Modified Glucose Absorption Equation in An Oral Minimal Model for Type 2 Diabetes Mellitus

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Abstract. The previously minimal model that has been developed by Bergman is known that blood uptake can be used to the calculations of insulin sensitivity and glucose effectivity in an intravenous glucose tolerance test (IVGTT). In this study, a minimal model Bergman has been modified by adding glucose absorption factors considering the rate of glucose concentration in the small intestine. Based on these present model results, subjects with type 2 diabetes mellitus (T2DM) have higher glucose concentrations and thus require greater insulin performance compared with subject pre-diabetes and normal subject. Besides, subjects with T2DM have lower insulin sensitivity and glucose effectivity compared with subject pre-diabetes and normal subjects. Fitting results obtained from these present model results are obtained using R2 values of glucose and insulin concentration, all values were above 0.90. This shows the validation results of the comparison of all simulation results and experimental data are good.

1. Introduction
Based on that observation in the intestinal wall of whole animal experiments, an appreciable fraction of the glucose that absorbed located in the intestinal. Since the glucose proportion which is absorbed in the intestinal wall is much higher at the ileum than at the jejunal end of the intestine. The high rates of glucose absorption in the intestinal wall suggest that this process may be a significant contributor to the dynamics system action of glucose [1].

Obesity and diabetes are associated with glucose absorption excess in the small intestine. Currently, the research on the mechanisms of intestinal glucose absorption is very limited. However, these researches are needed to describe the contributions of the glucose uptake and to explain the underlying mechanisms. All confirmations that truly play important roles in glucose absorption in small intestinal become novel targets to obtain the diagnosis model of obesity and diabetes which are serious human diseases commonly [2]. The understanding of the physiology of the digestive system during this century about the mechanism of glucose absorption in the small intestine [3]. Glucose is absorbed through the intestine by a transepithelial transport system. In this transepithelial transport process, the kinetics of transepithelial glucose transport can be assessed using oral glucose tolerance test (OGTT) [4].

To assess glucose absorption in humans can be not done directly, such as measurement invasively, nevertheless an approach based on mathematical modeling need to be developed to mimic absorptive conditions at the small intestine. The estimation of gut glucose absorption rates, the total glucose absorbed, and half-life in the gastrointestinal tract can be obtained using mathematical modeling and was compared by using the glucose absorption measurement standard. The World Health Organization (WHO) has recommended the standardized 75-g OGTT tests that used for diagnosis of impaired glucose tolerance (IGT) and T2DM as well as gestational diabetes mellitus. All plasma glucose measurements
will be done after 8-10 h fasting. After that, blood glucose and insulin concentrations are measured within 2-3 hours. If the range of blood glucose concentration in fasting subjects is 70-99 mg/dl, then the subject is still normal. If it is 100-125 mg/dl, then the subject is pre-diabetic, and the subject has diabetes if the blood glucose concentration is above 125 mg/dl. Based on the diagnosis, impaired glucose metabolism does not only indicate a higher possibility develops into T2DM but also followed with simultaneously increased cardiovascular risk [5].

Diabetes is a metabolic disorder characterized by the body’s inability to use glucose, fat, and protein due to insulin deficiency or insulin resistance increasing blood glucose and glycosuria levels. Metabolic disorders in T2DM will also cause hyperglycemia and can cause long-term complications, including damage and malfunctioning of organs such as kidneys, eyes, nerves and the risk of cardiovascular disorders and increased mortality. Medical treatment can be done by giving external insulin from outside the body by injection or orally which aims to balance the sugar levels in the body, but the early diagnosis will be better for preventing this T2DM disease.

The OMM is a minimal modification of the Bergman model by considering glucose orally [6, 7]. The formulation of the OMM has been developed in previous studies, but this model does not specifically explain the external glucose rate equation. The OMM can provide information about glucose effectiveness and insulin sensitivity as two important parameters. Glucose effectiveness is the ability of a person’s glucose to reduce their concentration in plasma without the help of insulin, whereas insulin sensitivity is the ability of insulin to accelerate the loss of glucose from plasma.

Research on T2DM has been carried out by various methods, one of them is the mathematical model method. Because mathematical models can provide an overview of the dynamics of glucose-insulin systems in the human body. In this study, the OMM model will be modified, then this model will be applied to the OGTT test result data. Modification of the glucose absorption equation in the OMM model will be proposed in this study.

Modification of glucose absorption equation in OMM is expected to be able to describe the dynamics of glucose and insulin in the human body, such as the results of OGTT experimental data. Determination of the value of glucose effectiveness and insulin sensitivity of the modified OMM equation in the glucose absorption equation from OGTT experimental data can be done.

The benefit of this study is to predict the subject's condition whether in normal, pre-diabetic, or T2DM conditions by processing the OGTT test results using OMM modification in the glucose absorption equation, so this model is expected to be able to diagnose and prevent.

2. Method

2.1. Minimal model Bergman

The minimal model was first introduced by Bergman et al. [6]. The model is a simple model that describes the rate of change in glucose in the blood that is only influenced by a few parameters. The minimal model Bergman assumes that the human body is a compartment (or tank). The glucose concentration and the resulting insulin concentration meet in a compartment (or tank) commonly called interstitial. The minimal model contains two model functions, the first function explains the glucose kinetics (minimal model of glucose), how the blood glucose concentration reacts to the blood insulin concentration. Whereas, the second function explains insulin kinetics (minimal model of insulin), how blood insulin concentration reacts to blood glucose. The two functions of this model successively receive glucose and insulin data as input. The two functions of this model are more often used to interpret the intravenous glucose tolerance test (IVGTT) [8]. The ordinary differential equations which describe the minimal model Bergman are represented as follows:

$$\frac{dG(t)}{dt} = -[p_1 + X(t)]G(t) + p_1 G_b, \quad G(0) = G_b$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3[I(t) - I_b], \quad X(0) = X_0$$

2.2. Modification of glucose absorption equations in the minimal model Bergman
One method for predicting glucose effectiveness ($S_G$) and insulin sensitivity ($S_I$) in OGTT tests with OMM models. The OMM model is a mathematical model that can calculate glucose effectiveness ($S_G$) and insulin sensitivity ($S_I$) from oral glucose tests. The glucose absorption equation is added to the minimal model Bergman:

$$\frac{dG(t)}{dt} = -[p_1 + X(t)]G(t) + p_1G_b + \frac{k_{abs}G_{gut}}{V}, \quad G(0) = G_b$$  \hspace{1cm} (3)

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3[I(t) - I_b], \quad X(0) = X_0$$  \hspace{1cm} (4)

The amount of glucose in the gut after the ingestion of a meal containing carbohydrate equivalent with millimoles of glucose [9, 10]. Therefore, the glucose absorption equation in the gut is defined by:

$$\frac{dG_{gut}(t)}{dt} = R_{ge}(t) - k_{abs}G_{gut}$$  \hspace{1cm} (5)

$$R_{ge}(t) = -D \frac{df(t)}{dt} = D \cdot k \cdot \beta \cdot \exp(-kt)^\beta$$  \hspace{1cm} (6)

The definition of variables and parameters in the OMM model that has been modified with the glucose absorption equation is shown in Table 1. The OMM model can provide information about glucose effectiveness and insulin sensitivity as two important parameters. In the OMM model, the glucose effectiveness ($S_G$) and insulin sensitivity ($S_I$) is given by:

$$S_I = \frac{p_3}{p_2}$$

$$S_G = p_1.$$  \hspace{1cm} (7)

### 2.3. An oral minimal model of insulin

The level of change in plasma insulin concentration ($dI/dt$) is represented by a component of insulin secretion in the pancreas ($R_I$) and the level of circulating insulin is calculated from a one-compartment model with $p_{i1}$ (min$^{-1}$) level parameters for the process of insulin loss [11]:

$$\frac{dI(t)}{dt} = -p_{i1}[I(t) - I_b] + R_I, \quad I(0) = I_b$$  \hspace{1cm} (8)

$$R_I = R_{i1} + R_{i2}$$

$R_{i1}$ (U.ml$^{-1}$.min$^{-1}$) is a representation of the secretion of insulin stored in beta cells in response to an increase in glucose levels can quickly be expressed by the following equation:

$$R_i = \begin{cases} \frac{dG}{dt}, & \frac{dG}{dt} > 0 \\ 0, & \frac{dG}{dt} \leq 0 \end{cases}$$  \hspace{1cm} (9)
where the $p_{I2}$ parameter (U.ml$^{-1}$.mg.dl$^{-1}$) represents the dynamics of insulin sensitivity secretion by beta cells. $R_{I2}$ (IU.ml$^{-1}$,min$^{-1}$) is a newly taken insulin secretion in response to glucose levels can be expressed by the following equation (with $R_{b2} = 0$):

$$
R_{I2} = \begin{cases} 
- \frac{1}{p_{I2}} \left[ R_{I2} - p_{I4}(G(t) - G(0)) \right] & G(t) - G(0) > 0 \\
- \frac{1}{p_{I2}} R_{I2} & G(t) - G(0) \leq 0 
\end{cases} 
$$

(10)

The parameter $p_{I4}$ (U.ml$^{-1}$.mg.dl$^{-1}$.min$^{-1}$) illustrates the insulin sensitivity static with beta cells to glucose levels with a time constant parameter $p_{I3}$ (min) and $R_I$ is not negative.

### Table 1. Definition of variables and parameters in the modification of the OMM model.

| Symbol | Unit | Description |
|--------|------|-------------|
| $G(t)$ | mg/dL | glucose concentration at time $t$ |
| $I(t)$ | μU/ml | insulin concentration at time $t$ |
| $X(t)$ | min$^{-1}$ | insulin action returns glucose concentration to basal level at time $t$ |
| $G_b$ | mg/dL | basal glucose concentration |
| $I_b$ | μU/mL | basal insulin concentration |
| $p_1$ | min$^{-1}$ | glucose effectiveness ($S_G$) is glucose absorption without the aid of insulin in the body tissues |
| $p_2$ | min$^{-1}$ | a constant rate of decrease in the ability to absorb glucose or in other words the rate of insulin fraction that appears in the interstitial plasma |
| $p_3$ | min$^{-2}$ (μU/mL)$^{-1}$ | increased insulin-dependent ability to absorb insulin in tissues per unit of insulin concentration above basal insulin, in other words, the cleansing fraction of insulin from the interstitial compartment |
| $k_{abs}$ | min$^{-1}$ | glucose absorption constant |
| $G_{gut}$ | kg | glucose mass in the small intestine |
| $V$ | dL/kg | the volume of plasma glucose distribution per unit of body weight |
| $k$ | min$^{-1}$ | constant of rate |
| $\beta$ | | state parameter |
| $G_{gut}$ | kg | glucose mass in the small intestine |
| $k_{abs}$ | min$^{-1}$ | glucose absorption constant |
| $R_{ge}$ | mg/min | the rate of abdominal lymph removal expressed by glucose flux into the intestine from the distal abdomen |
| $D$ | gram | the amount of glucose ingested |
| $f(t)$ | | a function of time |
2.4. Experimental OGTT test data

The healthy and non-smokers with no family history of diabetes have participated in OGTT tests. The OGTT tests were criteria standard that is used by the American Diabetes Association Expert Committee. The participated volunteers in this OGTT test are required to abstain from alcohol, caffeine, and strong physical activity for 24 h and to fast for 8-10 h before glucose and insulin concentrations are taken. At time zero, the participated volunteers were asked to drink a solution containing 75 grams of anhydrous glucose diluted in 250 ml of water over 1-2 min. Then, the blood samples would be taken and measured the concentration of the glucose and insulin in plasma of the participated volunteer before the glucose starts to rise. Plasma samples for measurement of glucose and insulin concentrations were carried out at 0, 10, 20, 30, 60, 90, 120, 150, 180, 240 and 300 min relative to the time after ingesting glucose. In this study, experimental OGTT test data were taken from a Dissertation by Møller [12, 13] with 120 Japanese subjects registered at Tokyo University Hospital, Japan.

3. Results and Discussion

The simulation program was created using Matlab software. The Matlab programming language is needed to facilitate numerical calculations and also makes it easy to graph solutions of equations of the rate of change in glucose and insulin concentrations of this present model. A numerical solution is done because this present model is difficult to solve analytically. In this study, the mathematical model is many couples of ordinary differential equations, so the most accurate numerical method is Runge Kutta order 45th. The program is validated by comparing the results obtained from simulation with experimental data of the OGTT test to get a fit curve. Analysis of deterministic coefficient ($R^2$) is needed to determine the validation of the values between the simulation results and the experimental data which is formulated as:

$$R^2 = 1 - \frac{X^2}{SST}$$

where $X^2$ and $SST$ are as follows:

$$X^2 = \sum_{i=1}^{n} \left[ \frac{y_i - y(t_i, \theta_1, \ldots, \theta_M)}{\sigma} \right]^2$$

where $y_i$ is the result of experimental data with a standard deviation of $\sigma$, $y(t_i, \theta_1, \ldots, \theta_M)$ is the result of this model data, $N$ is the amount of data, and $\bar{y}$ is the average value of the sum of experimental data and this model data.

The simulation results of this model are shown in Figures 1, 2 and 3. Experimental data for Japanese subjects (shown in Figure 1) show that when glucose enters the body through oral administration, glucose concentration rises at the highest level, then slowly decreases towards normal conditions within 300 min as well as insulin concentration. Fitting results for normal Japanese subjects obtained the glucose concentration curve has an $R^2$ value of 0.96 while the insulin concentration curve has an $R^2$ of 0.94. These results can already be presented that this model can describe the performance of glucose and insulin in the blood properly. Figure 1 shows that when the glucose concentration starts to rise to the highest level, then the insulin concentration also rises from the normal level, then the two curves return slowly down to the 300th min. This can explain that the concentration of insulin production is good in the body so that it can compensate for the level of glucose concentration in the body in normal subjects.

In Figure 1, the simulation results from the OGTT test data illustrate that the $S_G$ value shows that the ability of glucose absorption without the help of insulin in the subject is fairly good, while the $S_I$ value obtained at insulin concentration proves that the ability of glucose uptake in blood plasma by insulin in body tissue is still very so the glucose level in the blood can return to normal. These $S_G$ and $S_I$ values indicate a great influence on the body of a normal subject. Based on the glucose absorption value
that glucose uptake in normal subjects increases in the range of 0-15 min, then the glucose uptake value decreases in the range of 15-120 min, then rises in the range of 120-200 min and returns down in the range of 200-280 min. This shows that the working of insulin in the body of normal subjects is very good.

Simulation results for Japanese pre-diabetic subjects (shown in Figure 2) show that when glucose enters the body through oral administration, glucose concentration rises to the highest level, then slowly decreases to normal conditions within 300 minutes as well as concentration insulin. Simulation results from OGTT test data show that the $S_G$ and $S_I$ values obtained are smaller than the $S_G$ and $S_I$ values in normal subjects. The curve shows that the decrease in blood glucose concentration in pre-diabetic subjects is slower. This is thought to be caused because the amount of insulin secretion by beta cells has decreased. The $S_I$ value obtained is also smaller so that the insulin concentration curve is seen shows that the ability of glucose absorption in blood plasma by insulin is not good because the insulin response to glucose is still slow, but can still reduce glucose levels back to normal. Fitting results obtained from this simulation for glucose concentration of $R^2$ are 0.95 and the insulin concentration of $R^2$ is 0.96, this shows the validation results of both simulations are good.

The $G_b$ and $I_b$ values from the simulation results shown in Figure 3, when matched with the previous literature show that the profile of the subject entered into a T2DM state due to basal glucose in high subjects and low enough basal insulin causing glucose levels in the blood to increase. Simulation results from the OGTT test data obtained a smaller value compared to the value of $S_G$ and $S_I$ in normal and pre-diabetic subjects. This shows that the ability of glucose absorption without the help of insulin in the subject is not good. $S_I$ values obtained are relatively small and basal insulin is low, subjects need additional insulin (external insulin) to reduce the concentration of glucose in the blood. Insulin concentration curves show that the ability of glucose uptake in blood plasma by insulin in the body's tissues is not good but can still restore glucose levels in the blood to normal conditions with the time required for longer than normal subjects and pre-diabetes. The fitting results obtained from this simulation for glucose concentration of $R^2$ were 0.96 and the insulin concentration of $R^2$ was 0.91, indicating the results of validation from both simulations were quite good.

| Normal subject | Pre-diabetic subject | T2DM subject |
|----------------|----------------------|--------------|
| $G_b$          | 90                   | 110          | 135          |
| $I_b$          | 11                   | 8            | 5            |
| $S_I$          | $6.5 \times 10^{-5}$ | $3.0 \times 10^{-5}$ | $9.4 \times 10^{-6}$ |
| $S_G$          | 0.0201               | 0.0140       | 0.0039       |
Figure 1. The simulation results of glucose and insulin concentrations in normal Japanese subjects with values of $R^2 = 0.96$ and $R^2 = 0.94$. 
Figure 2. The simulation results of glucose and insulin concentrations in pre-diabetic Japanese subjects with values of $R^2 = 0.95$ and $R^2 = 0.96$. 
Figure 3. The simulation results of glucose and insulin concentrations in T2DM Japanese subjects with values of $R^2 = 0.96$ and $R^2 = 0.91$. 
4. Conclusion
The dynamics system of glucose and insulin in the human body can be described using a modified OMM simulation. In this study, the OMM model was modified with the addition of a factor of glucose absorption, glucose uptake and insulin secretion in the small intestine to describe the concentration rate of glucose and insulin in the body close to reality. The value of glucose effectiveness and insulin sensitivity can be predicted as a determinant of subjects under normal circumstances, pre-diabetes, or have been exposed to T2DM. Further research related to the application of the glucose absorption equation in the modified OMM model is more multiplied by the source of the subject to see the accuracy of this modified model.

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