Diabetic Complications Consortium

Application Title: Gastric Emptying and Glycemia in Type 1 Diabetes Mellitus

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1. Project Accomplishments:

Project Overview:
Approximately 50% of patients with type 1 diabetes mellitus (T1D) have delayed or rapid gastric emptying (GE), which can be measured by the emptying of a radiolabeled meal (i.e., scintigraphy), or with the ^{13}C-Spirulina gastric emptying breath test (GEBT). GEBT is extensively validated, FDA-approved, and a more practical office-based test that does not entail radiation exposure.

Poor glycemic control is attributed to several factors (e.g., nonadherence to therapy, suboptimal adjustment of insulin dose during exercise, erratic absorption of insulin, and errors in estimating caloric intake) but not GE. Artificial pancreas (AP) automated insulin delivery systems use algorithms to automatically increase, decrease, and suspend insulin delivery using CGM data streams, but these algorithms do not take GE into account. While AP systems have improved glycemic control, few patients attain the American Diabetes Association goal of an A1c < 7%.[1] Based on these considerations, *our overall long-term objective is to utilize GE to optimize the dose and timing of insulin delivery and thereby improve glycemic control in DM.*

Our data suggest that subcutaneous glucose values, measured with CGM sensors, for 4 hours after a meal can be accurately predicted with a mathematical model that incorporates *fasting* glucose, ingested calories, insulin delivery, and GE measured with scintigraphy or the GEBT. Moreover, the *predicted* postprandial glucose values approximate closely to *actual* postprandial CGM-glucose values *more closely* if the equations use the actual GE values for that patient. This strongly suggests that GE is necessary to accurately predict postprandial glucose values. Prompted by these preliminary findings, **our hypothesis is that GE is necessary to accurately predict CGM-glucose.**

Overview of Accomplishments:
We have refined and finalized mathematical models that incorporate GE measured with scintigraphy to predict postprandial continuous CGM glucose levels. We have evaluated these models on patient data sets with simultaneous CGM, scintigraphy, and GEBT measurements, all for four hours after a meal. The results show that incorporating actual GE values rather than population-normal GE values does indeed improve the quality of the CGM predictions. The results also show that using GEBT measurements alone (and converting these to effective scintigraphy values) lowers the quality of the CGM predictions only slightly.

2. Specific Aims:

Specific Aim 1. To refine and finalize mathematical models that incorporate GE measured with scintigraphy to predict postprandial continuous CGM glucose levels, to assess the closeness of fit between predicted and actual postprandial CGM values, and to establish the importance of GE values to achieving accurate predictions.

Results: Our goal is not optimal prediction of CGM, but rather a model that is as simple as possible while still being sufficient to predict CGM values fairly well, and to demonstrate the importance of accounting for GE. We have refined our model and evaluated various options for which parameters to fix based on literature values and which to fit to individual patient data, and have finalized a model that incorporates only two fitted parameters (p2 and p3, related to active insulin clearance and insulin-dependent glucose uptake). This simplifies the model, reduces computation time, and makes the model more robust. The fitted parameters also remain within physiologically reasonable values.

We evaluated the goodness of fit of this model based on the area under the CGM curve from 0 to 120 minutes post-prandial (AUC), and the RMS difference between the actual and predicted CGM values. Using the measured GE values, 93% of the data sets analyzed to date had predicted AUC values within 7% of the actual values, and the average RMS difference in CGM between the actual and predicted values (across all patients and times) was 9.20. When population normal rather than patient specific values for GE were used, only 71% of the data sets had predicted AUC values within 7% of the actual values, and the RMS difference was 10.55. Thus, the measured values did indeed yield better results than the population normal values. However, this difference did not currently reach statistical significance when analyzed with the Wilcoxon signed-rank test. Analysis of additional data sets is ongoing.

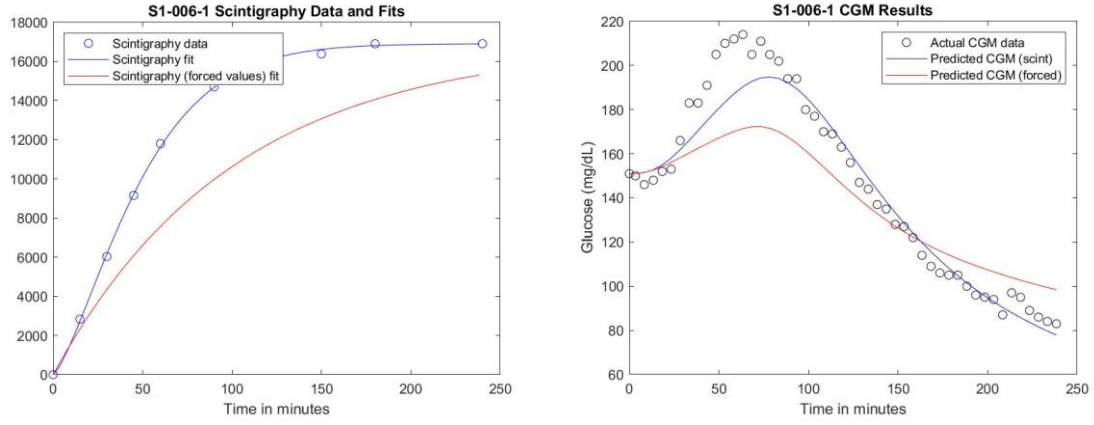

Fig. 1 – Left: Sample fits to scintigraphy data (blue) and GE curve using population normal values (red). For this case the time at which the stomach is half empty (tH) is 40.95 min, whereas the population normal value was taken to be 70 min. Right: Fits to CGM data using the GE fits at left. The differences in AUC from the actual data are -3.74% and -11.63%, and the RMS differences are 9.76 and 20.09 respectively.

Specific Aim 2. To develop mathematical models that incorporate GE measured with a gastric emptying breath test (GEBT) to predict postprandial CGM-glucose levels and to assess the closeness of fit between predicted and actual postprandial CGM values.

Results: The data sets above were for patients that had simultaneous scintigraphy and GEBT measurements. The GEBT measurements are safer and much more convenient, as described above, but give only indirect and delayed measurements of GE. We adapted a previously published regression-based equation that relates GEBT measurements to scintigraphy-based GE values, ran our model on these data sets using GE values based on the GEBT measures (converted to scintigraphy), and compared these predictions to those using the actual scintigraphy measurements. With the GEBT measurements, 86% of these data sets had predicted AUC values within 7% of the actual values, and the average RMS difference in CGM between the actual and predicted values was 9.66. These numbers compare favorably to the results (93% and 9.20) obtained when using the actual scintigraphy values, given how much simpler and patient-friendly the GEBT test is.

Given the closeness of these results, we do not see a need for exploring more advanced methods for converting GEBT measurements to scintigraphy values. We are currently analyzing a much larger number of data sets that have GEBT only, and will both evaluate these results and compare them to population-normal GE values (as in Aim 1 above).

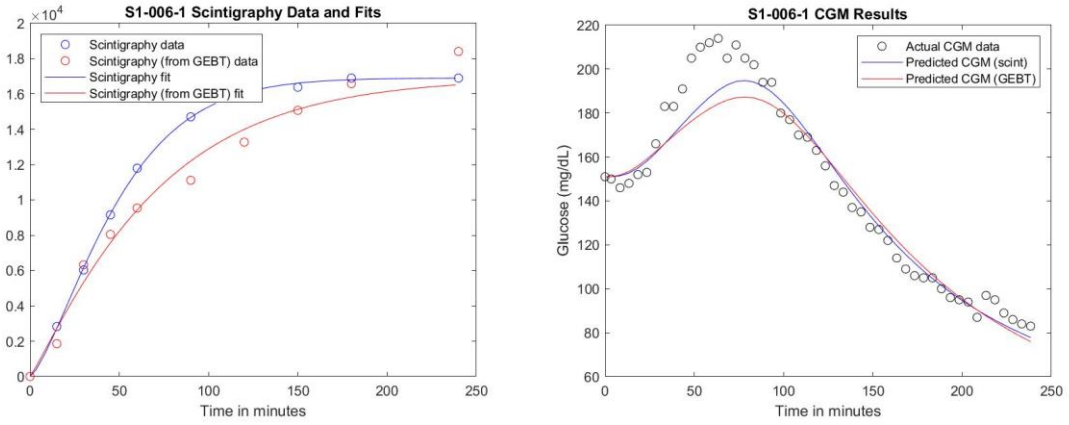

Fig. 2 - Left: Sample fits to scintigraphy data (blue) and GE curve using population normal values (red). For this case the time at which the stomach is half empty (tH) is 40.95 min with scintigraphy but 52.54 min using GEBT data. Right: Fits to CGM data using the GE values at left. The differences in AUC from the actual data are -3.74% and -5.40%, and the RMS differences are 9.76 and 12.03 respectively.

3. Publications:

None.