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Clinical trial

Performance of Dexcom-G5 and Freestyle Libre tested simultaneously in persons with type 1 or 2 diabetes and advanced chronic kidney disease.

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Abstract

BACKGROUND

Advanced chronic kidney disease (CKD) is a common complication for persons with type 1 and 2 diabetes and can often lead to glucose instability. Continuous glucose monitoring (CGM) helps users to monitor and stabilise their glucose. So far CGM and intermittent scanning CGM is only approved for persons with diabetes but not for those with advanced CKD.

AIM

To compare performance of Dexcom-G5 and Freestyle libre sensors in adults with type 1 or 2 diabetes and advanced CKD.

METHODS

This is a non-randomised clinical trial that took part at two outpatient clinics in western Sweden. All Patients with type 1 or 2 diabetes and estimated glomerular filtration rate (eGFR) of <30 mL/min/1,73m^2 were invited to participate. Forty patients (Full

Aanalysis Set=33) carried Dexcom G5 sensor for 7 days and Freestyle Libre sensor for 14 days simultaneously. For referencing measured capillary blood glucose (SMBG) with a high accuracy glucose meter (HemoCue) during the study period. At the end of the study all patients were asked to answer a questionnaire on their experience of using the sensors.

RESULTS

Mean age was 64.1 (range 41;77) years, HbA1c was 7.0 (SD 3.2)%, diabetes duration was 28.5 (SD 14.7) years. 27.5% of the study population were on haemodialysis, 22.5% on peritoneal dialysis. Mean absolute relative difference for Dexcom G5 *vs* SMBG was significantly lower than for Freestyle Libre *vs* SMBG, 15.2% (SD 12.2) and 20.9% (SD 8.6), mean difference 5.72 (95%CI 2.11-9.32) ,p=0.0036). Mean absolute difference was also significantly lower for Dexcom G5 than for Freestyle Libre, 1,21mmol/L (SD 0.78) and 1,76 mmol/L (SD 0.78), mean difference 0.55 (95%CI 0.27-0.83, P = 0.0004), Mean difference (MD) was -0.107 mmol/L and -1.10 mmol/L (P = 0.0002), respectively. 66% of Freestyle Libre values were in the no risk zone on the surveillance error grid compared to 82% of Dexcom G5 values.

CONCLUSION

Dexcom-G5 produces more accurate sensor values than Freestyle Libre in persons with diabetes and advanced CKD and is likely safe to be used by persons with advanced CKD.

Key Words: Type 1 Diabetes; Type 2 Diabetes; Chronic Kidney Disease; Continuous Glucose Monitoring; Accuracy; Mean Absolute Relative difference

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Core Tip: This study bridges a needed gap within the diabetes device area for persons with diabetes and advanced chronic kidney disease and was done in a home setting for analyses as close to real life as possible. The study found that Dexcom G5 showed a greater accuracy both in relation to mean absolute relative difference and on a surveillance error grid but participants rated their user experience for Freestyle Libre higher, but rated no difference in feeling safe.

INTRODUCTION

For persons with diabetes, good glycaemic control is essential to avoid problems due to diabetes complications (1). To reach the recommended glucose levels it is important to monitor glucose levels and for several years self-measurement of blood glucose (SMBG) with capillary measurements has been the best way to do this (1, 2). Over the last decades continuous glucose monitoring (CGM) and intermittent glucose monitoring (isCGM) has become more common within diabetes management and has for many replaced the multiple capillary tests. Both systems are made up of a small sensor that is inserted under the skin where it measures glucose levels in the interstitial fluid. CGM measures glucose levels continuously and every 5 minutes sends a glucose value to a handheld receiver or mobile telephone. It will give alarms for high and low glucose levels. The isCGM collects data and when the user scans the sensor with a handheld receiver or a mobile phone it sends the glucose levels to the receiver (3, 4).

Within the diabetes field there are many discussions as to who should be given CGM and isCGM. So far CGM and isCGM are only approved for persons with diabetes but not with chronic kidney disease (CKD) (3, 4) and mainly recommended for persons with type 1 diabetes and those who have problems with recurrent hypoglycaemia (1).

Advanced CKD is a common complication for persons with type 1 and 2 diabetes, it is estimated that 20-40% of people with diabetes will develop diabetic kidney disease and it is the leading cause of end stage renal failure (5, 6). A recently published study shows that as many as 5.1% of persons with type 1 Diabetes in Germany and Austria had eGFR below 30 mL/min, for Sweden and USA the corresponding figures were 1.5% and 2.1% (7). Advanced CKD increases the risk of hypoglycaemia and great glycaemic variations and therefore can it be of help for persons to monitor their blood glucose with a CGM or isCGM (8, 9). So far there are very few studies available on the accuracy of CGMs or isCGMs for persons with advanced CKD(10). Two of the most common systems are Dexcom and Freestyle Libre. Neither of these systems are approved for persons in dialysis(3, 4).

The aim of this study was to compare the performance of Dexcom G5 and Freestyle libre in adults with type 1 or 2 diabetes with CKD and estimated glomerular filtration rate (eGFR) of < 30 mL/min/1,73m^2, including patients on maintenance dialysis.

MATERIALS AND METHODS

This study took place at the NU-Hospital group and Sahlgrenska University Hospital. This is a non-randomized, non-blinded clinical study over 14-day period to compare the performance of Freestyle Libre 1 and Dexcom G5 for persons with diabetes and advanced CKD in an at home situation. The protocol was approved by the regional ethical review board of Gothenburg.

Study procedures

All participants signed a written informed consent before study start. The inclusion criteria were: Type 1 or Type 2 diabetes, between 18 and 80 years old, and eGFR < 30 mL/min/1.73m^2 both person in and not in dialysis. The Exclusion criteria were pregnancy, patients with severe cognitive dysfunction or other disease which makes glucose monitoring use difficult, continuous use of paracetamol, history of allergic reaction to chlorhexidine or alcohol anti-septic solution, abnormal skin at the anticipated glucose sensor attachment sites, eGFR ≤ 30 mL/min/1,73 m^2.

After obtaining a written and informed consent, a diabetes nurse inserted the two different sensors in accordance with instructions from the manufacturer. Dexcom G5 was inserted in abdomen and Freestyle Libre on the upper arm. Participants were instructed on how they should use each monitor and instructed how to calibrate the Dexcom G5. Calibrations were done using a HemoCue® DM RD 201 (Ängelholm, Sweden). All HemoCue meters were calibrated before being assigned to participants using an absolute isotop dilution GC.MC measurement system (11). The total measurement error/reproducibility imprecision of HemoCue is less than 6.5% (12). Earlier studies using HemoCue showed a strong correlation between capillary and venous HemoCue concentrations and capillary concentrations were considered to be a suitable reference (13). All participants were instructed by a diabetes nurse on how to

use the HemoCue meter. Participants were instructed to simultaneously document their blood glucose measured by HemoCue and the value of the Libre and Dexcom G5 in a diary minimum 3 times per day. Participants were instructed to calibrate their Dexcom G5 twice daily in accordance with manufacturer instructions and to do so after recording its value in the diary. Participants on maintenance dialysis (peritoneal dialysis or haemodialysis) were also asked to register start and finish of each session in their diary. After 7 days the Dexcom G5 was removed by the participants but they continued to record results from the Freestyle Libre and HemoCue. After the 14-day period participants returned the meters to site. Study personnel downloaded data from the meters using Glooko-Diasend system. HemoCue measurements were validated by personnel manually going through each value and comparing to the diary. When each sensor was finished, participants rated their experience on a 10-item visual analogue scale. Similar questionnaires have been used in earlier studies (14, 15).

Predefined endpoints

All endpoints were predefined and registered on ClinicalTrials.gov. The primary endpoint was the difference of Mean Absolute Relative Difference (MARD) between Dexcom G5 and Freestyle Libre using HemoCue (capillary glucose meter) as reference. Secondary endpoints were difference of Mean Absolute Difference (MAD) between Dexcom G5 and Freestyle Libre, difference of Mean Difference (MD) between Dexcom G5 and Freestyle Libre, correlation between the different systems. Predefined subgroup analyses for glucose ranges below 3.9 mmol/L, between 3.9 and 10 mmol/L and above 10 mmol/L as well as for those without dialysis and undergoing dialysis.

Independence of the study

The manufacturers of Freestyle Libre and Dexcom G5 were not involved in the design, performance, data analysis or publication of the article. No support was received from the manufacturers.

Statistics

After the sample size analysis it was decided to include 40 patients in the study (see supplement). All main analyses between Dexcom G5 and Freestyle Libre were

performed with paired analyses. All statistical analyses were predefined in the statistical analysis plan before database lock. All participants having at least 10 matched time points, with evaluable blood glucose values from both sensors and HemoCue (the reference capillary value) during the whole study period were included in the Full Analysis set (FAS). All matching time points were used. For paired analysis regarding continuous variables Fisher's non-parametric permutation test for paired observations was used and for dichotomous and ordered categorical variables Sign test was used. For comparison between dialysis subjects and subjects not in dialysis Fisher's non-parametric permutation test was used for continuous variables.

The primary variable was MARD, which is the mean absolute relative difference between estimated sensor glucose value of Freestyle Libre or Dexcom G5 and blood glucose measured with HemoCue. For each individual mean of following differences from each time-point was evaluated for both sensors: **| (** [redacted] **-** [redacted] **) | /** [redacted].

The Secondary variables were MAD and MD.

MAD is the mean absolute difference between estimated sensor glucose value of Freestyle Libre or Dexcom G5 and blood glucose measured with HemoCue. For each individual mean of following differences from each time-point was evaluated for both sensors: **|** [redacted] **-** [redacted] **|**.

MD is the mean difference between estimated sensor glucose value of Freestyle Libre or Dexcom G5 and blood glucose measured with HemoCue. For each individual mean of following differences from each time-point was evaluated: **(** [redacted] **-** [redacted]**)**,

where i = time-point during the analysed days in study.

The mean difference between Dexcom G5 and Freestyle Libre with 95% confidence intervals was calculated based on Fisher's non-parametric permutation test for paired observations for continuous variables. All analyses for different glucose ranges were based on HemoCue values within respective range.

To study the covariation between Dexcom G5/Freestyle Libre and HemoCue Pearson

correlation coefficient between each of the devices and HemoCue was calculated for each subject. These correlations were also analysed both for Dexcom G5 and Freestyle Libre with Fisher's non-parametric permutation test one sample test. Agreement between each of the devices and HemoCue were analysed with Bland-Altman' methods. The main result was the limit of agreement. If one got a value measured with one of the sensors you can calculate an interval where 95% of the HemoCue values would have been. The distributions of the difference between each of the sensor and HemoCue was also given together with Intraclass correlation coefficient (ICC), Bland-Altman plots and scatterplots.
All significance tests were two-sided and conducted at the 5% significance level. All statistical analyses were performed with SAS System Version 9.4, Cary, NC, USA.

Post-hoc analyses

The Surveillance Error Grid graph for Dexcom G5/Freestyle Libre *vs* HemoCue was calculated by using https://www.diabetestechnology.org/seg/. The proportion of sensor values within 15%, 20%, and 30% of reference values HemoCue for blood glucose >100 mg/dL (5.6mmol/L) or within 15, 20, and 30 mg/dL (0.8, 1.1, 1.7 mmol/L) of reference values for blood glucose ≤100 mg/dL (5.6 mmol/L) respectively was calculated. MARD Freestyle Libre *vs* HemoCue first week was compared with second week with the same requirements as main study with Fisher nonparametric permutation test for paired observations.

RESULTS

The study included 40 participants with type 1 and 2 diabetes and advanced CKD, 33 (FAS) met the criteria for data analysis, at least 10 time-points with evaluable values from both systems and the HemoCue within 5 minutes during the whole study period. Of the 7 patients that were not included in FAS two chose not to participate after starting the study, 5 did not meet the criteria for data analysis described above, that is, they did not have 10 matched time points for both sensors. Mean HbA1c was 7.0

%, 25.6% were women, mean age was 64.1 (range 41-77) and 50% were on dialysis. Further baseline characteristics in table 1.

Accuracy evaluations

The Mean Absolute Relative Difference (MARD) analysed for all participants for Dexcom G5 was significantly lower than for Freestyle Libre *vs* SMBG, 15.2% (SD 12.2) and 20.9% (SD 8.6) respectively, mean difference 5.72 (95%CI 2.11-9.32) ,p=0.0036). The Mean Absolute Difference (MAD)was also significantly lower for Dexcom G5 than for Freestyle Libre, 1,21mmol/L (SD 0.78) and 1,76 mmol/L (SD 0.78), mean difference 0.55 (95% 0.27-0.83, P = 0.0004),There was even a significant difference between the systems Mean Differences (MD). There was a systematic Mean Difference (MD) between Freestyle Libre and HemoCue of -1.10 mmol/L (95%CI -1.55 to -0.66 mmol/L, p<0.0001) but no systematic Mean Difference (MD) between Dexcom G5 and HemoCue -0.107 (95%CI -0.439 to 0.225), P = 0.052 (table 2).

We found that for glucose values that were in range (3.9-10.0mmol/L) and above range (> 10 mmol/L) there was a significantly lower MARD, MAD and MD for Dexcom G5 than for Freestyle Libre (Table 2). For glucose values in range the MARD was 14.8% (SD 10.6) for Dexcom G5 and 22.6% (SD 8.9) for the Freestyle Libre, mean difference 7.83 (95%CI 4.32-11.33, p<0.0001). The MARD for hyperglycaemic values were 12.3% (SD 11.6) and 16.6% (SD 11.1) respectively, mean difference 4.22 (95%CI 1.06-7.39, P = 0.010). There were few values below range (<3.9 mmol/L), 14 values from 9 individuals, table 2.

Sub-group analyses: persons needing and not needing dialysis

Sub-group analyses for MARD, MAD and MD were done for persons requiring dialysis and persons not requiring dialysis. The MARD for Freestyle libre for persons in dialysis was 19.3% (SD 7.4) compared to 22.5% (SD 9.5) for persons not in dialysis (P = 0.29). The corresponding values for Dexcom G5 were 15.5% (SD 14.8) and 15.0% (SD 9.6)), respectively (P = 0.91). For persons not in dialysis there was a significant difference between the sensors MARD and MAD, P = 0.0033 and P = 0.0057 respectively. For persons in dialysis there was a significant difference between the systems MAD, P =

0.035, whereas a numerical difference was found between the sensors MARD, yet not statistically significant (table 2). In a further sub-group analysis with persons on peritoneal dialyses, it showed numerically lower MARD and MAD for Dexcom G5 compared to Freestyle Libre as in the total population and there was a significant systematic difference between Freestyle Libre and HemoCue -1.58 (P = 0.01). There were 7 persons on Haemodialysis and Dexcom G5 showed a numerically lower MARD and MAD compared to Freestyle Libre in this sub-group, but the differences were less- (table 2).

Correlation between the systems

Analyses were done to see how well the systems correlated to the capillary reference system. Values obtained by Dexcom G5 and Freestyle Libre correlated significantly to those obtained by the HemoCue capillary reference system (r= 0.784, p<0.0001, and 0.777, p<0.0001, respectively).

Interclass correlation coefficient (ICC) was 0.68 for Freestyle Libre and 0.88 for Dexcom G5 and limits of agreement (-3.54- 1.34) for Freestyle Libre and (-1.94- 1.73) for Dexcom G5 (Table S1). This can even be seen clearly on the Bland-Altman plot in figure 1 and figure S2.

Patient experience

After using the systems, participants evaluated their experience (table3). Participants were significantly more positive towards Freestyle Libre than Dexcom G5 in all factors excepts on feeling safe where there was no significance between the two systems, Freestyle Libre scored 7.94 out of 10 and Dexcom G5 7.19 out of 10, P = 0.32 (table 3).

Post-hoc analyses

For Dexcom G5, %20/20= 79.6, which implies that 79.6% of the values above 5.6mmol/L were within 20% of the reference instrument, and within 1.11mmol/L (20mg/dL) for values below 5.6 mmol/L. The corresponding figure for Freestyle Libre was 61.3%. For %15/15 the values were 70.3% for Dexcom G5 and 43.9% for Freestyle Libre. For %30/30 the corresponding figures were 89.1% and 84.6% respectively. The Surveillance error grid (Figure 2) shows that 82% of the values for Dexcom G5 are

within the no risk zone (green colour) and 66.3% of the values for Freestyle Libre. Data from the second week of Libre shows that there is a greater MARD during this week, 24.8% (95%CI 20.4-29.2mmol/L) compared to 19.4 %, $P = 0.0042$. MARD for participants with type 1 diabetes was 11.8 % (SD 10.0) for Dexcom G5 and 17.4% (SD 5.7) for Freestyle Libre mean differences 5.6 (95%CI (-0.4-11.8, $P = 0.068$). Corresponding results for participants with type 2 diabetes were 16.2 % (SD 12.7) for Dexcom G5 and 21.6% (SD 8.6) for Freestyle Libre mean differences 5.4 (95%CI (0.25-10.49, $P = 0.042$).

DISCUSSION

Dexcom G5 showed a greater overall accuracy than Freestyle libre. Dexcom G5 even showed a greater accuracy for glucose values within range (3.9-10mmol/L) and above range (>10mmol/L). Furthermore, in a subgroup analysis the Dexcom G5 showed a greater accuracy for persons not in dialysis. However, for persons in dialysis Dexcom G5 had a numerically lower Mean Absolute Relative Difference (MARD) and a significantly lower Mean Absolute Difference (MAD) compared with Freestyle Libre. On the surveillance error grid Dexcom G5 had 82% of values within the no risk zone while Freestyle Libre had 66%. Glucose values from both sensors correlated well with the reference instrument, HemoCue. Freestyle Libre showed a greater systematic deviation than Dexcom G5. Participants rated their user experience of Freestyle libre higher after a 2-week period than Dexcom G5 but did not experience a difference in safety.

Earlier studies with similar methodology and same reference instrument have shown that the Freestyle libre had a MARD of 13.2% and an earlier Dexcom sensor (Dexcom 4G) had a MARD of 13.8% when tested in persons with type 1 diabetes (14, 15). A recent study analysed how well Freestyle libre correlates to capillary measurements (Medisafe® Fit) during haemodialysis in persons with type 2 diabetes found that the Freestyle Libre had a MARD between 13-22% depending on the glycaemic range and that it showed a 18.4 mg/dL (1.0mmol/L) lower values than the capillary reference instrument, The same study found that the Medtronic iPro Enlite sensor had a MARD

between 5-30% depending on glycaemic values and showed a 4.7mg/dL (0.3mmol/L) lower value than the reference instrument (10). Previously it's been shown that the Freestyle Libre deviates systematically by -0.5 mmol/L for persons with type 1 diabetes using HemoCue capillary measurements as a reference (15). The Dexcom G5 was found to have a MARD of 7.1-15.7% when tested in persons with type 1 diabetes and using a Yellow Spring Instrument as a reference (16).

Persons with advanced CKD more frequently experience glycaemic excursions (15). During haemodialysis there's an increased risk for hypoglycaemia, while patients with peritoneal dialysis have an increased hyperglycaemia risk (17, 18). It's therefore important that this group of patients receives all possible help to monitor their glucose levels and to increase their possibility of better glycaemic control. It is possible to speculate if these increased glucose excursions can possibly be the cause to the lower accuracy of these sensors for persons with advanced CKD. This study found that the accuracy of Freestyle Libre and Dexcom G5 while being used by persons with advanced CKD is similar to the accuracy of earlier sensors which were used as glucose indicators and not for insulin dosing decisions (14, 15). An earlier study has found that when persons on dialysis used CGM it led to more frequent treatment changes and better glycaemic control (19).

This study shows that even persons undergoing peritoneal dialysis, which can have high glucose fluctuations, have a MARD which is similar to previous systems. The peritoneal dialysis fluids do not seem to affect the MARD.

Freestyle Libre had a higher MARD and MAD than Dexcom G5 and there was a greater percentage of values within the safe zone for Dexcom G5. This can partly be explained by the fact that the Freestyle Libre showed a systematic deviation of -1.1mmol/L. It's important that users of the system are aware of the systems tendency of reporting lower glucose values. This systematic deviation is not only evident when the sensor is used by persons with advanced CKD although it seems to be greater for this patient group(15). The surveillance error grid showed that only 66% of Freestyle libre values were in the no risk zone whilst 82% of Dexcom G5 values were within the no risk zone.

Participants rated the user experience of the Freestyle Libre significantly higher than for the Dexcom G5. They found the system easier to use and easier to interpret the data on the receiver. The sensor was more comfortable, and it was less painful to insert. There was a greater interest to use the system in their daily life. This might be different with Dexcoms latest sensors which do not require calibration by the user. It is important to note that the users did not experience any difference of safety when using the system.

The strength of this study is that it was done independently from the manufacturers of this study. The study was done in a real-life environment as patients used the sensors in their daily life. All analyses were predefined. The limitations of this study were the short duration the participants used the sensors, and the evaluation of the user experience might change if the users become more comfortable and confident in the use of the sensors, and the questionnaire used is not validated. For certain subgroup analysis the number of participants or values obtained was low, therefore these analyses have to be interpreted with caution. It should be noted that Dexcom G5 was calibrated with the same capillary method as the reference system, and it cannot be excluded that more novel generations of Dexcom sensors which do not need calibrations may have a greater systematic deviation from HemoCue. Neither Dexcom G5 nor Freestyle Libre are approved to be used by persons with advanced chronic kidney disease. Another limitation is that the most novel sensors often used today were not evaluated. However, these data must be viewed in the light that CGM accuracy data are overall lacking in persons with Diabetes and advanced CKD and data are therefore urgently needed.

CONCLUSION

In conclusion, this study supports that Dexcom G5 has a similar accuracy in persons with diabetes and advanced CKD as in persons with diabetes without advanced CKD. The Freestyle Libre system showed similar correlations between sensor value and blood glucose values as Dexcom, but a lower number of values in the no risk zone indicating

that greater caution should be taken to use it in the current population. The Freestyle Libre showed a systematic deviation at least partly explaining the lower accuracy.

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