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Accuracy of flash glucose measurement in hemodialysis patients with and without diabetes mellitus

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Abstract:
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Glucose and insulin metabolism are altered in hemodialysis patients and diabetes management is difficult in these patients. We aimed to validate flash glucose monitoring in hemodialysis patients with and without diabetes mellitus as an attractive option for glucose monitoring not requiring regular self-punctures.

Methods
We measured interstitial glucose using a Freestyle Libre device in 8 hemodialysis patients with and 7 without diabetes mellitus over 14 days and compared the results to simultaneously performed self-monitoring of capillary blood glucose.

Results
In 720 paired measurements, mean flash glucose values were significantly lower than self-measured capillary values (6.12 ± 2.52 vs. 7.15 ± 2.39 mmol/l, p=1.3 E-86). Overall, mean absolute relative difference was 17.4% and mean absolute difference 1.20 mmol/l. The systematic error was significantly larger in patients without vs. with diabetes (-1.17 vs. -0.82 mmol/l) and on dialysis vs. interdialytic days (-1.09 vs. -0.90 mmol/l). Compared to venous blood glucose (72 paired measurements), the systematic error of flash glucose monitoring was even larger (5.89 ± 2.44 mmol/l vs. 7.78 ± 2.25 mmol/l, p = 3.74E-22). Several strategies to reduce the systematic error were evaluated, including the addition of +1.0 mmol/l as a correction term to all flash glucose monitoring values, which significantly improved accuracy.

Conclusions
Flash glucose monitoring systematically underestimates blood glucose in hemodialysis patients but taking this systematic error into account, the system may be useful for glucose monitoring in hemodialysis patients with or without diabetes.

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### Tables

**Table 1. Characteristics of study participants**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=15)</th>
<th>With diabetes (n=8)</th>
<th>Without diabetes (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>71±11</td>
<td>76±7</td>
<td>65±13</td>
</tr>
<tr>
<td><strong>Sex (male)</strong></td>
<td>11 (73)</td>
<td>5 (63)</td>
<td>6 (86)</td>
</tr>
<tr>
<td><strong>Dry Weight (kg)</strong></td>
<td>80.8±15.8</td>
<td>87.9±11.6</td>
<td>72.9±16.8</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>28.6±6.0</td>
<td>32.5±4.0</td>
<td>24.5±4.0</td>
</tr>
<tr>
<td><strong>Dialysis vintage (month)</strong></td>
<td>43 [29]</td>
<td>47 [34]</td>
<td>36 [38]</td>
</tr>
<tr>
<td><strong>Residual Kidney function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urine Volume (ml)</strong></td>
<td>700 [950]</td>
<td>920 [820]</td>
<td>630 [1700]</td>
</tr>
<tr>
<td><strong>Predialysis creatinine level (µmol/l)</strong></td>
<td>621 [194]</td>
<td>540 [187.5]</td>
<td>621 [282]</td>
</tr>
<tr>
<td><strong>Vascular access</strong></td>
<td>12 (80) / 3 (20)</td>
<td>7 (88) / 1 (13)</td>
<td>5 (71) / 2 (29)</td>
</tr>
<tr>
<td><strong>Dialysis schedule,</strong></td>
<td>7 (47) / 8 (53)</td>
<td>5 (63) / 3 (38)</td>
<td>2 (29) / 5 (71)</td>
</tr>
<tr>
<td><strong>Haemoglobin (g/l)</strong></td>
<td>109±12</td>
<td>104±12</td>
<td>115±9</td>
</tr>
<tr>
<td><strong>Albumin (g/l)</strong></td>
<td>39±3</td>
<td>38±2</td>
<td>39±4</td>
</tr>
<tr>
<td><strong>Duration of diabetes (years)</strong></td>
<td></td>
<td>25.5 [7]</td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>6.9±0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment of diabetes</strong></td>
<td>4 (50) / 3 (38) / 1 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Insulin / OAD / none)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em><em>Primary disease</em> (n)</em>*</td>
<td>6 (40)</td>
<td>6 (75)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>4 (26)</td>
<td>1 (13)</td>
<td>3 (43)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>3 (20)</td>
<td>2 (25)</td>
<td>1 (14)</td>
</tr>
<tr>
<td><strong>Obstructive uropathy</strong></td>
<td>3 (20)</td>
<td>1 (13)</td>
<td>2 (29)</td>
</tr>
<tr>
<td><strong>Glomerulonephritis</strong></td>
<td>2 (13)</td>
<td>1 (13)</td>
<td>1 (14)</td>
</tr>
</tbody>
</table>

Values are n (%), means ± SD or median [IQR]. * In some patients ESKD is multifactorial.

Abbreviations: BMI, body mass index; UF/W, ultrafiltration volume per dialysis session (average of all dialysis sessions during the study period) divided by dry weight.
Table 2. Accuracy of FGM by patient characteristics and measurement time.

<table>
<thead>
<tr>
<th></th>
<th>Paired Measurements (n)</th>
<th>FGM, mean±SD (mmol/l)</th>
<th>SMBG, mean±SD (mmol/l)</th>
<th>Mean difference (mmol/l)</th>
<th>MAD (mmol/l)</th>
<th>MARD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>392</td>
<td>7.5 ± 2.6</td>
<td>8.3 ± 2.5</td>
<td>-0.8 ± 1.3</td>
<td>1.1 ± 1.0</td>
<td>14.0 ± 10.7</td>
</tr>
<tr>
<td>No diabetes</td>
<td>328</td>
<td>4.5 ± 1.1</td>
<td>5.7 ± 1.2</td>
<td>-1.2 ± 1.0</td>
<td>1.3 ± 0.8</td>
<td>21.5 ± 11.9</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.00018</td>
<td>0.042</td>
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<tr>
<td><strong>Fluid removal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no / minimal</td>
<td>258</td>
<td>5.6 ± 2.0</td>
<td>6.4 ± 2.0</td>
<td>-0.8 ± 0.8</td>
<td>1.0 ± 0.6</td>
<td>15.7 ± 10.2</td>
</tr>
<tr>
<td>yes</td>
<td>462</td>
<td>6.5 ± 2.7</td>
<td>7.6 ± 2.5</td>
<td>-1.1 ± 1.3</td>
<td>1.3 ± 1.0</td>
<td>18.3 ± 12.6</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.366</td>
<td>0.507</td>
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<tr>
<td><strong>Dialysis schedule</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis days</td>
<td>288</td>
<td>6.2 ± 2.7</td>
<td>7.3 ± 2.6</td>
<td>-1.1 ± 1.3</td>
<td>1.3 ± 1.0</td>
<td>18.6 ± 12.8</td>
</tr>
<tr>
<td>Interdialytic days</td>
<td>432</td>
<td>6.1 ± 2.4</td>
<td>7.0 ± 2.2</td>
<td>-0.9 ± 1.1</td>
<td>1.1 ± 0.8</td>
<td>16.6 ± 11.1</td>
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<tr>
<td>p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.029</td>
<td>0.0047</td>
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<tr>
<td><strong>Study period</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>First 5 days</td>
<td>278</td>
<td>6.3 ± 2.7</td>
<td>7.1 ± 2.4</td>
<td>-0.8 ± 1.1</td>
<td>1.1 ± 0.8</td>
<td>15.6 ± 10.9</td>
</tr>
<tr>
<td>Day 6 – end</td>
<td>442</td>
<td>6.0 ± 2.4</td>
<td>7.2 ± 2.4</td>
<td>-1.1 ± 1.2</td>
<td>1.3 ± 1.0</td>
<td>18.5 ± 12.3</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
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<td></td>
<td>0.000037</td>
<td>0.0021</td>
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<tr>
<td><strong>Relation to meals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Preprandial</td>
<td>86</td>
<td>5.6 ± 2.1</td>
<td>6.4 ± 1.8</td>
<td>-0.7 ± 1.1</td>
<td>1.0 ± 0.8</td>
<td>16.9 ± 13.6</td>
</tr>
<tr>
<td>Postprandial</td>
<td>75</td>
<td>7.1 ± 2.5</td>
<td>7.9 ± 1.9</td>
<td>-0.9 ± 1.3</td>
<td>1.3 ± 0.9</td>
<td>17.1 ± 11.1</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.441</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Fluid removal refers to the average ultrafiltration volume per dialysis session over the entire study period. Patients with no / minimal fluid removal had a sufficient residual diuresis and only a minimal ultrafiltration volume (< 250ml and < 5ml / kg per dialysis session) to account for dialysate infused during flushing procedures. Patients with fluid removal depended on ultrafiltration (> 1500 ml and > 18ml/kg per dialysis session) to treat hypervolemia.
Accuracy of flash glucose monitoring in hemodialysis patients with and without diabetes mellitus

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Short Running Title: Flash glucose monitoring in hemodialysis

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Glucose and insulin metabolism are altered in hemodialysis patients and diabetes management is difficult in these patients. We aimed to validate flash glucose monitoring in hemodialysis patients with and without diabetes mellitus as an attractive option for glucose monitoring not requiring regular self-punctures.

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We measured interstitial glucose using a Freestyle Libre device in 8 hemodialysis patients with and 7 without diabetes mellitus over 14 days and compared the results to simultaneously performed self-monitoring of capillary blood glucose.

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In 720 paired measurements, mean flash glucose values were significantly lower than self-measured capillary values (6.12 ± 2.52 vs. 7.15 ± 2.39 mmol/l, p=1.3 E-86). Overall, mean absolute relative difference was 17.4% and mean absolute difference 1.20 mmol/l. The systematic error was significantly larger in patients without vs. with diabetes (-1.17 vs. -0.82 mmol/l) and on dialysis vs. interdialytic days (-1.09 vs. -0.90 mmol/l). Compared to venous blood glucose (72 paired measurements), the systematic error of flash glucose monitoring was even larger (5.89 ± 2.44 mmol/l vs. 7.78 ± 7.25 mmol/l, p = 3.74E-22). Several strategies to reduce the systematic error were evaluated, including the addition of +1.0 mmol/l as a correction term to all flash glucose monitoring values, which significantly improved accuracy.

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Keywords
Hemodialysis, flash glucose monitoring, glucose monitoring, interstitial fluid glucose level, diabetes mellitus, Freestyle Libre
Introduction

Diabetes mellitus represents the leading cause for end stage renal disease (ESRD) [1] and accounts for about 20 % of patients requiring renal replacement therapy (RRT) in Europe [2]. In addition, many patients with ESRD due to other renal diseases suffer from comorbid diabetes mellitus.

Adequate glycemic control in haemodialysis patients is hampered by a number of factors. First, advanced chronic kidney disease (CKD) leads to altered insulin and glucose metabolism (reduced insulin secretion, insulin resistance, decreased insulin clearance, reduced renal gluconeogenesis), which predisposes to both, hyper- and hypoglycemia [3]. Second, the haemodialysis procedure itself can directly affect glucose and insulin levels [4]. Third, dialysis schedules often interfere with food intake, many dialysis patients suffer from gastrointestinal complaints and they have to adhere to a variety of dietary restrictions. Fourth, most oral antidiabetic medications are contraindicated in ESRD. Finally, glycated haemoglobin (HbA1c) is not a reliable measure in dialysis patients due to reduced erythrocyte survival and treatment with erythropoiesis stimulating agents (ESA). Given the unreliability of HbA1c and the frequent need for insulin treatment, many haemodialysis patients rely on self-monitoring of blood glucose (SMBG) using capillary blood. This is associated with further discomfort in patients who already experience regular punctures for the dialysis procedure.

In recent years, new devices have been introduced to measure interstitial glucose levels either continuously (continuous glucose monitoring, CGM) or on demand (flash glucose monitoring, FGM) using a transcutaneous sensor [5–8]. In haemodialysis patients, interstitial glucose levels might correlate less well with blood glucose levels, since volume overload is common and haemodialysis treatment induces rapid fluid shifts between different compartments. In addition, uremic toxins might interfere with the measurement method [9]. Several studies have been published recently that validated CGM in haemodialysis patients [4,10–12], in contrast, only very few data are available on FGM. Compared to CGM, FGM has several advantages: the sensor is cheaper and can be left in place for up to two weeks, as compared to 6 to 10 days [13,14]. Furthermore, FGM devices are factory calibrated and do not require concomitant SMBG [15]. The most frequently used FGM systems is the FreeStyle Libre (FGM, Abbott Diabetes Care, Alameda, CA) patch, which gets attached to the intact skin on the back of the upper arm. Interstitial glucose measurements are stored in 15 minute intervals and can be displayed up to eight hours back after scanning the sensor with a reader [16].

Haemodialysis patients without diabetes also experience alterations in glucose- and insulin metabolism and insulin sensitivity [3] with frequent hypoglycemic episodes [17]. Postdialysis fatigue is a common complaint [18] and glucose enriched dialysate has been found to
decrease postdialysis fatigue [19,20], suggesting that fluctuating glucose levels in haemodialysis patients may contribute to symptoms. Thus, FGM might be also useful to monitor the glucose profile of haemodialysis patients without diabetes, both, on an individual basis and in clinical studies.

The purpose of this study was to evaluate the accuracy of the FreeStyle Libre FGM system to monitor glucose levels in both, haemodialysis patients with and without diabetes mellitus.
Subjects, Materials and Methods

Study Design
We performed a prospective observational study in two dialysis units run by the same hospital-based nephrology division (the cantonal hospital of Frauenfeld, Switzerland). The study was initiated in December 2019, the last patient visit was in July 2020. The observation period for every patient started with the placement of a FreeStyle Libre FGM sensor and lasted for 14 days, corresponding to the lifetime of the sensor. The study was approved by the Ethics committee of Eastern Switzerland (Ethikkommission Ostschweiz, EKOS) and conducted in adherence to the Declaration of Helsinki. All patients gave written informed consent.

Study Population
All haemodialysis patients aged > 18 years of the two dialysis units who had been treated with chronic outpatient intermittent haemodialysis for at least three months were asked for participation in the study. Patients with impaired vision that might interfere with SMBG, reading FGM values and completing a study diary were excluded. Further exclusion criteria were history of allergic reaction to the material of FreeStyle Libre and regular intake of paracetamol as it potentially interferes with the measurement method [8,9,21]. Patient screening was based on patient history in the electronic health records.

Interventions and measurements
A FreeStyle Libre FGM sensor was placed on the back of the upper arm of participants and left in place over the entire duration of the study. The attachment was always conducted by the same internal medicine resident, which had been instructed by a trained diabetic nurse prior to the investigation. The attachment always took place during the first dialysis session after the long interdialytic interval (i.e. on Monday or Tuesday). At the same time, patients were instructed in using the FreeStyle Libre FGM sensor and performing SMBG. Patients with diabetes continued to use their own SMBG devices, whereas patients without diabetes were instructed to use Contour XT. To ensure the highest amount of correspondence, the participants were asked to start the glucose measurements on the following day. Blood glucose levels were measured four times daily (before every meal and before bedtime) by SMBG, immediately followed by scanning of the FreeStyle Libre sensor. Participants were asked to record the readings as well as meals, physical activities, change of medication, or acute illness in a specially designed diary. The dialysate glucose concentration was 5.55 mmol/l. On the second and the third day of the trial (i.e. on a dialysis and a non-dialysis day), participants were instructed to perform three extra measurements within 1-2 hours after every meal to measure postprandial glucose concentrations. In addition, we measured
venous blood glucose values in the central hospital laboratory (on a Cobas pro integrated solution analyzer, Roche diagnostics (Schweiz) AG, Rotkreuz, Switzerland) immediately prior to every hemodialysis session.

After 14 days, participants returned the devices and data from the FreeStyle Libre were downloaded using the FreeStyle Libre computer software. The readings in the diaries were verified by the authors, comparing them to the downloaded data. In case of a dislodged sensor, a new sensor was installed, and measurements were completed sticking to the priorly defined 14-day interval.

Statistical analysis
We separately analysed paired FGM and SMBG values obtained during the regular preprandial and nighttime measurements; the pre- and postprandial measurements from the second and third day of the study; and measurements obtained on dialysis and non-dialysis days. All participants with at least 50% paired measurements available over a period of at least 7 days were included in the primary analysis. Participants with less paired measurements during a shorter period of time or with unreliable data due to non-compliance, acute illness or prolonged use of paracetamol were excluded. We used Bland-Altman plots and paired t-tests to compare the difference between paired glucose values measured by SMBG vs. FGM. We further calculated mean absolute difference (MAD) and mean absolute relative difference (MARD) for each patient, for all measurements, and for subgroups of patients or measurement values, as defined. For the comparison of mean difference, MAD and MARD between dialysis vs. interdialytic days, between the first 5 days vs. the reminder of the study period, and between pre- vs. postprandial values, we used a t-test; for the comparison between patients with vs. without diabetes and patients with high vs. low ultrafiltration volume, we used a nested t-test. Agreement between FGM and SMBG readings was further analyzed using the Surveillance error grid [22], available at https://www.diabetestechnology.org/seg/. Statistical analyses were performed using Microsoft Excel version 2013 and R software, version 4.0.2 (R Core Team 2020. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).
Results

Patient characteristics

Eighteen patients were included in the study. The median recording time of the sensor was 13 days (interquartile range 7-13). Three patients were excluded from the analysis: one discontinued due to acute illness requiring hospital admission, and two were non-compliant with SMBG (Figure 1). Data from 15 patients were analysed, 8 with and 7 without diabetes mellitus. One FreeStyle Libre sensor had to be replaced during the study period due to sensor failure. Baseline characteristics of all patients included in the analysis are shown in Table 1, and characteristics, observation period, number of paired measurements and measurement results for individual patients are shown in Supplementary Table 1.

Overall accuracy of FGM results

In total, 795 paired glucose measurements were available for analysis, 720 of which were from the regular preprandial and bedtime SMBG measurements, 75 from postprandial measurements. Mean values of all paired preprandial and nighttime glucose measurements by SMBG and FGM over the entire study period are shown in Figure 2, mean glucose values over the entire study period by time of the day are shown in Supplementary Figure 1 and mean daily glucose profiles by diabetes status and hemodialysis vs. interdialytic days in Supplementary Figure 2. Overall, mean FGM values were 0.98 mmol/l lower than SMBG values (6.12 ± 2.52 vs. 7.15 ± 2.39 mmol/l, p=1.3 E-86). Bland-Altman plots and Surveillance error grids for the entire study population as well as by diabetes status are shown in Figure 3. 68.8% of FGM values fell into zone A, and 19.3% into zone B. Mean absolute difference (MAD) and mean absolute relative difference (MARD) were 1.20 ± 0.92 mmol/l and 17.4 ± 11.9%, respectively. Accuracy of the measurements varied considerably between patients (Supplementary Figure 3), but was relatively independent on blood glucose level (Supplementary Figure 4 and Supplementary Table 2).

For the comparison of FGM values with venous blood glucose values, 72 predialysis measurements were available. Mean FGM values were 1.87 mmol/l lower than venous BG values (5.89 ± 2.44 mmol/l vs. 7.78 ± 7.25 mmol/l, p = 3.74E-22). 44.4 % of FGM values were in zone A, whereas 51.4% fell into zone B of the Surveillance error grid (Supplementary Figure 5). MAD was 2.0 ± 0.99 mmol/l and MARD 26.3 ± 12.39 %, respectively.

Accuracy of FGM values by patient characteristics and measurement time

We next analyzed whether diabetes status and other variables had an influence on systematic and random measurement error. The systematic error was significantly larger in patients without vs. with diabetes mellitus, during dialysis vs. interdialytic days as well as with growing use time of the sensor and tended to be higher in patients with vs. without fluid
removal during hemodialysis (Table 2). However, these differences were rather small compared to the overall systematic measurement error. Patients performed postprandial SMBG on both, a dialysis and a non-dialysis day. The results of paired pre- vs. postprandial measurements performed on these two days are shown in Table 2 and the corresponding Bland Altman plots and Surveillance error grids in Supplementary Figure 6.

**Correction for the systematic bias of FGM**

Given that we found a systematic underestimation of blood glucose monitoring by FGM, we aimed to derive a correction term that might increase its accuracy in hemodialysis patients. Since the overall systematic bias was very close to 1 mmol/l, relatively independent of absolute glucose levels (Supplemental Table 2) and the effect of patient subgroup and measurement time was relatively small (Table 2), we tested whether the simple correction term of +1 mmol/l to glucose readings obtained by FGM would result in a meaningful improvement of accuracy. After this correction, mean difference, MAD and MARD for FGM vs. SMBG in all 720 preprandial or bedtime paired measurements were 0.02 ± 1.15 mmol/l, 0.82 ± 0.81 mmol/l and 11.9 ± 10.7%, respectively. Bland-Altman plots and Surveillance error grids for corrected FGM measurement values compared to SMBG are shown in Figure 4. 87.8 % of FGM values fell into zone A, and 10.4 % into zone B. We also evaluated whether individual calibration of the device might improve accuracy. An individual correction term for every patient, based on the first four paired measurements, resulted in a mean difference, MAD and MARD of -0.51 ± 1.11 mmol/l, 0.89 ± 0.84 mmol/l and 12.7 ± 10.8%, respectively. An individual correction term based on the first two measurement days resulted in a mean difference, MAD and MARD of -0.33 ± 1.06 mmol/l, 0.78 ± 0.80 mmol/l and 11.0 ± 10.1%, respectively.
Discussion

The main findings of our study are that FGM using the FreeStyle Libre sensor led to a systematic underestimation of blood glucose levels in chronic haemodialysis patients, yet after adding a simple correction term, measured values were reasonably accurate.

CGM has gained growing popularity in the treatment of type 1 (T1DM) and recently also in type 2 diabetes mellitus (T2DM) patients. Current devices accomplish MARD results between 10 and 20% [15,23–25]. ISO 1597:2013 defines that at least 95% of measurements have to lie within ± 15% of the reference glucose concentration for blood glucose values ≥ 5.6 mmol/l, or within ± 0.83 mmol/l for blood glucose values < 5.6 mmol/l [23]. Measurement of glucose in interstitial tissue by CGM results in a physiological time lag of approximately 10-15 min compared to blood glucose levels [26]. Deviation from blood glucose levels is greater during rapid glucose changes [15,23,24,27] and hypoglycemia [24,28,29], but this bias is outweighed by several benefits of CGM: an enormous increase in the number of measurements and visualization of trends of daily glucose fluctuation that help to anticipate hypoglycemia, with most of the devices including a warning system to prevent both hypoglycemia and hyperglycemia [13], thus extending time in euglycemia or in target range. Compared to CGM, FGM has the advantage of factory calibration, thus obviating the need for SMBG to calibrate the device; a longer lifespan of the sensor [15], compact and light weight design [24] and of lower cost.

Tight blood glucose control is not considered essential in hemodialysis patients who mostly suffer from advanced macrovascular complications. However, even reasonable glycemic control is often difficult to achieve in these patients. Several studies have validated CGM in hemodialysis patients and found a reasonable agreement with SMBG [4,10–12]. The use of FGM in hemodialysis patients, in contrast, has been reported only very recently. FGM would be particularly useful in hemodialysis patients due to its factory calibration eliminating the need for SMBG. A total of six studies have reported the use of FGM in hemodialysis patients so far [30–35], however, only three of these reported validation against SMBG [33–35]. Compared to these studies, we found a somewhat higher but similar precision of FGM, as expressed by MAD and MARD.

Mean difference reflects systematic error, MAD and MARD reflect a combination of systematic and random measurement error. We found a significantly and relevantly lower mean glucose level by FGM as compared to SMBG, which pointed to a systematic measurement error. The underestimation of glucose levels was relatively constant across the absolute range of blood glucose levels (i.e. not proportional to the glucose level), which
suggested that an additive term (rather than a correction factor) might be used to correct for the systematic measurement error. Since the mean difference between paired FGM and SMBG values was very close to 1 mmol/l, we evaluated the utility of simply correcting FGM values by adding 1 mmol/l. Indeed, this correction term considerably improved the performance of FGM and yielded a MARD and results on Surveillance's error grid which were equivalent to the respective measures reported for non-dialysis patients with T1DM and T2DM [6,25,28,36] and in agreement with current recommendations and standards for CGM (ISO 1597:2013). While our study is the first to evaluate a correction term for the systematic measurement bias of FGM in hemodialysis patients, all three studies that previously validated FGM in hemodialysis patients found a near-identical systematic bias (Yajima et al: -19.9 mg/dL = -1.10 mmol/l, Matoba et al: -18.4 mg/dL = -1.02 mmol/l; not reported in numbers by Gennia et al. but visible from the correlation graph) [33–35]. An individual correction term derived for every patient from a number of paired measurements might allow for a more precise, individualized correction, since mean difference, MAD and MARD between FGM and SMBG varied considerably between patients (Supplement Table 1). However, two consecutive calibration days were needed to improve accuracy over the use of the simple universal correction term and this would require complicate calculations to be performed by the patients, resulting in only minor improvements.

The reason for the systematic measurement error of FGM in hemodialysis patients remains unclear. It is likely that alterations in volume status might influence equilibration between blood and interstitial fluid. This should, however, theoretically influence random variation rather than introduce a systematic bias. In addition, the dialysis procedure itself might lead to fluid and electrolyte shifts. We tested these hypotheses by separately analyzing days with vs. without dialysis treatment and patients with relevant fluid removal during hemodialysis vs. those with sufficient residual renal function not requiring relevant fluid removal. We found a somewhat higher systematic bias, MAD and MARD on dialysis days compared to non-dialysis days, while the difference between patients with relevant fluid removal vs. those without was not significant. In addition, measurement bias somewhat increased with increasing use time of the sensors. However, these influences were not large compared to the overall systematic measurement error. Thus, other factors, such as interference by uremic toxins, likely contribute to the systematic underestimation of blood glucose levels by FGM. Further study will be required to evaluate whether the same systematic bias is also present in patients with advanced renal failure not treated by hemodialysis. The mentioned effects of ultrafiltration rate and dialysis day on accuracy of FGM needs also to be taken into account when interpreting individual patient data, but again, these influences on overall accuracy are relatively small.
We have used SMBG as the reference against which to compare FGM, because the Freestyle Libre device is intended to be a replacement for SMBG, which represents the current standard of care. Furthermore, SMBG as a comparator provides more reference points and mirrors real-life accuracy during daily use, as compared to venous glucose measurements. In addition, we did also compare FGM values to a smaller number of simultaneously performed venous blood glucose measurements and found an even higher underestimation of blood glucose by FGM compared to venous levels. Further study is needed to evaluate whether SMBG also leads to some systematic blood glucose underestimation in hemodialysis patients.

Our study is to our knowledge the first that evaluated FGM in hemodialysis patients without diabetes. While we found a somewhat reduced accuracy compared to patients with diabetes, overall accuracy was reasonable in patients without diabetes, particularly after considering the correction factor of +1mmol/l. Hemodialysis patients without diabetes are at increased risk for hypoglycemic episodes due to a number of factors, e.g. reduced insulin clearance and reduced food intake [3,37]. Thus, FGM might represent a valuable tool to evaluate hemodialysis patients without diabetes with suspected hypoglycemic episodes and FGM might be used to evaluate the effect of subclinical hypoglycemic episodes on perceived dialysis fatigue [18], both, on an individual patient level as well as in the setting of clinical studies. The higher systematic bias of FGM in hemodialysis patients without diabetes as compared to those with diabetes is not simply attributable to lower accuracy of FGM at low glucose values, since measurement error was largely independent on absolute blood glucose values. The use of different SMBG devices (Contour XT from Abbott by patients without diabetes vs. their own device by patients with diabetes) and patients without diabetes being less familiar with SMBG measurements are potential explanations. Probably more importantly, however, interindividual variability of measurement error was relatively high and the number of patients in our study relatively low, such that few patients without diabetes and with a high individual bias of their measurements may have influenced the overall comparison.

Our study has several limitations. First, the study population was relatively small. However, due to a comparatively long study period, it was possible to obtain an adequate amount of paired measurements. Second, patients with diabetes used their own SMBG devices due to optimal handling, and accuracy might depend on the device used. Third, since capillary glucose measurements were performed by the participants themselves, we cannot exclude technical errors by participants although they were carefully instructed. However, the latter
two limitations reflect the real-life setting of the study, which also represents a strength, since FGM was validated under real-life conditions. Finally, relatively few paired venous blood glucose measurements were available as the gold standard against which to compare FGM.

**Conclusion**

Our study shows that FGM systematically underestimates blood glucose levels in hemodialysis patients. The systematic error depended on diabetes status and dialysis schedule, but these influences were relatively small compared to the overall systematic error of the entire cohort. Importantly, accuracy of FGM can be improved in both, patients with and without diabetes, by correcting for the systematic error, e.g. via a correction term of +1mmol/l. Thus, our findings validate FGM as a potentially useful tool for glucose monitoring in hemodialysis patients, when considering and correcting for the systematic error.
Figure legends

Fig. 1. Study Flow Chart.

Fig. 2. Glucose values for paired measurements by FGM and SMBG over the entire study period. Triangles and solid lines represent the mean of all FGM values, crosses and dashed lines the mean of all SMBG results.

Fig. 3. Bland-Altman Plots & Surveillance Error Grids for paired glucose measurements. Solid lines represent the mean difference, dashed lines the upper and lower confidence interval in the Bland-Altman Plots. Risk levels in the Surveillance Error Grids are color-coded and range from non (dark green) over moderate (yellow) to extreme (dark red).

Fig. 4. Bland-Altman Plots & Surveillance Error Grids for paired glucose measurements, after adding a correction term of +1mmol/l to all FGM values.
Funding

This investigator-initiated study did not receive external funding.

Conflict of interest

PW reports has participated at advisory board and received lecture fees from Abbott, Switzerland. The other authors have no conflict of interest to declare.

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Author contributions

MRW: investigation, formal analysis, visualization, writing – original draft; MD: formal analysis PW: conceptualization, resources, writing – review & editing, supervision; ADK: conceptualization, methodology, formal analysis, resources, data curation, writing – original draft, supervision, project administration

All authors have read and approved the final manuscript.
References


Monitoring

Parts of the data have previously been presented at the 77th Scientific Sessions of the American Diabetes Association in San Di. Diabetes Technol Ther 2018; 20: 541–549. doi:10.1089/dia.2018.0105


**Supplemental Files**

**Accuracy of flash glucose measurement in hemodialysis patients with and without diabetes mellitus**

Michèle R. Weber, Matthias Diebold, Peter Wiesli and Andreas D. Kistler

**Supplemental Table 1.** Individual study participants’ characteristics

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<th>DM history</th>
<th>Trial duration</th>
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<th>Mean FGM</th>
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<th>Mean Diff.</th>
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</table>
**Supplemental Table 2.** Systematic error according to blood glucose level. We used two different categorizations, by 2 mmol/l intervals (upper panel) and by normal vs. extreme (<3.9 / > 10.0 mmol/l) levels (lower panel).

<table>
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<tr>
<th>Blood Glucose Level</th>
<th>Matched pairs, n</th>
<th>Mean difference, mmol/l ± SD</th>
<th>MAD, mmol/l ± SD</th>
<th>MARD, %</th>
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<td>SMBG &lt;5 mmol</td>
<td>114</td>
<td>(-0.6) ± 0.9</td>
<td>0.9 ± 5.8E-01</td>
<td>19.9 ± 13</td>
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<td>SMBG 5-7 mmol</td>
<td>297</td>
<td>(-0.9) ± 0.8</td>
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<td>SMBG 7-9 mmol</td>
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<td>(-1.3) ± 1.3</td>
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<td>19.2 ± 12.9</td>
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<tr>
<td>SMBG 9-11 mmol</td>
<td>91</td>
<td>(-1.1) ± 1.5</td>
<td>1.5 ± 1.1</td>
<td>15.6 ± 11.8</td>
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<tr>
<td>SMBG &gt;11 mmol</td>
<td>60</td>
<td>(-1.0) ± 1.7</td>
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<td>10.4 ± 10.9</td>
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<td>SMBG &lt;3.9 mmol/l</td>
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<td>(-0.3) ± 1.2</td>
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<td>SMBG 3.9-10 mmol/l</td>
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<td>SMBG &gt;10 mmol/l</td>
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<td>10.9 ± 10.1</td>
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</table>

**Supplemental Fig. 1.** Mean glucose values by time of the day

**Supplemental Fig. 2.** Average glucose values by time of the day

**Supplemental Fig. 3.** Bland-Altman plots & Surveillance Error Grids in individual patients. Numbers refer to patient numbers in Supplemental Table 1.

**Supplemental Fig. 4.** Correlation of the mean difference between paired measurements with SMBG (left) and the mean of SMBG and FGM (right). Both correlations – in opposite directions – were statistically significant, but very weak.

**Supplemental Fig. 5.** Bland-Altman Plot (left) & Surveillance Error Grid (right) for paired measurements by FGM and venous glucose in the central laboratory.

**Supplementary Fig. 6.** Bland-Altman plot (left) & Surveillance Error Grid (right) for paired values by FGM vs. SMBG measured before vs. after meals on two consecutive days
60 patients were screened for eligibility
25 with diabetes 35 without diabetes

5 patients were not eligible
due to regular intake of paracetamol

55 patients were offered participation
22 with diabetes 33 without diabetes

18 patients gave written informed consent
11 with diabetes 7 without diabetes

3 did not complete the study
2 incompliant with SMBG
1 acute illness requiring hospital admission

15 patients included in analysis
8 with diabetes 7 without diabetes
A. All Patients

B. Patients with diabetes

C. Patients without diabetes

SMBG (mmol/l)

FGM (mg/dl)

Mean of SMBG and FGM
A. All Patients

B. Patients with diabetes

C. Patients without diabetes

Mean of SMBG and FGM
A Patient with diabetes

1. Difference Measurement vs. SMBG
2. Difference Measurement vs. CGM
3. Difference Measurement vs. SMBG
4. Difference Measurement vs. CGM
5. Difference Measurement vs. SMBG
6. Difference Measurement vs. CGM
7. Difference Measurement vs. SMBG
8. Difference Measurement vs. CGM

Mean of SMBG and CGM
Mean of SMBG and CGM
Mean of SMBG and CGM
Mean of SMBG and CGM

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B Patients without diabetes
FGM vs. Plasma Glucose Levels (PGL)

A  Preprandial Measurements

B  Postprandial Measurements