Dermal Glucose Sensing: Enhancing Precision in Diabetes Management

Clinical Results From the Laxmi Novel CGM Sensing in the Dermis

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INTRODUCTION

Commercial CGM devices are designed to measure glucose in the interstitial fluid of the hypodermis (subcutaneous lipid layer). It is well known that the interstitial fluid glucose is delayed compared to blood, this delay has been reported to be between 10 and 20 minutes in humans. Additional delays arise from membrane mass transfer and digital signal processing. To eliminate physiological time delays, we developed a novel CGM that measures glucose in the dermis rather than the subcutaneous layer. Based on skin physiology, with a capillary bed above and below the dermis, we expected to observe minimal time lag between the blood and the ISF of the dermis.

METHODS

The CGM developed by Laxmi is an electrochemical sensor based on glucose oxidase (Gox) chemistry where glucose reacts with Gox to create hydrogen peroxide, which is detected via amperometry. The sensor is inserted into the dermis using a patented inserter which reliably places the sensor in the dermal space (1.8 to 2.4 mm below the skin). To evaluate the accuracy of the sensor and its associated physiological time constant, we conducted a prospective, open label, single-center, non-significant risk study, where 10 subjects with type-I DM were enrolled at a US-based clinical site. Subjects wore our novel Laxmi CGM, simultaneously, subjects wore a commercial CGM (FreeStyle Libre 3). The total intended wear duration of both CGMs was 7 days. We compared data from both CGMs to plasma glucose (converted from whole blood using the factor 1.12) obtained by frequent YSI whole-blood samples over three in-clinic sessions on days 2, 4 and 7 of the study. In each clinic session, participants arrived in a fasting state, and after the 2nd YSI measurement was taken, they consumed a standardized meal (570-650 calories, 12-15 g protein,15-17 g total fat (9-11 g saturated), 97-107 g carbohydrate (62-85g sugars)) to induce hyperglycemia. A total of 40 YSI measurements were performed in each clinic session over a duration of 8 hours. Data from both the Laxmi and the FreeStyle Libre 3 (FSL3) CGMs was compared against the YSI data, during euglycemia, hypoglycemia and hyperglycemia. All data was downloaded to Laxmi database after every clinic day. Data from both CGMs was analyzed comparing accuracy (MARD) over various glucose Rates of Change (RoC).

RESULTS

Sensor performance was evaluated by MARD, MEDARD, Error Grid Analysis and performance according to ISO standards. MARD and MEDARD were computed for both Laxmi and FSL3. Error Grid analysis was performed using both the Clark and Consensus error grids. Using the ISO performance guidelines, data is shown in the tables below. We included calculations based both on FSL3 historical data on a 5-minute interval and data from FSL3 scan which was reported on a 1-minute time scale. In the table, 15/15 means 15 mg/dl below 100 mg/dl and 15% above 100 mg/dl. The data clearly demonstrates that dermal sensing is more accurate. The overall MARD for all Laxmi Sensors was 5.91% while the overall MARD for FSL3 was 9.67%. MEDARD was 4.50% for Laxmi and 8.20% for FSL3 while the standard error of prediction was 11.84 mg/dl for Laxmi and 16.77 mg/dl for FSL3. Data are shown in Figure 4 for the Clarke error grid, as the consensus grid is nearly identical. We also calculated sensors physiological time lags using Laxmi developed software to evaluate the 2-compartment model, shown graphically below in Figure 2. Glucose arrives in the ISF via diffusion from the capillary blood. The constant K21 is for arrival. Similarly, glucose leaves the ISF to the local tissue via K02. Panel B shows the response of ISF glucose to a step change in blood glucose. Note that in general the ISF glucose is lower than blood glucose except at steady state. The Laxmi sensor (and all CGM sensors) measures ISF glucose but blood glucose is more useful for insulin dosing. ISF depends on blood glucose through a diffusion relationship; this relationship must be inverted to convert tissue glucose to the equivalent blood glucose at that time. There is no analytical method to convert tissue glucose to blood glucose using the 2-compartment model. We have developed an iterative model incorporating the differential equations of the model. In our implementation, we used the YSI data as a truth reference then used a range of physiological time constants to convert the tissue glucose to the blood. We minimized mean square error and t value, the minimum squared error was our estimate of the true time constant. For the evaluable sensors (n=17) 12 had an estimated t value of 0 or 1 minute, median =0, mean=0.8 SD=1.14 min). The longest t was 4 minutes.

TABLE 2: ISO COMPARATORS

ISO Comparator	Laxmi	Libre 3 History	Libre 3 Scan
ISO 5/5	55.74%	37.50%	35.19%
ISO 10/10	82.88%	64.46%	59.81%
ISO 15/15	95.32%	85.62%	81.11%
ISO 20/20	98.38%	94.67%	92.59%
ISO 30/30	99.68%	99.68%	98.89%
ISO 40/40	99.87%	100.00%	100.00%

TABLE 3: ISO RANGE

ISO Range	Laxmi N	Laxmi %	Libre N	Libre %
<= 5% or 5 mg/dL	349	56.4%	219	35.4%
> 5 - 10% or mg/dL	187	30.2%	166	26.8%
> 10 - 15% or mg/dL	55	8.9%	129	20.8%
> 15 - 20% or mg/dL	20	3.2%	56	9%
> 20% or 20 mg/dL	8	1.3%	49	7.9%
Bias		0.9%		6.1%

CONCLUSIONS

This small (n=10) study was designed to evaluate the clinical performance of a novel CGM system measuring ISF in the dermis. In a clinical, YSI based study the sensor was more clinically accurate overall and during high glucose rates of change. There are several caveats to the study; factory calibration is not ready for the Laxmi sensors, so they were calibrated using the first YSI value as a bias correction. The insertion and electronics (transmitter) system for Laxmi is not a final product but rather both are prototypes. Several visits (8/25) were removed from the study due to high signal noise (likely due to transmitter-sensor connection issues). Despite these issues, the Laxmi dermal sensor performed with excellent clinical accuracy and negligible physiological time lag. Future work will be aimed at testing in more T1 subjects and to begin to address techniques for factory calibration.

FIGURE 1: DATA FROM ONE CLINIC SESSION

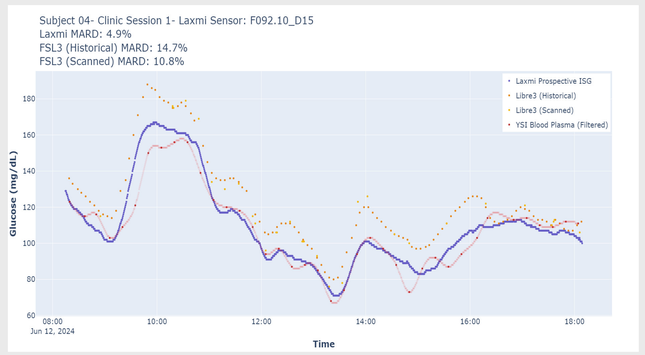


FIGURE 2: CALCULATION OF TIME LAG

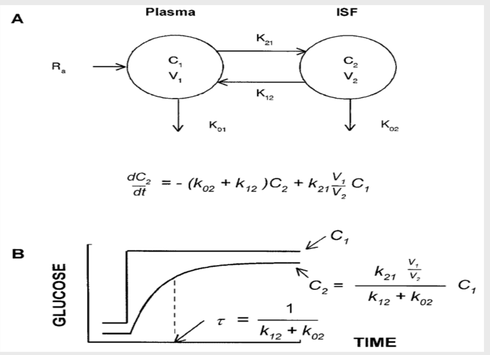


FIGURE 3: RELATIVE DIFFERENCE OVER ROC

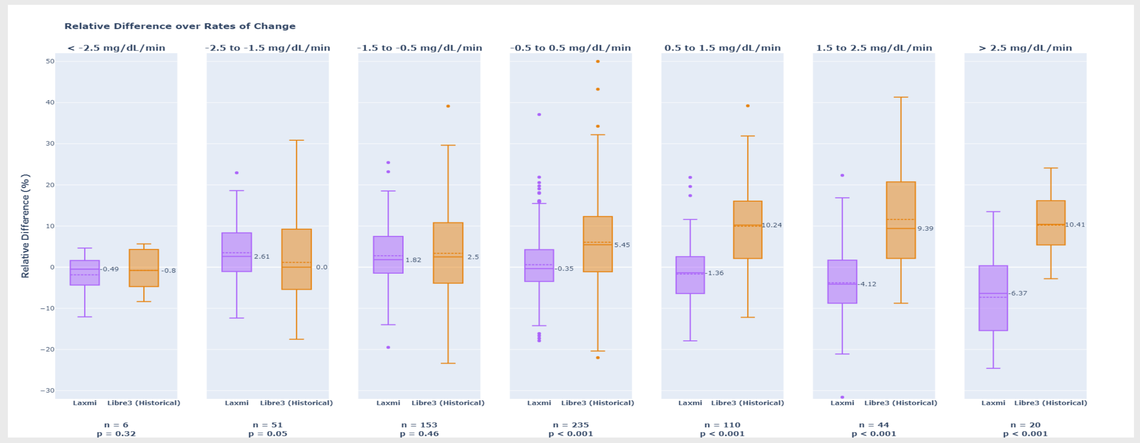
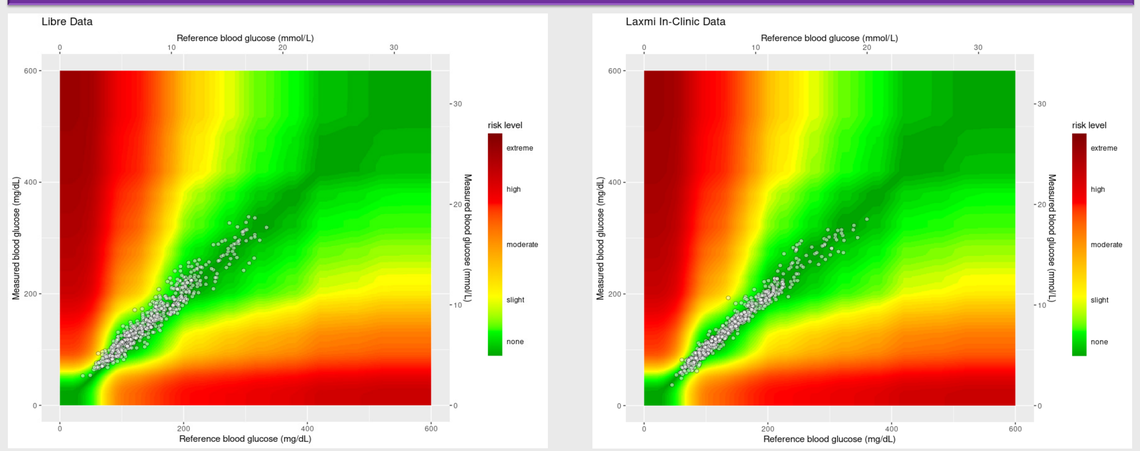


FIGURE 4: LAXMI VS. FREESTYLE LIBRE 3 IN-CLINIC DATA



Note that the two error grids are similar, as the area of agreement is greater than ISO 20/20.

TABLE 1: DEMOGRAPHICS

Sub ID	Gender	Age	Race	Duration of Diabetes Years	HbA1C
1	Male	44	Asian	19	6.80%
2	Female	43	More than one race	18	6.90%
3	Male	44	More than one race	40	8.20%
4	Male	29	Black	23	6.90%
5	Female	30	Unknown	9	7.80%
6	Male	30	White	4	5.90%
7	Female	31	More than one race	6	7.70%
8	Male	41	Black	13	7.40%
9	Female	36	Black	19	7.20%
10	Female	35	White	19	7.70%