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Using a Cageside Device for Testing Glycosylated Hemoglobin in Cynomolgus Macaques (*Macaca fascicularis*)

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Nonhuman primates naturally develop type 2 diabetes mellitus and exhibit clinical features that are similar to those observed in humans, including obesity, insulin resistance, dyslipidemia, and pancreatic pathology. The glycosylated hemoglobin (HbA1C) test is the primary test used for diabetes management in humans because it reflects the average blood glucose levels over the previous 3 mo. The HbA1C results are a better predictor of potential risk of complications than are single or episodic measures of glucose levels. HbA1C levels have proven useful for the diagnosis and monitoring of blood glucose levels in NHP, but for testing by a commercial laboratory, the test requires a vial of whole blood, results are not available for several days, and the test is expensive. The cageside device requires a single drop of blood, it displays the HbA1C percentage in 5 min, and the cost per sample is less than for sending it to a commercial lab. We therefore assessed the correlation between a cageside test using a handheld unit and the commercial lab test for measuring HbA1C in cynomolgus macaques. From both normal and confirmed diabetic animals, 4 mL blood was collected from a peripheral vessel and sent to a commercial lab for HbA1C testing. At the same time, a drop of capillary blood was collected and tested immediately in the HbA1C cageside test. A comparison of the results revealed significant correlation between the cageside and commercial lab tests. Therefore, we feel that the HbA1C test using handheld device may help to rule out nondiabetics and indicate which animals require additional testing.

Abbreviations: T2DM, type 2 diabetes mellitus

The prevalence of diabetes in humans has increased exponentially in the last 20 y due to an increase in type 2 diabetes mellitus (T2DM).[2] Morbidity associated with T2DM results from hyperglycemia-related complications including microvascular (retinopathy, neuropathy, nephropathy) and macrovascular (cerebrovascular, coronary artery, peripheral vasculature) diseases.[3] Evidence found by the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study indicates that better glycemic control was associated with lower incidence of complications and better clinical outcome. Additional evidence supported the translation of HbA1C into glycemic control and long-term risk assessment.[23,24] Daily glucose measurements do not provide accurate measures of long-term average blood glucose concentrations. The best method for assessing long-term glycemic control is the measurement of HbA1C levels,[21] which reflect the attachment of glucose to hemoglobin and thus the average of a person's blood glucose levels over the RBC lifespan (that is, approximately 3 mo).[17] Therefore, optimal treatment of diabetes in human patients involves control with insulin combined with routine HbA1C monitoring.[23]

Several NHP species naturally develop diabetes and exhibit clinical features that are similar to those observed in humans, including obesity, insulin resistance, dyslipidemia, and pancreatic pathology.[4,16,26] This similarity makes NHP excellent models for studying T2DM in humans. The most widely studied NHP that develop spontaneous diabetes are macaques, and the most extensive research involving the development, characteristics, and comorbidities of diabetes has been conducted in cynomolgus and rhesus macaques.[7] Because HbA1C values are strongly correlated with blood glucose levels and the risk of developing complications, this indicator is a useful parameter to screen for and monitor diabetes in nonhuman primates.

Recently, the use of reference labs to measure HbA1C levels has proven useful for diagnosis and monitoring of chronic blood glucose levels in NHP. However, the test requires a vial of whole blood, results take several days, and the per-sample cost can be prohibitive. The aim of the current study was to validate a cageside handheld device that is used in human medicine for use in cynomolgus macaques, to ameliorate these constraints by requiring a single drop of blood, displaying results in 5 min, and drastically reducing the per-sample cost.

Materials and Methods

Animals. The study population comprised 38 (29 male and 9 female) adult cynomolgus macaques (*Macaca fascicularis*). Eight of these animals are part of a confirmed type 2 diabetic colony used for studying diabetes and plasma glucose concentrations and ranged in age from 13 to 26 y. These animals are individually housed indoors in an AAALAC-accredited facility and are allowed free access to their daily allotment of high protein monkey diet (LabDiet 5047, St. Louis, MO) and water. They are supplemented with fresh fruits and vegetables and are provided with enrichment activities daily. All animals are screened yearly for *Macacine herpesvirus 1* and 3 times a year for tuberculosis by intrapalpebral tuberculin. The macaques are classified as

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diabetic and started on insulin therapy once they exhibit fasting glucose levels greater than 150 mg/dL, a HbA1C greater than 5%, and weight loss. Their blood glucose level is measured every morning after fasting overnight, and they are treated with insulin glargine (Lantus, Aventis Pharmaceuticals, KS City, MO); dosing is individualized with the goal of maintaining morning glucose levels between 100 and 200 mg/dL.

The remaining 30 animals (age, 3.5 to 8.5 y) are nondiabetic and used on gene therapy protocols. These macaques are housed indoors in pairs in an AAALAC-accredited facility, are fed twice daily (Teklad Diets 2050, Madison, WI), and have unrestricted access to water. They are supplemented with fresh fruits and vegetables and are provided with environmental enrichment daily. All animals are screened semiannually for *Macacine herpesvirus 1*, SIV, simian retroviruses 1 and 2, simian T-lymphotropic virus, and measles. In addition, they are tested semiannually by intrapalpebral tuberculin for tuberculosis. One of these animals had diabetes induced with streptozotocin after the initial testing and was tested subsequently.

Housing and care for all animals are provided in accordance with the standards set forth in the *Guide for the Care and Use of Laboratory Animals*[9] and the Animal Welfare Act.[1] All procedures for this study were approved by the Novartis East Hanover Animal Care and Use Committee and by the University of Pennsylvania and The Children's Hospital of Philadelphia IACUC.

Blood collection and testing. The 8 diabetic animals were trained to present a hindlimb for conscious blood collection. The other 30 animals were sedated with ketamine and dexmedetomidine for blood collection on unrelated protocols. In each animal, approximately 4 mL blood was collected from a peripheral vein and placed into an EDTA anticoagulant tube (Monoject, Covidien, Minneapolis, MN). The tubes were immediately placed on ice and sent overnight to Jefferson University Hospitals (Philadelphia, PA). There the samples were tested for HbA1C percentage (Premier Hb9210 HbA1c Analyzer, Trinity Biotech, Jamestown, NY) by using boronate affinity technology. This method is certified by the National Glycohemoglobin Standardization Program, whose purpose is to standardize hemoglobin A1C test results to those of the Diabetes Control and Complications Trial and United Kingdom Prospective Diabetes Study,[23,24] which established the direct relationships between HbA1C levels and outcome risks in patients with diabetes.

After the 4-mL sample was collected, a single drop of capillary blood was collected and used to run the cageside test (A1CNow$^+$ System, PTS Diagnostics, Indianapolis, IN). This device was chosen because of its proven accuracy and precision when monitoring HbA1C in diabetes management.[11,14] The cageside test uses both immunoassay and chemistry technology to measure A1C and total hemoglobin, respectively. Once the blood sample is introduced, blue microparticles, which are conjugated to antiA1C antibodies, migrate along the reagent strip. These blue microparticles are captured on the strip, and the amount captured reflects the amount of A1C present in the sample. For the measurement of total hemoglobin, the diluent converts hemoglobin to methemoglobin. The intensity of methemoglobin on the reagent strip is then measured and is proportional to the concentration of hemoglobin in the sample. The test results are expressed as A1C%, obtained by dividing the amount of A1C by the total hemoglobin in the sample and multiplying by 100.[18] Results were available from the cageside unit within 5 min and were recorded immediately.

Statistical analysis. The purpose of our study is to establish the relationship between a cageside HbA1C testing device and the laboratory test in cynomolgus macaques. To this end, we examined the correlation between the 2 measures to determine whether the A1C readings differ between them. Given we had data on one animal in 2 states (that is nondiabetic and then diabetic after induction), we used only one value in each analysis, as appropriate. We describe our data, calculating average values and counts as appropriate for different population characteristics. Given the small number of animals, we also provide the data for individual animals in a separate table. Our primary analysis implemented a logistic regression to generate a slope and *P* values for the slope using the data set including all measured values that did not hit the ceiling value for either measure. As a sensitivity analysis, we performed the same analysis using all data, specifying the maximal reading of 13 for the cageside levels and the actual values of the laboratory readings. Finally we examined the relationship of measures only in animals that were not diabetic, given our strong interest in using the new measure to determine the status of animals in the nondiabetic range.

To determine the magnitude of the difference in values for the measures, we subtracted the blood laboratory measure from the cageside value and calculated the average difference and the 95% CI for this value. We calculated this number for the nondiabetic animals separately, given our particular interest in those values. Because only 2 animals yielded values in the diabetic range, no statistical value could be calculated for this group, but the differences in cageside compared with laboratory values were observed for any potential trend as the blood values increased. All of the analyses were conducted in SAS (version 9.4, SAS Institute, Cary, NC) with graphs created by using Excel 2010 (version 14, Microsoft, Redmond, WA).

Results

In 7 of the 9 confirmed diabetic animals, the cageside device gave an HbA1C result of greater than 13%, which is the upper limit of the device, thus limiting the usefulness of these values in our analysis. The values for the remaining 2 of the diabetic animals were 12.8% and 9.4%; the commercial lab values for those animals were 9.3% and 7%, respectively. The nondiabetic animals had cageside HbA1C values of 4.9% to 6.4%, compared with values of 3.9% to 4.7% from the commercial lab (Table 1).

Correlation of results. When the data from all of the animals with interpretable cageside values less than 13% were used in the analysis, the correlation of the 2 methods was 0.978 ($P < 0.001$), making them very highly correlated with a slope of 0.683 (Figure 1). To analyze sensitivity, we included the animals whose cageside HbA1C value was out of range, assigning them a value of 13%. Although the ceiling effect clearly reduces the variability of a single parameter, adding these animals did not substantially affect the correlation (0.983, $P < 0.001$) but did increase the slope (0.873), as expected (Figure 2). A second analysis that assessed only the nondiabetic animals was then conducted. The smaller range resulted in increased variability, with a lower but still moderate correlation (0.486; $P = 0.007$; Figure 3).

Differences between measures. Overall, the differences between the 2 measures were consistent, with the cageside HbA1C values always higher. For the nondiabetic animals, the average difference between the measures was 1.39% (95% CI, 1.3% to 1.5%), with a range of 0.5% to 2.0%. However, the difference between the measures in the diabetic range was 2.4% at the 9.4% HbA1C level and 3.5% at the 12.8% HbA1C level, suggesting that the relationship is not constant, consistent with the slope of 0.683. Applying the 1.39% difference to the 5.0% cutoff for diabetes (that is, a cutoff of 6.39% for the cageside

Table 1. Individual data from all macaques in the study population

	HbA1C (%)	
	Cageside device	Commercial lab
Nondiabetic animals		
1	5.2	3.9
2	5.6	4.0
3	6.0	4.0
4	5.2	4.1
5	5.3	4.1
6	5.6	4.1
7	5.3	4.2
8	5.3	4.2
9	5.6	4.2
10	5.7	4.2
11	5.8	4.2
12	5.4	4.3
13	5.5	4.3
14	5.5	4.3
15	5.7	4.3
16	5.7	4.3
17	5.7	4.3
18	5.8	4.3
19	5.8	4.3
20	4.9	4.4
21	5.4	4.4
22	5.7	4.4
23	6.0	4.4
24	6.1	4.4
25	6.1	4.4
26	6.2	4.4
27	5.6	4.5
28	5.7	4.5
29	6.4	4.5
30	6.4	4.7
Diabetic animals		
28	9.4	7
31	12.8	9.3
32	>13	9.3
33	>13	10.2
34	>13	10.8
35	>13	11.5
36	>13	11.5
37	>13	11.5
38	>13	11.7

Note that 7 of the macaques have values of that exceed 13%, the upper limit of the cageside device. In addition, animal 28 is listed twice, indicating his values both before and after induction of diabetes.

test) indicated that 2 (6.7%) of our 30 animals would have been misclassified as diabetic.

Discussion

Our results demonstrate a high degree of correlation between the cageside HbA1C level and the blood levels obtained from the commercial lab, thus suggesting that the cageside test may well be useful in routine testing of diabetes state in cynomolgus macaques. However, the cageside reading was consistently higher by 1.39% in the nondiabetic range, potentially leading to a misclassification rate of nondiabetic animals as diabetic of 6.7%. In addition, because none of the animals' laboratory values were just above the cutoff value for diabetes, we could not estimate the likelihood of misdiagnosis as normal in those diabetic macaques whose HbA1C values were just above the

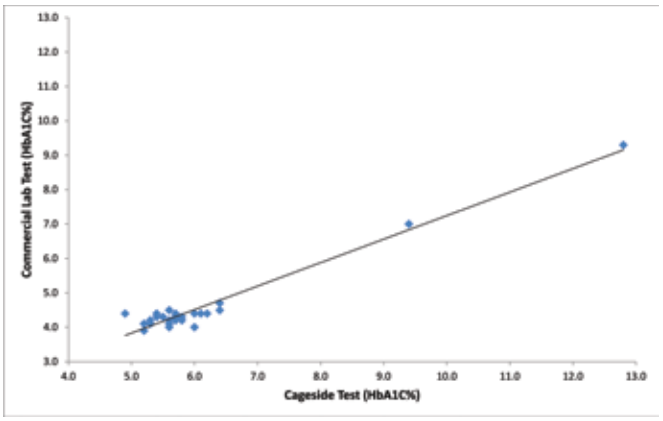

Figure 1. This model includes all cynomolgus macaques with readings lower than 13%. For the animal tested twice, only the values obtained after induction of diabetes are included here. The correlation is 0.978 ($P < 0.001$), making the 2 tests very highly correlated.

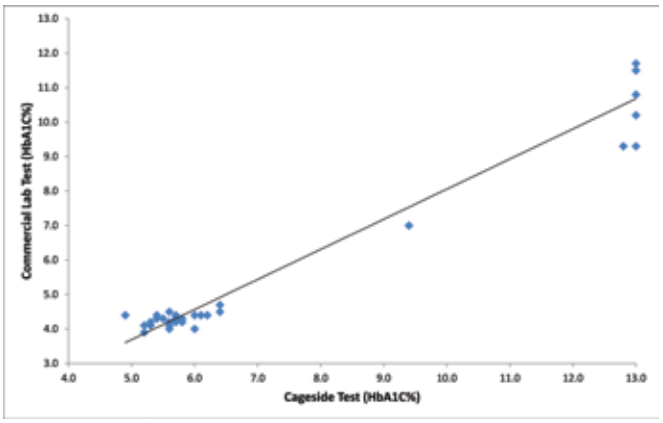

Figure 2. This sensitivity analysis includes all of the macaques; a value of 13% was assigned to those animals whose readings exceeded the upper limit of the cageside device. The correlation is 0.983 ($P < 0.001$). The correlation is not markedly different from that in Figure 1.

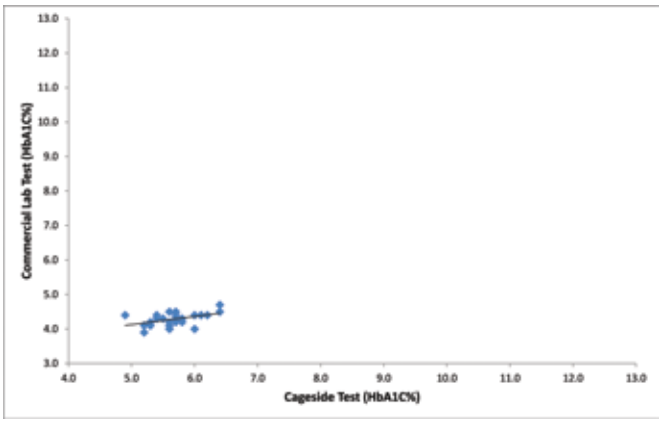

Figure 3. This model includes only the nondiabetic animals. For the animal tested twice, only the values obtained before induction of diabetes are included here. The correlation is 0.486 ($P = 0.007$). The correlation is lower than that obtained previously but is still moderate.

cutoff. As such, additional work is necessary to precisely establish the cageside HbA1C levels that indicate the cut-off for the diabetic state.

Given the reasonably narrow 95% CI, we can propose a conservative guidance for the use of this test, with the clear understanding that confirmatory testing by a commercial laboratory is necessary for a range of intermediate values. In this regard, for the diagnosis of a nondiabetic state, the lower bound of the 95% CI (1.3%) is added to the blood value cutoff of 3.5% to give a value of 4.8%, below which it is highly likely the animal will not be diabetic. For the diagnosis of diabetes, the higher bound of the 95% CI (1.5%) is added to the 5.0% cutoff, for a minimal value of 6.5%. However, because of the insufficient data from animals whose HbA1C values were just above the diabetic threshold, we recommend using a value of 7.0% to be conservative regarding the diagnosis of diabetes.

To put these findings in context, the ability of HbA1C measurement to capture the degree of glucose exposure over time is related more intimately to the risk of complications than are single or episodic measures of glucose levels.[10,22] In NHP, traditional tests for the detection and characterization of diabetes mellitus have included the measurement of fasted plasma glucose, urine glucose, urine ketone, serum fructosamine, and fasted plasma insulin concentrations as well as oral and intravenous glucose tolerance tests.[5,13,20,25,27] In NHP, these tests can present various challenges, including difficulty in sample collection, the necessity for anesthesia, potential alterations due to anesthetics, multiple confounding factors (for example, activity, duration of food withholding, diet), and stress hyperglycemia attributable to restraint or sedation.[8,12,19] For this reason, HbA1C measurement has been a valuable tool in monitoring long-term glycemic control in NHP because it is insensitive to many of those factors. Serum fructosamine is used to monitor long-term glycemic control as well, because it allows the assessment of the average blood glucose levels for the preceding 2 to 3 wk and is useful in patients with blood loss, hemolytic anemia, or hemoglobinopathies.[28] However, these tests do not come without challenges. They require an entire vial of whole blood, which must be refrigerated. If the NHP is not well trained to sit still and present an extremity for blood draws, the animal must be sedated each time the test is performed. The samples must be shipped to a commercial lab, and results may be unavailable for 5 to 10 d. In addition, these tests can be expensive. Using the cageside device is simpler, faster, and more cost-effective. The device we chose required only a single drop of blood (which can be collected via ear stick or another way, similar to daily blood glucose monitoring) and yields results in 5 min. This immediate feedback better enables disease management, given that necessary medication changes can be made sooner. In addition, the cost of the cageside test is significantly less than that charged by commercial labs for both HbA1C and serum fructosamine.

The goal of this study was to compare the HbA1C cageside test values with those from a commercial lab to assess correlation. This analysis revealed a significant relationship between the cageside and commercial lab tests for evaluating HbA1C in cynomolgus macaques. According to long-term longitudinal studies of adult rhesus monkeys before and during the development of T2DM, HbA1C concentrations exceeding 4.7% appear to be diagnostic of early or preT2DM in rhesus macaques and an HbA1C greater than 5.0% is diagnostic of overt diabetes.[6] The normal HbA1C in cynomolgus macaques is 3.5% to 5.0%.[15] The commercial lab values were appropriate with each animal's diabetic state: the nondiabetic macaques had values of 3.9% to 4.7%, whereas the diabetic animals had values greater than 5%. However, using the cageside device would lead to incorrectly classifying several animals as diabetic. Using the 95% CI as we described earlier makes the values more meaningful. The cageside device is therefore useful for ruling out nondiabetic animals or for indicating which animals merit further screening for diabetes.

The cageside device offers several advantages over a commercial lab. One of those is cost. The cageside test comes in a box with the device and 20 tests, and the cost per test, at the time of writing, is as much as 85% less than the cost of sending the sample to a commercial lab. Another advantage is the timing of results. With the cageside device, the reading is displayed within 5 min after loading the sample, such that the results are available nearly immediately. In contrast, several days elapse between collecting a sample for HbA1C analysis at a commercial lab and obtaining the results. Lastly, the cageside test presents a refinement to animal wellbeing, because only a single drop of blood is needed, which can easily be obtained from a tail, ear, or finger prick. This benefit eliminates the need for multiple sedation events when using HbA1C percentage to screen animals over time.

Although these results are promising, the current study has several limitations, and more work is needed to further assess the usefulness of the cageside device and in the establishment of more precise cutoff values. One of the limitations is the small data set. Additional animals and multiple measures from the same animals, especially as they progress from the nondiabetic to the diabetic state, are needed to increase the accuracy of the diabetic cutoff values from the cageside device. The lack of animals with an HbA1C percentage between 4.7% and 7.0% (according to the commercial laboratory test) limits our ability to specify appropriate cutoff values. For future studies, having a larger sample that includes animals representing the entire range of HbA1C values would be informative. An additional limitation is the cageside device's upper limit of 13%. Although animals whose readings exceeded 13% were still correctly identified as diabetic, the exact correlation and relationship of values between the 2 tests would have been improved if we had true HbA1C values from the cageside device for those animals. In the future, it would be helpful to test a larger population of confirmed diabetic animals and to use dilutions to get a true numeric value in excess of 13%. Lastly, only cynomolgus macaques were tested for this study, and knowing whether the same results can be obtained when using the cageside device on other macaque species would be helpful.

The data in the current study show that the cageside device has real potential for less traumatic and less costly testing of HbA1C levels in cynomolgus macaques, with good correlation to the laboratory 'gold standard.' Despite our limited data, the cageside device may be useful for ruling out nondiabetics and for indicating which animals warrant further screening for diabetes. Additional work is needed to better determine the values of the cageside device that indicate prediabetes and true diabetes. In addition, further studies are merited to assess the cageside test across a wider range of HbA1C values and in different species.

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