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ORIGINAL ARTICLE

Rationale and Design for a GRADE Substudy of Continuous Glucose Monitoring

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Abstract

Background: The **G**lycemia **R**eduction **A**pproaches in **D**iabetes: A Comparative **E**ffectiveness (GRADE) study has enrolled a racially and ethnically diverse population with type 2 diabetes, performed extensive phenotyping, and randomly assigned the participants to one of four second-line diabetes medications. The continuous glucose monitoring (CGM) substudy has been added to determine whether there are racial/ethnic differences in the relationship between average glucose (AG) and hemoglobin A1c (HbA1c). CGM will also be used to compare time in target range, glucose variability, and the frequency and duration of hypoglycemia across study groups.
Methods: The observational CGM substudy will enroll up to 1800 of the 5047 GRADE study participants from the four treatment groups, including as many as 450 participants from each of 4 racial/ethnic minority groups to be compared: Hispanic White, non-Hispanic White, non-Hispanic African American, and non-Hispanic Other. CGM will be performed for 2 weeks in proximity to a GRADE annual visit, during which an oral glucose tolerance test will be performed and HbA1c and glycated albumin measured. Indicators of interindividual variation in red blood cell turnover, based on specialized erythrocyte measurements, will also be measured to explore the potential causes of interindividual HbA1c variations.
Conclusions: The GRADE CGM substudy will provide new insights into whether differences exist in the relationship between HbA1c and AG among different racial/ethnic groups and whether glycemic profiles differ among frequently used diabetes medications and their potential clinical implications. Understanding such differences is important for clinical care and adjustment of diabetes medications in patients of different races or ethnicities.

Keywords: Type 2 diabetes, Glycated hemoglobin, Interracial differences, Continuous glucose monitoring, Average glucose.

Background

Interindividual differences in the relationship among average glucose (AG) levels, glycated hemoglobin, and other measures of glycemic control, including interracial and interethnic differences, have been suggested[1–6] but remain controversial.[7–10] Most studies to date, with rare exceptions,[11,12] have not collected reliable measures of average glycemia or explored plausible mechanisms for the putative differences. Interindividual variability in red blood cell (RBC)

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turnover and genetic variation in hemoglobin glycation[13–17] have been proposed as explanations for any interindividual differences in the relationship between AG and glycated hemoglobin levels. Understanding whether such putative differences exist among racial and ethnic groups is important because of the potential to overtreat or undertreat subgroups of patients based on the incorrect translation of hemoglobin A1c (HbA1c) into AG levels, which could in turn result in excess hypoglycemia or increased risk for long-term micro- and macrovascular complications, respectively.

The **G**lycemia **R**eduction **A**pproaches in **D**iabetes: A Comparative **E**ffectiveness (GRADE) Study has recruited participants with type 2 diabetes (T2D) with a large representation of African Americans and Hispanic Americans as well as non-Hispanic Whites (NHWs).[18] The study is primarily directed at comparing glycemic effects, based on HbA1c, of four of the most commonly used diabetes medicines when added to metformin. We describe herein a continuous glucose monitoring (CGM) Substudy added to GRADE which, with its diverse population, will definitively address whether the relationship between AG and HbA1c differs among racial and ethnic populations. In addition, the random assignment to different diabetes therapies in GRADE provides the opportunity to examine potential differential effects of diabetes medications on glucose profiles, including their relative risk for hypoglycemia and postprandial hyperglycemia. Putative differences in glucose profiles between diabetes medications beyond mean glycemia achieved have also been suggested as a risk factor for long-term complications,[19] but comparative effectiveness studies with random treatment assignment and reliable measurements of glycemic profiles have been extremely limited.

Methods

Population and setting

The design of the GRADE study has been described in detail.[18] In brief, the GRADE study, a pragmatic, parallel design clinical trial, recruited participants ≥30 years of age with diabetes duration <10 years. At the time of randomization eligible participants were treated with at least 1000 mg of metformin per day for the preceding 8 weeks, but with no other diabetes medications, and had HbA1c levels between 6.8% and 8.5%. Eligible participants were randomly assigned to the sulfonylurea glimepiride, the DPP-4 inhibitor sitagliptin, the GLP-1 receptor agonist liraglutide, or the long-acting insulin analog glargine. Recruitment ended in August 2017 with a cohort of 5047. Participant race is self-reported according to seven categories and ethnicity as Hispanic or not. The CGM study will be an observational substudy within the GRADE clinical trial.

CGM substudy cohort

Approximately 1800 participants of the GRADE parent study will be recruited to enroll in the CGM substudy, including up to 450 members of each of the four racial and ethnic minorities of interest that will provide adequate power to allow comparisons. We expect that this selection will also provide similar distributions across the treatment groups. The four racial/ethnic groups considered are Non-Hispanic African American (NHAA), Hispanic White, NHW and Non-Hispanic Other (NHO), where the NHO group includes American Indians, Asian Americans, and Pacific Islanders, and participants who report race/ethnicity as ''other.''

Measurements

Continuous glucose monitoring. CGM will be performed for 2 weeks on the selected subcohort in close proximity (about 2–4 weeks prior) to the time of a scheduled annual year 1, 3, or 5 visit (Fig. 1: Study Overview) to have information on metabolic progression over time. Owing to practical scheduling challenges, a small number of ''year one'' participants will be studied after the first year annual visit at months 15, 18, or 21.

The Abbott Freestyle Libre™ Pro CGM Professional model (Abbott Diabetes Care, Alameda, CA), was selected for its ease of use (small and lack of need for calibration) and the masked nature of the glucose data collected (results not visible to the participants to avoid influencing diabetes management). Staff training will be provided centrally at CGM substudy start-up for all sites with a didactic and hands-on demonstration and practice. The selection of staff to insert the sensor will be based on local guidelines and scope of practice and all staff engaged in the CGM substudy will be required to review the manual of procedures and complete a certification quiz.

The CGM sensor will be inserted on the back of either upper arm, activated with the CGM reader and worn for 10 to 14 days. At the time of sensor placement, study staff will review with participants an instruction sheet that covers care of the CGM sensor, sensor removal, diary completion, and how to return the sensor to the GRADE clinical site. The sensor is removed either at the time of the follow-up visit if it occurs on day 14 of CGM use, or by the participant at home depending on the timing of the completion of monitoring (Fig. 1). If the sensor is dislodged before the 14-day study period is completed and the participant is willing, a second sensor will be placed within the study period. The data from the two sensors will be combined. Ten or more days of CGM readings will be considered a complete study for inclusion in the main analyses. If participants have experienced an acute illness likely to affect glycemia or have been treated with systemic glucocorticoids during the CGM collection, the GRADE Coordinating Center is alerted and those results will be censored. All sensors are read by the GRADE Central Biochemical Laboratory (CBL) at the Advanced Research and Diagnostic Laboratory, Department of Laboratory Medicine and Pathology, University of Minnesota in Minneapolis, Minnesota.

During the 14-day monitoring period, each participant will keep a diary of any symptomatic episodes consistent with hypoglycemia, including the date, time, and treatment of the episode and the date of sensor removal/dislodgement. CGM results will be blinded to both the participant and the clinical site staff during the monitoring period; however, after the CGM results have been analyzed, alert levels (defined as two episodes, each with two or more consecutive CGM values ≤54 mg/dL) (with readings recorded every 15 min so an episode is at least 30 min in duration) will be reported to the centers so that appropriate adjustments in lifestyle or medication may be considered.

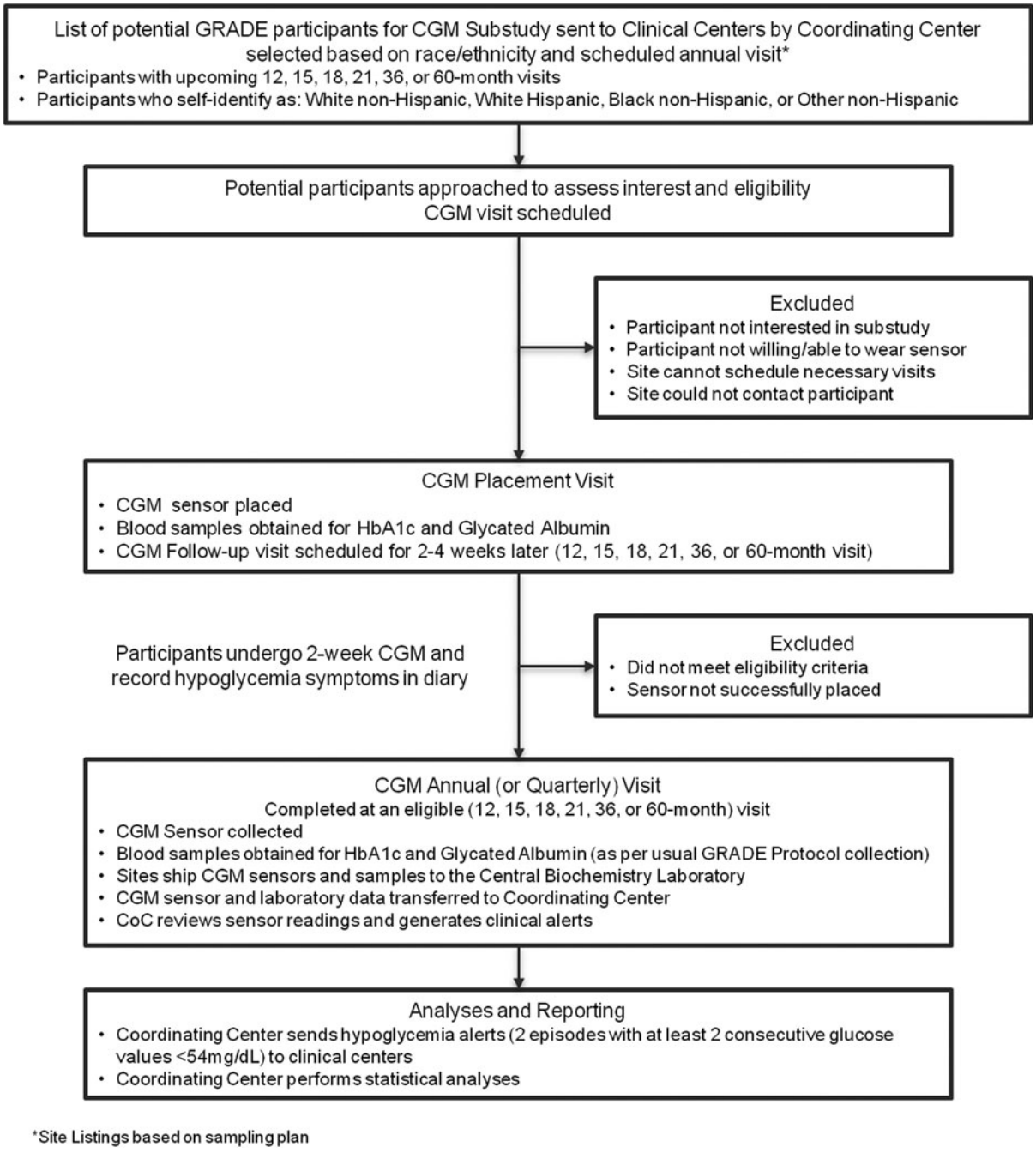

FIG. 1. Continuous glucose monitoring substudy overview.

Besides AG, other features of interest will be the time spent in the designated hyperglycemic ranges of >180 and >250 mg/dL, time spent in the target range of 70–180 mg/dL, and the time spent in the designated hypoglycemic ranges of <70 and <54 mg/dL. In addition, we will measure the number of episodes of hypoglycemia (<70 and <54 mg/dL), where an episode is defined as two events, each of which has two or more consecutive glucose levels <54 mg/dL. Glycemic variability will be captured with derived measures such as the mean amplitude of glycemic excursion and the continuous overall net glycemic action, the mean of daily differences, coefficients of variation, and standard deviations.[20]

Laboratory measurements. Blood samples for HbA1c and glycated albumin[21] will be obtained at the time of the CGM insertion and approximately 2 weeks later when the CGM is completed. These blood samples will also be used to assess the mean RBC ages and turnover among participants. Blood samples obtained subsequently may be analyzed similarly. All measurements are performed in the GRADE CBL. Glycated hemoglobin is measured in EDTA whole blood using the Tosoh HPLC Glycohemoglobin Analyzer, which is an automated high-performance liquid chromatography method (Tosoh Medics, Inc., San Francisco, CA). Calibration of this method is evaluated utilizing standard

values derived by the National Glycohemoglobin Standardization Program (NGSP). The interassay coefficients of variation in the GRADE Central Laboratory are 1.16% at a HbA1c value of 5.34% and 0.55% at a HbA1c value of 10.11%. Glycated albumin will be measured using a multienzyme, stepwise assay (Asahi Kasei, Inc.,Tokyo, Japan) in serum and expressed as the percentage of albumin that is glycated. The interassay coefficient of variation (CV) of glycated albumin in the GRADE Central Laboratory is 4.4% at a mean concentration of 0.45 g/dL and 2.8% at a mean concentration of 1.64 g/dL; the interassay CV of albumin is 2.4% at a mean concentration of 4.45 g/dL and 1.9% at a mean concentration of 3.86 g/dL.

Estimation of red blood cell age and turnover

Two approaches will be used to estimate each participant's RBC age and turnover and their potential extraglycemic influence on HbA1c. First, CGM and HbA1c will be combined with a mechanistic model of hemoglobin glycation to provide an indirect estimate of the subject's mean RBC age (eMRBC).[22] Second, single-RBC volume and hemoglobin concentration will be measured (ADVIA 2120i, Siemens AG or CELL-DYN Sapphire; Abbott Diagnostics, Abbott Park, IL). These measurements provide quantitative estimates of RBC age and turnover.[23,24] Each measurement of RBC turnover will be used to identify participants whose RBC turnover is relatively faster or slower than the norm and in whom the AG/HbA1c relationship may be altered accordingly.

Statistical analyses

Initial analyses will compare the characteristics of the racial/ethnic groups, including the distribution of HbA1c and the distribution of CGM results (including AG) with an adjustment for six pairwise comparisons. A linear model will regress the HbA1c on AG, calculated from CGM, with a class effect for racial/ethnic group and AG by group interaction. A 2-degrees of freedom joint test of the equality of intercepts and slopes will investigate differences among groups in the HbA1c to AG regression lines with an adjustment for six pairwise comparisons. The principal comparison of NHW versus NHAA will also be conducted secondarily for males and females with a test of homogeneity. Similar analyses will be performed using glycemic measures derived from the oral glucose tolerance test, and with glycated albumin instead of HbA1c, and employing measures of HbA1c and AG corrected for variation attributed to estimated mean RBC age.

Additional analyses will compare these relationships among the four treatment groups under the intention-to-treat principle, using all available data, and additional terms for racial group and interactions of AG with treatment group.

Cox proportional hazards models stratified by the year of the CGM assessment (1, 3, or 5), with and without adjustment for AG, HbA1c, and other risk factors (such as sex and age) will assess the association between the level of glucose variability and selected incident GRADE outcomes observed after the CGM evaluation. Outcomes of interest will include the time-to-occurrence of the GRADE primary, secondary, and tertiary metabolic outcomes[18] and time to an episode of severe hypoglycemia (defined as requiring assistance), as well as time to microvascular complications (such as micro- and macroalbuminuria defined as an albumin excretion: urine creatinine ratio >30 and 300 mg/g, respectively) and the risk of cardiovascular disease (CVD).

Multiple comparisons conducted across subgroups will be adjusted for multiplicity using the Holm procedure.[25]

Power calculations and sample size. The sample size for the study was based on an assessment of the power to detect a difference in intercepts of 4 mg/dL and slopes of 1 mg/dL/% between racial/ethnic groups (NHW vs. NHAA) when regressing HbA1c on AG, the primary aim. The calculations employed estimates from the A1c-Derived Average Glucose (ADAG) study,[11] allowing for nonhomogeneous (homoscedastic) random errors over the range of HbA1c. These quantities were then employed in the expression for the noncentrality parameter for the 2 df chi-square test of the difference in slopes and intercepts to calculate sample size and power.

A sample size of 86 per racial/ethnic group within each treatment group would provide $\sim$90% power to detect the difference described above in intercepts and slopes for the comparison of 2 racial/ethnic groups adjusting for 6 pairwise comparisons. Allowing for possible model misspecification through a 1.2 variance inflation factor, and 10% missing data yields a sample size of 112 participants in each of the 4 racial/ethnic groups within each of the four treatment groups, for a total sample size of 1800 participants, 450 within each racial group evenly divided among the four treatment groups (112 each) and 450 within each treatment group evenly divided among the four racial groups (112 each).

This sample size will provide excellent power (>90%) to detect a meaningful difference between two racial groups within one of the four treatment groups. The power to determine whether glycemic variability contributes to or affects the outcomes in GRADE, including microvascular and CVD events, is a function of the effect sizes (i.e., hazard ratios) and the number of participants who have the event. The latter will be limited.

Conclusions

Many epidemiologic studies over the past 20 years have demonstrated higher HbA1c levels in African Americans than Whites.[26] Until the mid-2000s, the observed differences in HbA1c by race were universally attributed to health disparities, that is, differences in health care in different population groups. Subsequent studies that compared HbA1c by race and statistically adjusted for sociodemographic and clinical factors, and controlled for access to care and quality of care, were unable to explain the observed differences in HbA1c by race.[27,28] More recently, differences in HbA1c have been demonstrated in African American and White adults who were selected to have the same fasting and postchallenge glucose levels.[4,29–31] Still, unmeasured differences in diet and physical activity between African Americans and Whites might have resulted in chronic differences in glucose levels and thus in HbA1c. To address the limited measurements of actual mean glycemia in prior studies, a recent study of African American and White patients with type 1 diabetes (T1D) used CGM to provide a complete assessment of AG levels.[12] It demonstrated that HbA1c was 0.8% higher in African Americans than Whites. Approximately one-half of the difference was explained by differences in glycemia, but

the remaining ~0.4% difference was not explained by average glycemia. In contrast, no significant racial differences were found in the relationship between mean glucose and glycated albumin or fructosamine.

Racial differences in single nucleotide polymorphisms that are associated with HbA1c, but operate through nonglycemic mechanisms, have been proposed as an explanation for the differences in HbA1c between African Americans and Whites.[32] To date, however, no polymorphisms have been identified to explain more than a small proportion of the observed difference in HbA1c by race. Racial differences in red cell turnover have also been invoked to explain the racial differences in HbA1c,[33] although there is no direct evidence of racial differences in red cell turnover to date, owing in part to the difficulty in its measurement.[16]

CGM provides frequent real-time reliable measurements of glucose levels that allows calculation of AG. Other key features added by CGM glucose analysis beyond AG levels include the ability to quantitate hypoglycemia and glucose variability. While the GRADE CGM substudy is measuring a single 2-week period of glucose control, this period of CGM has been shown to be a good reflection of 30–90 days of CGM in most individuals.[34]

Most trials to date studying the added value of using CGM have focused on individuals with T1D who are using pump therapy or multiple daily insulin injections.[12,35] Only a few studies have used CGM to characterize glucose metrics in T2D patients or examined the value of CGM in T2D management.[36] No studies to date have characterized or compared CGM metrics or glucose profiles in a large number of T2D patients randomized to commonly used T2D medications, as will be done in the GRADE CGM substudy. A key component of diabetes management today is focused on minimizing hypoglycemia in both T1D and T2D, since hypoglycemia has been clearly demonstrated to be potentially dangerous, as well as disruptive to the quality of life and costly to the health care system.[37,38] While some T2D medications carry a low risk of hypoglycemia, sulfonylureas and insulin have been associated with an increased risk of hypoglycemia. CGM is the only practical way to compare rates of hypoglycemia 24 h/day, and capture all the episodes of hypoglycemia whether they are symptomatic or asymptomatic.

Glucose variability, the other key glucose profile metric not captured by an HbA1c, has been associated with an increased risk for hypoglycemia, diabetes complications, and reduced quality of life.[19,39] Few studies have been performed in T2DM, and the GRADE CGM substudy will greatly expand the characterization of glucose variability across four major diabetes treatment regimens. Similarly, the relationship between microvascular and macrovascular complications and glucose variability is based on a few observational studies.[40,41] GRADE is measuring renal microvascular disease and cardiovascular risk factors, allowing us to determine if these outcome measures are related to glucose variability.

In summary, the GRADE CGM substudy will provide a large and diverse population of patients with T2D to determine whether, and the extent to which, the relationship between AG and HbA1c differs among racial and ethnic groups. The additional measurement of glycated albumin and RBC profiling should help to distinguish the contribution of abnormalities in RBC turnover from differences in glycation. This substudy will also provide new insights into whether glycemic profiles and measures of time in target range, hypoglycemia, and glucose variability differ among frequently used diabetes medications.

Acknowledgments

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