T1D Exchange

RACIAL DIFFERENCES IN MEAN CGM GLUCOSE IN RELATION TO HBA1C

A T1D Exchange Clinic Network Protocol

Version 1.3
9/04/14

TABLE OF CONTENTS

CHAPTER 1: BACKGROUND INFORMATION AND STUDY SYNOPSIS

1.1 Background and Rationale

Racial differences in glucose control have been reported in people with type 1 diabetes (T1D). The SEARCH for Diabetes in Youth study reported that African American youth with T1D were more likely to have an HbA1c >9.5% than Caucasian youth (35.5% versus 12.3%) (1). Similarly, in the T1D Exchange clinic registry, mean HbA1c was reported to be higher in non-Hispanic African Americans compared with non-Hispanic Whites (9.6% versus 8.4%).

Although it has been presumed that the higher HbA1c levels in African Americans represents worse glycemic control, it also has been hypothesized that the higher HbA1c levels could be an artifact due to race-based genetic differences in the glycation of hemoglobin at the same glucose levels. Biological differences to explain variability in the association of mean blood glucose with HbA1c has been referred to as a "glycation gap." Previous reports suggest that genetic differences may account for up to 62% [95% CI: 47-75%] of variability (2) in the association of mean glucose and HbA1c (3).

Several studies have used continuous glucose monitoring (CGM) or home blood glucose meter data to assess the relationship between mean glucose and HbA1c (4-7). A 3-month observational study of 10 clinical centers in the U.S., Europe, and Africa demonstrated strong support for a linear relationship between mean glucose and HbA1c levels, with some evidence that African Americans might have lower mean glucose per any given HbA1c level (4). A 6-month observational study conducted in the U.S. noted fairly constant measures of glycability consistent with what one might expect to see from individual differences, however, these differences in glycability explained less than half of the differences in HbA1c levels (5). In an analysis of CGM data from the JDRF CGM RCT, mean glucose ranged from 128 to 187 mg/dl for an HbA1c level of 7.0±1.0% (6). Previous studies included too few African Americans to make a meaningful assessment as to whether racial differences exist in the glycation gap or whether HbA1c levels in African-Americans tend to overestimate mean glucose compared with Whites. Herman and Cohen have reviewed the literature on racial differences in the relationship between HbA1c and blood glucose and make a compelling case for the existence of true differences and the need for data to definitively address this issue (8).

Several studies have evaluated the optimal sampling duration for using CGM data to estimate mean glucose (9) and other studies (5, 10). Consistently, the studies have shown that at least 14 days of CGM glucose data are needed to have a stable estimate of mean glucose. Xing et al (9) assessed different sampling strategies over a three-month period and concluded that a 12-15 day period of monitoring every three months may be needed to optimally assess overall glucose control.

An understanding of whether HbA1c reflects glycemic levels (as estimated by mean glucose) with similar accuracy in African Americans as in Whites is critical for patient management since HbA1c levels typically are used as the metric to determine the effectiveness of treatment. Thus, this study was designed to assess whether differences exist in the HbA1c-mean glucose relationship between non-Hispanic African Americans and non-Hispanic Whites.

1.2 Study Objective

The primary objective of the study is to determine whether a racial difference exists in the association of mean glucose with HbA1c between non-Hispanic African Americans and non-Hispanic Whites with T1D, and in particular to determine whether HbA1c levels overestimate mean glucose in non-Hispanic African Americans compared with non-Hispanic Whites.

1.3 Study Summary

This multi-center observational study will include up to 225 individuals with T1D with approximately equal numbers of non-Hispanic African American and non-Hispanic White participants, stratified in two age groups of 8 to <18 years old and ≥18 years old. At enrollment, blood will be drawn for measurement of HbA1c, fructosamine, glycated albumin, hemoglobin electrophoresis, total CBC with indices, reticulocyte counts, serum creatinine, and total bilirubin. Additional samples may be collected for storage in the T1D Exchange Sample Repository. A blinded CGM device will be worn as continuously as possible for 12 weeks, with a clinic visit every 14 days to change the sensor. The sensor to be used in the study is a modified, investigational version of Abbott Diabetes Care's Flash Glucose Monitoring system that has a 14-day memory sensor (see section 2.5). A log will be completed by the participant for at least 7 days on three occasions, recording meal times, insulin dosing, and exercise. During the periods where a daily log will be kept, participants may be asked to wear an accelerometer to record activity. Blood will be drawn for measurement of HbA1c level, blood glucose, fructosamine, and glycated albumin at two of the follow-up visits and at the final visit.

CHAPTER 2: STUDY PROTOCOL

2.1 Recruitment and Informed Consent

Up to 225 participants are expected to be enrolled, with approximately 100 participants in each of the two age strata (8 to <18 years old; ≥18 years old) and within each age strata, approximately 50 non-Hispanic African American and 50 non-Hispanic White participants. Participants with abnormal lab results (i.e., hemoglobinopathy or anemia) will remain in study follow up, but may be replaced as may participants with insufficient CGM data.

For eligible participants, the study will be discussed with the potential participant and, for those <18 years old, with the parent/legal guardian (referred to subsequently as 'parent'). Informed consent will be obtained from the potential participant (and parent for minors) according to IRB requirements prior to performing any study-specific procedures that are not part of the potential participant's routine care. Assent will be obtained from minors according to IRB requirements.

2.1 Eligibility Criteria

2.1.1 Inclusion Criteria

Potential study participants must meet all of the following inclusion criteria:

1. T1D Exchange clinic registry participant (meeting eligibility criteria for presumed autoimmune T1D)
   - If an individual is not currently participating in the T1D Exchange, he/she must join the T1D Exchange clinic registry in order to participate in this study (see section 3.6).
2. Age ≥8 years old
3. Duration of T1D ≥ 2.0 years
4. Self-identified race as non-Hispanic African American or non-Hispanic White; those selecting multiple race designations on the race/ethnicity form (see Appendix A) would be excluded
   - If parental race/ethnicity is known, both parents must be non- Hispanic African American or both parents must be non-Hispanic White in order for the participant to meet eligibility criteria.
5. Most recent HbA1c: 6.0% to 12.0% within 3 months prior (most recent may be from point of care measurement on day of visit)
6. Insulin regimen has been stable for the last two months, with no plans to switch the modality of insulin administration during the next 3 months (e.g., injection user switching to a pump, pump user switching to injections, or the addition of Lantus (Glargine) insulin)
7. Current CGM users are eligible as long as CGM has been used for at least 3 months and individual is willing to use blinded study CGM as well.
8. Ability to read, write and speak English

2.1.2 Exclusion Criteria

Study participants must NOT have any of the following exclusion criteria:

1. Females: pregnant or intending to become pregnant within the next 3 months
2. Known hemoglobinopathy
3. Known to have anemia, particularly hemolytic anemia
4. History of blood transfusion in the last 3 months or planned blood transfusion during the course of the study

5. Use of erythropoietin
6. Renal disease defined as history of dialysis, renal transplant, or known GFR <60 ml/min/1.73 m^2
7. History of islet cell transplant or pancreas transplant
8. Known active liver disease
9. Extensive skin changes or diseases that would inhibit wearing a sensor
10. Allergy to adhesives or other products involved with CGM use
11. Recent substantial improvement or worsening in glycemic control (i.e., a change in HbA1c exceeding 1% in the last 3 months)
12. Unable or unwilling to complete study procedures
13. Any current or previous medical condition or medication use that the investigator considers would interfere with the ability of the subject to complete study procedures
14. Concurrent participation in another study that could affect glycemic control

2.2 Enrollment Examination

At the enrollment examination, history will be elicited from the participant/parent and extracted from available medical records. Data may be collected with regard to the participant's diabetes history and current diabetes management, family history including parental race and ethnicity, socioeconomic indicators, current medications, and current medical conditions.

Physical examination will include body weight and height for all participants and Tanner Staging for participants <18 years old.

A blinded CGM sensor will be inserted and worn for 14 days (±2 days). Care instructions will be provided. A blood glucose meter and test strips for use with study blood glucose meter will be provided for use during CGM wear.

Non-fasting blood samples will be obtained for: measurement of hemoglobin electrophoresis, HbA1c level, fructosamine, glycated albumin, total CBC with indices, serum creatinine, reticulocyte counts and total bilirubin. A fingerstick blood glucose check and a laboratory measurement of blood glucose may be done at the time blood samples are obtained.

Additional blood samples may be collected for storage in the T1D Exchange Sample Repository, including DNA, RNA, peripheral blood mononuclear cells (PBMC), serum and plasma.

A pregnancy test may be performed for female participants.

2.3 Follow-up Visits

Follow-up visits will occur 14 days (±2 days) from the prior visit for placement of CGM sensors, for an expected total of 6 follow-up visits over a time period of 12 weeks to a maximum of 16 weeks (if one or more visits are delayed). Participants may receive reminder phone calls prior to follow-up visits. Visit week designations are titled according to ideal follow-up schedule, but may not correspond exactly depending on actual follow-up schedule.

The 4 and 8 week visits will include a blood draw for measurement of HbA1c level, blood glucose, fructosamine, and glycated albumin. A fingerstick blood glucose check may be done at the time blood samples are obtained.

The final visit will include point of care HbA1c measurement and a blood draw for measurement of HbA1c level, blood glucose, fructosamine, and glycated albumin. A fingerstick blood glucose check may be done at the time blood samples are obtained. At the final planned visit, the CGM data will be reviewed to determine if there is at least one week of data in the two week use period. If not, a new sensor will be placed and the final visit will be deferred. A food questionnaire may be administered at one or more visits.

A log will be completed by the participant for at least 7 days on three occasions, recording information such as, but not limited to, meal times, insulin dosing, sleep pattern, and exercise. Participants may be given an accelerometer to wear during the time the log is being kept.

There is no management or support during the study other than what would normally be provided as part of usual care. The downloaded CGM data and blood glucose monitoring data from the study will be reviewed with the participant at conclusion of the study or at a subsequent usual care office visit. Feedback on the format in which the CGM data are provided for review at the end of the study might be requested from the participant.

2.4 Blood Sample Collection

At the time of enrollment, non-fasting blood samples will be obtained for: measurement of hemoglobin electrophoresis, HbA1c level, fructosamine, glycated albumin, total CBC with indices, reticulocyte counts, serum creatinine, and total bilirubin. A fingerstick blood glucose check and a laboratory measurement of blood glucose may be done at the time blood samples are obtained. Additional samples may be collected for storage in the T1D Exchange Sample Repository, including DNA, RNA, peripheral blood mononuclear cells (PBMC), serum and plasma.

At 4 and 8 weeks, non-fasting blood samples will be drawn for measurement of HbA1c level, blood glucose, fructosamine, and glycated albumin. A fingerstick blood glucose check may be done at the time blood samples are obtained.

The 12-week visit will include a point of care HbA1c and a non-fasting blood draw for measurement of HbA1c level, blood glucose, fructosamine, and glycated albumin. A fingerstick blood glucose check may be done at the time blood samples are obtained.

2.5 Continuous Glucose Monitoring

The CGM that will be used in the study is a modified, investigational version of Abbott Diabetes Care's Flash Glucose Monitoring system that has a 14-day memory sensor. The system uses a wired enzyme-based sensor to measure glucose levels. No calibration by the user is needed. The sensor automatically measures and stores glucose levels every 15 minutes. The sensor has a simple and low pain sensor application, with a small low-profile sensor patch on the skin. Although the device is investigational, an IDE from the Food and Drug Administration is not required. An IDE is not required for device studies that are considered to have less than significant risk. Since the sensor is blinded, meaning that the subject cannot see the glucose values, there is no risk of the subject making a real-time change in insulin delivery or any other aspect of diabetes management based on glucose values from the sensor.

A sensor will be worn as continuously as possible for 12 weeks throughout the course of the study. The CGM will be placed by a member of the study team every 14 days (±2 days) and participant/parent will be instructed on the use and return of the device.

Minimum CGM data requirements for analyses are detailed in Chapter 4. If insufficient data are obtained in the final 2-week period (weeks 10-12), the participant may be asked to extend sensor wear for an additional 2 weeks and return for a final visit.

A blood glucose meter and test strips will be provided for use during CGM wear. If participants use a personal CGM or insulin pump these data may be downloaded at study visits.

2.6 Accelerometer

Participants may be asked to use an accelerometer during the time the log is being kept.

Participants will receive instructions on how to wear the device.

	Screening & Baseline visit 0 weeks	**2 weeks***	**4 weeks***	**6 weeks***	**8 weeks***	**10 weeks***	**12 weeks***
Window		(±2 days)	(±2 days)	(±2 days)	(±2 days)	(±2 days)	(±2 days)
Informed consent	X						
Focused medical history and physical exam	X						
Point of Care HbA1c	X *(only if HbA1c from prior 3 mos not available)*						X
Fingerstick blood glucose reading	X		X		X		X
Blinded CGM training and placement (wear for 14 days)	X	X	X	X	X	X	X *(only if insufficient data from 10-12 weeks period)*
Blood Glucose Meter (BGM) for use throughout study	X	X	X	X	X	X	X *(only if insufficient CGM data from 10-12 weeks period)*
Daily Log Start (daily log kept for at least 7 days)		X		X		X	
Accelerometer Use Start (may be worn while log is completed)		X		X		X	
Food Questionnaire (may be included)		X	X	X	X	X	X
<u>Labs (Central):</u> HbA1c; fructosamine; glycated albumin; blood glucose at follow up (may also be included at baseline)	X		X		X		X
<u>Labs (Central):</u> Hemoglobin Electrophoresis; Serum Creatinine; Reticulocyte counts; Total bilirubin; (Local Lab) Total CBC with indices;	X						
T1D Exchange Sample Repository	X						

*This is an estimation of weeks. Next visit will actually occur 14 days (±2 days) following the prior visit.

2.7 Quality Assurance and Monitoring

The primary outcome data for the study will be HbA1c from the laboratories performing these analyses. Monitoring with include duplicate samples for quality control assessment.

2.8 General Considerations

This study is being conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki and with the standards of Good Clinical Practice.

CHAPTER 3: MISCELLANEOUS CONSIDERATIONS

3.1 Adverse Events

The only adverse events to be collected will be those related to the study procedures. Hypoglycemia will be considered an adverse event only if severe (defined as needing assistance of others due to altered consciousness) and hyperglycemia will be considered an adverse event only if it results in diabetic ketoacidosis. Each investigator is responsible for informing his/her IRB of serious study-related adverse events and abiding by any other reporting requirements specific to his/her IRB.

3.2 Benefits for Participants

Results of this study will provide important new knowledge that will be generalizable to individuals with T1D.

In addition, the results may have specific relevance for the participant with respect to determining how well HbA1c levels reflect mean glucose levels. Retrospective review of the CGM data also may be useful for improving glycemic control.

3.3 Risks

The risks of the study are minimal. The blood draws could result in discomfort or bruising, or rarely an infection. For children <18 years the maximum blood volume will not exceed 5 cc/kg body weight over a 1-month period. The exact blood volumes collected may vary according to local IRB regulations. The maximum blood volume collected from adults >18 years will not exceed 250cc over a 1-month period.

The risks of wearing the CGM are minimal. Participant may experience mild or moderate symptoms associated with the CGM sensor application or the adhesive used to keep the sensor in place. These include swelling, rash, itching, bruising, pain, bleeding and hardening of the skin. Infection, inflammation or bleeding at the sensor insertion site are also possible risks of applying a sensor to the skin.

The risk of disclosure of protected health information is very small. Efforts are taken to assure that this does not occur, in compliance with HIPAA/HITECH/future privacy regulations.

3.3.1 Special Consideration for Children

The study procedures are minimal risk, and the study is likely to yield general knowledge about T1D that is of importance for the understanding and amelioration of T1D in children. Assent of children along with consent of the parents will be obtained prior to any study procedures, in accordance with IRB requirements. This research proposal in children is therefore consistent with United States Department of Health and Human Services, Protection of Human Subjects, subpart D, section 46.404.

3.4 Participant/Parent Reimbursement

Participants will be reimbursed $50 per study visit for their transportation and time in the study. Additionally, participants who record the daily log will receive $50 for each of the 3 logs. Minimum criteria for daily log completion includes record of awakening time, bedtime and each insulin dose.

3.5 Pregnancy

Individuals who are known to be pregnant will not be able to participate in this study as metabolic changes associated with pregnancy may make data interpretation difficult. A pregnancy test may be completed as part of this study.

3.6 T1D Exchange Clinic Registry

If a participant is not already enrolled in the T1D Exchange clinic registry, he/she will become part of the registry when joining this study. As a registry participant, information from their medical record will be entered following enrollment and may be entered into the registry database at least once a year and they will have an opportunity to provide their email address to be contacted in the future about other studies for which they may be eligible. Participants also may be asked to complete a questionnaire(s) either on a computer, paper, or via telephone. Participants may be given the option to have questionnaires emailed to them and may decide whether or not to complete a questionnaire each time they are asked. For current registry participants, an annual registry update will be completed during study follow up. For all participants, the medical record data extraction for the registry is needed since such data complement the data being collected solely for this protocol and will be used in the analyses.

Participants who do not wish to continue to have medical record data entered into the registry database annually will have the opportunity to withdraw from registry as does any registry participant.

3.7 T1D Exchange Sample Repository

The T1D Exchange Sample Repository is designed to support ongoing and future research by qualified investigators by collecting information and biosamples from people with T1D. Samples will be used only for the study of T1D and its complications. Within this overarching purpose, multiple T1D Exchange studies will collect blood samples specifically for the T1D Exchange Sample Repository, whose policies and procedures will govern the release of data and samples to investigators. The T1D Exchange Sample Repository is directed by the Biobank Operations Center at Benaroya Research Institute, Seattle, WA and the Jaeb Center for Health Research (JCHR) who are responsible for the oversight of the operations of this database and biosample repository. Specifically, the JCHR IRB reviews and approves specific protocols under which data and samples may be obtained and shared, and ensures that adequate provisions protect the privacy and confidentiality of participants and data.

Enrolled participants will have samples collected for storage in the T1D Exchange Sample Repository. Blood will be drawn at enrollment and may include DNA, RNA, peripheral blood mononuclear cells (PBMC), serum and plasma. Although blood samples will need to be collected as part of this study, participants will have the option of declining storage of biosamples for future use.

3.8 Study Costs

All study-specific visits, procedures, and supplies will be paid for by the study.

3.9 Participant Withdrawals

Participation in the study is voluntary, and a participant may withdraw at any time.

3.10 Confidentiality

The participant's T1D Exchange identification number will be used to identify all data. Data will be entered on the Jaeb Center for Health Research's secure website through an SSL encrypted connection. The Jaeb Center websites are maintained on Unix and Linux servers running Apache web server software and on a Windows server running IIS, all with strong encryption. The study website is password-protected and restricted to users who have been authorized by the Jaeb Center to gain access.

Samples will be labeled with a code that will have no components that could identify the participant. The code of each sample will be linked in the Jaeb Center's database to the participant's T1D Exchange identification number.

Samples will be sent to multiple facilities for specimen storage and analyses. All laboratories and sample storage facilities will have an agreement with the Jaeb Center that will require compliance with HIPAA/HITECH/future regulations.

CHAPTER 4: STATISTICAL CONSIDERATIONS

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study.

4.1 Sample Size

Data from prior studies were used to construct a linear regression model for CGM-measured mean glucose as the dependent variable and HbA1c as the independent variable from which the estimated slope was 20 mg/dl per 1% change in HbA1c with a corresponding standard error of 1.18 mg/dl per 1%. This translates into a standard deviation of $1.18 \times \sqrt{(455)} \approx 25$ mg/dl per 1%.

With these assumptions, a minimum sample size of 200 participants (100 White and 100 African American) will provide 80% power to detect a difference in slopes of 10 mg/dl per 1% HbA1c.

4.2 Analysis Plan

4.2.1 Primary Analysis

The primary analysis will utilize HbA1c at 12 weeks and the prior 12 weeks of CGM values.

The following steps will be undertaken prior to the statistical modeling stage:

1) Weighted summary values for daily CGM averages (based on equal weights to each of the 24 hours measurements) up to 84 days will be computed using the formula provided by Tahara and Shima (1993) (11).
2) Individual weighted CGM averages and HbA1C values at 12 weeks will then be summarized by racial groups
    - Race-specific graphical depictions of CGM values vs. HbA1c values will be constructed to develop an understanding of the unadjusted shape of such relationship.
3) Diagnostics and assumptions will be checked for the proper modeling approach
    - Normality checks of the HbA1c (or CGM summary values) and/ or the residuals from any proposed model will be assessed using Q-Q plots and/or Wilk & Shapiro tests. Constancy of the variance will be assessed using standard F-test and plots checks.

4.2.2 Analytic Methods

Modeling Approach

The primary analysis model will have CGM weighted averages as dependent variable, which will be modeled as a function of HbA1c and race as well as the interaction between them. If normality and constancy of variance hold, a simple least square regression model will be

followed for analysis. However in the event of violation of these conditions, a robust modeling approach like the generalized linear mixed model will be pursued to accommodate any departure from normality and/or constancy of variance. It is expected that relationship of CGM data vis-à-vis HbA1c will be linear and the ultimate test in the interaction model is to determine if the slopes between the whites and blacks are significantly different.

4.2.3 Missing Data

HbA1c: Participants without a 12-week central laboratory HbA1c will be excluded from the primary analysis.

CGM: A minimum of two weeks of data is required within each one-month period, with at least one week required in the final 2-week period. Also, if insufficient data are obtained in the final 2-week period (weeks 10-12), the participant may be asked to extend sensor wear for an additional 2 weeks and return for a final visit. Additionally, based on volume of missing data, an imputing approach might be pursed to estimate missing observations.

4.3 Secondary Analyses

4.3.1 Age Groups

The primary analysis will be replicated in two subgroups based on age (<18 and ≥18 years old).

4.3.2 Other Subgroups

Exploratory analysis will investigate the mean glucose-HbA1c relationship according to gender and HbA1c level.

4.4 Additional Analysis/ Summaries:

4.4.1 Baseline Tabulations:

Summary statistics will be generated by racial groups and racial by age groups for demographics parameters of age, gender, duration of diabetes, BMI, fructosamine, HbA1c, insulin delivery method, and glycated albumin. Laboratory abnormalities will be tabulated.

4.4.2 Amount of CGM data:

The amount of CGM data over the course of the study by racial group will be tabulated.

4.4.3 Comparison of CGM and Blood Glucose Meter (BGM)

CGM and BGM glucose measurements will be compared using usual accuracy metrics. In addition, study BGM measurements made in the clinic will be compared with central lab glucose measurements done at the time of blood draws.

4.4.4 Additional CGM Data Analyses

The CGM data may be used for additional assessments such as glucose levels on awakening in the morning and patterns of glucose levels during the day.

4.4.5 Other Measures of Glucose Control

Similar to the primary analysis methods above, the relationship between weighted mean glucose and each of fructosamine and glycated albumin and whether this relationship differs by race will be assessed.

Additionally, paired correlations (Spearman or Pearson) of HbA1c, fructosamine, glycated albumin and mean glucose will be examined for African Americans and Whites. Also additional k-spline smoothing techniques will be pursued to relate CGM weighted values to HbA1c within each of the racial groups.

4.5 Adverse Events

Reportable adverse events will be tabulated.

CHAPTER 5: REFERENCES

1. Petitti DB, Klingensmith GJ, Bell RA, Andrews JS, Dabelea D, Imperatore G, et al. Glycemic control in youth with diabetes: the SEARCH for diabetes in Youth Study. J Pediatr. 2009; 155:668-72 e1-3.
2. Snieder H, Sawtell PA, Ross L, Walker J, Spector TD, Leslie RD. HbA(1c) levels are genetically determined even in type 1 diabetes: evidence from healthy and diabetic twins. Diabetes. 2001; 50:2858-63.
3. Cohen RM, Snieder H, Lindsell CJ, Beyan H, Hawa MI, Blinko S, et al. Evidence for independent heritability of the glycation gap (glycosylation gap) fraction of HbA1c in nondiabetic twins. Diabetes Care. 2006; 29:1739-43.
4. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. Translating the A1C assay into estimated average glucose values. Diabetes Care. 2008; 31:1473-8.
5. Wilson DM, Kollman. Relationship of A1C to glucose concentrations in children with type 1 diabetes: assessments by high-frequency glucose determinations by sensors. Diabetes Care. 2008; 31:381-5.
6. Wilson DM, Xing D, Beck RW, Block J, Bode B, Fox LA, et al. Hemoglobin A1c and mean glucose in patients with type 1 diabetes: analysis of data from the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. Diabetes Care. 2011; 34:540-4.
7. Wilson DM, Xing D, Cheng J, Beck RW, Hirsch I, Kollman C, et al. Persistence of individual variations in glycated hemoglobin: analysis of data from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Randomized Trial. Diabetes Care. 2011; 34:1315-7.
8. Herman WH, Cohen RM. Racial and ethnic differences in the relationship between HbA1c and blood glucose: implications for the diagnosis of diabetes. J Clin Endocrinol Metab. 2012; 97:1067-72.
9. Xing D, Kollman C, Beck RW, Tamborlane WV, Laffel L, Buckingham BA, et al. Optimal sampling intervals to assess long-term glycemic control using continuous glucose monitoring. Diabetes Technol Ther. 2011; 13:351-8.
10. Mazze RS, Strock E, Wesley D, Borgman S, Morgan B, Bergenstal R, et al. Characterizing glucose exposure for individuals with normal glucose tolerance using continuous glucose monitoring and ambulatory glucose profile analysis. Diabetes Technol Ther. 2008; 10:149-59.
11. Tahara Y, Shima K. The response of GHb to stepwise plasma glucose change over time in diabetic patients. Diabetes Care. 1993; 16:1313-4.

Appendix A:
Race/Ethnicity Form

RACE ETHNICITY VERIFICATION

Ethnic Category:

☐ Hispanic or Latino

☐ Not-Hispanic or Latino

Definitions are as follows:

Hispanic or Latino: *A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can be used in addition to "Hispanic" or "Latino."*

Not Hispanic or Latino: *A person not of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.*

Racial Category:

☐ American Indian or Alaska Native

☐ Asian

☐ Black or African American

☐ Native Hawaiian or Other Pacific Islander

☐ White

☐ Other _____

Definitions are as follows:

American Indian or Alaska Native: *A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment.*

Asian: *A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.*

Black or African American: *A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black" or "African American."*

Native Hawaiian or Other Pacific Islander: *A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.*

White: *A person having origins in any of the original peoples of Europe, the Middle East or North Africa.*