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 offer 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 and not severity, 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 too short-term to relate to meal. We chose to initially address the typical scenario of a non-insulin-dependent intermittent high-intensity exercise (HIE). The model 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 Mathematical Simulator (DiMMS.R, The Epsilon Group).

**Methods**

**General Approach**

In T2DM subjects, the literature indicates that exercise affects glucose utilisation (GU) and endogenous glucose production (EGP), with an increase in GU seen during, and for a few hours after, an exercise session, and an increase in EGP corresponding very closely to the timespan of the exercise session\(^{2}\). A decrease in EGP is seen in the day after HIE, presumably to support replenishment of glycogen stores\(^{3}\).

The increased GU during HIE is known to be insulin independent, because (1) it occurs independently of insulin levels, (2) it is seen with high and low glucose levels that induced insulin mediated, and (3) it is dependent on muscle contraction\(^{4}\). The increased GU after HIE is expected to be insulin dependent, as the effects of the insulin waves above mentioned very quickly after exercise completion.

Dalla Man\(^{1}\) provides sufficient data to model exercise effects with HIE, in the specific case of an 80 minute session beginning 45 minutes after a meal. In this case, unlike others involving HIE, the increase in GU did not outpace the increase in BG. The difference may be accounted for by the relatively short time between the meal and the intervention in Larsen’s study. Our model attempted to match Larsen’s first 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 HIE.

**Model Derivation**

Interpreting Larsen’s data (including total GU, BG, and plasma insulin concentration, \(\text{I}_0\)) in the context of the Dalla Man\(^{1}\) 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 restricted the equations to independently represent the insulin-dependent and insulin-independent portions of GU (GU\(_D\) and GU\(_I\), respectively) as follows:

\[
\text{GU}(t) = \text{GU}\_I(t) + \text{GU}\_D(t)
\]

Where GU\(_D\) is the glucose mass in slowly equilibrating tissues, \(\text{I}(t)\) is insulin action, and \(\text{I}_0\) and \(\text{GU}\_D(t)\) and \(\text{GU}\_I(t)\) are defined as follows:

\[
\text{GU}\_D(t) = \frac{\text{GU}\_D(0) \cdot e^{-t/\tau}}{1 + \text{GU}\_D(0) \cdot e^{-t/\tau}}
\]

Where \(\text{GU}\_D(0)\) is the insulin-dependent GU at \(t=0\), and \(\frac{1}{\tau}\) is the time-constant of GU\(_D\).

\[
\text{GU}\_I(t) = \frac{\text{GU}\_I(0) \cdot \text{I}(t) \cdot e^{-t/\tau}}{1 + \text{GU}\_I(0) \cdot \text{I}(t) \cdot e^{-t/\tau}}
\]

Where \(\text{GU}\_I(0)\) is the insulin independent GU at \(t=0\), and \(\frac{1}{\tau}\) is the time-constant of GU\(_I\).

For \(\text{GU}\_D(t)\), we performed a simulation to establish a typical mapping between BG and \(\text{GU}\_D(t)\). For \(\text{GU}\_I(t)\), we assumed Larsen’s testing \(\text{I}(t)\) as the basal insulin level \((\text{I}_0)\) in the Dalla Man model, and used this along with \(\text{GU}\_I(0)\) to compute \(\text{GU}\_I(t)\) from Dalla Man’s equations.

We then established time-varying profiles for \(\text{GU}\_D(t)\), during exercise, and for \(\text{GU}\_I(t)\) in the post-exercise period as follows:

\[
\text{GU}\_D(t) = \frac{\text{GU}\_D(0) \cdot e^{-t/\tau}}{1 + \text{GU}\_D(0) \cdot e^{-t/\tau}} + \text{GU}\_D(t)
\]

Where \(\text{GU}\_D(t)\) is the glucose mass in slowly equilibrating tissues, \(\text{I}(t)\) is insulin action, and \(\text{GU}\_D(0)\) and \(\text{GU}\_D(t)\) are defined as follows:

\[
\text{GU}\_D(t) = \frac{\text{GU}\_D(0) \cdot e^{-t/\tau}}{1 + \text{GU}\_D(0) \cdot e^{-t/\tau}}
\]

Where \(\text{GU}\_D(0)\) is the insulin-dependent GU at \(t=0\), and \(\frac{1}{\tau}\) is the time-constant of GU\(_D\).

For \(\text{GU}\_I(t)\), we first established \(\text{GU}\_I(t)\) over the post-exercise period for both (the exercise and non-exercise) arms by using equation 2 while mapping Larsen’s BG data to \(\text{GU}\_I(t)\). We then found \(\text{GU}\_I(t)\) by subtracting \(\text{GU}\_D(t)\) from Larsen’s data for total GU. We used this equation, and per our approach to calculate the required \(\text{GU}\_I(t)\) values over the post-exercise period. This was done for both the exercise and non-exercise arms.

Since the \(\text{GU}\_D(t)\) change is attributable to muscle contraction, we assumed it would vary very quickly after the start of exercise and disappear very quickly after the end of exercise within 1 minute. Using the DiMMS.R simulator, we performed an iterative optimization process to find a \(\text{GU}\_D(t)\) multiplicative factor that resulted in a BG effect which closely matched that seen by Larsen for the 46 minute post-exercise period (Figure 3 and 4). It should be noted that the additional effects induced by exercise were not limited to our specific postexercise scenario, and Larsen does not provide sufficient data to quantify it. As a result, our approach of tuning \(\text{GU}\_D(t)\) to match the BG response will have the effect of empirically compensating for EGP during exercise.

**Results**

The BG curve for the model was fit to the targeted curve, with a correlation of \(r^2=0.887\) and a RMS error of 7.3 mg/dl and MAID of 3.3% (Figure 4).

In the design of the model, when the \(\text{GU}\_D(t)\) multiplication factors were calculated over the post-exercise period, the effective \(\text{GU}\_D(t)\) value was computed independently for the exercise and nonexercise cases, based on Larsen’s data. As a supplementary validation of our approach to this calculation, we confirmed that the calculated \(\text{GU}\_D(t)\) value remained much more constant over the applicable timespan in the nonexercise case. We found that calculated nonexercise \(\text{GU}\_D(t)\) in this period to 120 to 180 minutes after meal time, where good data was available and \(\text{GU}\_D(t)\) was large enough to allow a meaningful calculation had a mean of 0.548 and standard deviation of 0.043 mg/kg/min/(also the same standard deviation for the exercise case was 0.5 times this amount.

**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 was to that seen at the same time in a simulation without exercise was 2.2:1. Qualitatively we do not have enough data to evaluate this effect, but qualitatively, it is consistent with expectations.

**Conclusions**

A model for the acute effects of postprandial exercise in people with T2DM has been incorporated into the DiMMS.R simulator. This model addresses the specific case of a high-intensity intermittent exercise, during which the model relies on an increase in insulin independent GU during exercise, and an increase in insulin dependent GU after, persisting until 180 minutes after the session completes. The effects on BG have been shown to match expectations over the 250 minute span starting when exercise begins (with MAID ≤ 3.3%).

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 effects of ongoing work, which will be incorporated into a more comprehensive model in DiMMS.R.

References:

1. Diabetic’s Health: Transactions on Biomedical Engineering 2007; 54(1):1745-1749
7. IUBMB Life 2009; 61(5): 473-484

Contact: meinheimer@tegernsia.com