baseline ($n=17$, 18.3%). The number of subjects experiencing severe hypoglycemia was reduced only in the NVS-D subgroup with the highest score (from 93 [18.3%] to 26 [6.9%] after 12 months, $p<0.001$).

The number of subjects experiencing hypoglycemic coma remained stable across the PEAK/NVS-D subgroups.

The number of individuals reporting absenteeism decreased at 12 months only in the PEAK subgroup with the highest score (from 28 [11.4%] to 6 [3%], $p=0.002$). Likewise, absenteeism at 12 months decreased significantly in the high scoring NVS-D subgroup (from 52 [10.4%] to 13 [3.1%], $p<0.001$) (Tables 2 & 3).

Multiple regression analyses showed that the change in the frequency of severe hypoglycemia, hypoglycemic coma, and that for school/work absenteeism did not show any association with baseline HbA1c, PEAK or NVS-D score, scanning frequency or any other parameter.

DISCUSSION

In this large bicentric prospective cohort study, we assessed whether diabetes knowledge and health literacy would impact glycemic control, severe hypoglycemia, hypoglycemic coma and days of work or school absenteeism in PWD1 starting with isCGM during 1 year of routine clinical follow-up. Important to note is that, although individuals were followed in specialized diabetes centers, no in- or exclusion criteria

were used, thereby avoiding selection bias. Indeed, these people do reflect the overall type 1 diabetes population in Belgium (21).

In the total population, HbA1c slightly improved after 6 and 12 months compared to baseline with, however, a small statistically significant increase at 12 months compared to 6 months. The clinical relevance of this evolution is marginal. Also, T<70 and T<54 were reduced by respectively 20.2 and 7.6 minutes a day after 12 months. The IMPACT-trial showed a similar decrease in time spent in hypoglycemia, albeit more pronounced, which is possibly due to the selection of highly motivated and well-controlled individuals in that trial (6). In our study, the reduction of time spent in hypoglycemia was fairly consistent in nearly all PEAK/NVS-D subgroups.

TIR did not change throughout the study in the complete cohort, but we did observe an increase in T>180 by 31.7 minutes a day. The decrease in HbA1c in combination with a decreased time spent in hypoglycemia, a stable TIR and an increase in T>180 seems counter-intuitive. This may be due to the definition of TIR. It is possible that patients spent more time in the lower ranges of TIR (70-140mg/dl) than in the higher ranges (140-180mg/dl). This would go undetected. Furthermore, baseline measurement of time in ranges were taken after 2 weeks of unblinded use of isCGM. Improvement in glycemic control might have occurred during this short time period. This could result in an underestimation of the beneficial effects of isCGM and might partly explain the observed discrepancy between evolution of HbA1c and the time in ranges. Finally, we also noted a decrease in frequency of severe hypoglycemia and work/school absenteeism in the total group.

isCGM provides a comprehensive picture of glucose profiles, allowing patients to make therapeutic adjustments to improve metabolic control and it has been shown to reduce time in hypoglycemia, increase time in range, improve HbA1c and quality of life (6-9). However, the abundance of data that people using isCGM see and have to interpret can also be perceived as challenging or sometimes overwhelming. Therefore, we hypothesized that adequate health literacy and diabetes knowledge are needed to achieve favorable results with this new technology.

Previous studies on this topic report conflicting results: some report no association between health literacy/diabetes knowledge and glycemic control (11-16), while others did find a significant association (17-19). Studies in this area are heterogeneous, using different study designs, studying different populations and using different measures of health literacy and diabetes knowledge, and are thus difficult to compare. To the best of our knowledge, this is the first study assessing in detail whether diabetes knowledge and health literacy impact outcomes in adults with type 1 diabetes starting with isCGM. In order to be able to evaluate in detail knowledge about insulin titration skills, correction factor, carbohydrate counting, physical activity, and interpretation of glucose trends, we developed this new PEAK questionnaire. We observed that the favorable evolution of HbA1c only manifested itself in subgroups with a higher score on the PEAK/NVS-D questionnaire, suggesting that diabetes knowledge and health literacy do have an influence on HbA1c in patients starting with isCGM. However, multiple linear regression analysis

identified HbA1c at start, gender, age, level of education, and scan frequency as the most important factors. PEAK score was identified as one of the factors predicting both TIR and time in hyperglycemia (both $T > 180$ and $T > 250$), besides scan frequency and HbA1c at start.

Importantly, in the total cohort we observed a decrease in frequency of the number of people reporting work/school absenteeism or severe hypoglycemia. The number of subjects experiencing hypoglycemic coma remained stable during the study period, irrespective of PEAK/NVS-D score, but numbers were very low. The number of subjects experiencing severe hypoglycemia at 12 months decreased only in the PEAK subgroups with a low to moderate score. These people showed room for improvement.

Absenteeism from work/school significantly decreased at 12 months only in the highest scoring PEAK/NVS-D subgroups. A decrease in the other subgroups was observed, however significance was not reached because the small size of the subgroups and the infrequency of events. These findings suggest that diabetes knowledge and health literacy, as assessed in this study, have no serious impact on more distal health outcomes such as work/school absenteeism, hypoglycemic coma and severe hypoglycemia in our study population. Literature in this area is scarce and prone to bias because events are often self-reported by study participants. In our study, all medical interventions, hospitalisations and emergency admissions were confirmed using hospital records. Nevertheless, in the general population low health literacy levels are associated with a multitude of adverse health outcomes such as increased number of hospitalisations, emergency admissions and, among elderly individuals, an increase in mortality (22).

Our study has limitations. Our analysis to determine the influence of diabetes knowledge and health literacy was hampered by the fact that the large majority of individuals had high scores on both questionnaires. Indeed, 81.5% of participants had a score ≥ 7 (45.1% had a very high score of 9-10) on the PEAK questionnaire and 83.4% had a score ≥ 4 on the NVS-D questionnaire. Nevertheless, in general, higher scores were associated with better outcomes in terms of HbA1c reduction, time spent in hypoglycemia, and absenteeism from work/school. We used a newly developed tool, the PEAK questionnaire, to assess diabetes knowledge from a practical point of view, inquiring about aspects that are relevant for daily management of type 1 diabetes. In our population, it showed a fairly good internal consistency, a good discriminative power, and a good correlation with NVS-D score. In addition, results for evolution of HbA1c, hypoglycemia, and TIR were concordant between questionnaires, which suggest that the PEAK questionnaire has a value in assessing diabetes literacy. The high scores on both questionnaires are probably the result of the high level of diabetes literacy in PWD1 in Belgium. It would be interesting to utilize these questionnaires in PWD1 in a different setting, to evaluate the influence of organization of the healthcare system. We note that about a quarter of the participants did not fill out the PEAK questionnaire correctly. This may either be accidental (e.g. lapse in concentration) or intentional (e.g. fear of failing the test in

people with a lower educational level). We did however notice that these people had a lower level of education than those who filled it out, but HbA1c and other glucometrics were comparable. However, we cannot assume a less optimal evolution of glucometrics in this group. But if this would be the case, it would strengthen our observations.

Strengths of the study are the large sample size and the paucity of exclusion criteria. Our study population reflects a real-world population of individuals living with type 1 diabetes.

Conclusion

isCGM is a new technology and offers patients more insight in glycemic trends. isCGM resulted in reduced time spent in hypoglycemia, with, however, an increase in T>180. HbA1c evolved favourably, but the reduction was marginal. Our findings suggest that diabetes knowledge and health literacy affect glucometrics and work/school absenteeism in individuals starting with isCGM, and as such emphasize the importance of education.

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Author contributions

C.D.B., S.C., C.Ma, and P.G. designed this study. S.C., N.B, B.B, and C.Mo collected the data. S.C. and B.B. analyzed the data and performed statistical analyses. B.B. wrote the first draft of the manuscript and made Figures/Tables. All authors discussed the data and edited the manuscript. B.B., S.C., P.G. and C.D.B. are guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data Availability: Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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Legends to figures

Figure 1: A. Evolution of HbA1c during the study period. B. Evolution of HbA1c during the study period according to PEAK subgroup. C. Evolution of HbA1c during the study period according to NVS-D subgroup. Linear mixed model analysis. Reported values: mean $\pm$ SE. * $p < 0.05$. X-axis: 0 = start of study (2 weeks), 6 = 6 months, 12 = 12 months.

Figure 2: A. Evolution of time <70 and time <54 during the study period. B. Evolution of time <70 and time <54 during the study period according to PEAK subgroup. C. Evolution of time <70 and time <54 during the study period according to NVS-D subgroup. Linear mixed model analysis. Reported values: mean $\pm$ SE. * $p < 0.05$. X-axis: 0 = start of study (2 weeks), 6 = 6 months, 12 = 12 months.

TABLE 1: Baseline characteristics and glucometrics according to PEAK SCORE

	PEAK 0-6 (group 0)	PEAK 7-8 (group 1)	PEAK 9-10 (group 2)	p-value
Sex (Male) N (%)	79 (65.8)	141 (59.7)	122 (41.8)	Between-group difference (p<0.001)
Age (year)	47.5 [44.5; 50.4] (N=120)	45.6 [43.6; 47.5] (N=236)	39.0 [37.4; 40.6] (N=292)	Between-group difference: groups 0, 1 vs 2 (p<0.001)
BMI (kg/m²)	25.5 [24.7; 26.2] (N=115)	25.5 [24.9; 26.0] (N=232)	25.2 [24.7; 25.7] (N=290)	NS
Diabetes duration (year)	26.3 [23.4; 29.1] (N=119)	25.6 [23.7; 27.5] (N=236)	21.6 [20.2; 23.0] (N=289)	Between group-difference: groups 0 vs 2 (p=0.007) and groups 1 and 2 (p=0.004)
Education (higher) N (%)	36 (35.3)	118 (52.4)	181 (67.3)	Between-group difference (p<0.001)
Treatment (MDI) N (%)	95 (81.9)	202 (86.0)	201 (69.3)	Between group-difference: groups 0, 1 vs 2 (p<0.001)
Basal insulin (U)	23.5 [21.1; 25.9] (N=105)	24.2 [22.4; 25.9] (N=208)	23.1 [21.7; 24.6] (N=265)	NS
Bolus insulin (U)	26.1 [22.6; 29.5] (N=51)	30.4 [27.2; 33.6] (N=87)	28.4 [25.9; 30.9] (N=80)	NS
Hba1c (%)	7.9 [7.7; 8.1] (N=100)	8.0 [7.8; 8.2] (N=235)	7.9 [7.7; 8.1] (N = 290)	NS*
Time <54 (%)	4.5 [3.5; 5.5] (N=88)	4.8 [4.1; 5.4] (N=197)	3.7 [3.2; 4.1] (N=252)	Between group-difference: groups 1 vs 2 (p=0.022)
Time <70 (%)	9.7 [8.3; 11.1] (N=88)	10.6 [9.6; 11.6] (N=197)	8.9 [8.1; 9.6] (N=252)	Between group-difference: groups 1 vs 2 (p=0.018)
Time in range (%)	50.8 [47.8; 53.8] (N=88)	52.0 [49.9; 54.1] (N=197)	53.2 [51.5; 54.9] (N=252)	NS
Time >180 (%)	39.5 [36.1; 42.9] (N=88)	37.4 [35.0; 39.8] (N=197)	37.9 [35.9; 39.9] (N=252)	NS
Time >250 (%)	17.3 [14.7; 19.8] (N=88)	16.6 [14.7; 18.5] (N=197)	15.7 [14.3; 17.1] (N=252)	NS
Scan frequency 12 months N (95% CI)	9.3 [8.1; 10.6] (N=94)	9.8 [8.9; 10.7] (N=190)	10.7 [9.8; 11.7] (N=231)	NS

* NS = non significant

One-way ANOVA: HbA1c, time in different glycemic ranges, basal/bolus insulin, BMI, age and diabetes duration.

χ^2 -test: sex, education and treatment

Table 2 – Evolution of acute events for the PEAK subgroups

	PEAK score 0-6					
	Baseline	6 months	p-value	12 months	p-value	
			baseline		baseline	6 months
Severe hypoglycemia */† (N = 43)	22 (24.0)	9 (12.5)	0.065	3 (4.0)	<0.001	0.125
Hypoglycemic coma * (N = 43)	5 (5.6)	0 (0)	NS ‡	0 (0)	NS	NS
Work absenteeism * (N = 42)	8 (9.0)	5 (6.6)	NS	1 (1.3)	NS	NS
	PEAK score 7-8					
	Baseline	6 months	p-value	12 months	p-value	
			baseline		baseline	6 months
Severe hypoglycemia */** (N = 115)	46 (22.3)	19 (11.2)	0.170	13 (7.2)	0.001	1.0
Hypoglycemic coma * (N = 115)	8 (3.9)	3 (1.8)	NS	2 (1.1)	NS	NS
Work absenteeism * (N = 114)	21 (10.2)	9 (5.4)	NS	5 (2.7)	NS	NS
	PEAK score 9-10					
	Baseline	6 months	p-value	12 months	p-value	
			baseline		baseline	6 months
Severe hypoglycemia */** (N = 135)	43 (16.7)	20 (9.6)	0.031	17 (8.3)	0.078	0.549
Hypoglycemic coma * (N = 131)	4 (1.6)	3 (1.4)	NS	2 (1.0)	NS	NS
Work absenteeism * (N = 122)	28 (11.4)	17 (8.2)	0.189	6 (3)	0.002	0.065

* Severe hypoglycemia/hypoglycemic coma/work or school absenteeism: participants experiencing an event (N (%))

† Severe hypoglycemia = help from third parties for hypoglycemia

‡ NS = non significant

Outcomes are the result of Cochran's Q-test (with post-hoc McNemar's test).

Table 3 – Evolution of acute events for the NVS-D subgroups

	NVS-D score 0-3					
	Baseline	6 months	p-value	12 months	p-value	
			baseline		baseline	6 months
Severe hypoglycemia */† (N = 43)	21 (23.6)	9 (12.5)	NS ‡	5 (6.7)	NS	NS
Hypoglycemic coma * (N = 43)	8 (9.0)	1 (1.3)	NS	1 (1.3)	NS	NS
Work absenteeism last * (N = 39)	7 (8.3)	5 (7.1)	NS	2 (2.6)	NS	NS
	NVS-D score 4-6					
	Baseline	6 months	p-value	12 months	p-value	
			baseline		baseline	6 months
Severe hypoglycemia */** (N = 256)	93 (18.3)	40 (10.1)	0.006	29 (6.9)	<0.001	0.186
Hypoglycemic coma * (N = 252)	15 (3.0)	6 (1.5)	NS	4 (1.0)	NS	NS
Work absenteeism * (N = 245)	52 (10.4)	26 (6.5)	0.043	13 (3.1)	<0.001	0.064

* Severe hypoglycemia/hypoglycemic coma/work or school absenteeism: participants experiencing an event (%).

† Severe hypoglycemia = help from third parties for hypoglycemia

‡ ‡ NS = non significant

Outcomes are the result of Cochran's Q-test (with post-hoc McNemar's test).

A

B

C

A

B

C