The Modified Oral Minimal Model to Know Incretin Hormone Effect in Type 2 Diabetes Mellitus

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Abstract: Simulation of glucose, insulin and incretin hormones concentrations in the blood is described using the modified oral minimal model that can be learned easily. In this study, the modified oral minimal model can also describe the kinetics of incretin hormone concentration to determine the level of insulin secretion in the body. Incretin hormone has been recognized as a major stimulus for insulin secretion after an oral glucose load. Based on the results of this study, subjects with type 2 diabetes have the smallest of incretin hormone concentration (115 ng/dL). The normal subjects have the highest of incretin hormone concentration (300 ng/dL). The simulations which have been done show that the deterministic coefficient (R^2) value of each simulation has reached above 90%, meaning that all the simulations results are good.

1 INTRODUCTION

When glucose is infused intravenously, insulin secretion is stimulated much less than it is when glucose is taken orally so as to result in similar glucose concentrations. The incretin hormones function has the key physiological impact on glucose homeostasis after oral glucose. The secretion of insulin after ingestion of glucose compared to the isoglycemic intravenous glucose challenges is called the incretin effect. This effect is estimated to be responsible for 50 to 70% of the insulin response to glucose. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are the two intestinal insulin-stimulating hormones caused mainly the incretin effect. Incretins are peptide hormones that originate in the gut and increase the effectiveness of insulin secretion after glucose ingestion in a glucose-dependent manner. GLP-1 and GIP are the two dominant incretin hormones. They play an essential role in maintaining normal glucose homeostasis and in particular postprandial glucose levels (Tura et al. 2014; Kaur & Gautam 2006; Vilsbøll & Holst 2004; Ahren 2011).

In subjects with type 2 diabetes mellitus (T2DM), the incretin effect is either greatly impaired or absent, and it is assumed that this could contribute to the inability of these subjects to adjust their insulin secretion to their needs. In studies of the mechanism of the impaired incretin effect in T2DM subjects, it has been found that the secretion of GIP is generally normal, whereas the secretion of GLP-1 is reduced, presumably as a consequence of the diabetic state. It might be of even greater importance that the effect of GLP-1 is preserved whereas the effect of GIP is severely impaired (Michaliszyn et al. 2014).

Two types of minimal model for the glucose and insulin dynamics and incretin effect have been developed according to the different routes of glucose administration: intravenous glucose tolerance test (IVGTT) and oral glucose tolerance test (OGTT). The IVGTT-based minimal model consists of glucose and insulin subsystems, where insulin in the plasma compartment passes the endothelium and enters a remote interstitial compartment to exert insulin action. However, the intravenous administration of glucose is far from the physiologic way of glucose intaking, which necessitates further improvement of the model by incorporating the physiology of oral glucose intake. The most common oral administration test, the standard method to determine glucose tolerance status, is the oral glucose tolerance test (OGTT). This test is vital for the characterization of the metabolic syndrome and natural progression from normal glucose tolerance (NGT) to prediabetes (impaired glucose tolerance (NGT)) to T2DM. The

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OGTT-based minimal model, is commonly called the oral minimal model, can be easily applied to examine the dynamic physiology of glucose homeostasis. The oral minimal model can also be readily adapted to various situations by modifying its structure (Lim et al. 2016; De Gaetano et al. 2013).

The OGTT test is characterized by uncertainty both in the amount of glucose absorbed and in its absorption rate, which results in the time course of exogenous glucose delivery to plasma. In the OGTT-based minimal model, the time course of the rate of appearance (R_a) of exogenous glucose in plasma cannot be specified a priori. Given the ingested dose, indeed, several factors contribute toward affecting the R_a: the rate of gastric emptying of ingested glucose, the extent of intestinal absorption during the intestinal transit, and the hepatic uptake of portal glucose. Because of these uncertainties, the R_a time course in the OGTT test has been represented by a piecewise linear function, with the time of breakpoints assigned and values that are estimated from the data. The rate of gastric emptying and the small intestine transit time appear to be the main factors in determining the glucose R_a profile (Salinari et al. 2011; Wilbaux et al. 2017).

Mathematical models of the glucose and insulin dynamics have been used to represent the relationship mainly between glucose and insulin. The glucose profiles during OGTTs are difficult to predict due to highly variable factors such as the rate of glucose absorption from the intestine and the temporal delay of insulin action. Furthermore, the incretin hormones have been recognized as a major insulin secretory stimulus after an oral glucose load. In the present model, the modified oral minimal model that includes the incretin effect has been developed to describe the glucose, insulin and incretin hormone dynamics during the OGTT [Kim et al. 2014; Brubaker et al. 2007; Seike et al. 2011).

This research introduced a modified oral minimal model based on the incretin mechanisms for investigating the incretin hormones. This study was performed in healthy and subjects with T2DM that the glucose excursion is very similar after ingestion of 75 g due to an increase in the incretin effect matching the increased glucose load.

2 MATERIALS AND METHODS

2.1 The Oral Minimal Model

The classic single-compartment IVGTT-based minimal model was first introduced by Bergmann and co-author. Minimal model is a one compartment model, which means that the body is described as a compartment with a basal concentration of glucose and insulin. This model contains two minimal models. The first model describes glucose kinetics, how blood glucose concentration reacts to blood insulin concentration and the second model describes the insulin kinetics, how blood insulin concentration reacts to blood glucose concentration. However, the IVGTT used to obtain parameters in this model is invasive and requires considerable cooperation on the part of the patient [Bergman et al. 1981; Bergman et al. 1979; Kartono 2013).

The OGTT is a much simpler procedure to perform, with both decreased invasiveness and reduced burden on the patient. The OGTT tests are thus routinely performed in clinical laboratories to diagnose prediabetes (IGT) to T2DM. The OGTT-based minimal model is commonly called oral glucose minimal model resembles the IVGTT-based minimal model but has a new element, the gastrointestinal tract, which has as input the oral dose.

The oral glucose minimal model has two ordinary differential equations that represent the changes in plasma glucose and insulin concentrations. Variables and Parameters Of Oral Minimal Model shows in Table 1. The general model equations are described as follows (Cobelli et al. 2014):

$$\frac{dG(t)}{dt} = -[p_1 + X(t)]G(t) + p_1 G_b + \frac{R_\alpha(t)}{V}, \quad G(t_0) = G_0, \tag{1}$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3[I(t) - I_b], \quad X(t_0) = 0, \tag{2}$$

$$R_\alpha(t) = \begin{cases} \alpha_{i-1} + \dfrac{\alpha_i - \alpha_{i-1}}{t_i - t_{i-1}}(t - t_{i-1}), \\ 0, \\ t_{i-1} \le t \le t_i, i = 1,...,8 \\ others \end{cases}. \tag{3}$$

Table 1: Variables and Parameters Of Oral Minimal Model.

Symbol	Unit	Notes
$G(t)$	mg/dL	glucose concentration when t after given input glucose by orally
$I(t)$	μU/mL	insulin concentration when t after input glucose is given orally
$X(t)$	min^{-1}	insulin action gives back glucose concentration to basal level when t after given input glucose orally
G_b	mg/dL	basal glucose concentration before given input glucose orally
I_b	μU/mL	basal insulin concentration before input glucose given orally
G_0	mg/dL	theoretic glucose concentration in plasma when t equals zero which is soon after input glucose is given orally
I_0	μU/mL	theoretic insulin concentration in plasma when t equals zero, more than I_b, is soon after input glucose is given orally.
p_1	min^{-1}	S_G is effectivity of glucose, which is glucose absorption without insulin in tissue.
p_2	min^{-1}	constant of increment of glucose absorption ability, in other words, the fraction of the velocity of insulin which shows in interstitial plasma
p_3	min^{-2} $(\mu U/mL)^{-1}$	improving the ability of glucose-dependent insulin absorption in tissue per unit insulin concentration above basal insulin, in other words, cleaning fraction insulin from interstitial compartment
$R_\alpha(t)$	mg. $kg^{-1}min^{-1}$	the rate of input endogen glucose to the systemic circulation
V	dL/kg	the volume of distribution of glucose
α_i	mg. $kg^{-1}min^{-1}$	the amplitude of glucose absorption
t_i	min	time of glucose absorption

The rate of plasma insulin secretion concentration (dI/dt) is represented by the pancreatic insulin secretion R_I can be described as the sum of two components: dynamic insulin secretion (R_{I1}) and static insulin secretion (R_{I2}). The insulin circulation rate of a single-compartment model with a rate parameter p_{I1} (min^{-1}) for insulin disappearance is defined by the following equation:

$$R_I = R_{I1} + R_{I2}, \tag{4}$$

$$\frac{dI(t)}{dt} = -p_{I1}(I(t) - I_b) + R_I, \tag{5}$$

The secretion of rapidly releasable insulin stored in β-cells in response to elevations in the glucose level is represented by the parameter R_{I1} (μU mL^{-1} min^{-1}) can be written as follow:

$$R_{I1} = \begin{cases} p_{I2}\dfrac{dG(t)}{dt} & \text{if, } \dfrac{dG(t)}{dt} > 0 \\ 0 & \dfrac{dG(t)}{dt} \le 0 \end{cases} \tag{6}$$

where the sensitivity of dynamic insulin secretion by the β-cells is described by the parameter p_{I2} (μU mL^{-1} mg^{-1} dL). The secretion of newly recruited insulin in response to an elevated glucose level is represented by the parameter R_{I2} can be written as follow:

$$R_{I2} = \begin{cases} -\dfrac{1}{p_{I3}}\left[R_{I2} - p_{I4}(G(t) - G_b)\right] & G(t) > G_b \\ -\dfrac{1}{p_{I3}}R_{I2} & G(t) \le G_b \end{cases} \text{ if} \tag{7}$$

The sensitivity of static insulin secretion by β-cells to an elevated glucose level with a time constant parameter p_{I3} (min) is described by the parameter p_{I4} (μU mL^{-1} mg^{-1} dL min^{-1}).

2.2 The Modified Oral Minimal Model

2.2.1 The Incretin Hormones Model

The GLP-1 hormone is produced by L cell which is available in ileum and colon, while GIP hormone is produced by K cell in duodenum tract and jejunum. Secretion of these hormones can increase quickly after subjects consume food which contains carbohydrate and lipid. Carbohydrate and lipid can stimulate the secretion of incretin hormones. The GLP-1 hormone can stimulate β-cells in the pancreas to produce insulin and directly inhibit glucagon secretion, so that blood glucose level decreased.

To design the incretin hormones model, it is needed to know how glucose enters the body. Glucose entry into the body during OGTT involves two main compartments. These compartments are the gastrointestinal (GI) tract and mesenteric circulation. In the GI tract, liquid glucose is very

rapidly emptied from the stomach into the duodenum. The equation to describe the rate of delivery of glucose to the duodenum the duodenum ($Duod_G$) with a 75 g load OGTT is described by:

$$Duod_G = \begin{cases} 0 & t < 5 \\ 5.1014 - 0.0307, & 5 \le t \le t_{\max 75g} \\ 0 & t > t_{\max 75g} \end{cases}. \quad (8)$$

where $t_{\max 100g}$ = 166.1 min, t is time since the start of the simulation, and $t_{\max}$ is the t-intercept of the straight lines. The OGTT simulations began after 5 min of basal metabolism; that $t_{\max}$ is used only to refer to the intercepts of these curves and nowhere else in the model; and that these straight lines are simple mathematical descriptions of experimentally measured glucose delivery rates (mmol min^{-1}). Duodenal delivery rates cannot be negative. Furthermore, when the units are converted from mmol back to grams:

$$\int_5^{166.1} Duod_G dt = 414.27 \text{ mmol} = 74.58 \text{ g}, \quad (9)$$

thus retrieving the ingested doses of glucose. $Duod_G$ is used subsequently to determine the rate of release of incretins

These equations determine the rate of secretion of incretin hormones and the rate of absorption of glucose into mesenteric circulation. There is an additional ordinary differential equation to describe more about incretin concentration which is written below:

$$\frac{dInc(t)}{dt} = \frac{Ra_{Inc}}{V} + k_5 Duod_G - k_6 Inc(t), \quad (10)$$

where $Ra_{Inc} = k_6 V Inc_b$ and basal plasma levels of incretins (Inc_b) were 200 ng/dL. The equations above describe the concentration of incretin hormones is based on GIP concentration during the OGTT. Ra_{Inc} is the basal rate of appearance of the incretin, Inc_b is the basal concentration determined by the average fasting total GIP of all subjects and k_6 is the degradation which gives effect to the rate of incretin hormones concentration. Parameter k_5 is the rate of appearance of incretin due to $Duod_G$

2.2.2 Modified Insulin Secretion Model

The equation of insulin concentration kinetics in this present model is from Brubaker and co-authors which has some absorption parameters (Brubaker et al. 2007). These absorption parameters give effect to insulin kinetics in the body. The equation from Brubaker and co-authors is modified by adding constant R_I from Seike et al. (2011). These are the modified equations which describe insulin secretion in pancreas and rate of insulin concentration:

$$\frac{dI(t)}{dt} = k_7 G(t) + k_8 Inc(t) - k_9 I(t) + \beta + R_I, \quad (11)$$

$$R_{I2} = \begin{cases} -\frac{1}{p_{I3}} Inc_b [R_{I2} - p_{I4}(G(t) - G_b)] & \text{if } G(t) > 0 \\ 0 & G(t) \le 0 \end{cases} \quad (12)$$

Parameter k_7 is the rate of appearance of insulin due to $G(t)$, k_8 is the rate of appearance of $I(t)$ due to $Inc(t)$, k_9 is the measure of degradation/clearance of I and β is effects of additional regulators of $I(t)$ on insulin appearance.

3 RESULTS AND DISCUSSION

The simulation of the modified oral minimal model is made using the Matlab language programming. It is needed to simplify the numerical calculation and simplify to make the graphic of the glucose, insulin, and incretin hormones concentration. Numerical analysis is also needed to be done because it is very difficult to solve these analytical equations. In this research, the mathematical model used is the ordinary differential equation (ODE). Since this research using ODE, the most accurate numerical method is Runge-Kutta 45 or ode45. Analysis deterministic coefficient (R^2) is needed to figure out the validation value between data from the model to data from the experiment which is formulated by:

$$R^2 = \sum_{i=1}^{N} \left[\frac{y_i - y(t_i)}{\sigma} \right], \quad (13)$$

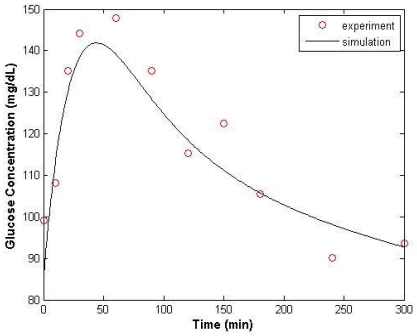
$$SST = \sum_{i=1}^{N} \left[\frac{y_i - \bar{y}}{\sigma} \right], \quad (14)$$

$$R^2 = 1 - \frac{X^2}{SST}, \quad (15)$$

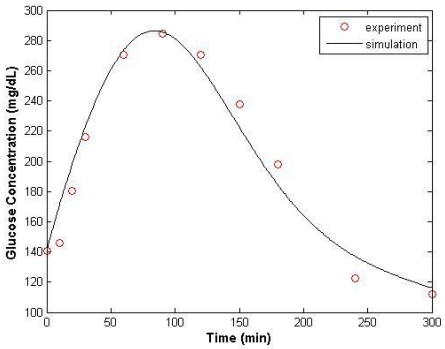
where y_i is experiment data which contains deviation standard σ, $y(t_i)$ is modeling data, N is the data and $\bar{y}$ is the average value of the sum from experimental data and model data.

These data were taken from 120 Japanese subjects who were listed at Tokyo University Hospital, Japan.

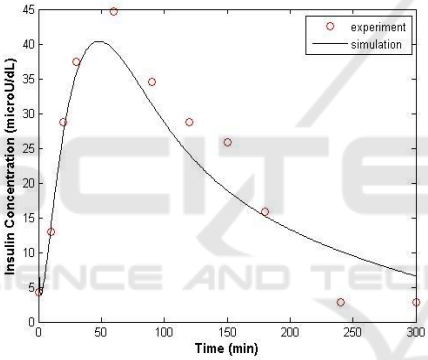
The potential subjects (male and female) were at age 40 to 65 years. All subjects were given 75 g sampled OGTT. After all, subjects fasted for approximately 10 hours, their venous sample blood was taken at 0 min. These samples were taken to measure glucose, insulin, and incretin hormones concentration during 10, 20, 30, 60, 90, 120, 150, 180, 240 and 300 min (Møller 2012).



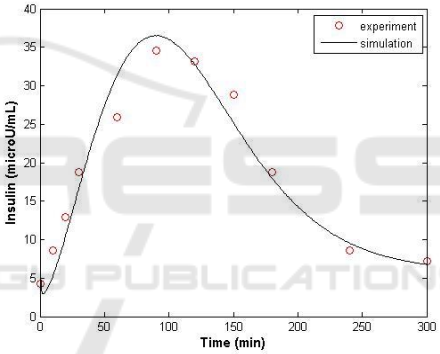
Normal Japanese subjects.



T2DM Japanese subjects.



Normal Japanese subjects.



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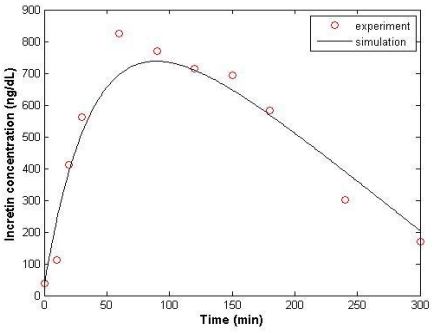

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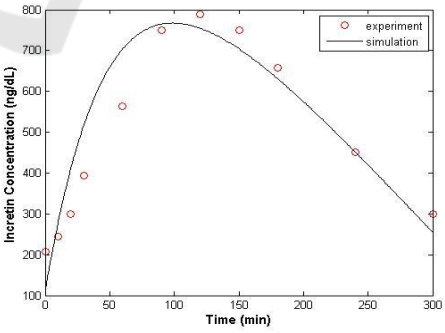

T2DM Japanese subjects.

Figure 1: Simulation results of the glucose, insulin and incretin hormone concentration of the normal and T2DM Japanese subjects and the deterministic coefficient (R^2) is = 91%.

The simulation results of the modified oral minimal model for glucose, insulin and incretin hormones concentration of normal Japanese subject data show good results. This can be proved by the deterministic coefficient R^2 from the simulation. The results of fitting data which is represented by R^2 value are more than 90%. The parameter G_b value is 85 mg/dl. This value shows that right value for the normal subject because according to statistics data, the G_b value for the normal subject is 80-100 mg/dL. In the rate of glucose concentration, as seen in Figure 1, the glucose level slowly increased, then it decreased after 60 min. In the normal subject, the ability of insulin to accelerate the losing glucose from plasma is good. As seen in Fig. 1, the rate of insulin concentration increased until 60 min, after an oral glucose load. This research also determined the parameter basal incretin hormones Inc_b. The parameter Inc_b value is 300 ng/dL, according to statistical data for the normal subject, the Inc_b value is more than 200 ng/dl. This parameter value can be concluded as the normal subject because it is more than 200 ng/dL.

The simulation results of the modified oral minimal model for glucose, insulin and incretin hormones concentration of T2DM Japanese subjects' data show also good results. The deterministic coefficient results of fitting data which is represented by R^2 value is more than 90%. The parameter G_b value is 140 mg/dL. This value shows that right value for the T2DM subject because, according to statistics data, the G_b value of the T2DM subject is 130-150 mg/dL. In this simulation, the G_b value is even higher than the previous simulation results of the normal subject. This results can show that the absorption of glucose in the body for normal subjects is the highest than the T2DM subjects.

The parameter Inc_b value of T2DM subjects is 115 ng/dL, according to statistical data for the T2DM subject, the Inc_b value is less than 200 ng/dL. So, this parameter value can be determined as T2DM subjects. This parameter Inc_b can show that the incretin hormones response is even slower than the normal subject. The summary of values and units for constants used in the present model shows in Table 2. As seen from Figure 1, the rate of incretin concentration slowly increased from 0-120 min, after input glucose orally, that it increased by 150 min and kept decreasing until 300 min.

Table 2: Values and units for constants used in the present model.

Constant	Value	Units
G_b	85-140	mg/dL
I_b	10-11	µU/dL
Inc_b	115-300	ng/dL
p_1	0.01-0.05	min^{-1}
p_2	0.002-0.005	min^{-1}
p_3	0.0015-0.0025	min^{-1}
k_5	2.5-3.0	$ng\ dL^{-1}\ mmol^{-1}$
k_6	0.018-0.024	min^{-1}
k_7	0.009-0.03	$mU\ min^{-1}\ mmol^{-1.3}\ dL^{-0.3}$
k_8	0.003-0.004	$mU\ min^{-1}\ ng^{-1}$
k_9	1.3-1.6	min^{-1}

4 CONCLUSIONS

Kinematics of glucose, insulin and incretin hormones concentration in the blood can be described using a mathematical model. In this study, the present model used is the modified oral minimal model. Oral minimal model is modified to be able to describe the rate of incretin hormones concentration so that the level of secretion of insulin in the body can be seen. Incretin hormones serve as a primary stimulus of insulin secretion if there are incoming glucose orally. The OGTT test data can show two parameter values of the Incb and Gb from fit between the present model and the OGTT experimental results. Subjects with T2DM have the highest basal glucose value parameter (G_b), while normal subjects have G_b values lower than the T2DM subject. Based on this study, subjects with T2DM have an incretin hormone basal (Inc_b) parameter is the smallest (Inc_b = 115 ng/dL). Normal subjects have Inc_b value exceeding 200 ng/dL.

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