In Silico Comparison of Minimal Monitoring Frequency Using Two Glucose Monitoring Systems

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Background

Glucose Monitoring is essential for people with T1DM. Sensor-based glucose monitoring (sensor) systems have found increasing use, in addition to strip-based blood glucose monitoring ("BGM") systems. A new sensor-based system was recently assessed relative to BGM-based care, in a 6-month RCT[1] enrolling 328 participants. Those in the sensor-based care group checked between 5.5 and 38.5 times daily. An *in silico* analysis complementing this RCT, where virtual subjects check four times daily (pre-meal and pre-bedtime) is of interest.

Methods and Protocols

One hundred virtual T1DM subjects were enrolled in a 420- day study using the UVA/Padova T1DM Simulation platform. Subjects underwent "parallel-universe" sensor-based and BGM-based study arms; where each random element, not directly caused by the glucose monitoring system choice, is experienced by a particular subject in a consistent manner across all studies, allowing for a direct comparison of the relative outcomes of study arms. The sensor modeling applies a method described by Breton and Kovatchev[2], to clinical study data collected from 72 subjects with type 1 diabetes[3].

To more closely reflect a community-based population study with lifestyles and treatment choices representative of actual populations, additional modeling adjustments were made:

T1D Exchange Population

HbA1c values empirically observed in the T1D Exchange Registry[4] (T1DEx) were used to establish a desired mean BG distribution across the population[5]. The T1DMs subjects' basal BG concentrations (G_b) were adjusted via Johnson transform[6] to match this distribution, but with the mean Fasting BG representative of the fasting BG values expected for the overall mean BG. Basal insulin infusion rates in the T1DM subjects were adjusted to achieve these fasting levels, and CR and CF treatment parameters were reestablished via an iterative calibration process to achieve the mean BG values originally estimated from the T1DEx's HbA1c data, (Figure 1) [7]. The calibration process was guided by month-long simulations. All other per-subject parameters not derived from G_b remained unchanged to preserve the glucose-insulin response.

Lifestyle Variability

All simulations incorporate the following factors affecting glucose variability:

- Mixed meal effect was created by varying the glucose rate of appearance for each meal by factors of 0.5, 1.0, and 1.5 with probabilities of 30%, 50% and 20%, respectively.
- CHO counting errors assumed a beta distribution (a=0.2, b=0.45), resulting in under-estimation 63% of the time[8].
- Meal CHO amounts varied randomly: Breakfast (40-75 gm); lunch (60-80 gm); and dinner (60-90 gm).
- Exercise occurred randomly, 3 times/week, affecting insulin sensitivity by +50%[9,10].
- Sick days occurred randomly 5% of the days, affecting insulin sensitivity by -20% and +20%[11].

BGM

BGM is modeled to meet the 2013 ISO 15197 standard with all error resulting from Gaussian white noise[12].

Analysis

The proxy for assessing risk of hypoglycemia is the duration true BG ≤ 55 mg/dL. The proxy for assessing risk of hyperglycemia is the duration true BG > 240 mg/dL. The proxy for assessing time in target range is the %time between 70 and 180 mg/dL. These metrics were calculated for each subject in each study arm and compared for statistical significance by the Wilcoxon Rank Sum/Mann Whitney U test[13] (Figure 2). In addition, time ≤ 70 mg/dL and > 180 mg/dL were calculated but not considered proxies for risk.

T1D Exchange Population

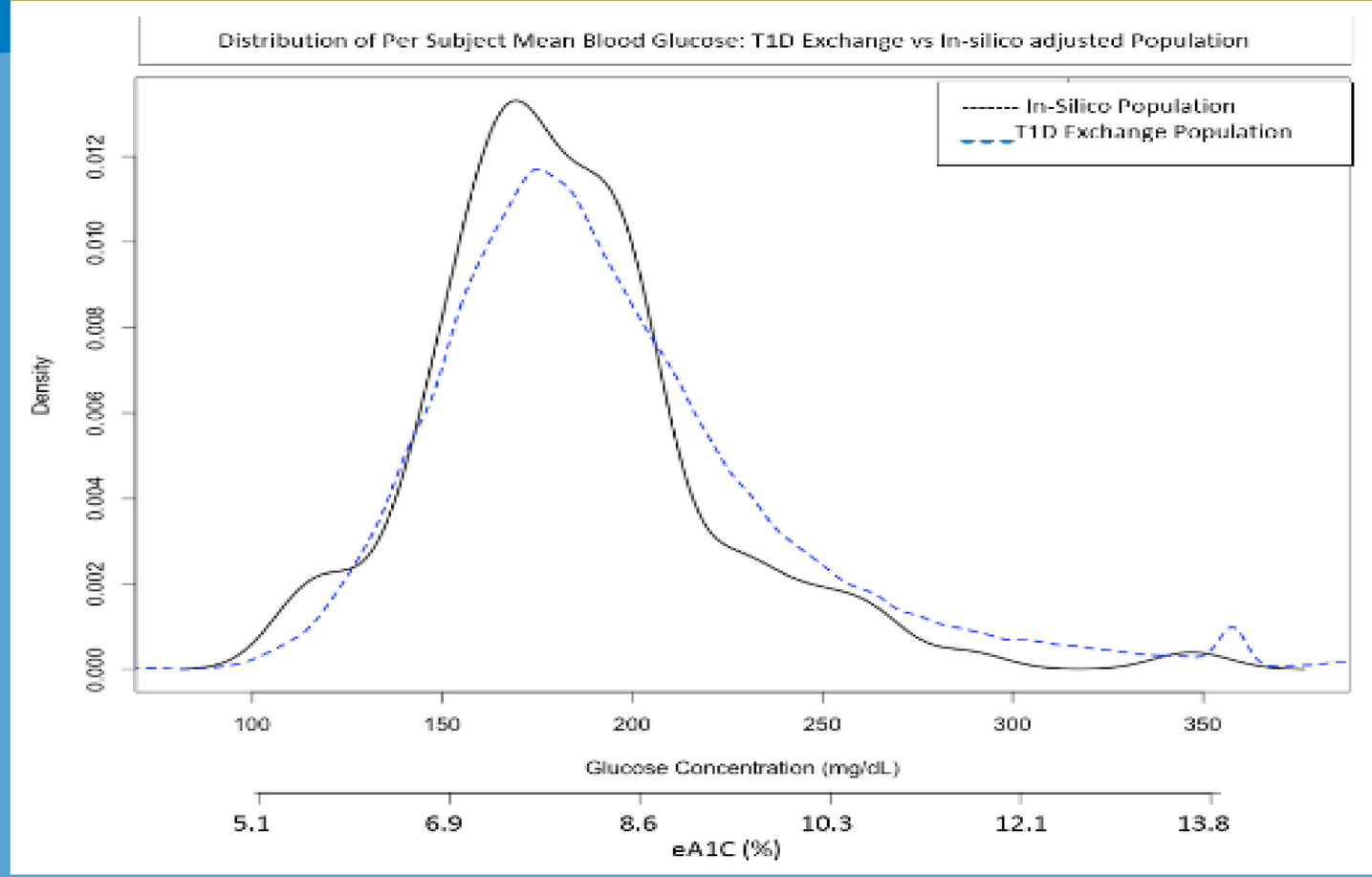

Figure 1. Comparison of baseline Mean BG of the *in silico* T1DMS subjects relative to the HbA1c-based eAG data from the T1D Exchange Registry. A Secondary axis shows the eA1c of the T1DEx *in silico* population.

Per-subject Comparison of Outcome Metrics

Mean and standard deviation of the calculated metrics are shown in Table 1. There were no significant differences in hypoglycemia risk (0.3% ± 0.56% vs 0.3% ± 0.55%; BG ≤ 55 mg/dL), time in range (40.6% ± 23.5% vs. 41.0% ± 23.3%; 70 <BG<180 mg/dL), and hyperglycemia risk (22.9% ± 22.8% vs. 22.4% ± 22.5%; BG > 240 mg/dL) between the two parallel study arms.

Table 1. The percent of time BG readings remained within the specified ranges were similar when using real-time glucose readings available to subjects 4 times per day when compared to time-in-range using 4 BG readings per day. Values are expressed as Mean ± Standard Deviation of expected % of time in a day among the 100 subjects in each study arm.

	BGM-based care, 4x/day	Sensor-based care, 4x/day
BG ≤ 55mg/dL [% time]	0.3 ± 0.6	0.3 ± 0.6
70 < BG ≤ 180mg/dL [% time]	41.0 ± 23.3	40.6 ± 23.5
BG > 240mg/dL [% time]	22.4 ± 22.5	22.9 ± 22.8
BG ≤ 70mg/dL [% time]	1.2 ± 2.3	1.3 ± 2.3
BG > 180mg/dL [% time]	57.8 ± 24.2	58.1 ± 24.5

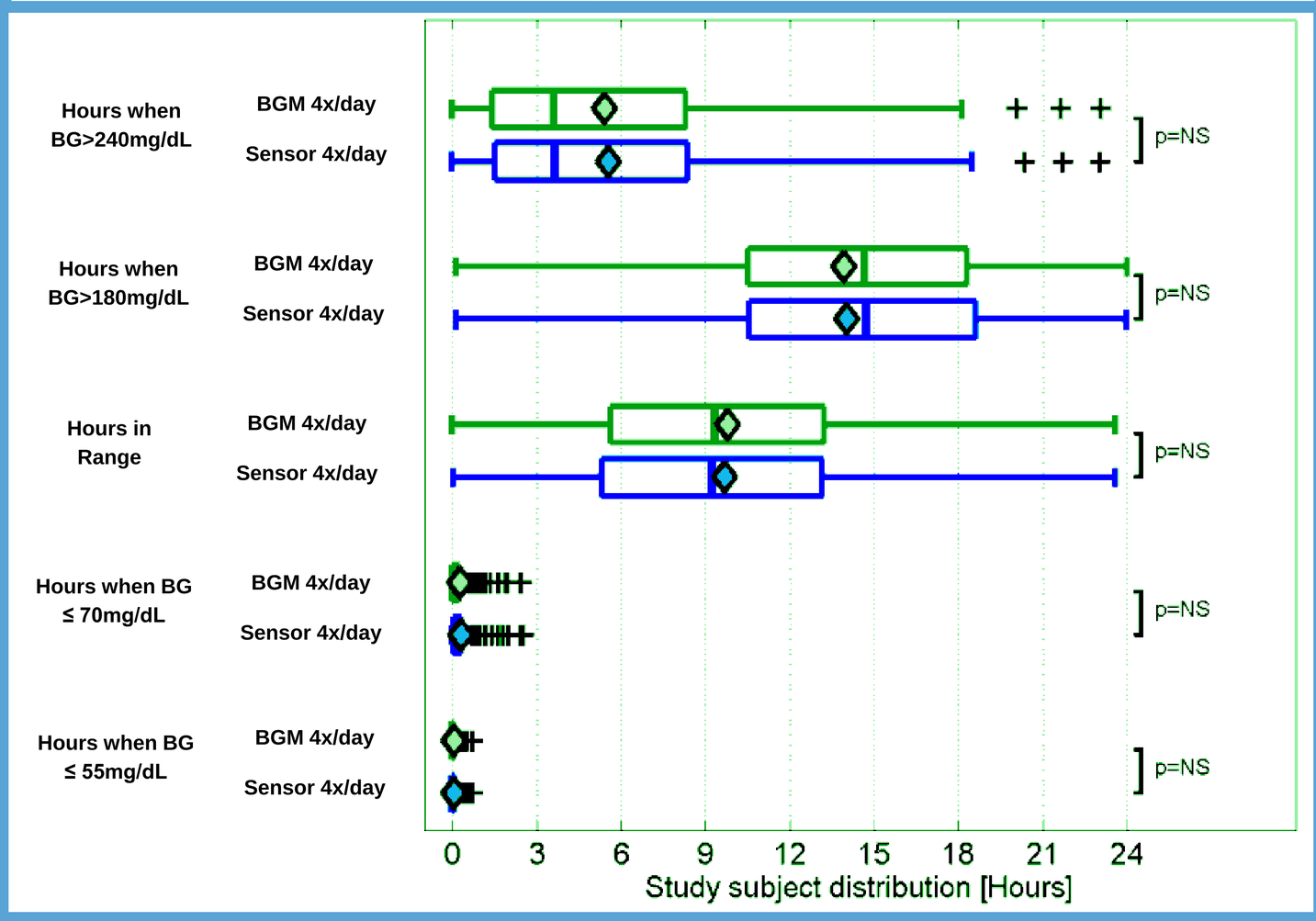

Figure 2. Per-subject comparison of outcome metrics for using 4 sensor readings per day versus 4 BG readings per day. Values are expressed as the expected hours in a day. All comparisons demonstrate no statistical significance.

Conclusions

In this "parallel-universe" simulation setting, the study population can experience realistic variations in meal size and timing, carbohydrate counting error, and variable insulin sensitivity in tandem across study arms. This demonstrates that checking glucose with the sensor-based system, even less frequently than what occurs in a real-world RCT, and without the benefit of the trend arrow nor glucose history, presents similar hypoglycemia risk, time in target range, and hyperglycemia risk, relative to BGM-based care in the identical setting.

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