The accuracy of current Dexcom G4 Platinum CGM System and potential advantages of routine blood glucose monitoring (BGM) in subgroups that require careful glucose monitoring: A follow-up investigation on the REPLACE-BG study.

Introduction:

Continuous glucose monitoring (CGM) technologies allow for better management of diabetes by offering patients access to real-time trends in glucose fluctuations. Initially, the FDA approved CGM devices as an adjunct-only tool, whereby, routine blood glucose monitoring (BGM) was required to confirm glucose levels for making insulin dosing decisions. Nevertheless, many CGM users often made insulin dosing decisions without the use of confirmatory BGM. The accuracy of the CGM devices have improved over the years,[1] which may warrant their use as a stand-alone diagnostic for making diabetes treatment management decisions. Along these lines, the REPLACE-BG clinical trial recently concluded that CGM without the regular use of confirmatory BGM was as safe and efficacious in maintaining glucose levels within a normal range in adults with well-controlled type 1 diabetes.[2] In this report, we followed up the REPLACE-BG study by examining the accuracy of the CGM devices used in the study, the Dexcom G4 Platinum CGM System with an enhanced algorithm (Software 505). We found that the instantaneous accuracy of the devices can be approximated by an exponential distribution a mean absolute relative difference of 10.3% compared to BGM measurements. This indicates that at any given moment the accuracy of the device is on average off by 10.3% and is off by more than 20% nearly 15% of the time. Because there is still have room for improvement in the accuracy of CGM devices, it begs the question if certain subgroups with difficult-to-manage glucose levels could still benefit from routine BGM. One potential subgroup could be premenopausal females, as many women have difficulty maintaining euglycemia during certain phases of their menstrual cycle. To this end, we specifically compared females under 35 years in the CGM+BGM and CGM Only groups from the REPLACE-BG dataset.[3,4] Our analysis reveals that females in the CGM+BGM group had lower mean glucose levels, spent a longer time within a normal glucose range (70-180mg/dL), and had lower HbA1c levels at the conclusion of the 26-week trial compared to the CGM Only group. These findings suggest that in addition to CGM, certain subpopulations may benefit from routine BGM to guide their treatment decisions.

Accuracy of the Dexcom G4 Platinum CGM System

The Dexcom G4 CGM devices provide real-time [glucose] measurements every 5 minutes, which requires twice-daily calibrations with BGM measurements. Subjects also made BGM measurements for guiding diabetes management decisions to different degrees in the CGM+BGM and CGM Only group. Thus, all subjects had a plethora of BGM measurements throughout the 26-Week trial that we utilized to assess the accuracy of CGM devices. We correlated each BGM measurement with a CGM measurement that preceded it if one occurred within a 5-minute interval. Only the first BGM measurement was used for analysis if multiple BGM measurements were made within a 10-minute interval. This yielded 294,904 pairs of CGM-BGM measurements from 217 subjects for which we assessed the absolute relative difference (ARD) using **equation 1**:

$$ARD = 100\% \times \frac{|\,[Glucose]_{CGM} - [Glucose]_{BGM}|}{[Glucose]_{BGM}}$$

Equation 1

Fig. 1A shows a histogram of the absolute relative differences in the measurements which follows an almost perfect exponential distribution as delineated by the exponential fit (black trace in **Fig. 1A**). We found that the mean ARD of all points was 10.31% which coincided with the mean derived from the exponential fit (mean ±95% CI: 10.31 ± 0.074%), again reinforcing that the sensor accuracy is well described by an exponential distribution. This functional form allows for simple calculations of expected sensor accuracy. For instance, if we wanted to know the relative amount of time the sensor accuracy was off by >20%, it would be ~14.37% of the time (`1-expcdf(20,10.31)`). We suggest that the variability in accuracy from this large real-world dataset can serves as a benchmark for future generations of CGM devices or for testing the effectiveness of incorporating more calibrations within a day.

We next examined how much intra-subject variability there was in sensor accuracy. **Fig. 1B** shows a histogram of the mean absolute relative difference (MARD) of CGM vs. BGM for each subject, which follows a log-normal distribution with $\sigma^2 = 13$. Given that there are hundreds, if not thousands, of CGM-BGM measurement pairs for each subject, it was surprising to see such a broad distribution of MARDs. This suggests that factors within subjects may systematically impact sensor accuracy.

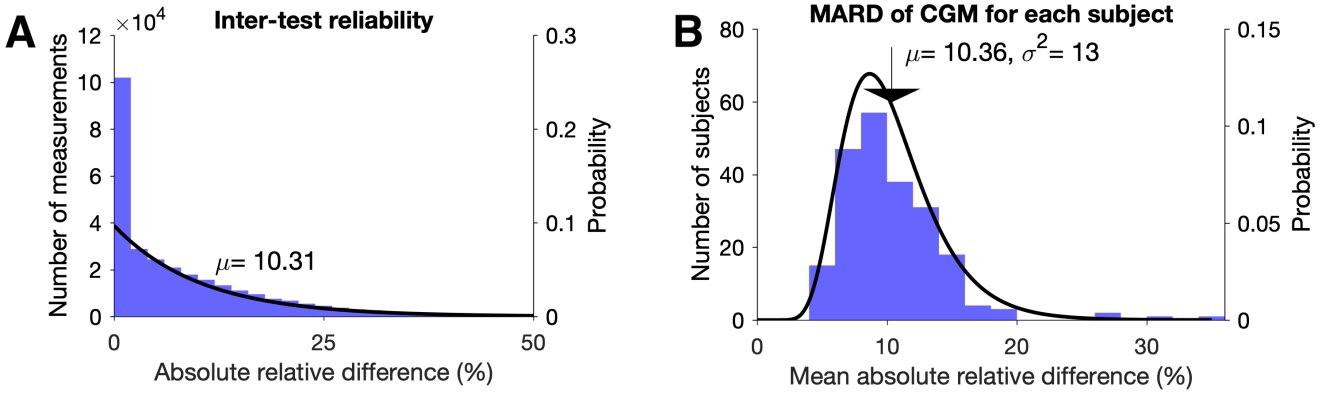

Fig. 1: Accuracy of the Dexcom G4 Platinum CGM System

Potential benefit of routine BGM for females <35 years with type 1 diabetes using CGM devices

CGM devices report glucose concentrations every 5 minutes, and thus provide invaluable information about fluctuations in glucose levels. However, the amount of variability in sensor accuracy may cause reason for concern for certain patient populations that require careful monitoring of their absolute glucose concentrations. While Aleppo et al. demonstrated that routine BGM did not appear to offer benefits in regulating glucose levels overall and in several subgroups stratified by baseline factors in the REPLACE-BG study,[3] we specifically focused our analysis to a subgroup that may particularly benefit from accurate absolute glucose measurements. As many women have difficulty maintaining euglycemia during certain phases of their menstrual cycle, we examined females in the CGM Only and CGM+BGM groups that were <35 years of age at the time of enrollment in the REPLACE-BG study. In addition to examining time within a normal glucose range (70-180mg/dL) and coefficient of variation (CV) of glucose concentrations, we also assessed mean and standard deviation glucose concentrations because we found these parameters had stronger relationships to HbA1c values (see supplementary **Fig. S1**).

The CGM Only and CGM+BGM groups had similar HbA1c levels at initial screening (7.39 ±.13 vs. 7.33 ±.19 mmol/mL, respectively p=0.81) (**Fig. 2A**). HbA1c levels did not increase in either group, but the CGM+BGM group had lower HbA1c levels compared to the CGM Only group (6.64 ±.14 vs. 7.07 ±.11, respectively, p<0.05) (**Fig. 2B**). This suggests that females <35 may have benefited from the routine BGM in addition to CGM in the clinical trial.

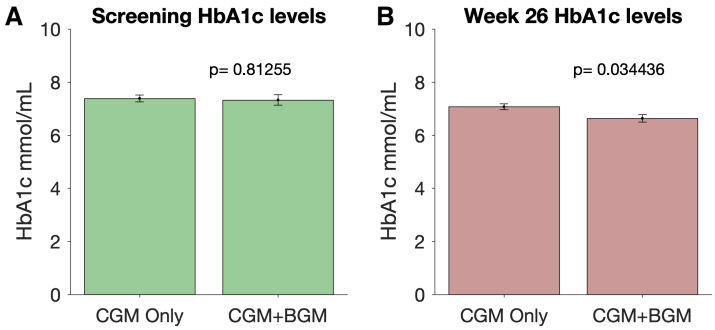

Fig. 2: HbA1c levels at Screening and Week 26

We next examined the effect of treatment group on CGM-measured glucose levels. There was a clear difference in the pooled distribution of glucose measurements, whereby the CGM Only group appeared to have a lower mean and greater spread (**Fig. 3A**). The mean, standard deviation, and CV of glucose concentrations, and Time in Range was calculated for each subject in both groups. We found a significant decrease in the mean glucose concentration (p<0.05) (**Fig. 3D**) and a trend showing increased Time in Range (p=0.051) (**Fig. 3B**) in the CGM+BGM group, suggesting that females <35 benefited from routine routing BGM. No significant effects were found on the standard deviation or CV. Lastly, we examined the daily fluctuations in glucose levels between the two groups by taking the mean glucose concentration of each subject at 1-hour time bins over the duration of the entire post-enrollment period and then taking the mean across subjects in each group. This allows us to see stereotypical daily fluctuations in glucose levels. While there were no qualitative differences in the fluctuations in glucose rhythms between the groups, the CGM+BGM was offset to lower glucose levels throughout the day (**Fig. 3C**).

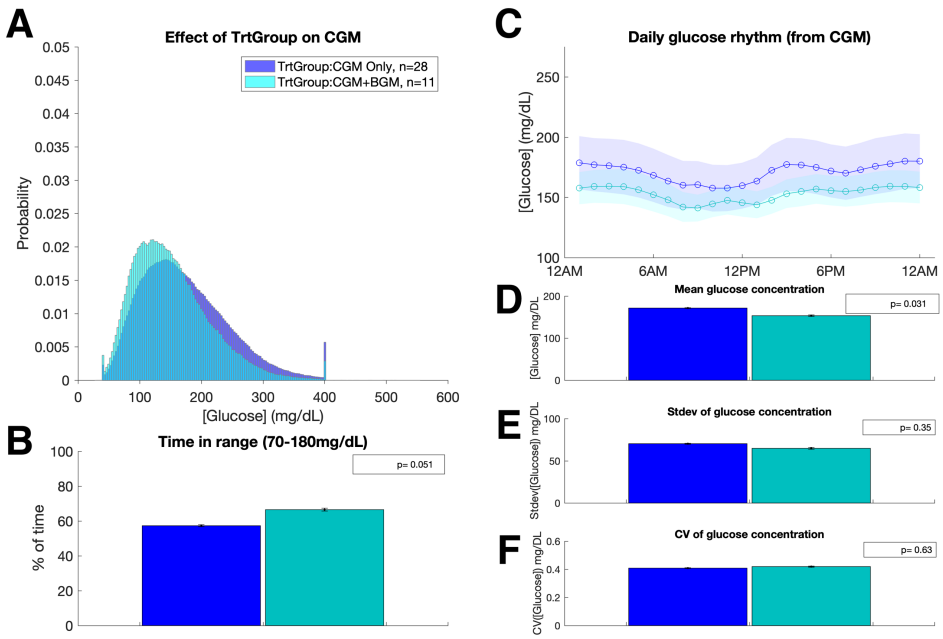

Fig. 3: Effect of routine BGM on CGM-measured glucose levels in females <35years

Conclusion:

This report characterized the accuracy of modern CGM devices from the large REPLACE-BG dataset. While accuracy of CGM devices have improved over the years, there is still room for improvement as glucose measurements can be off by >20% nearly 15% of the time. Patients that require careful monitoring of their absolute glucose levels may still benefit from routine BGM measurements to guide diabetes management decisions, as we demonstrated for the female <35 subgroup from the REPLACE-BG clinical trial.

References

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2. Aleppo, G. *et al.* REPLACE-BG: A randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in adults with well-controlled type 1 diabetes. *Diabetes Care* (2017). doi:10.2337/dc16-2482
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4. Valdes, C. T. & Elkind-Hirsch, K. E. Intravenous glucose tolerance test-derived insulin sensitivity changes during the menstrual cycle. *J. Clin. Endocrinol. Metab.* (1991). doi:10.1210/jcem-72-3-642

Supplementary Material

HbA1c levels positively correlate with mean and standard deviation of [glucose] and inversely correlate with Time in Range

The HbA1c test is a biological assay to measure the concentration of glycosylated hemoglobin (HbA1c), which gets glycosylating by glucose in the bloodstream. As this test directly measures how much glucose binds to an endogenous protein, it serves as a useful biomarker for glucose burden. Because red blood cells have a half-life of about 2 months, the HbA1c test reflects some information about the glucose fluctuations over the past several months. Using the REPLACE-BG dataset we explored how and which characteristics of CGM-measured glucose levels after the enrollment period correlated with HbA1c levels at week 26. The main idea is that parameters that correlate with HbA1c may serve as useful biomarkers related to glucose burden. **Fig. S1A** shows probability distributions of CGM-measured glucose levels stratified by patients' Week 26 HbA1c levels. There is a clear increase in the mean and variance as HbA1c levels increased (cool to warm colors). The Time in Range was determined for each subject, and we found significantly lower mean Time in Range as HbA1c levels increased (**Fig. S1B**, $p<0.005$). Similar to Fig. S1A, each subject had their own distribution of glucose values, which could be fit to a log-normal distribution function using the `lognfit` function in MATLAB to determine the mean, standard deviation, and coefficient of variation (CV) of glucose levels. The group mean ± SEM of each of those parameters are shown in **Fig. S1 D,E, and F**, respectively. This analysis highlights that the mean and standard deviation increases proportionally with HbA1c levels ($p<0.005$ for both). Interestingly, the CV does not significantly correlate with HbA1c levels since the mean and standard deviation covary; thus, CV may have limited utility in identifying if a certain treatments or interventions have beneficial or detrimental effects on maintaining glucose levels. Lastly, we examined how HbA1c levels were related to daily glucose rhythms, shown average hourly glucose levels in each group stratified by Week 26 HbA1c levels (**Fig. S1C**). Glucose levels fluctuated similarly in all groups, but the higher HbA1c groups were offset to higher circulating glucose levels throughout the day.

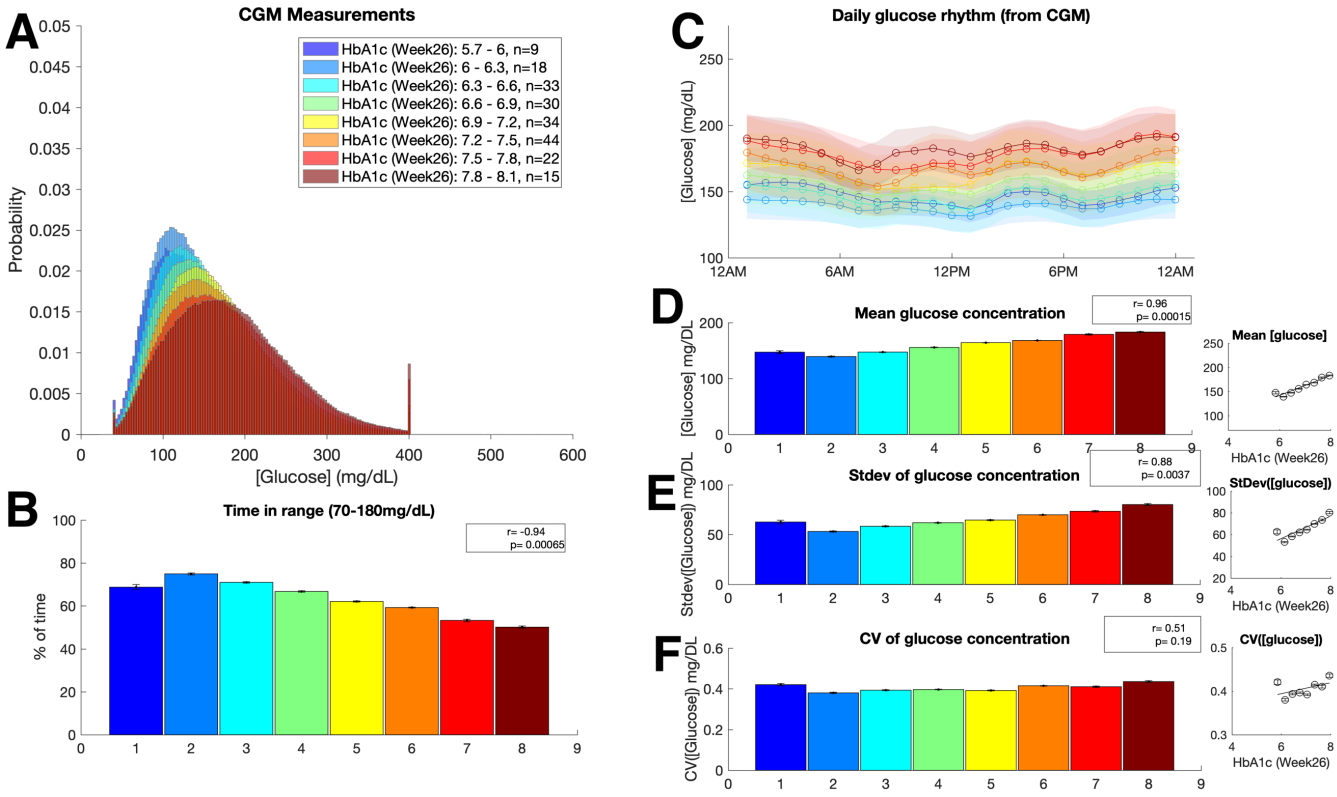

Fig. S1: The relationship between Week 26 HbA1c and CGM-measured glucose concentrations