Glucose Measurements Using Blood Extracted from the Forearm and the Finger

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Abstract. *Using the FreeStyle blood glucose monitor that measures glucose in a 0.3 µl blood sample, blood from the fingertip and blood from the forearm were measured for glucose concentration. There was a difference in glucose concentration between these sites. A linear regression of glucose measurements from the arm versus those from the finger in blood samples from diabetic patients taken at random times during the day gave an intercept of 19.4 mg/dL, a slope of 0.913 and a correlation coefficient of 0.956. Further studies indicated that changes in blood glucose are first detected in the finger sample and the changes lag in the arm measurements. This difference can be significantly reduced by rubbing the test site on the forearm to increase blood perfusion. Using this technique the correlation of arm to finger was nearly ideal with an intercept of -0.5 mg/dL, a slope of 1.027, and a correlation coefficient of 0.971.*

The accuracy of FreeStyle was assessed using venous blood versus YSI. The regression statistics were: intercept = 7.1 mg/dL, slope = 0.923, and correlation coefficient = 0.992. A Clarke Error Grid analysis yielded 99.6% of the measurements in Zone A and 0.6% in Zone B. Using capillary blood from the finger the regression statistics versus YSI were: intercept = 6.6 mg/dL, slope = 0.934, and correlation coefficient = 0.982. Zone A of the Clarke Error Grid contained 98.3% of the measurements with the remaining 1.7% in the B Zone. When arm measurements were compared to YSI measurements of finger capillary blood the regression statistics were: intercept = 9.0 mg/dL, slope = 0.945, and correlation coefficient = 0.967. Zone A of the Error Grid contained 87.7% of the measurements, Zone B 11.4%, and Zone D 0.8%. There would be very little difference in therapeutic decisions when the arm is used as the lancing site rather than the finger.

Introduction

Self-monitoring of blood glucose (SMBG) is a necessary part of the treatment plan of people with diabetes mellitus. The goal of glycemic control is greatly enhanced by intensive insulin therapy, which requires frequent testing of blood glucose[1]. Barriers to frequent testing include the pain associated with the finger stick necessary to obtain blood for the test and the accumulated trauma to the fingers. New glucose monitoring systems have recently been developed that allow sample extraction from other sites than the finger in order to overcome this barrier. Since the fingertip tissue is highly perfused, it is relatively easy to extract an adequate sample for glucose testing. Unfortunately the finger is dense in pain receptors as well, which leads to the pain associated with blood extraction. The development of off-finger glucose monitors requires the extraction of an adequate blood sample from tissue less highly perfused.

The FreeStyle blood glucose monitoring system was designed to use a very small sample size, 0.3 µl. Early in the development of the product it was clear that it was possible to obtain sufficient blood from the forearm to perform the glucose measurements with excellent precision. It was also observed that the glucose results from the arm and finger were not perfectly correlated. A series of studies was designed to characterize the observed differences.

Study Designs

Study 1.
One hundred subjects with Type 1 or Type 2 diabetes were tested during a normally scheduled clinic visit. A trained technician obtained two FreeStyle glucose readings from finger sticks and two FreeStyle glucose readings from arm sticks. The readings were taken as close in time as possible.

Study 2.
Six subjects with Type 1 diabetes were brought into a clinic in the morning and tested for blood glucose every fifteen minutes for five to six hours during which one meal was consumed. Each blood glucose test included two FreeStyle glucose readings from the finger and two FreeStyle glucose readings from the arm all performed by a trained technician. The readings were taken as close in time as possible.

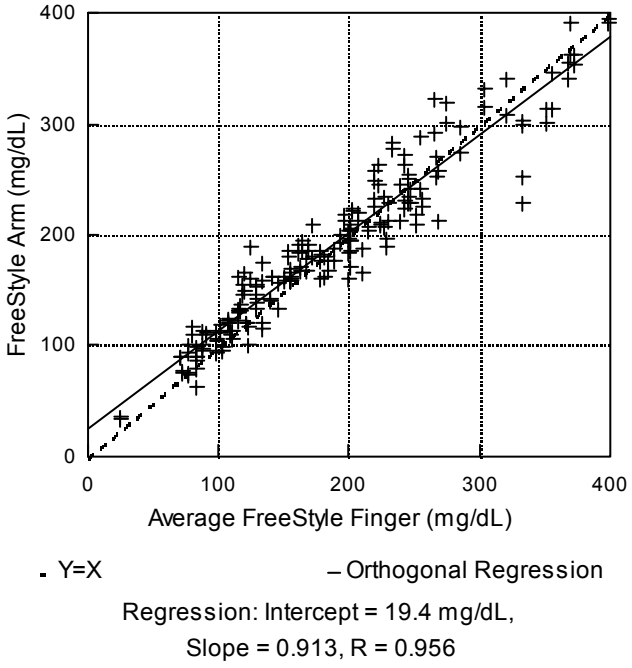
Study 3.
Two subjects with Type 1 diabetes were brought into a clinic in the morning and tested for blood glucose every fifteen minutes for five to six hours during which one meal was consumed. Each blood glucose test included two FreeStyle glucose readings from the finger and two FreeStyle glucose readings from the arm all performed by a trained technician. The readings were taken as close in time as possible. Before the second FreeStyle test on the arm, the arm was rubbed vigorously to increase blood perfusion to the puncture site. Two subjects were tested.

Study 4.
One hundred twenty subjects with Type 1 or Type 2 diabetes were tested during a normally scheduled clinic visit. A trained technician obtained two FreeStyle glucose readings from finger sticks and two FreeStyle glucose readings from arm sticks. The arm was rubbed vigorously before each test on the arm to increase blood perfusion to the puncture site. A large sample of capillary blood was extracted from the finger, and plasma from this sample was analyzed for glucose on the YSI model 2300 Blood Glucose Analyzer. Care was taken that all tests were performed over a short time period to avoid changes in blood glucose concentrations during the readings. A heparinized venous sample was also drawn, and the glucose was analyzed by FreeStyle and YSI. Duplicate FreeStyle readings were taken, and the YSI reading was performed on plasma separated from the whole blood sample.

Results and Discussion

In *Study 1* there was a difference between the glucose results from the arm and those from the finger as shown in *Figure 1*. An orthogonal regression was used to assess the correlation in order to account for the expected error in both the x- and y-axes. The correlation coefficient of 0.956 suggests a high degree of correlation, but the intercept of the regression equation is significantly greater than zero, 19.4 mg/dL, and the slope is less than one, 0.913.

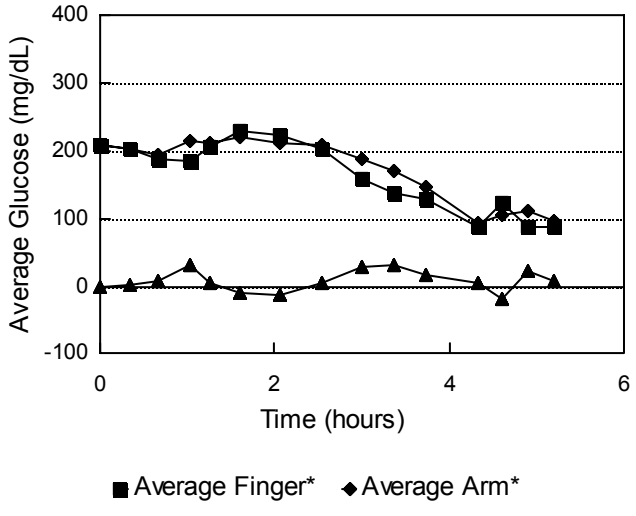
Figure 1: Study 1 — FreeStyle Capillary Arm Blood versus FreeStyle Capillary Finger Blood



In light of these results, exploratory experiments were performed that suggested the difference between the arm and the finger were caused by a lag in the arm response to a rapid change in

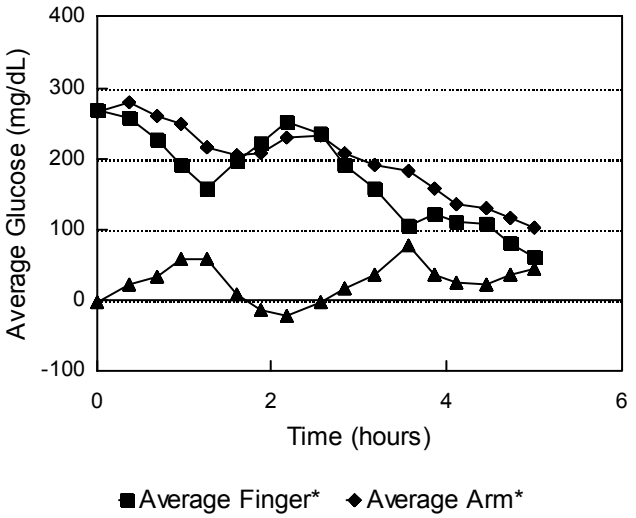
glucose concentration. *Study 2* was designed to verify this hypothesis. Type 1 patients were enrolled in *Study 2* since they are more likely to experience rapid changes in glucose concentrations.

Figure 2a: Study 2 — Glucose Profile with a Small Change in Glucose Concentration



* The data points are the average of duplicate measurements.

Figure 2b: Study 2 - Glucose Profile with a Large Change in Glucose Concentration



*The data points are the average of duplicate measurements.

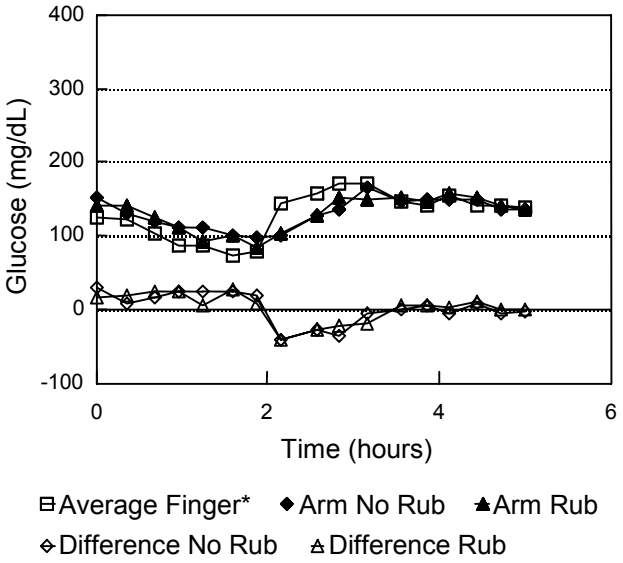
Two typical glucose profiles from *Study 2* are shown in *Figures 2a* and *2b*. The profile in *Figure 2a* exhibits a change in glucose, but the change is gradual and covers a limited glucose range, 86-229 mg/dL. The difference between the arm and finger for this subject under these conditions is insignificant. In *Figure 2b* the changes are more rapid and encompass a larger range, 60-268 mg/dL. For this subject the difference in glucose concentrations between arm and finger are much more pronounced. The data fits the hypothesis that the arm glucose concentration lags that of the finger. The net effect on all glucose readings is that the glucose concentration from the arm never reaches as high a peak as the finger, nor does it experience as low a valley. Similar to *Study 1*, a regression of all the arm readings in the study versus those on the finger gave a high intercept (34.3 mg/dL) and a low slope (0.873) suggesting that the extremes in glucose readings from finger capillaries tend to be damped in capillary blood from the arm.

Total blood flow of 33 ±10 ml/100 gm·min at 20°C has been reported for fingertips, while 6-9 ml/100 gm·min is reported for forearm, leg, and abdominal skin[2]. Stimulating blood flow at the surface of the arm was proposed as a possible strategy to mitigate the difference between the measurements of glucose from the arm and the finger. Heating the arm or rubbing vigorously were two methods for stimulating blood flow that showed promise in exploratory studies. Since rubbing the site is convenient under nearly any circumstance, this technique was employed in *Study 3*.

Results from *Study 3* are shown in *Figure 3a* and *Figure 3b*. In *Figure 3a* the glucose concentration change is modest with a range of 74-172 mg/dL. Rubbing the arm had virtually no effect on the readings, but the difference between arm and finger readings were relatively small. In *Figure 3b* the glucose concentration change is much larger with a range of 58-303 mg/dL. The lag in the arm readings is readily apparent in this case, and

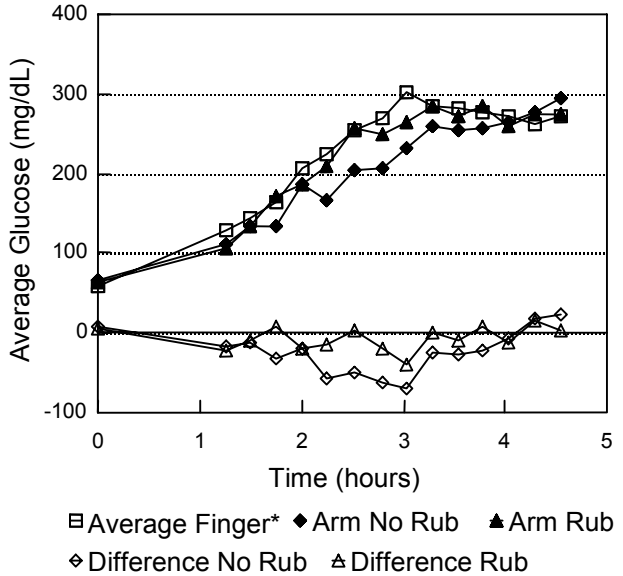
stimulating blood flow by rubbing the puncture site has a clearly beneficial effect — the large differences are significantly reduced.

Figure 3a: Study 3 — Glucose Profile with a Small Change in Glucose Concentration



*The data points are averages of duplicate measurements.

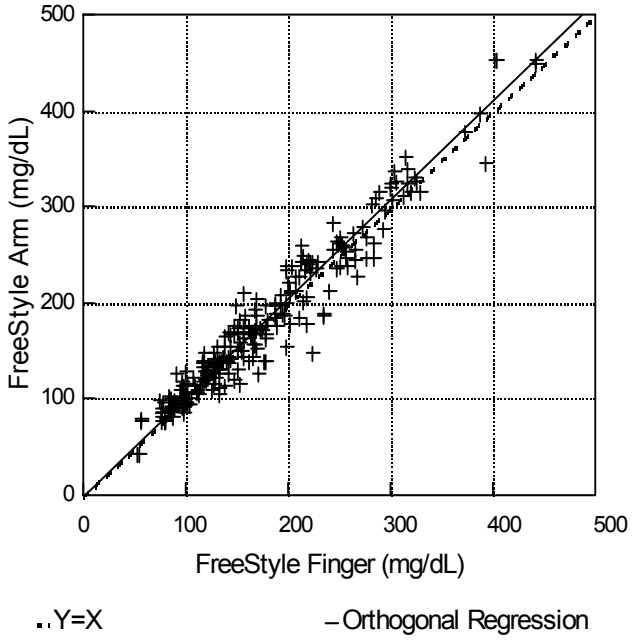
Figure 3b: Study 3 - Glucose Profile with a Large Change in Glucose Concentration



*The data points are the average of duplicate measurements.

Study 2 and *Study 3* support the hypothesis that the finger provides the leading indicator of blood glucose changes versus the arm. But these studies were conducted with a limited number of patients, and further study is necessary to determine whether the rate and magnitude of the glucose changes are the greatest influence on the observed difference between arm and finger. Furthermore, it is not clear that this difference is consistent from person to person. The results of *Study 3* suggest that stimulating blood flow at the puncture site on the arm can diminish the lag in the glucose readings. An added benefit of the rubbing technique is that the increased blood flow makes it easier to obtain a sufficient blood sample for the glucose test.

Figure 4: Study 4 — FreeStyle Capillary Arm Blood versus FreeStyle Capillary Finger Blood



Regression: Intercept = -0.5 mg/dL,
Slope = 1.027, R = 0.971

To confirm the benefit of the rubbing technique over a larger range of patients, *Study 4* was designed similarly to *Study 1*. The correlation between arm and finger when the rubbing technique is employed is shown in *Figure 4*. There is a modest improvement in correlation coefficient compared to *Study 1*, 0.971 versus 0.956, but there is significant improvement in the regression line. When rubbing is employed the intercept is nearly zero, -0.5 mg/dL, and the slope is near unity, 1.027. A simple method to stimulate additional

blood flow to the puncture site can greatly improve the agreement between glucose readings from the arm and finger in a study with a large number of subjects (n = 120).

Comparing a glucose monitor to a laboratory method is the traditional manner for determining clinical utility of the monitor. In 1987 Clarke, *et al.* introduced the Error Grid Analysis as a means of interpreting laboratory comparisons as they relate to therapeutic decisions[3]. The assumptions upon which the Error Grid was constructed were that glucose values should be kept within an ideal range of 70-180 mg/dL, that glucose below 70 mg/dL should be treated by ingestion of carbohydrate, and that glucose above 180 mg/dL should be treated by insulin injection. The readings of a glucose monitor are compared to a laboratory method on a scattergram and the graph is divided into zones that represent the error as it would relate to therapy. The Clarke Error Grid is shown in *Figure 5* and the zones of the Grid are defined as follows:

Zone A — Clinically accurate, within ±20% of the laboratory.

Zone B — Error greater than ±20%, but would lead to benign or no treatment.

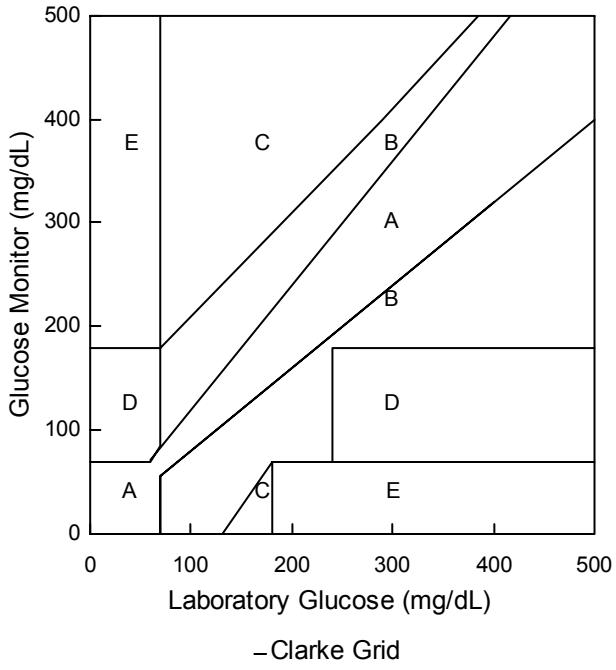
Zone C — Errors would lead to unnecessary corrective treatment.

Zone D — Potentially dangerous failure to detect hypo- or hyperglycemia.

Zone E — Erroneous treatment of hypo- or hyperglycemia.

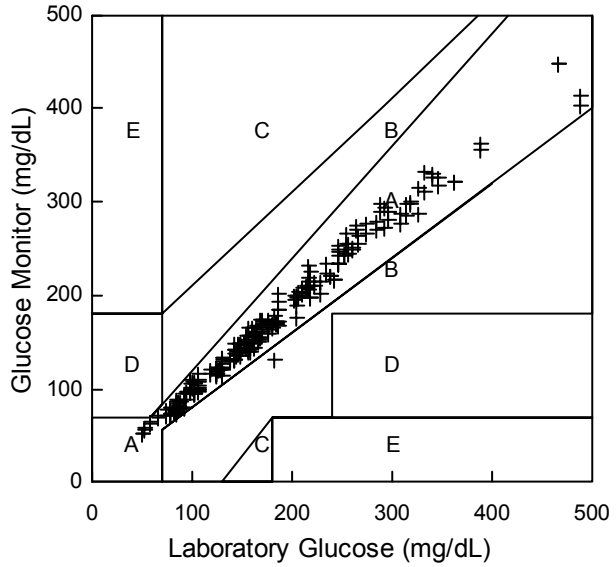
Using this tool, FreeStyle glucose measurements from *Study 4* were assessed with YSI plasma readings as the laboratory method. In *Figure 6* the analysis of venous samples is shown. When a homogeneous sample of venous blood is analyzed by both methods, the agreement between FreeStyle and the lab method is excellent. The A Zone of the Clarke Error Grid contains 99.6% of the measurements, and the other 0.4% are in the B Zone. The regression statistics give a slope of 0.923, and intercept of 7.1 mg/dL and a correlation coefficient of 0.992. The FreeStyle measurement technology is capable of very accurate glucose determination.

Figure 5: Clarke Error Grid



–Clarke Grid

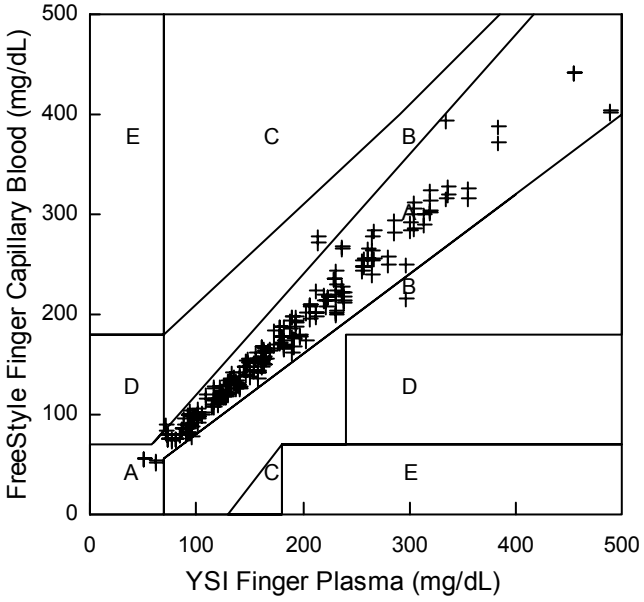
Figure 6: Freestyle with Venous Blood versus YSI with Venous Plasma



Regression: Intercept = 7.1 mg/dL,
Slope = 0.923, R = 0.992

Figure 7 reports measurements performed on a blood sample extracted from the finger. The points are slightly more scattered – the value of R for the finger test is 0.982 versus 0.992 for the venous regression. But 98.3% of the points are within the A zone of the Clarke Error Grid with the remaining 1.7% in the B zone. Unlike the venous test, the finger tests were performed on different samples – the blood for the YSI and that for the FreeStyle tests were taken from different lance sites and at slightly different times. The increase in scatter is likely due to slight differences in glucose concentration of the extracted blood.

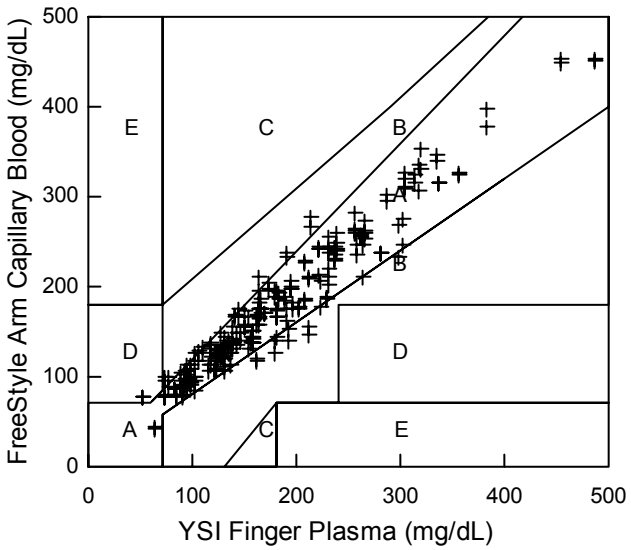
Figure 7: Freestyle with Finger Capillary Blood versus YSI with Finger Plasma



Regression: Intercept = 6.6 mg/dL,
Slope = 0.934, R = 0.982

In *Figure 8* the results of the FreeStyle arm tests are graphed versus the YSI plasma sample extracted from the finger. There is clearly more scatter in this regression with R equal to 0.967. Despite the physiological difference between the arm and the finger, 87.7% of the readings are within the A zone of the Clarke Error Grid, 11.4% are in the B zone, and 0.8% in the D zone. There is very little difference in the therapeutic decisions when the arm is used as the lance site rather than the finger.

Figure 8: Freestyle with Arm Capillary Blood versus YSI with Finger Plasma



Regression: Intercept = 9.0 mg/dL,
Slope = 0.945, R = 0.967

There are additional factors to consider in comparing the use of arm tests versus finger tests. In the practice of blood glucose monitoring, measurements are generally taken before a meal or before bed in order to determine the proper insulin dosage. This is the time when the blood glucose is least likely to be in rapid transition. The blood glucose should not be rising rapidly from recent ingestion of carbohydrate, nor should it be falling rapidly from administered insulin. This is the physiological condition when the difference between glucose concentration at the finger and the arm is at a minimum. The arm site is ideal for these tests. If postprandial glucose is measured the patient is more likely to be in a transitional mode, but the timing of the test is more critical in this case than is the testing site. When the glucose is changing rapidly a difference in 15 minutes in the time the sample is taken can have a more significant impact than the difference between arm and finger.

There is a condition, however, when the difference between finger and arm could be significant. If the blood glucose concentration is falling

rapidly into a state of hypoglycemia, the lag in the glucose change at the arm could cause a delay in the detection of hypoglycemia. This is the point at which the accuracy of the glucose monitor is most critical as witnessed by the narrow area of the A Zone in the Error Grid at the point where hypoglycemia is detected. The glucose data from the finger in *Figure 7* has relatively low scatter at low glucose, and the measurements are sufficiently accurate to detect hypoglycemia. The data from the forearm in *Figure 8* exhibits greater scatter, and there is a greater likelihood of points falling into the D zone, which indicates failure to detect hypoglycemia. There are many occasions when a person with diabetes is performing a test with the express purpose of detecting hypoglycemia — if experiencing hypoglycemic symptoms, if a meal is delayed after an insulin injection, or before driving or operating heavy equipment. Under these circumstances it may be preferable to extract blood from the finger to perform the glucose test.

Conclusion

Alternate site testing with the FreeStyle Blood Glucose Monitoring System generally gives blood glucose readings that compare well with the widely accepted fingerstick testing. However, during times of glucose changes the concentration on the arm can lag behind the concentration change occurring at the fingertip. A significant well-recognized difference between the tissue of the arm and that of the fingertip is the rate of blood flow. Rubbing the skin of the arm vigorously for a few seconds stimulates blood flow at the skin surface and minimizes the differences in glucose concentration. Using the rubbing technique, blood glucose measurements made on the forearm, as compared to measurements made on the finger, do not lead to significant differences in therapeutic decisions except during times of rapid blood glucose changes. When testing for the purpose of detecting hypoglycemia, it may be preferable to test on the finger.

References:

1. American Diabetes Association, *Medical Management of Type 1 Diabetes*, Third Edition, 1998, pp. 71-72
2. Johnson, P. C., *Peripheral Circulation,* John Wiley & Sons, 1978, p. 198
3. Clarke, W.L., et al, Evaluating clinical accuracy of systems for self-monitoring of blood glucose, *Diabetes Care*, 1987 Sept-Oct, 10(5), 622-8