Modeling Glucose Regulation in Postprandial Intermittent High Intensity Exercise with T2DM Patients

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Background and Objective

Exercise is an important lifestyle factor that impacts glucose control for patients with Type 2 diabetes mellitus (T2DM), and a mathematical model of its effects would open valuable new lines of inquiry for *in silico* studies performed on these patients. Current exercise models used with such studies of diabetes are only applicable to Type 1. These models, which involve effects on insulin sensitivity, cannot be assumed to extend to T2DM where insulin resistance is involved.

We attempted to create a mathematical model representative of exercise's acute effects in people with T2DM, in a way that supports integration into the metabolic model defined by Dalla Man[1]. An initial survey of the literature showed that these effects are very dependent on exercise intensity, and probably its timing relative to meals. We chose to initially address the typical scenario of a single postprandial session of intermittent high-intensity exercise (IHE). The modeling effort reported here was limited to effects seen during and within a few hours following the session.

The model was developed with, and incorporated into, the Diabetes Mellitus Metabolic Simulator (DMMS.R, The Epsilon Group).

Methods

General Approach

In T2DM subjects, the literature shows that IHE affects glucose utilization (GU) and endogenous glucose production (EGP), with an increase in GU seen during, and for a few hours after, an exercise session[2], and an increase in EGP corresponding very closely to the timespan of the session[3,4]. A decrease in EGP is seen the day after IHE, presumably to support replenishment of glycogen stores[5].

The increased GU during IHE is known to be insulin independent, because (1) it occurs independently of insulin levels[3], (2) it exists with high catecholamine levels which inhibit insulin mediated GU[3,6], and (3) it is dependent on muscle contraction[7]. The increased GU after IHE is expected to be insulin dependent, as the effects of the last 2 items above disappear very quickly after exercise completion[3,4,6].

Larsen, et al. provides sufficient data to model GU associated with IHE, in the specific case of a 46 minute session beginning 45 minutes after a meal. In this case, unlike others involving IHE, the increase in EGP did not outpace the increase in GU[2,3]. The difference may be accounted for by the relatively short time between the meal and the exercise session in Larsen's study. Our model attempted to match Larsen's final BG responses by exclusively addressing the GU effects. For this analysis we limited the timespan of this model to that of continuous data from Larsen's study (about 4 hours), and so did not address the EGP reductions of the day after IHE.

Model Derivation

Interpreting Larsen's data (including total GU, BG, and plasma insulin concentration, I_{pc}) in the context of the Dalla Man model, we established the metabolic parameters associated with GU, applicable to Larsen's subjects during the control arm, in which exercise was not present. We restructured the equations to independently represent the insulin-dependent and insulin independent portions of GU (GU_{id} and GU_{ii}, respectively) as follows:

$$GU_{id}(t) = V_{mx} \cdot X(t) \cdot \frac{G_t(t)}{K_{m0}+G_t(t)} \quad (1)$$

$$GU_{ii}(t) = F_{cns} + V_{m0} \cdot \frac{G_t(t)}{K_{m0}+G_t(t)} \quad (2)$$

Where $G_t(t)$ is the glucose mass in slowly equilibrating tissues, $X(t)$ is insulin action, and V_{mx}, V_{m0}, K_{m0}, and F_{cns} are model parameters. To resolve the time-varying signals in these equations ($X(t)$ and $G_t(t)$) we took two approaches: For $G_t(t)$, we performed a simulation in DMMS.R to establish a typical mapping between BG and $G_t(t)$. For $X(t)$, we assumed Larsen's fasting I_{pc} as the basal insulin level (I_b in the Dalla Man model), and used this along with his real time I_{pc} data to compute $X(t)$ from Dalla Man's equations.

We then established time-varying profiles for V_{m0} during exercise, and for V_{mx} in the post-exercise period as follows:

For the V_{mx} change, we first established $GU_{ii}(t)$ over the post-exercise period (for both the exercise and non-exercise arms) by using equation 2 while mapping Larsen's BG data to $G_t(t)$. We then found $GU_{id}(t)$ by subtracting $GU_{ii}(t)$ from Larsen's data for total GU. With this, we used equation 1 and our derived $X(t)$ to calculate the required V_{mx} values over the post-exercise period. This was done for both the exercise and non-exercise arms.

Since the V_{m0} change is attributable to muscle contraction, we assumed it arose very quickly after the start of exercise and disappeared very quickly after the end of exercise (within 1 minute). Using the DMMS.R simulator, we performed an iterative optimization process to find a V_{m0} multiplication factor that resulted in a BG effect which closely matched that seen by Larsen for his 46-minute postprandial exercise period (figures 1 and 2). It should be noted that the EGP is expected to be elevated during the exercise session, though this effect is reduced in our specific postprandial scenario, and Larsen does not provide sufficient data to quantify it. As a result, our approach of tuning V_{m0} to match the BG response will have the effect of empirically compensating for EGP changes during exercise.

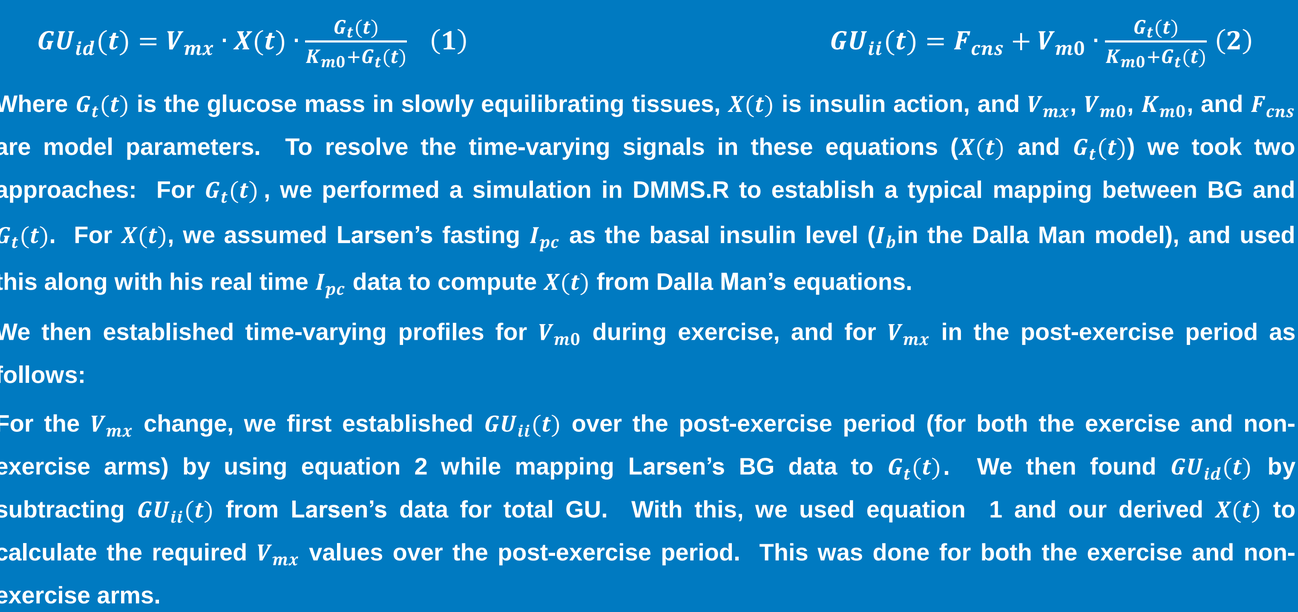

Figure 1 Clinical data from the Larsen study, showing BG on the non-exercise day vs. BG on the exercise day, with non-exercise day data "normalized" – adjusted to match that of the exercise day at the start of the meal.

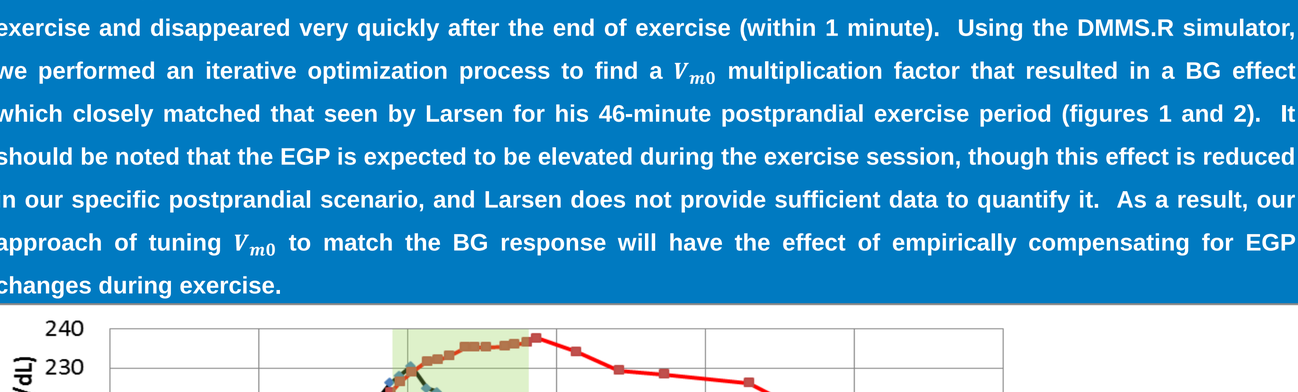

Figure 2 Difference in BG concentration on the exercise day, relative to the non-exercise day, as a percentage of the concentration on the non-exercise day. This is used to establish an expected BG target applicable during the exercise session, using results of a postprandial simulation without exercise.

Methods – Model Evaluation

Performance of the model was evaluated by creating a simulation in DMMS.R with a protocol matching that used in Larsen, and comparing the simulated BG curve to a target simulated BG curve. The target curve was established by performing a simulation that included the meal, but not the exercise, and by then applying the differences in BG concentration attributable to exercise (based on Larsen's data) from the start of exercise until 280 minutes after the start of the meal. The simulated meal was made to match, in carbohydrate content, the meal used in the Larsen study.

Model Definition

A time-profile for a multiplier to be applied to the V_{mx} parameter was defined to peak 219 minutes after the start of the meal at a value of 3.55, and return to 1 after another 32 minutes. The multiplier applied to the V_{m0} parameter rose to 5.67 one minute after the start of exercise, and returned to 1 within 1 minute of exercise completion. Both profiles are shown in Figure 3.

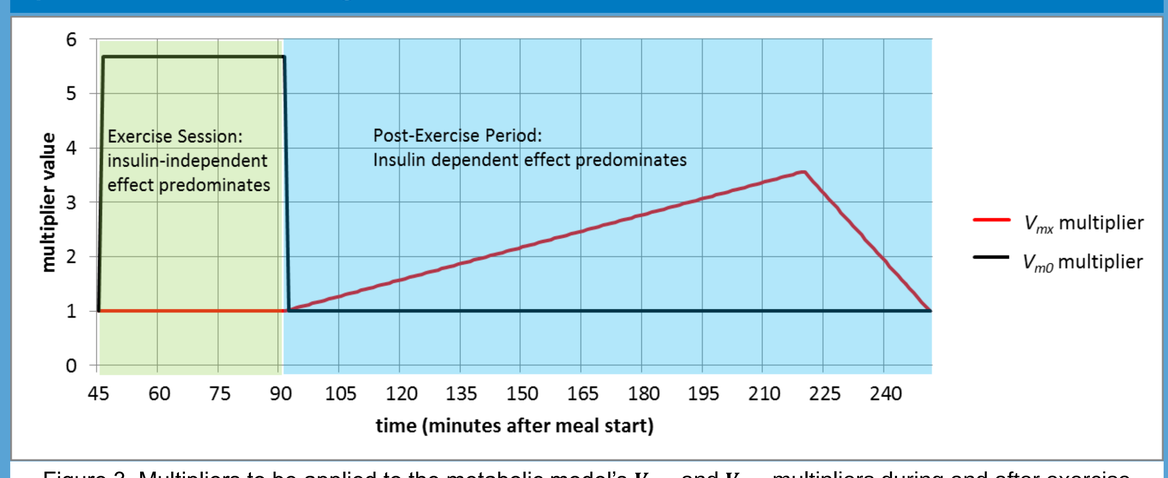

Figure 3 Multipliers to be applied to the metabolic model's V_{mx} and V_{m0} multipliers during and after exercise

Results

The BG curve for the model was found to fit the targeted curve, with a correlation of r=0.987, an RMS error of 7.3mg/dL, and MARD of 3.36% (figure 4).

In the design of the model, when the V_{mx} multiplication factors were calculated over the post-exercise period, the effective V_{mx} value was computed independently for the exercise and non-exercise cases, based on Larsen's data. As a supplementary validation of our approach to this calculation, we confirmed that the calculated V_{mx} value remained much more constant over the applicable timespan in the non-exercise case. We found that calculated non-exercise V_{mx} (in the period from 120 to 236 minutes after meal time, where good data was available and $X(t)$ was large enough to allow a meaningful calculation) had a mean of 0.048 and standard deviation of 0.0043 mg/kg/min/(pmol/L). The same standard deviation for the exercise case was 6.9 times this amount.

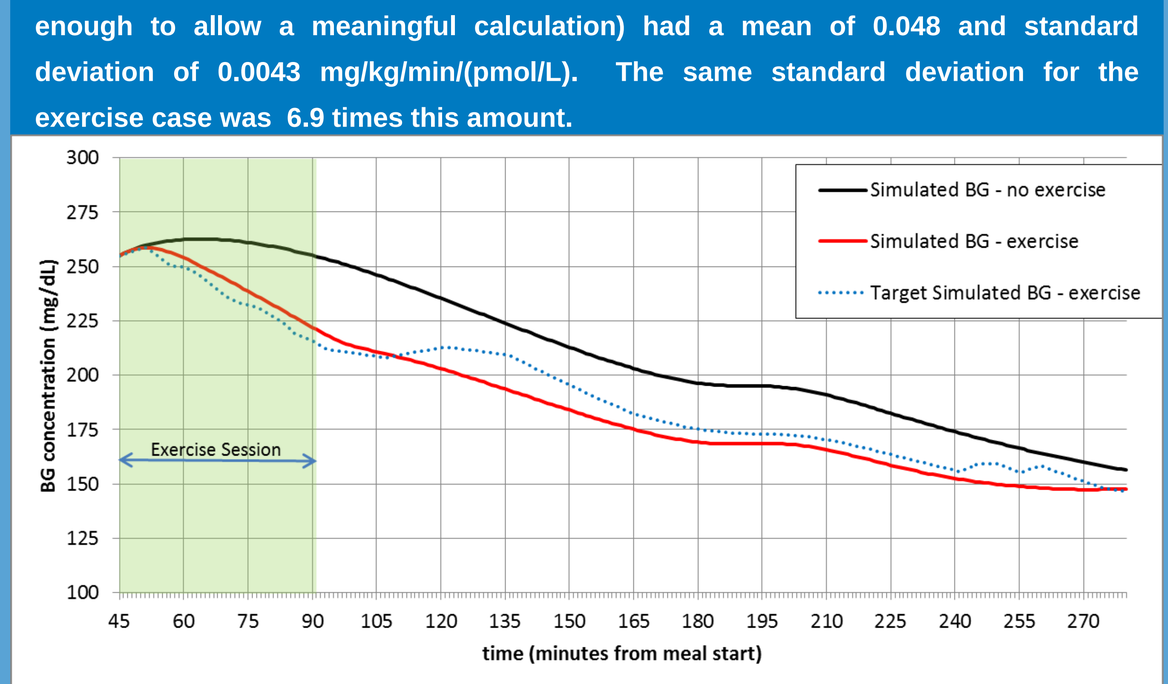

Figure 4 Modeled BG response to exercise compared to the desired response as was targeted by the modeling process.

Results – Discussion

Though the model relies exclusively on metabolic parameters that effect GU, it does result in an increase in EGP, as a natural consequence of the change in BG. The observed effect is shown in figure 5. The maximum ratio of EGP seen with exercise to that seen at the same time in a simulation without exercise was 2.2:1. Quantitatively, we do not have enough data to evaluate this effect, but qualitatively, it is consistent with expectations.

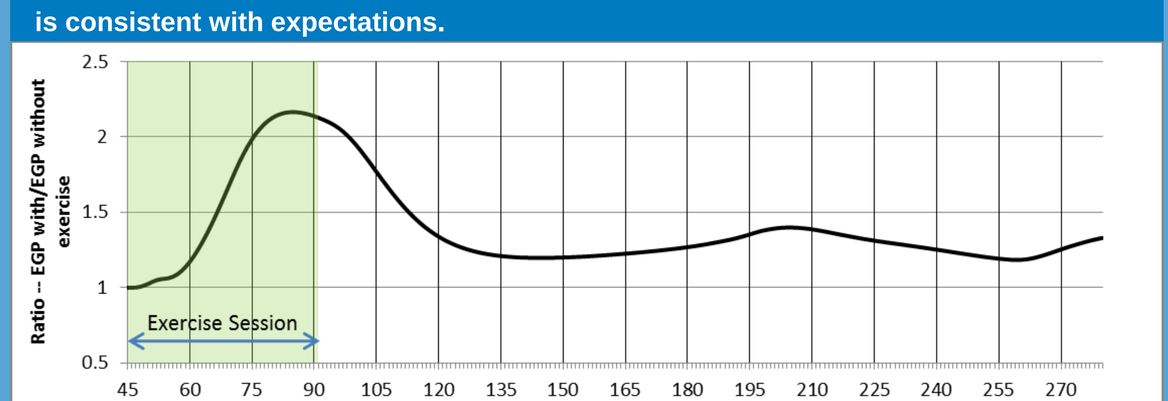

Figure 5 In the simulated scenarios, ratio of EGP on the exercise day to that on the non-exercise day, during the same time period. This effect arises entirely as a consequence of the changes to utilization.

Conclusions

A model for the acute effects of postprandial exercise in people with T2DM has been incorporated into the DMMS.R simulator. This model addresses the specific case of a 46-minute IHE session beginning 45 minutes after a meal. The model relies on an increase in insulin independent GU during exercise, and an increase in insulin dependent GU after, persisting until 160 minutes after the session completes. The effects on BG have been shown to match expectations over the 235 minute span starting when exercise commences (with MARD = 3.36%).

The literature indicates that exercise effects are very dependent on both intensity and timing of exercise relative to meals, so expanding the scope of this model to address a range of these factors would be valuable. The EGP effects during exercise and EGP reductions that happen hours or days after exercise are the topic of ongoing work, which will be incorporated into a more comprehensive model in DMMS.R.

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