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Modeling the effect of non-exercise activity on peak post-prandial glucose in diabetes

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***Abstract*— The timing, intensity, and duration of post-prandial exercise are important factors that reduce glucose excursions. When exercise is of moderate intensity, performed between 25 and 55 minutes after a meal, it results in greater attenuation of glucose. However, the potential glucose reduction for shorter-duration, non-exercise activity thermogenesis (NEAT) (such as activities of daily living) may also be beneficial, particularly in cases where exercise is neither feasible nor prudent. Therefore, we designed a system to capture blood glucose and activity intensity through internet of medical things devices and modeled the impact of the timing and duration of NEAT on peak glucose. This work designed a linear mixed effects model to evaluate the impact of NEAT on peak, post-prandial glucose in a study of data captured on varied participants with or without diabetes. We found at least 25 minutes of NEAT starting 30 minutes after the meal most effectively reduced peak post-prandial glucose.**

***Clinical Relevance*— This work establishes the impact of NEAT on reducing post-prandial peak glucose in free-living environments as another method of controlling glucose surges.**

I. Introduction and Related Works

Diet and exercise are critical components of treatments to prevent and manage type 2 diabetes (T2D) [1]. The American Diabetes Association identifies exercise, in relationship with diet, to be a critical component to controlling blood glucose [2], and notes that with the advent of continuous glucose monitors (CGMs) individuals with T2D may be more willing to perform exercise without fear of inducing hypoglycemia [2]. A number of studies have examined these recommendations promoting moderate to vigorous intensity exercise after meals which demonstrated a reduction in the peak of the postprandial glucose response (PPGR) [3-6]. Particularly, exercise of moderate intensity 30 to 60 minutes after a meal leads to the greatest attenuation in glucose [4, 7], especially if the exercise lasts at least 20 minutes. As long as the pre-meal, pre-exercise glucose levels are not already at hyperglycemic levels, moderate exercise improves glucose control, reducing episodes of hyperglycemia [8]. However, the American Diabetes Association indicates that individuals with diabetes may be hesitant to conduct moderate or vigorous exercise, even with CGMs, because of potential adverse effects on glucose control [2]. For these cases, the American Diabetes Association identifies any break in sedentary behavior as potentially beneficial. Therefore, it is important to understand the effects of light intensity exercise to help individuals with diabetes.

Light intensity exercise, while less studied, has been also been shown to have beneficial effects on glycemic control (reducing hyperglycemia), where periods of walking help reduce PPGRs [9], even if higher intensity activities produced larger attenuation of glucose [10]. A review by Hatamoto et al. [3] found that brief, periodic exercise may have additional reductive effects than longer, sustained periods, which is also applied to repeated short walking, as a low intensity activity [11]. In addition to interval-based activity, such as walking, any interruption in sedentary behavior has been shown to improve glycemic response [9]. Even though many studies have approved the benefits of shorter-duration, non-exercise activity thermogenesis (NEAT), such as activities of daily living (including walking) on PPGRs, studies have primarily focused on varying the timing, duration, and interval nature of moderate to vigorous intensity exercise and resistance training [6]. Therefore, it is very hard to examine the benefits of NEAT with no prescribed activity, and whether this non-exercise activity has a relationship with PPGRs and if so, does NEAT lead to quantifiable peak glucose attenuation.

To address this challenge, we propose a technological and computational approach to model the impact of NEAT on PPGRs using commercially available CGMs and smartwatches. We present results from a study in which participants wore a CGM (Dexcom G6) and a fitness tracker (Fitbit Sense) for ten days, while they consumed a variety of prescribed meals with known macronutrients, but exercise was neither prescribed nor required. We sought to evaluate how NEAT in free-living environments impacted post-prandial peak glucose. For this purpose, we used linear mixed effects models [11] to quantify the contribution of meal composition and post-prandial NEAT on peak PPGR, and identify the optimum timing and duration of NEAT that would lead to the greatest attenuation of postprandial glucose.

II. Methods

A. Experimental protocol

Experimental data for this work was obtained as part of a larger study in which participants were monitored in free-living conditions for 10 days (Advarra IRB Pro00049227; ClinicalTrials.gov NCT04991142). Participants were provided breakfast shakes of known meal macronutrient compositions; a variety of lunches from a fast, casual restaurant chain (Chipotle Mexican Grill, Inc.), also with known meal macronutrient composition; were allowed their choice of dinners; and asked not to consume anything for three hours after any meal. Participants wore three devices: a Fitbit Sense smartwatch, an Abbott Freestyle Libre Pro CGM on their upper arm, and a Dexcom G6 Pro on their abdomen. In addition, we analyzed participants' gut microbiome using

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TABLE I. MACRONUTRIENT COMPOSITION OF THE BREAKFAST SHAKES.
THE FIRST COLUMN DENOTES MACRONUTRIENT AMOUNTS (HIGH/LOW) IN THE ORDER OF: CARBS, PROTEIN, FAT, FIBER.

Meal #	Carbs (g)	Protein (g)	Fat (g)	Fiber (g)
B01 HLLL	66	22	10.5	0
B02 HHLL	66	66	10.5	0
B03 HLHL	66	22	42	0
B04 HHHH	73	66	42	7
B05 LLLL	24	22	10.5	0
B06 HLLL	66	22	10.5	0
B07 HHLL	66	66	10.5	0
B08 HLHL	66	22	42	0
B09 LLLL	24	22	10.5	0
B10 HLHH	73	22	42	7

a commercial service (Viome Life Sciences, Inc.), though this information is not being used in the current study. The macronutrient ("macro" for short) composition of the meals were varied between low and high carbohydrates (carbs), protein, fat, and fiber, based on the average American diet [12]. While the study is ongoing, at the time of this writing we have collected data on 27 participants. Based on HbA_{1c} measurements taken at the initiation of the study, 10 participants did not have pre-diabetes or T2D, 12 had pre-diabetes, and five had T2D.

Our current study used data from (1) the Fitbit Sense, which provided estimates of physical activity on a minute-by-minute basis; and (2) the Dexcom G6 Pro[5], which provided interstitial glucose readings every five minutes. Except for one overnight period for charging, participants wore the watches for the entire study. Further, we focused our analysis on the breakfast shakes because they contained precise quantities of macro, and the period of consumption of the shakes (~5 min) was relatively short. The macro composition of the breakfast shakes is shown in Table I. As we sought to capture intra-individual variability to identical meals, several of the breakfasts in Table I were repeated.

B. Quantifying and parameterizing NEAT

To quantify NEAT, we used data captured by the Fitbit Sense smartwatch, which provided activity data, heart rate, and calorie expenditure estimates on a minute-by-minute basis. Activity was captured by a triaxial accelerometer and gyroscope. The Fitbit then generated an estimate of energy expenditure from these sensors, and provided that estimate to us as a measure of the metabolic equivalent of task (MET). In brief, the MET is an estimate of energy expenditure relative to the mass of an individual, with 1 MET representing the resting metabolic rate. Typically, any measure above 1 MET is considered activity of either light (METs < 3), moderate (3<METs<6), or vigorous (METs > 6) intensity. To determine the intensity and duration of NEAT, we parameterized the postprandial NEAT by taking a series of windows at start time (T) relative to the end of the meal and with fixed duration (D), and for each window we computed the area under the curve (AUC) of the MET curve[6]. Fig. 1 shows the average MET across all participants and breakfasts (with 95% confidence intervals (CI)).

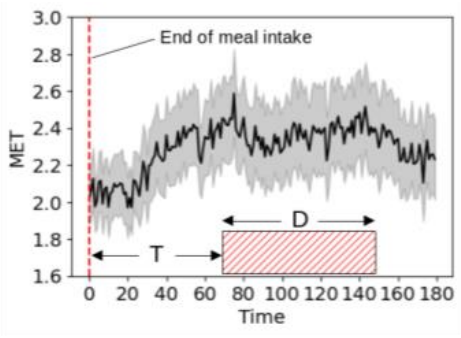

Fig. 1. Mean and 95% CI of post-breakfast METs across all participants in the study. The bottom shows the windowing function used to parameterized timing (T) and duration (D) of activity.

C. Modeling the effect of NEAT on postprandial glucose

After extracting activity data from the Fitbit, we sought to model the relationship between macros, participant HbA_{1c}, and measure of non-exericse activity and postprandial glucose response to the breakfasts. As a measure of postprandial glucose, we computed the peak glucose up to three hours after the meal. To capture the impact of NEAT on peak post-prandial glucose, we used a linear mixed effects model [11]. Linear mixed effects models are a statistical modeling approach well-suited to modeling correlations between repeated measures in a longitudinal study and a response variable and allow us to quantify the variance in the response variable explained by these repeated measures. In a linear mixed effects model, these measures are represented as fixed and random effects, where fixed effects are fixed, non-random quantities (e.g., macros in a meal) and random effects are random variables. In biostatistics, specifically, fixed effects represent fixed, known quantities across the population and random effects are unknown, latent variables representing subject-specific effects. Linear mixed effects models are particularly useful at identifying individual effect sizes [11]. In our study, the fixed effects considered were the meal macros, the participant HbA_{1c}, and the AUC of the MET curve for start time T and duration D, and a random effect was added representing each subject. Our model predicted the peak postprandial glucose after a meal as:

$$G_{ij} = \mathrm{G}_0 + \sum_k \beta_k x_{ijk} + \alpha_i + \epsilon_i$$

where G_{ij} is the peak postprandial glucose for subject i and meal j, x_{ijk} is the kth fixed effect (i.e. carbohydrate quantity) for the ith person and jth breakfast, β_k is the regression coefficients (effect size) for the kth fixed effect, α_i and ϵ_i are the random effect and residual for the ith subject.

D. Evaluation metrics

We used several evaluation metrics to determine the ideal timing and duration of NEAT for peak postprandial glucose attenuation. We used the coefficient of determination (R^2) for the linear mixed effects model and computed the change in R^2

[5] The Pro model is blinded, so participants were unable to see their blood glucose levels during the study. This reduced the potential for patients to alter their normal exercise and eating behavior based on CGM information.

[6] We calculated this for each participant and breakfast resulting in 213 MET curves.

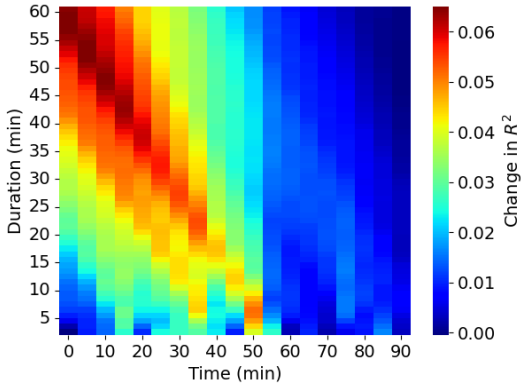

Fig. 2. Explained variance of peak PPGR with AUCs of METs starting at time after breakfast and with width covering durations.

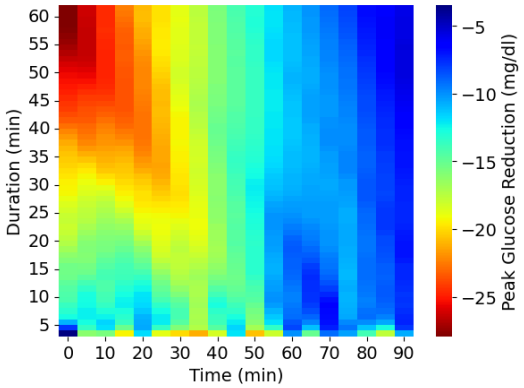

Fig. 4. Expected peak glucose reduction from NEAT starting at time after breakfast and with width covering durations.

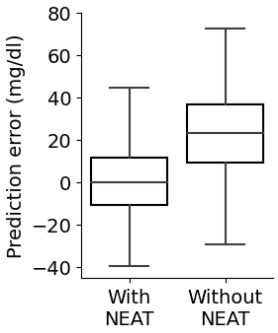

Fig. 3. Box plots showing the prediction error of peak post-prandial glucose estimation of models with and without NEAT.

when the linear mixed effects model had NEAT as a fixed effect versus when it did not. Additionally, we computed the average reduction in peak glucose from NEAT. Finally, we evaluated the effect size of the NEAT regression coefficients and evaluated the statistical significance of these coefficients in the linear mixed effects model using a t test. All analysis was conducted in R using the lmerTest package (version 3.1) for modeling and testing for significance of effects [13].

III. Experiments and Results

We sought to determine, with a linear mixed effects model that had fixed effects for meal macros and participant HbA_{1c}, if including NEAT: (1) better explained the variance in peak postprandial glucose across all participants and breakfasts, (2) had an attenuating effect on peak postprandial glucose, and if so (3) what the optimal timing and duration of NEAT were to achieve the greatest reduction in peak postprandial glucose. Fig. 2 illustrates the heat map of increase in explained variance (R^2) by including NEAT in the linear mixed effects model. The base model (without NEAT) had a coefficient of determination of 0.47. We see that the inclusion of NEAT provides an increase in the explained variance if that non-exercise activity occurs prior to 60 minutes after the completion of the meal. This validates that a linear mixed effects model with a fixed effect representing activity level does better explain peak postprandial glucose than models that do not have measurements of NEAT included. We compared the accuracy of peak glucose estimation of this model with and without the fixed effects representing NEAT. Illustrated in Fig. 3 is the model with the highest increase in R^2. We concluded that the inclusion of NEAT resulted in more accurate estimation of the peak postprandial glucose.

Then we sought to determine if NEAT had an attenuating effect on peak postprandial glucose. To estimate reduction, we provided the mean MET level for each window starting at time T for any duration D (2.279 in our study) to the linear mixed effects models trained with NEAT and compared the difference in peak glucose to the same model with only the resting metabolic rate (MET of 1) and compared the difference in estimated peak glucose. The heatmap for these estimations is provided in Fig. 4. The inclusion of NEAT provided an attenuating effect on peak postprandial glucose, particularly if occurring prior to 60 minutes after the meal.

Finally, we reviewed the findings of both increased explained variance in the linear mixed effects models (Fig. 2**)** and attenuation of peak glucose (Fig. 4**)** to determine the optimal timing and duration of non-exercise activity to reduce peak postprandial glucose. From the changes in explained variance, we found that the largest increase in explained variance comes from non-exercise activity that started immediately after the meal (start time T=0) with a 55-minute duration, with an increase of 0.06 to the R^2 measure. However, non-exercise activity that began as late as 35 minutes after the start of the meal (start time T=35) with at least a 20-minute duration had a similar increase in explained variance (increase in R^2 of 0.05). This indicates that NEAT in the period between 30 and 55 minutes provides the greatest peak postprandial glucose attenuation.

Similarly, when evaluating the greatest reduction in peak postprandial glucose, we found that the largest decrease in peak postprandial glucose came when non-exercise activity occurred immediately after the meal (start time T=0) with a 55-minute duration, with a decrease of 28 mg/dl of peak postprandial glucose. However, as with the explained variance, non-exercise activity that began as late as 25 minutes after the meal (start time T=25) with at least a 30-minute duration had a similar decrease in peak postprandial glucose (at least 20 mg/dl reduction in peak postprandial glucose). This suggests that the period between 25 and 55 minutes was most critical in glucose attenuation. Together, these findings suggest that non-exercise activity of at least 20

TABLE II. COMPARISON OF BASELINE MODEL TO MODELS WITH 20-MINUTE DURATIONS IN 20 MINUTE INCREMENTS

Model	R^2	Effect size of MET (mg/dl)	*p*
Baseline (Macronutrients + HbA1c)	0.47		
Baseline + MET AUC 0	0.50	-0.393	<0.001
Baseline + MET AUC 20	0.52	-0.408	<0.001
Baseline + MET AUC 40	0.51	-0.387	<0.001
Baseline + MET AUC 60	0.48	-0.211	<0.001
Baseline + MET AUC 80	0.48	-0.204	<0.001
Baseline + MET AUC 100	0.47	-0.140	0.012

minutes in duration beginning as late as 35 minutes after the meal have a significant reductive effect on peak glucose.

Alternative times and duration may also have been effective, with the tradeoff being smaller reductions in peak glucose. We compared the significance of the effect size of windows of duration D=20 minutes starting at different times. The comparisons with the baseline model are seen in Table II. When a model with the inclusion of a MET window was no longer significant, the R^2 of the model returned to that of the baseline model, and the magnitude of the effect size diminished. The results in Table II, along with the results illustrated in Figs. 2 and 4 are consistent with studies that indicate peak glucose occurs within the first 90 minutes [3], and that physical activity that starts after 100 minutes has no statistically significant effect on glucose attenuation.

IV. LIMITATIONS AND FUTURE DIRECTIONS

This work has several limitations in providing additional guidance on the impact of NEAT on past-meal glucose excursions. First, it assumes a linear effect for HbA_{1c} values, and does not take into consideration the contribution of endogenous glucose production to achieved HbA_{1c} levels. Second, the variation in NEAT intensities and durations can provide personalized effect and should be investigated on a person-by-person basis. Third, the accuracy and amount of error in the MET levels requires further study to determine. Finally, we can also evaluate the impact of NEAT on the incremental area under the curve of the entire 3-hour glucose response.

V. CONCLUSION

In this work, we have demonstrated that NEAT captured in free-living environments can effectively reduce peak glucose. We determined that NEAT is an important factor for estimating the peak post-prandial glucose levels. In addition, any NEAT that captures the period from 25 to 55 minutes after a meal has the strongest reductive effect on peak post-prandial glucose. This indicates that even NEAT can have a beneficial effect on controlling glucose surges and should be a part of any health regimen for glycemic control.

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