CGM in Non-Diabetic Populations

CONSIDERATIONS & INSIGHTS

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Numerous market players, from established medical device vendors such as Abbott, to startups like Levels, have developed solutions built on continuous glucose monitors (CGMs). Exos Human Performance Lab clients and partners also have an interest in understanding this technology. This Insights Paper shares some insights and information gleaned from HPL's work in launching and executing a study of CGM usage in non-diabetics.

INTRODUCTION

Wearable sensors are increasingly used to monitor wellness behaviors and biometrics by consumers in nonclinical settings. Continued advancements in biomedical technology and widespread use of wearable devices present a unique opportunity to better understand the feasibility of combined use and tolerance of these devices in nonclinical populations. The growing evidence for the use of these devices in research and coaching focused on diet and physical activity behavior change is promising but needs further investigation[1].

INSIGHTS

- Current CGM technology is designed to detect fluctuations in blood glucose of the magnitude associated with disease at sampling rates of every 5 minutes (Dexcom). Advancements should focus on detection of much smaller magnitudes of change over shorter durations (i.e. increased sensitivity) to feasibly inform non-diabetic CGM users.
- Blood glucose is tightly regulated in the absence of disease (DMI or DMII) which challenges the ability to detect an eating event in a non-diabetic population.
  - Normal glycemic profile: Data has shown that the body primes itself for a meal/eating event -- the messages go to the digestive system and turn on the Insulin response before a meal is consumed, largely muting the glucose response observed in non-diabetic individuals compared to individuals with DM.
  - Agreement between glucose meter and serum blood glucose readings have been reported to be within 15%[2].
- The points above emphasize the reliance on time stamped data entry and tracking.
  - Time synced entries of nutritional intake to the minute are needed for meaningful correlative analysis with blood glucose or CGM values.

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CONSIDERATIONS & INSIGHTS

INSIGHTS (CONT.)

- Challenges with tracking nutritional intake in free-living populations continue to be pervasive. The lack of adherence to physical activity and dietary guidelines remains unresolved as well[1]. New technologies and/or platforms that limit user burden, ensure accessibility and ease of use are important for consistent engagement. Nutrition tracking platforms sourced from validated nutrition databases (i.e. USDA) can also improve the accuracy of nutrition information reported by users. A final feature with implications for engagement, accuracy, and accountability is photo capture and storage.
- Pros and Cons of Crowd Sourced Nutrition Tracking. Crowd sourced data is not connected to a nutrition database which creates a major issue for reliability. Typically these platforms are used as a tracker or to deliver a prescribed meal plan and are relatively user friendly. Users can add notes and photos which are helpful in creating a positive user experience. The largest challenge with nutrition logging apps that rely on crowd sourcing for their nutrient content is that the data must be translated into NDSR (Nutrition Database for Standard Reference) to be of value.
- Efforts to make improvements across the board have accelerated and largely focused on the use of software programs and mobile based apps. Several options are currently available, each with their own limitations. Five platforms were evaluated for use in the Exos CGM Pilot Study. Our primary considerations for the pilot study included:
  - Cost per user
  - Photo logging capabilities
  - Photo storage
  - Date and time meal tracking
  - Verification of micro and macronutrient composition
  - Voice journaling
  - 3rd party integration (e.g. Fitabase)
  - Customizable
- A bespoke white-label nutrition application was selected.
  - Selection results: This platform was selected due to its date and time stamp capabilities, photo storage feature, and most importantly, because it is backed by the verifiable USDA database. Food items, brands, and micro and macronutrients are not based on crowd-sourced data as with other commercially available platforms (e.g. MyFitnessPal), making nutrition logging through this platform more reliable. Added benefits of this platform include the ability to schedule tasks and provide links to digital content (i.e. videos, device instructions, etc.) on the app's homepage.

CGM Pilot Study Details

OBJECTIVES

The primary objectives include:

1. Evaluate the feasibility of routine use of blinded CGM devices by non-diabetics, user experience, and the acceptability of study protocols, that will inform product development and future studies.
2. Use data collected from the study for power calculations and the development of novel hypotheses for future studies and product development.
3. Determine the feasibility of correlating CGM values or trends from current Fitbit Production metrics (HRV, HR, activity, sleep, etc.)
4. Collect a developmental dataset with raw data logging with hypertension status (from ABPM).

The secondary objectives include:

1. Determine the feasibility of correlating glucose and trends from 24-hour raw data collected from current sensors (PPG, accelerometer).
2. Examine the relationship between glucose levels, heart rate metrics, activity, and sleep.
3. Isolate specific foods causing glucose spikes and assess the variability of responses.

Primary Outcome Variables

To assess the correlation between blood glucose, sleep, stress, blood pressure, and physical activity:

Table 1. Primary outcome variables

BIOMETRICS			COLLECTION CADENCE				
Outcome	**Assessment Tool**	**Collection Method**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Post**
Glucose (mg/dL)	Dexcom	Passive, blinded, daily	x	x	x	x	

Secondary Outcome Variables and Covariates

To assess the correlations and covariates that influence the relationship between nutrition intake and blood glucose:

Table 2. Secondary Measures

NUTRITION			COLLECTION CADENCE				
Outcome	**Assessment Tool**	**Collection Method**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Post**
Nutrition Intake	Vitabot	Manual tracking, pictures	x	x	x	x	

CGM Pilot Study Details

DATA COLLECTION

Six methods of data collection will be used for this study. Participants will receive two (2) biometric assessment devices (blinded CGM and blood pressure) and two (2) wearable devices (Fitbit Sense; production and raw data logging) that capture activity and sleep data. A brief description of the biometric assessment and wearable devices is provided below. Participants will be asked to use a web based and/or mobile application for nutrition logging throughout the observation period. Participants will be asked to complete a daily survey to inform nutrition logging compliance, and ambulatory blood pressure compliance and data quality (week 1 only). Participants will be asked to complete surveys before and after completion of the observation period. Pre and/ or post-observation surveys will include measures of menstrual cycle (female participants), medication use, recovery/sleep, and general feedback regarding theyour experience.

In an effort to decrease participant burden, a study phone will be provided for use during the observation period. This study phone will be preloaded with the mobile apps needed for the study and configured with the appropriate connectivity settings to ensure compatibility with study devices, as appropriate. Participants will be asked to limit the use of the study phone to study activities only. Phones will be shipped to participants with other study materials and equipment. Participants will be asked to return the study phone to the research team at the end of the observation period.

Wearable Activity Tracking Devices.
Each participant will receive two wearable smart devices (Fitbit Sense watch - i.e. production device and Fitbit Sense with custom Firmware - i.e. raw data logger device) provided by the study. All participants will be asked to meet a wear-time minimum for the devices averaging at least 90% of the time throughout the duration of the study. Participants will be asked to complete a 'Wear Log' anytime the device is removed outside of being charged. They will be asked to provide the date and times on/off per record in the 'Wear Log'. Standard exceptions for when the device should not be worn only include during showering as this is when the device should be charging. The device is waterproof so participants are expected to wear the device while swimming. Known exceptions should be reported as well.

Data from wearable devices will be made accessible for the study via Fitabase (www.fitabase.com) for the production Fitbit. Participants will control their own Fitbit account that is associated with their study device. Data from the raw data logger device will be downloaded directly from the device upon receipt. The data will be erased from the device before being reused or shipped to another participant.

Dexcom Continuous Glucose Monitor (CGM).
Participants will receive a blinded Dexcom Continuous Glucose Monitor (Dexcom G6 Pro; https://www.dexcompro.com/products/) for use during the study. Dexcom CGM devices (3 G6 PRO kits, 10 day use) will be shipped to each participant. Participants will be instructed to apply and remove the transmitter 3 times over the duration of the study. Data from the blinded Dexcom CGM device will be made accessible for the study via direct download upon receipt. Participants will use return shipping labels provided to return the blinded CGM devices to the research team (Exos Phoenix, AZ) so that the anonymous data can be downloaded by a healthcare provider.

CGM Pilot Study Details

DATA COLLECTION

Blood Pressure Monitoring.
An ABPM blood pressure cuff such as, Welch Allyn ABPM 7100 Ambulatory Blood Pressure Monitor (https://www.hillrom.com/en/products/abpm-7100/), will be sent to each participant for use during the first week of observation. Once participants have completed one 24 hour ambulatory blood pressure monitoring period, they will be instructed to ship the blood pressure device back to the research team so the data can be offloaded.

Nutrition Logging.
Participants will be asked to maintain their usual dietary behaviors and use Vitabot, a custom, white-labeled nutrition logging application (https://vitabot.com/web/) to record all nutritional intake throughout the duration of the study. They will use the photo feature to take pictures of each meal or snack and upload it for review. Participants will access the Vitabot platform through the mobile app. A dietitian/nutritionist will be available to review all nutrition records and photos on a regular basis. Data from Vitabot will be accessed directly through the administrator website and then manually downloaded and entered into a de-identified dataset for analysis.

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SURVEYS

Participants will complete a series of surveys over the course of the study. All participants will complete the same surveys according to the same cadence (outlined below). Qualtrics (www.qualtrics.com) platform will be used to develop, administer, and manage surveys and survey responses. Survey links will be sent to participants via email and/or text message to complete digitally. Participants will be given the opportunity to opt into SMS text delivery for surveys. Surveys will not be administered by an interviewer; however, Exos research staff will be available by phone and/or email to answer questions or provide clarification, as needed. Participant subject ID numbers will be used to track unique responses per participant.

Baseline Survey.
Participants will be asked to complete a survey immediately after completion of the consent process. This survey will be used for descriptive purposes and to determine final eligibility for the study. This survey will include the basic demographic information, health and medication history, and usual nutrition behaviors described in the measures section above.

Daily Survey.
Participants will be asked to complete a survey once a day throughout the observation period. This survey will be used for descriptive purposes and to determine weekly compliance for the study. This survey will ask about nutrition logging and blood pressure compliance described in the measures section above.

End of Observation Survey.
Participants will be asked to complete a survey at the completion of the study. This survey will include a shorter, modified version of the baseline survey to assess user experience, and satisfaction, and gather general feedback regarding the biomedical and fitness tracking devices, and nutrition logging platform after 4 weeks of nutrition and blood glucose monitoring. This survey will also ask about their current medications and medications taken during the observation period. Finally, female participants will be asked to report the start and end dates of any menstrual cycles experienced during the observation period.

CGM Pilot Study Details

REFERENCES

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    a. Study design and Target population. A 7-day observational study in 30 nondiabetic adults. All participants wore a CGM sensor throughout the observation period. Physical activity and diet were tracked manually through the CGM receiver and MyFitnessPal. Physical activity was also tracked using an accelerometer. A 10-item survey was used to evaluate the acceptability of each study tool. Results. Summary acceptability scores were 4 out of 5 (5-point scale), on average, for the CGM sensor, receiver, and MyFitnessPal. The accelerometer was rated a 3/7 out of 5. Ratings were based on ease of use, usefulness, and relevance of information of interest.
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    a. Study design and Target population. This study aimed to investigate associations between circadian rhythm of blood pressure and glucose tolerance status. This was a cross-sectional study of 67 normotensive and non-diabetic adults aged 35-79 years. Participants completed a 75g oral glucose tolerance test and 24 hours of ambulatory blood pressure monitoring. Results. Patterns of mean diurnal-nocturnal systolic BP (SBP) differed between participants classified as glucose tolerance impaired (n=31) or normal glucose tolerance (n=36), but not significantly. When controlling for other factors, the reduction of SBP during the nighttime hours was significantly smaller in the impaired glucose tolerance (IGT) group compared to the normal glucose tolerance (NGT) group, 7.19 and 9.8 mm Jg, respectively. It was concluded that IGT status is associated with a less pronounced decrease in nocturnal BP in normotensive, non-diabetic participants.

CGM Pilot Study Details

REFERENCES

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    a. Study design and Target population. A 6-day cohort study in 327 nondiabetic adults to outline and predict responses to a variety of foods considering an individual's unique physiology and microbiome, and elements of foods eaten. Measurements included anthropometry, CGM blood glucose readings (5 min interval, iPro2; Medtronic), and gut microbial composition. Participants logged food and activity throughout the study using the DayTwo Food & Activity Logger available in Google Play and iTunes App Stores. The DayTwo Food logger is powered by the curated full MyNetDiary food database. Nutritional values in the MyNetDiary database were used to report nutritional values of meals reported Results. Post-meal glycemic response varied across participants. Model predictability was higher (R=0.62) when considering clinical, physiological, and microbiome factors in addition to traditional approaches that use nutrition content alone (R=0.34 calories and R=0.40 carbohydrates). Personalized tools to manage glycemic responses to foods may lead to better maintenance of healthy blood glucose levels.
5. Zahedani AD, Torbaghan SS, Rahili S, Karlin K, Scilley D, et. al. Improvements in glucose regulation using a digital tracker and continuous glucose monitoring in healthy adults and those with type 2 diabetes. Diabetes Ther. (2021) 12:1871-1886.
    a. Study design and Target population. 10-day combined observation and study in 1022 non-diabetic or non-insulin dependent type 2 diabetic (T2D) adults. This study investigated the effect of CGM use, food and activity logging on hyper- and hypoglycemia in a diverse population. Based on data quality (minimum requirement 9 days of CGM wear and 33% daily coverage) only 665 participants were included in the study. All participants wore a Freestyle Libre CGM, tracked physical activity, food consumption, and heart rate data using an app. Participants completed three standard nutrient challenges to assess patterns of glycemia independent of variability of nutrients consumed. Results. Short-term use of CGM with guidance for lifestyle modifications can be beneficial for regulating glucose in non-diabetic, prediabetic, and non-insulin dependent T2D. Long-term studies needed to determine sustainability of effects.
6. Bent B, Cho PJ, Henriquez M, Wittmann A, Thacker C, et. al. Engineering digital biomarkers of interstitial glucose from noninvasive smartwatches. npj Digital Medicine (2021)4:89; https://doi.org/10.1038/s41746-021-00465-w.
    a. Study design and Target population. Prospective data analysis of 25,000 concurrent interstitial glucose and wearable smartwatch measures in 16 non diabetic or prediabetic adults (aged 35-65 yrs) to explore the feasibility of non-invasive approaches to manage glycemic health. All participants completed baseline HbA1c measures in the clinic, wore a Dexcom G6 CGM sensor, logged food and drink consumption, and wore an Empatica smartwatch for an 8-10 day period. A standardized breakfast meal was ingested every other morning during the study. Results. Methods for data-driven and domain-driven predictions of interstitial glucose from noninvasive wearables were demonstrated. The ability to predict glucose deviations (84%) and interstitial glucose values (87%) with greater than 80% accuracy was shown.