Differences in glucose level between right arm and left arm using continuous glucose monitors

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Abstract

Background: Continuous glucose monitoring (CGM) measures interstitial glucose levels through a sensor with a thin filament inserted under the skin. It is customary for patients to rotate sensor application sites between arms to minimize skin irritation. However, there is limited data regarding the degree of inter-arm differences with CGM technology.

Methods: Self-proclaimed right-handed (n = 5) and left-handed (n = 5) participants, regardless of concurrent comorbidities, were enrolled for CGM. Participants wore a FreeStyle Libre Pro sensor on each arm for a maximum of 14 days. Muscle mass and body fat analysis was conducted using a multi-frequency segmental body composition analyzer. Glucose levels from both arms were time-matched with the first 12 hours eliminated from analysis. Mean glucose and time in target range were compared between readings from the right and left arm.

Results: A total of 9830 paired glucose levels were included for analysis. In all participants (n = 10), mean glucose on the right arm was 89.1 mg/dL (SD, 19.9) and 85.3 mg/dL (SD, 19.3) on the left arm (P < 0.001). Glucose was out of target range (70-180 mg/dL) for 12.7% of the time in the right arm compared to 18.5% in the left arm (P < 0.001).

Conclusions: In a group of 10 nondiabetic and diabetic adults, there was a statistically significant difference in CGM readings between the right and left arms. Time in target range may differ based on arm selection when using a CGM. Arm dominance did not explain the inter-arm glucose level discordance.

Keywords

Continuous glucose monitoring, blood glucose self-monitoring, diabetes mellitus, time in range, body composition

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Background

Continuous glucose monitoring (CGM) is an emerging technology that allows for improved glycemic control in both type 1 and type 2 diabetes.[1] By inserting a sensor with a thin filament under the skin into the subcutaneous tissue, CGM measures interstitial fluid (ISF) glucose and estimates blood glucose levels. Depending on the device, CGM can provide real-time glucose readings, glucose trend information, and alerts for the detection of glucose range excursions. With increasing evidence of CGM's clinical benefit, payers have agreed to full or partial reimbursement for CGM in at least 14 countries including the United States.[2]

The FreeStyle Libre Pro (Abbott Diabetes Care Inc., Alameda, CA, USA) is a popular CGM system

specifically designed for healthcare professionals.[3] The patient wears the sensor on the back of either upper arm for up to 14 days. At the end of the collection period, the healthcare provider can download the data onto a computer, review trends and patterns in the results with the patient, and adjust treatment accordingly. It is customary for patients to rotate the

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FreeStyle Libre sensor application sites between arms to minimize skin irritation. There is limited data on the degree of inter-arm differences with CGM technology and whether any observed inter-arm differences are due to system precision or physiologic causes. The operator's manual of the FreeStyle Libre Pro reported a study of precision in which subjects wore two separate sensors, one on the back of each upper arm, and calculated the mean percent absolute relative deviation (PARD).[4] The general formula for PARD is reported as $100 \frac{yCGM1 - yCGM2}{mean\ (yCGM1,\ yCGM2)}$.[5] The resulting PARD of 8.6% with a coefficient of variation of 6.1% suggests that system precision may contribute to inter-arm differences in CGM readings.

Another study of CGM reproducibility with sensors worn simultaneously on the right and left sides of the abdominal subcutaneous tissue found that clinical evaluation of the glucose range provided by the two sensors was concordant for 65% of the evaluated periods. The authors proposed that variability in subcutaneous fat content in individuals may affect the reproducibility of readings.[6] Likewise, multiple studies have explored the relationship between glucose exchange and tissue type. In a glucose uptake study using positron emission tomography in both obese and non-obese subjects during normoglycemic hyperinsulinemia, insulin-stimulated glucose uptake per kilogram tissue of femoral skeletal muscle was greater than that of femoral subcutaneous adipose tissue.[7] In contrast, an investigation assessing transcapillary glucose exchange efficiency in human skeletal muscle and adipose tissue under fasting conditions found no statistical difference in glucose concentrations between muscle and adipose tissue ISF.[8]

A pilot study in which 2 right-handed participants wore the FreeStyle Libre Pro on each arm for 10 days found that the right arm glucose was greater than the left arm for 96% of the time.[9] If the right and left side of the body have physiological differences that affect energy requirements and glucose exchange, they may possibly impact the difference in CGM reading on each arm. Physiological differences that increase asymmetry may include usage of the dominant arm, and increased muscle or fat on one side of the body.[10] The present trial was designed to compare CGM readings from the right and left arms (inter-arm). We also planned to explore the associations of arm dominance, arm muscle mass, and fat content to differences in arm CGM readings.

Methods

This prospective trial was conducted at a university campus in the United States. The protocol was approved by the Institutional Review Board at University of the Pacific. All participants gave informed consent prior to inclusion in the study. Ten participants were recruited to wear a CGM sensor on each arm simultaneously for 10–14 days. Half of the participants had to self-identify as right-handed and the other half left-handed.

Study participants

Participants were 18 years of age or older and included regardless of concurrent comorbidities. Participants were excluded if they had any dermatological condition on the upper arms, a current systemic infection, an implanted medical device, or plans to receive high-frequency electrical heat treatment, magnetic resonance imaging, or computed tomography scans. Additionally, participants who were pregnant, breastfeeding, or planning to become pregnant within 30 days after screening were excluded.

Study design

Participants attended a total of 3 study visits. On Day 1, each participant underwent simultaneous insertion of two CGM sensors (FreeStyle Libre Pro Flash Glucose Monitoring System, Abbott Diabetes Care Inc., Alameda, CA, USA), one on the back of each upper arm. The CGM system measured glucose concentrations from interstitial fluid in the range of 40 to 500 milligrams per deciliter (mg/dL) every 15 minutes until the sensors fell off or the end of study (10–14 days). Participants received general instructions on sensor care and hygiene and were instructed to continue their normal lifestyle habits. Body composition analysis, including measurements of muscle mass and body fat percentage in each arm, was conducted with the Tanita MC-780U multi-frequency segmental body composition analyzer (Tanita Corp., Tokyo, Japan).

Follow-up visits occurred once between Days 5–8 for CGM data download, and between Days 10–14 for final CGM data download and sensor removal.

Endpoints

The primary endpoint was the difference in CGM-derived glucose levels between the right arm and left arm (inter-arm comparison). The co-primary endpoint was the glucose difference between arms in right-handed participants compared to the difference between arms in left-handed participants.

Additional endpoints included percentage of CGM readings signifying time in range, and correlation between inter-arm glucose difference and inter-arm muscle or fat difference. Subgroup analysis was performed by BMI $\geq 30 \, \text{kg/m}^2$ and by diabetes (self-reported). Hypoglycemic episodes, defined as 1 or

more consecutive CGM reading(s) less than 70 mg/dL (interrupted by no more than one reading greater than or equal to 70 mg/dL), were compared on the right and left arm.

Statistical analysis

We planned to enroll 10 participants giving a total of 12,960 right arm – left arm glucose reading pairs in an ideal scenario. The CGM system manual reported a clinical study of system performance comparing CGM results and laboratory results of venous blood glucose in 12323 data pairs.[4] Given the frequency of CGM reading is every 15 minutes and a study duration of up to 14 days, a sample size of 10 participants would ensure a comparable number of data pairs as the study in the operator's manual. All participants' data were included in analysis regardless of duration of participation. CGM readings from the right and left arms were time-matched, with the first 12 hours of data eliminated from analysis to account for acclimation of the CGM system to the participant's body.

Glucose levels between the left arm and right arm were analyzed with a paired student's t-test with the unpaired t-test performed for comparison between right-handed and left-handed individuals. A Fisher's exact test was used to compare categorical data. Appropriate correlation tests (Pearson's or Spearman's rank) were determined by skewness and kurtosis tests for normality.

Standard deviations are reported for means where applicable. Analyses were conducted with Stata version 13.1. $P < 0.05$ was considered statistically significant for all analyses.

Results

A total of 10 participants (5 right-handed and 5 left-handed participants) were enrolled in this study and 9 participants completed the study through Day 10 or later. One participant discontinued at day 5 due to the CGM sensors falling off. In total, 9830 paired CGM readings from all 10 participants were available for analysis and the maximum difference in the time-matched readings were up to 6 minutes apart.

Participants' baseline characteristics were balanced with regards to sex (5 males and 5 females), with majority under age 45 and of Asian race (Table 1). The majority of participants (n = 8) did not report any pre-existing medical conditions. One participant self-reported type 2 diabetes treated with metformin, glipizide, and semaglutide. Another participant self-reported thalassemia without ongoing treatment.

The glucose level in the right arm was higher than the left arm in 67% (range 46–98%) of all time-matched readings. The range of 46–98% reflects

Table 1. Baseline characteristics of the study population.

	Study participants (n = 10), No. (%)
Age, y	
18–<25	5 (50)
25–<45	4 (40)
45–<60	1 (10)
Mean (SD) [range]	29 (10) [21–53]
Sex	
Male, %	5 (50)
Female,%	5 (50)
Self-reported race(s) among Hispanic or Latino/a participants	
Asian, %	1 (10)
Self-reported race(s) among non-Hispanic or Latino/a participants	
Asian, %	7 (70)
White, %	1 (10)
Asian and White, %	1 (10)
Physical characteristics	
Height, mean (SD), cm	169 (8.7)
Weight, mean (SD), kg	68 (12)
BMI, mean (SD), kg/m²	24 (5)
RA muscle mass, mean (SD), kg	2.7 (0.7)
LA muscle mass, mean (SD), kg	2.8 (0.8)
RA fat percentage, mean (SD), %	22 (14)
LA fat percentage, mean (SD), %	22 (15)
Medical history	
Type 2 diabetes mellitus	1 (10)
Thalassemia	1 (10)

Abbreviations: LA, left arm; RA, right arm; SD, standard deviation.

individual participant data (n = 10), and is not weighted by the number of readings per participant. Figure 1 shows the magnitude of inter-arm difference plotted by time of day.
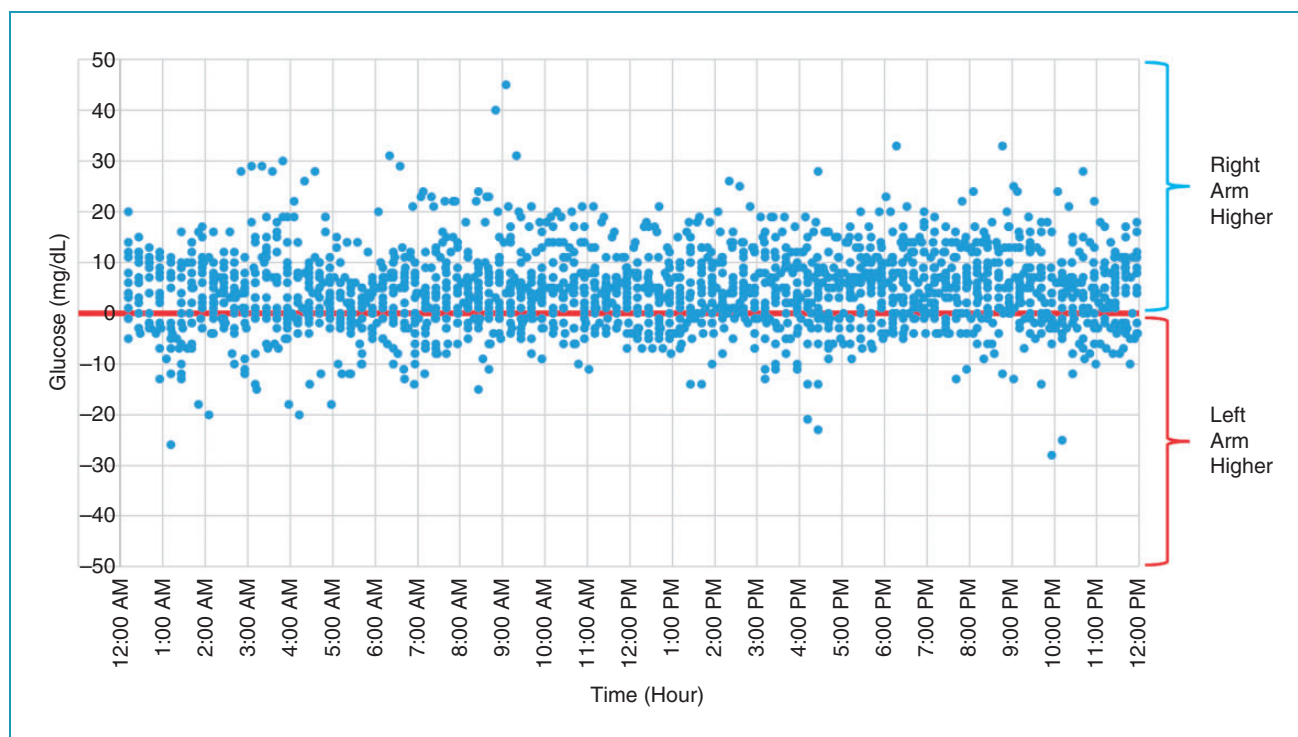
Figure 1. Inter-arm differences in CGM-derived glucose readings by time of day.

A scatterplot of 9830 CGM data pairs from all participants. Difference in glucose was calculated by taking the right arm reading minus the left arm reading. Points above the x-axis represent a time-matched data pair in which the right arm reading was greater than the left arm reading. Conversely, points below the x-axis represent a time-matched data pair in which the left arm reading was greater than the right arm reading.

In all participants (n = 10), mean glucose on the right arm was 89.1 mg/dL (SD, 19.9) and 85.3 mg/dL (SD, 19.3) on the left arm (P < 0.001) (Table 2). In right-handed participants (n = 5), mean glucose on the right arm was 88.7 mg/dL (SD, 21.9) and 85.0 mg/dL (SD, 21.4) on the left arm (P < 0.001). In left-handed participants (n = 5), mean glucose on the right arm was 89.5 mg/dL (SD, 17.8) and that on the left arm was 85.6 mg/dL (SD, 17.1) (P < 0.001). There was no significant difference in inter-arm glucose difference between right-handed and left-handed groups (3.7 vs 3.8 mg/dL, respectively, P = 0.54).

Glucose levels were out of range for 12.7% of the time in the right arm compared to 18.5% in the left arm (P < 0.001) (Table 3). Glucose levels were below range for 12.5% of the time in the right arm compared to 18.4% in the left arm (P < 0.001). Glucose levels were above range for 0.20% of the time in the right arm compared to 0.15% in the left arm (P = 0.10)

Inter-arm differences between glucose, muscle mass, and fat percentage were significantly skewed (P < 0.001).

No correlation was found between inter-arm glucose difference and inter-arm muscle difference (r = 0.24), inter-arm glucose difference and inter-arm fat difference (r = -0.19), and inter-arm fat difference and inter-arm muscle difference (r = −0.41). The absolute difference in glucose between the right and left arms was >10 mg/dL, >20 mg/dL, and >30 mg/dL, for 19.4%, 3.4%, and 0.32% of all readings, respectively.

Obese participants (n = 3) were identified by body composition analysis in the study. Mean glucose on the right arm was higher than that on the left arm by 3.9 mg/dL in nondiabetic participants, by 3.1 mg/dL in the one diabetic participant, by 3.2 mg/dL in non-obese participants, and by 5.4 mg/dL in obese participants (P < 0.001 for each subgroup) (Table 2). In obese participants, there was a 10.3% inter-arm difference in time in range (TIR); in non-obese participants, there was a 4.3% difference (Table 3). Among all participants, a total of 199 hypoglycemic episodes were counted from readings on the right arm and 323 hypoglycemic episodes from those on the left arm.

Discussion

The present study demonstrates significantly different CGM-derived glucose readings on the right and left arms. Glucose levels on the right arm were significantly greater than those on the left arm in both right-handed and left-handed participants. Since there were only

Table 2. Subgroup analysis of mean CGM-derived glucose, by dominant hand, diabetes status, and obesity.

Subgroup	RA glucose (mean ± SD) (mg/dL)	LA glucose (mean ± SD) (mg/dL)	Inter-arm glucose difference (mean ± SD) (mg/dL)
All participants* (n = 10)	89.1 ± 19.9	85.3 ± 19.3	3.8 ± 7.8
Right-handed participants* (n = 5)	88.7 ± 21.9	85.0 ± 21.4	3.7 ± 8.5
Left-handed participants* (n = 5)	89.5 ± 17.8	85.6 ± 17.1	3.8 ± 7.1
Nondiabetic participants* (n = 9)	88.5 ± 19.1	84.6 ± 18.4	3.9 ± 7.9
Diabetic participant* (n = 1)	93.6 ± 24.7	90.5 ± 24.3	3.1 ± 7.3
Non-obese participants* (n = 7)	89.6 ± 19.2	86.4 ± 18.4	3.2 ± 7.0
Obese participants* (n = 3)	87.6 ± 21.7	82.2 ± 21.4	5.4 ± 9.6

Abbreviations: LA, left arm; RA, right arm; SD, standard deviation.
*$P < 0.001$ for time-matched inter-arm glucose difference.

Table 3. Distribution of CGM-derived glucose across a target range of 70–180 mg/dL.

	Time below range, < 70 mg/dL (time/day)	Time in range, 70–180 mg/dL (time/day)	Time above range, >180 mg/dL (time/day)
All participants (n = 10)			
RA readings	12.5% (3 h)	87.3% (20 h 57 min)	0.20% (3 min)
LA readings	18.4% (4 h 24 min)	81.5% (19 h 34 min)	0.15% (2 min)
Right-handed participants (n = 5)			
RA readings	15.5% (3 h 43 min)	84.1% (20 h 11 min)	0.43% (6 min)
LA readings	21.4% (5 h 8 min)	78.3% (18 h 47 min)	0.32% (5 min)
Left-handed participants (n = 5)			
RA readings	9.8% (2 h 21 min)	90.2% (21 h 39 min)	0% (0)
LA readings	15.6% (3 h 44 min)	84.4% (20 h 16 min)	0% (0)
Non-obese participants (n = 7)			
RA readings	11.4% (2 h 44 min)	88.5% (21 h 14 min)	0.11% (2 min)
LA readings	15.7% (3 h 46 min)	84.2% (20 h 13 min)	0.05% (1 min)
Obese participants[†] (n = 3)			
RA readings	15.8% (3 h 48 min)	83.7% (20 h 5 min)	0.48% (7 min)
LA readings	26.1% (6 h 16 min)	73.4% (17 h 37 min)	0.44% (6 min)

Abbreviations: LA, left arm; RA, right arm.
[†]All three obese participants were right-handed.

minor inter-arm differences in muscle and fat, our population was not diverse enough in the context of body composition.

No correlation was found between inter-arm glucose difference and inter-arm muscle or fat difference. Due to the different energy requirements of muscle and fat tissue, a correlation was expected with either variable.[7] Although individual tests of correlation resulted as nonsignificant, inter-arm differences in muscle and fat may both contribute to inter-arm glucose difference as in a multi-factorial model.[11] Additionally, the energy demands and glucose flux of the local subcutaneous tissue may approximate to a balanced level on both sides despite differences in muscle and fat content.[8]

A 2019 international consensus report, endorsed by the American Diabetes Association, recommended time in ranges (TIRs) as clinical targets and outcome measurements in clinical practice with CGM.[12] While 70-180 mg/dL is the glycemic target range for individuals with type 1 and type 2 diabetes, it was also considered appropriate for this study's objective of assessing variability of CGM results between arms without respect to diabetes status. The consensus report provided guidance for type 1 and type 2 diabetes patients to limit time below range (TBR, <70 mg/dL) to less than 4%. In this study, all subgroups analyzed had an inter-arm difference in TBR greater than 4%. Furthermore, the consensus report advised that each incremental 5% increase in TIR (70–180 mg/dL) is associated with clinically significant benefits for individuals with type 1 or type 2 diabetes. In all participants, the mean inter-arm difference in TIR was 5.8%. If diabetic patients have the magnitude of inter-arm differences observed in this study, it could correspond to clinically significant treatment decisions and long-term health outcomes.

In diabetes management, CGM is also considered useful in addressing the acute risk of hypoglycemia. In patients who have agreed with their healthcare provider to use CGM to guide treatment decisions, the inter-arm glucose difference is likely to make the largest impact when a reading from one side of the body is in target glucose range and the other is out-of-range. In all participants combined, the left arm recorded roughly 1.6-fold more hypoglycemic episodes than the right arm. Of note, all subgroups studied (all participants, nondiabetic, diabetic, non-obese, and obese) recorded a significantly lower mean glucose from the left arm. All subgroups also recorded more readings below range (<70 mg/dL) from the left arm than the right arm. When there is a difference in readings between arms, CGM data analysis could lead to potential treatment decisions such as acute rescue therapy and adjustments to chronic maintenance therapy, depending on the arm being used.

A potential limitation of this trial is that participants were able to enroll regardless of diabetic status. Hence, our results could be different in those with diabetes. While we had a high number of individual time-matched readings, we could benefit from a larger overall patient sample size. Interestingly, obese participants had the highest mean inter-arm glucose difference and TBR difference. Since obesity is common in patients with type 2 diabetes mellitus, this population may warrant further investigation. A study of insulin resistance found a significant inverse association between visceral abdominal tissue and acute insulin response in obese subjects, and concluded that fat distribution is an important determinant of both insulin resistance and insulin secretion.[13] It is plausible that, in obese individuals, fat depots may have an overall metabolic impact on insulin resistance and secretion, and thus glucose flux as well.

In conclusion, in participants wearing a CGM simultaneously on the right and left arms, a statistically significant difference between readings was evident. This finding is of particular importance when interpreting time in range in clinical practice and in clinical trials in light of the 2019 international consensus report.[12] Although no correlation was found between inter-arm glucose difference and inter-arm muscle or fat differences, the larger magnitude of difference in obese participants warrants further investigation.

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