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Study of Modified Oral Minimal Model using *n*-Order Decay Rate of Plasma Insulin for the Oral Glucose Tolerance Test in Subjects with Normal, Impaired and Diabetic Glucose Tolerance

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Abstract: In this present study, the modified Oral Minimal Model (OMM), with secretion of insulin from pancreas was assumed that the insulin decay rate was not always a first-orderly process in the Oral Glucose Tolerance Test (OGTT), had been developed to study Normal Glucose Tolerance (NGT), Impaired Glucose Tolerance (IGT or pre-diabetes) and type 2 Diabetes Mellitus (T2DM) subjects. The modified OMM model was used to assess physiological functions which were insulin sensitivity (S_I) and glucose effectiveness (S_G) from the OGTT data. The results of the modified OMM model fit to the measured glucose and insulin concentration-time profiles in the OGTT process of the subjects. The single-step fitting process to optimize the real pAarameters of the S_I and S_G index from the experimental data using the modified OMM. Our results showed that all NGT subjects had higher the S_I and S_G index than all IGT and T2DM subjects following the OGTT process. Basal and large peak glucose were lower in all NGT subjects than in all IGT and T2DM subjects. Insulin extraction was lower in all subjects with T2DM but was almost similar for the NGT and IGT subjects. The averaged correlation between measured and this present model, commonly called R^2 value, showed that these four cases were 0.96 which indicated good agreement.

Keywords: Glucose Effectiveness, Insulin Sensitivity, Mathematical Model, Oral Glucose Tolerance Test, Type 2 Diabetes Mellitus

Introduction

Many mathematical models had been proposed for the assessment of the S_I and S_G index by analyzing glucose tolerance test. The most familiar of these models was the classical minimal model proposed by Bergman *et al*. (1979), which analyses an Intravenous Glucose Tolerance Test (IVGTT) to optimize the S_I and S_G index. The classical minimal model described insulin release in response to glucose was injected through intravenous and glucose clearance in response to plasma insulin concentrations, assuming all other effects are unchanged or negligible. The model composed two coupled ordinary differential equations: One modeling the rate of glucose clearance based on the action of the remote insulin and the other giving the rate of a secretion of the remote insulin compartment. These mechanisms could help ameliorate the effects of noise in the glucose or insulin measures during the IVGTT on the calculated S_I and S_G index. However, the IVGTT process was described by the classical minimal model of these methods do not describe a physiological function experimentally since the rate of glucose and insulin perturbations of an IVGTT was not reflect the condition of daily living. Therefore, the IVGTT process was not highly recommended to have a method able to quantify the S_I and S_G index in a normal life (Dalla Man *et al*., 2004; Claudio *et al*., 2014).

An estimation of the S_I index from orally received glucose during an OGTT in normal subjects was introduced by Caumo *et al*. (2000). The classic minimal model of glucose kinetics was coupled with an equation describing the rate of absorption of glucose into the

circulation after oral glucose received. The model's Caumo provided an estimate of the *SI* index in a given normal subjects.

Toffolo and co-workers introduced the basic concept into more general practice in the mathematical models of an OGTT process. The mathematical models were used to analyze 11 blood samples obtained during a 5-h OGTT had been proposed and validated by comparison with direct measurement methods. They also proposed the second-phase (or static) insulin secretion index had been validated using a glucose clamp method (Toffolo *et al*., 2006a; 2006b).

Study of the extensions involving exogenous glucose ingestion incorporated the minimal model representation of insulin effects on glucose clearance, but add additional modeling to extract data on glucose rate of appearance of the plasma glucose profile. The estimation of the S_I and S_G index of glucose ingestion had been an interesting research in present years with a number of different models developed for the study of this situation. Mari *et al*. (2002) proposed a comparison of several OGTT-based methods, including one in which the glucose clearance was not described by the minimal model (Kim *et al*., 2014; Morton *et al*., 2017). Dalla Man *et al*. (2002) proposed a glucose tracer method to validate the S_I and S_G index from the OGTT methods.

Mathematical modeling techniques which used data from a more in accordance and also and also keep accuracy assessment with the OGTT procedures would have a greater chance of applying in a clinical test. Results of data test from 2-h OGTTs would be beneficial because the 2-h glucose level during an OGTT data had been used in mathematical modeling and as one of the clinical tests for diabetes by the World Health Organization (WHO) (Alberti and Zimmet, 1998).

In this study, we used the OGTT data from the NGT, IGT and T2DM to develop a modified OMM for the optimization and assessment of the S_I and S_G index. We developed a modified OMM was used to assess the results of the NGT, IGT and T2DM subjects capable of describing the physiological function which occurs during a standard OGTT. The purpose of this study was to provide an accurate method for assessing the S_I and S_G index in the NGT, IGT and T2DM from clinically available OGTT data. The scope of this present model was different from that of our previous models, which were mostly developed for describing a variety of intravenous glucose perturbations, like a various infusion of glucose and insulin or IVGTT process (Zheng and Zhao, 2005; Kartono, 2013; Kartono *et al*., 2017).

Materials

Four cases, including NGT, IGT and T2DM subjects during the OGTT process, were studied. The experimental data on the glucose and insulin concentration in these four cases were obtained from the published literature:

Study of Case 1

We used the experimental data from Dalla Man *et al*. (2004). In the standard OGTT, the database selected consisted 46 males and 42 females normal subjects. At time 0, subjects received a triple-tracer mixed meal containing 1±0.02 g kg^{-1} glucose. The meal was eaten within 10 min, so then glucose and insulin plasma samples were collected at times (t): 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, 240, 260, 280, 300, 360 and 420 min.

Study of Case 2

The OGTT data were taken from Campioni *et al*. (2007). In their study, experimental data were performed on 10 healthy subjects: 5 men and 5 women. All subjects were non-obese and had body weights that ranged from 68 to 99 kg for men and from 49 to 61 kg for women at the General Clinical Research Centre of the Mayo Foundation. In the first OGTT procedure, the subjects ingested 1 g of glucose/kg body at time 0 min, furthermore the blood for measurement of plasma glucose and insulin concentrations was obtained at times (t): 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 180, 210 and 240 min.

Study of Case 3 *and* 4

The OGTT data of Case 3 and 4 included 120 Japanese subjects enrolled at Tokyo University Hospital in Japan and 150 Caucasians subjects enrolled at Rigshospitalet, Copenhagen, Denmark was taken from Møller *et al*. (2014). The 270 subjects represented according to glucose tolerance state (NGT, IGT, or T2DM, as defined by WHO criteria). Firstly, all subjects received an oral bolus corresponding to 75 g of glucose and afterward, plasma glucose and insulin samples were collected at times (t): 0, 10, 20, 30, 60, 90, 120, 150, 180, 240 and 300 min for determination of glucose and insulin plasma.

Methods

Modified Oral Minimal Model

The OGTT test was recommended by the WHO for the diagnosis of diabetes in the presence of elevated fasting plasma glucose. The OGTT process consisted of an oral ingestion of 75 g glucose dissolved in water and a single measure of plasma glucose and insulin concentration after 2-5 h. For this reason, an orally administered glucose function, $R_\alpha(t)$, was incorporated into the classical minimal model. A mathematical function of $R_\alpha(t)$ represented the variable rate of glucose absorption. The rate of change in glucose absorption was

the piecewise-linear function with known breakpoint time t_i and amplitude α_i:

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

A present model had been recently developed to estimate the S_I and S_G index together with the glucose rate of appearance during an OGTT test. In the present model, the glucose compartment of classical minimal model coupled with the variable rate of glucose absorption. The present study was that the modified OMM model provided values of parameter *n* was the order decay rate of the remote insulin compartment function:

$$\frac{dG(t)}{dt}=-\left[p_1+X(t)\right]G(t)+p_1G_b+\frac{R_\alpha(t)}{V}\;G_0=G_b \tag{2}$$

$$dX(t)=-p_2X(t)+p_3\left[I(t)-I_b\right]^n\;X_0=0 \tag{3}$$

Time-dependent variables in modified OMM were defined by $G(t)$ was the plasma glucose concentration (mg dl^{-1}), $I(t)$ was the plasma insulin concentration (μU ml^{-1}), $X(t)$ was a variable in a remote insulin compartment where insulin was active in accelerating glucose disappearance (min^{-1}) and $R_\alpha(t)$ was the variable rate of glucose absorption after an oral glucose ingestion (mg dl^{-1} min^{-1}). A zero subscript in variables represented a value at a time 0 after the oral glucose ingestion ($G_0 = G(0)$ and $X_0 = 0$ and $I_0 = I(0)$).

Parameters in modified OMM were defined by $p_1 = S_G$ was glucose effectiveness: A measure of the fractional ability of glucose to lower its own concentration in plasma independent of increased insulin (min^{-1}), p_2 was the rate constant describing the dynamics of insulin action (min^{-1}) and p_3 was the parameter governing the magnitude of insulin action (ml μU^{-1} min^{-1}) and V was distribution volume (dl kg^{-1}). The $S_I = p_3/p_2$ was insulin sensitivity, as the ability of insulin to enhance glucose utilization and inhibit glucose production. It was an important parameter to assess the efficiency of the glucose regulatory system.

The rate of change in the plasma insulin compartment was represented by the sum of pancreatic insulin secretion (R_I) and the insulin circulation rate was calculated from an insulin compartment model with a rate parameter p_{I1} (min^{-1}) for the *n*-order decay rate of the insulin disappearance:

$$\frac{dI(t)}{dt}=-p_{I1}\left[I(t)-I_b\right]^n+R_I\;I_0=I_b \tag{4}$$

The variable rate of pancreatic insulin secretion (R_I) was described as the sum of dynamic insulin secretion (R_{I1}) and static insulin secretion (R_{I2}):

$$R_I=R_{I1}+R_{I2} \tag{5}$$

The rate of change of dynamic insulin secretion (R_{I1}) represented the secretion of rapidly replaceable insulin stored in beta-cells in response to elevations in the glucose level (μU ml^{-1} min^{-1}), according to the following equation:

$$R_{I1}=\begin{cases}p_{I2}\dfrac{dG}{dt} & if\quad \dfrac{dG}{dt}>0\\ 0 & if\quad \dfrac{dG}{dt}<0\end{cases} \tag{6}$$

where, the parameter p_{I2} described the sensitivity of dynamic insulin secretion by the beta-cells (μU ml^{-1} dl mg^{-1}). The rate of change of the secretion of newly recruited insulin in response to an elevated glucose level (μU ml^{-1} min^{-1}) was represented by R_{I2}, according to the following equation (with $R_{Ib} = 0$):

$$\frac{dR_{I2}}{dt}=\begin{cases}-\dfrac{1}{p_{I3}}\left\{R_{I2}-p_{I4}(G-G_b)\right\} & if\quad G-G_b>0\\ -\dfrac{1}{p_{I3}}R_{I2} & if\quad G-G_b\le 0\end{cases} \tag{7}$$

The sensitivity of static insulin secretion by beta-cells to an elevated glucose level was described by the parameter p_{I4} (μU ml^{-1} mg^{-1} dl min^{-1}) with a time constant parameter p_{I3} (min). R_I was always positive value and when $R_{I1} + R_{I2} < 0$ and $R_I = 0$ (Toffolo *et al*., 2001; Seike *et al*., 2011).

Particle Swarm Optimization Parameter Estimation Techniques

In 1995, Kennedy and Eberhart introduced Particle Swarm Optimization (PSO) algorithm. The PSO was a method of optimization solutions that was adapted from the behavior of animals such as birds flock movements were then each object animal considers to be a particle. A particle in dimensional space had a position that was encoded as vector coordinates. A particle had a constant speed and a position of a particle visualized trail would form a straight line. This position vector was considered as a condition of the particle in the search space. Each position in the search space was an alternative solution that could be evaluated using the objective function. Each particle moved with a certain speed and each particle was assumed to know the best position of any other

particles. External factors in question included the best position ever skipped a particle and the best position of the entire particles (Kennedy and Eberhart, 1995; Eberhart and Kennedy, 1995).

In this research, to optimize the parameters of p_1, p_2, p_3, p_{I1}, p_{I2}, p_{I3} and p_{I4} in the modified OMM were used the PSO algorithm. Then each parameter considered to be a particle. With the external factors of an experimental data of OGTT test that alter the line would then move the parameters in the search space, it was expected that the parameters could lead, approached and ultimately achieve an optimal point. The coefficient of determination, R^2, was calculated from parameter estimates. The residuals between the best-fit curve and the experimental data, $y_i - \hat{y}_i$, were used:

$$R^2 = 1 - \frac{\sum_{i=1}^{n}\left(y_i - \hat{y}_i\right)^2}{\sum_{i=1}^{n}\left(y_i - \bar{y}_i\right)^2} \quad (8)$$

where, y was experimental data, $\hat{y}$ was the prediction of the non-linear least-squares fit and $\bar{y}$ was the averaged experimental data.

Results and Discussion

The optimized parameters obtained by fitting the modified OMM to the experimental data of the four cases were listed in Fig. 1-8 and Table 1-3. The values of R^2 between measured and calculated plasma concentrations were also shown in the figures and tables. The averaged R^2 value, including glucose and insulin concentrations for these four cases, was 0.96; this means that the single-step fitting was a good agreement. This could be explained by the increased flexibility of the modified OMM, because of the introduction that the insulin decay rate was not always a first-order process, which exactly reflected the actual OGTT situations mathematically in the present model.

The optimized parameters α_i and t_i of R_α (t) provided by the modified OMM was estimated with good precision of the S_I and S_G index: α_1 = 5.36±0.33 mg kg^{-1} min^{-1} (t_1 = 5 min), α_2 = 7.78±0.24 mg kg^{-1} min^{-1} (t_2 = 10 min), α_3 = 6.00±0.28 mg kg^{-1} min^{-1} (t_3 = 30 min), α_4 = 5.05±0.22 mg kg^{-1} min^{-1} (t_4 = 60 min), α_5 = 4.77±0.28 mg kg^{-1} min^{-1} (t_5 = 120 min), α_6 = 3.52±0.19 mg kg^{-1} min^{-1} (t_6 =150 min), α_7 = 2.09±0.09 mg kg^{-1} min^{-1} (t_7 = 180 min) and α_8 = 0.34 ± 0.03 mg kg^{-1} min^{-1} (t_8 = 300 min) (Dalla Man *et al*., 2004).

Table 1. Optimized parameters for measuring glucose and insulin concentrations using the modified OMM for the healthy or NGT subjects

Parameters	Case 1	Case 2	Case 3	Case 4
G_b (mg dl^{-1})	85	90	94	90
I_b (μU ml^{-1})	5	10	5	5
S_I ((μU/ml)$^{-1}$ min^{-1})	11.68×10^{-4}	11.68×10^{-4}	11.65×10^{-4}	26.50×10^{-4}
S_G (min^{-1})	0.055	0.035	0.055	0.050
n	1.18	0.92	0.99	1.08
R^2 for glucose	0.94	0.96	0.98	0.95
R^2 for insulin	0.95	0.97	0.98	0.97

Table 2. Optimized parameters for measuring glucose and insulin concentrations using the modified OMM for Japanese subjects

Parameters	NGT	IGT	T2DM
G_b (mg dl^{-1})	94	105	140
I_b (μU ml^{-1})	5	9	5
S_I ((μU/ml)$^{-1}$ min^{-1})	11.65×10^{-4}	9.60×10^{-4}	4.50×10^{-4}
S_G (min^{-1})	0.055	0.051	0.011
n	0.99	0.94	0.99
R^2 for glucose	0.98	0.97	0.96
R^2 for insulin	0.98	0.96	0.97

Table 3. Optimized parameters for measuring glucose and insulin concentrations using the modified OMM for Caucasians subjects

Parameters	NGT	IGT	T2DM
G_b (mg dl^{-1})	90	105	143
I_b (μU ml^{-1})	5	7	10
S_I ((μU/ml)$^{-1}$ min^{-1})	26.50×10^{-4}	6.50×10^{-4}	5.15×10^{-4}
S_G (min^{-1})	0.050	0.045	0.012
n	1.08	1.07	0.95
R^2 for glucose	0.95	0.97	0.96
R^2 for insulin	0.97	0.98	0.97

In Case 1 regarding a healthy (NGT) subject, the experimental result and simulation of plasma glucose and insulin concentration curve were shown in Fig. 1. In this OGTT process, the plasma glucose concentration achieved the highest concentration in 40 min afterward glucose concentration declined immediately to the basal line in 120 min. The corresponding plasma insulin concentration stimulated by the ingested glucose raised to form the highest glucose, then an approximately exponential declined afterward and finally a secondary peak appears. The R^2 value between experimental and calculated plasma glucose concentrations was 0.94 and the R^2 value of plasma insulin profiles was 0.95.

The simulation results of Case 2 were shown in Fig. 2. In the modified OMM with a received of oral glucose bolus at 0 min, the blood glucose concentration of the healthy human slowly returned to the basal lines in 240 min regardless of the ingestion. There was a large peak after 20 min, both the experimental and calculated glucose concentrations shown a higher response to the insulin, the peak caused by stimulation by a glucose ingestion. This was due to significantly higher dynamic rate of insulin from 10 to 50 min and significantly lower dynamic rate from 60 to 120 min. The values of $R^2 = 0.96$ for glucose and $R^2 = 0.97$ for insulin between experimental and calculated plasma concentrations indicated that the simulation using the proposed model was a good agreement.

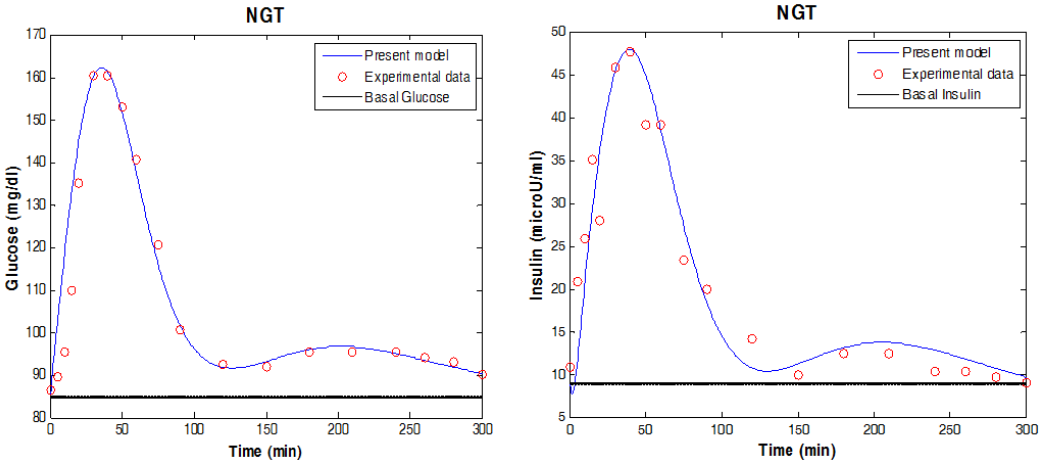

Fig. 1. Measured and calculated plasma glucose concentrations of plasma glucose and insulin level in Case 1, with parameters: G_b = 85 [mg dl^{-1}], I_b = 5 [μU ml^{-1}], $p_1 = S_G$ = 0.055 [min^{-1}], p_2 = 0.009 [min^{-1}], S_I = 11.68×10^{-4} [(μU/ml)$^{-1}$ min^{-1}], p_{I1} = 0.5 [min^{-1}], p_{I2} = 0.2 [μU ml^{-1} dl mg^{-1}], p_{I3} = 2.5 [min], p_{I4} = 0.55 [μU ml^{-1} mg^{-1} dl min^{-1}], V = 1.56 [dl/kg], n = 1.18, R^2 for glucose = 0.94 and R^2 for insulin = 0.95

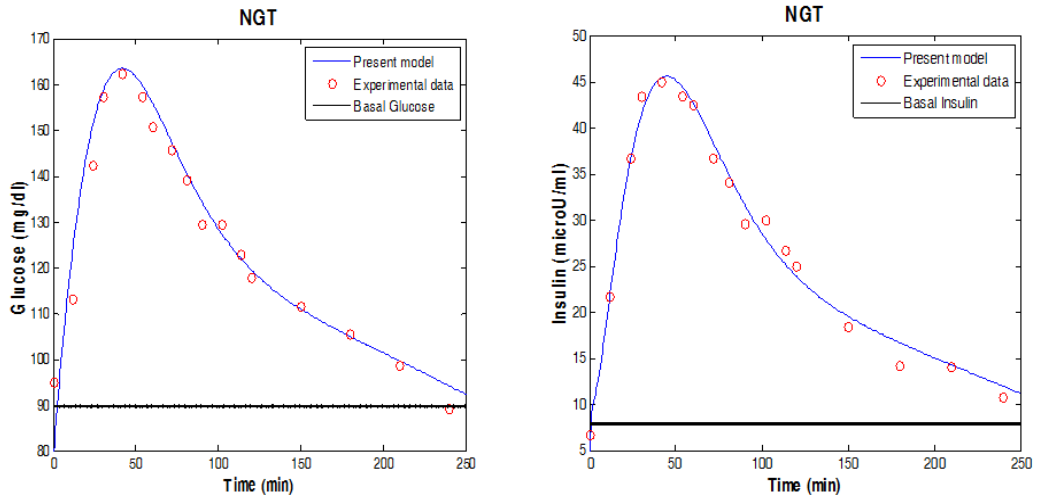

Fig. 2. Measured and calculated plasma glucose concentrations of plasma glucose and insulin level in Case 2, with parameters: G_b = 90 [mg dl^{-1}], I_b = 10 [μU ml^{-1}], $p_1 = S_G$ = 0.035 [min^{-1}], p_2 = 0.012 [min^{-1}], S_I = 11.68×10^{-4} [(μU/ml)$^{-1}$ min^{-1}], p_{I1} = 1.65 [min^{-1}], p_{I2} = 0.002 [μU ml^{-1} dl mg^{-1}], p_{I3} = 4.0 [min], p_{I4} = 0.6 [μU ml^{-1} mg^{-1} dl min^{-1}], V = 1.56 [dl/kg], n = 0.92, R^2 for glucose = 0.96 and R^2 for insulin = 0.97

The Case 3 was about Japanese subjects. The modified OMM was the same as in Case 1 and 2. As shown in Fig. 3-5, the blood glucose took more than 250 min to return to the basal line in spite of an oral glucose ingestion at 0 min. In Fig. 4 and 5, there was a great insulin peak from 80 to 100 min for IGT and T2DM subjects. In NGT subjects, there was a large peak after 20 min, because of a much higher insulin caused by stimulation by a glucose ingestion. As expected, stimulated insulin concentrations, which form the first insulin peak of T2DM subjects were lower than in NGT and IGT subjects shown in Fig. 3-5. In Table 2, a lower the S_I index in IGT subjects compared to NGT subjects was observed in the Japanese subjects. A decrease of the S_I and S_G index from NGT to IGT and T2DM subjects also had been reported for Japanese. The present model described well the actual OGTT operation and reached the averaged R^2 values of 0.96 for plasma glucose and 0.97 for insulin.

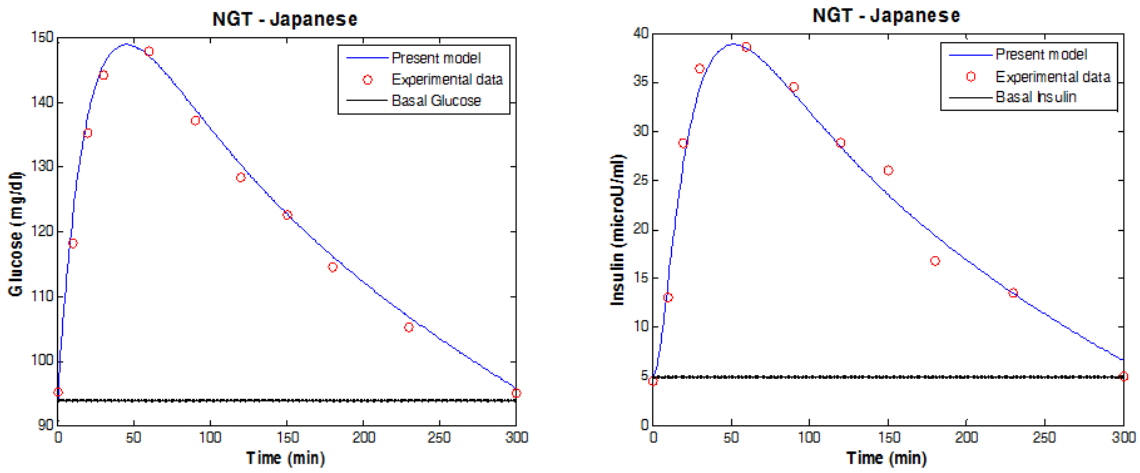

Fig. 3. Measured and calculated plasma glucose concentrations of plasma glucose and insulin level in Case 3 (NGT-Japanese), with parameters: G_b = 94 [mg dl^{-1}], I_b = 5 [μU ml^{-1}], p_1= S_G = 0.055 [min^{-1}], p_2 = 0.002 [min^{-1}], S_I = 11.65×10^{-4} [(μU/ml)$^{-1}$ min^{-1}], p_{I1} = 1.5 [min^{-1}], p_{I2} = 0.002 [μU ml^{-1} dl mg^{-1}], p_{I3} = 5.0 [min], p_{I4} = 0.9 [μU ml^{-1} mg^{-1} dl min^{-1}], V = 1.56 [dl/kg], n = 0.99, R^2 for glucose = 0.98 and R^2 for insulin = 0.98

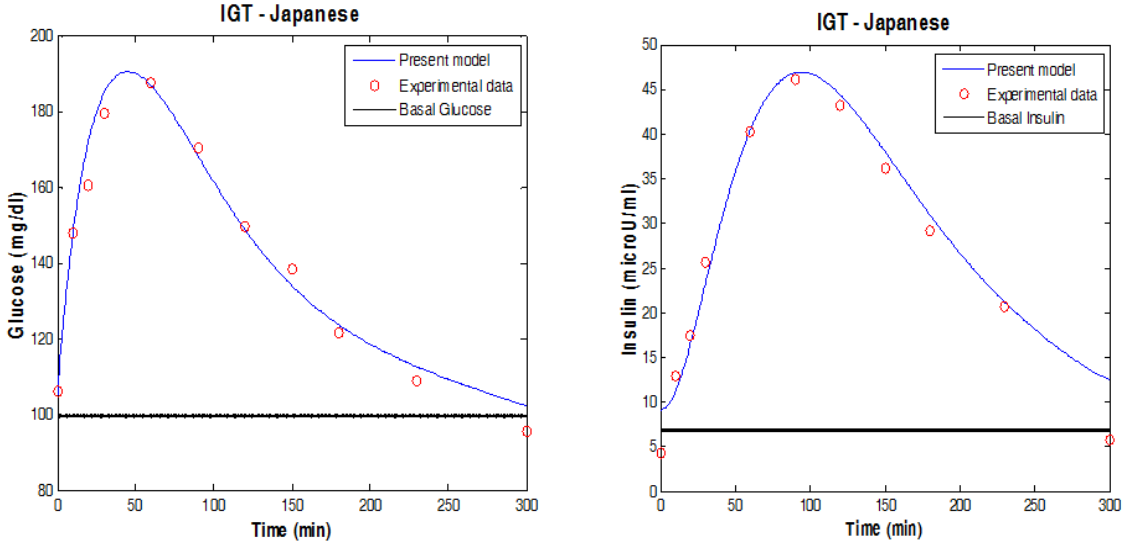

Fig. 4. Measured and calculated plasma glucose concentrations of plasma glucose and insulin level in Case 3 (IGT-Japanese), with parameters: G_b = 105 [mg dl^{-1}], I_b = 9 [μU ml^{-1}], p_1= S_G = 0.051 [min^{-1}], p_2 = 0.008 [min^{-1}], S_I = 9.60×10^{-4} [(μU/ml)$^{-1}$ min^{-1}], p_{I1} = 2.0 [min^{-1}], p_{I2} = 0.075 [μU ml^{-1} dl mg^{-1}], p_{I3} = 50.0 [min], p_{I4} = 1.0 [μU ml^{-1} mg^{-1} dl min^{-1}], V = 1.56 [dl/kg], n = 0.94, R^2 for glucose = 0.97 and R^2 for insulin = 0.96

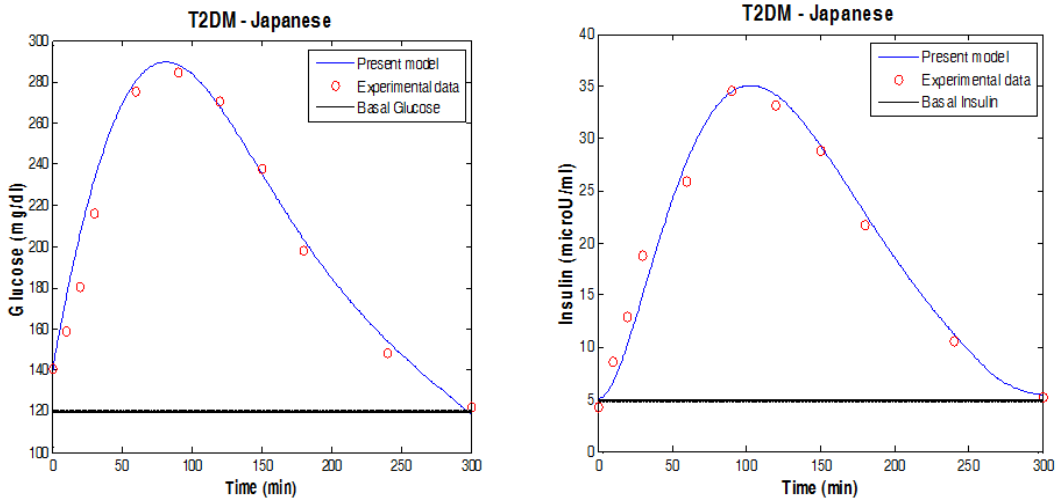

Fig. 5. Measured and calculated plasma glucose concentrations of plasma glucose and insulin level in Case 3 (T2DM-Japanese), with parameters: G_b = 140 [mg dl^{-1}], I_b = 5 [μU ml^{-1}], p_1= S_G = 0.011 [min^{-1}], p_2 = 0.009 [min^{-1}], S_I= 4.50×10^{-4} [(μU/ml)$^{-1}$ min^{-1}], p_{I1} = 4.25 [min^{-1}], p_{I2} = 0.1 [μU ml^{-1} dl mg^{-1}], p_{I3} = 20.0 [min], p_{I4} = 0.9 [μU ml^{-1} mg^{-1} dl min^{-1}], V = 1.56 [dl/kg], n = 0.99, R^2 for glucose = 0.96 and R^2 for insulin = 0.97

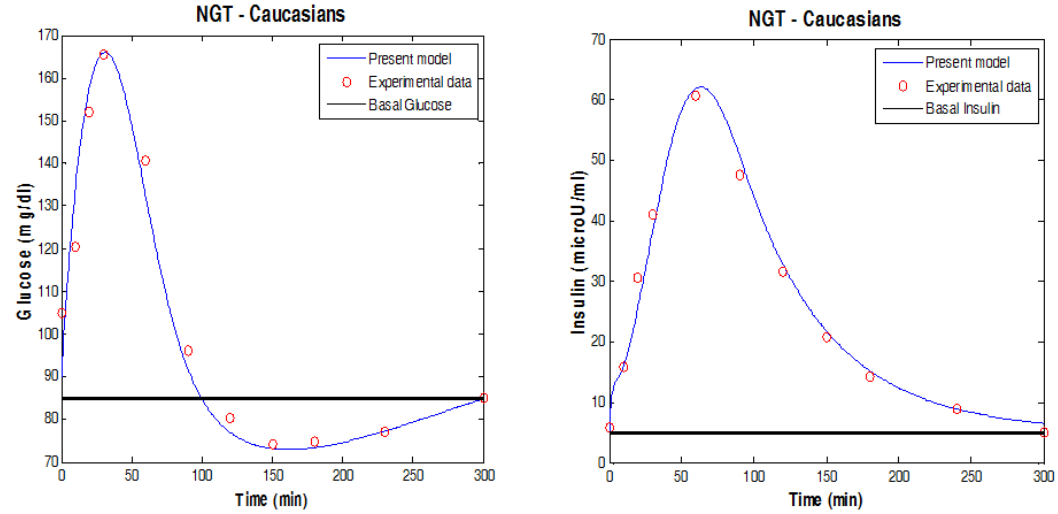

Fig. 6. Measured and calculated plasma glucose concentrations of plasma glucose and insulin level in Case 3 (NGT-Caucasians), with parameters: G_b = 90 [mg dl^{-1}], I_b = 5 [μU ml^{-1}], p_1 = S_G = 0.050 [min^{-1}], p_2 = 0.006 [min^{-1}], S_I= 26.50×10^{-4} [(μU/ml)$^{-1}$ min^{-1}], p_{I1} = 0.45 [min^{-1}], p_{I2} = 0.9 [μU ml^{-1} dl mg^{-1}], p_{I3} = 55.0 [min], p_{I4} = 0.9 [μU ml^{-1} mg^{-1} dl min^{-1}], V = 1.56 [dl/kg], n = 1.08, R^2 for glucose = 0.95 and $R^2$for insulin = 0.97

In Case 4 regarding Caucasians subjects, the present model simulated the rate of pancreatic release of insulin by the introduction of exogenous orally administered glucose using gradually reduced ingestion on rates during the OGTT. Although the exogenous oral glucose bolus was received at 0 min, the time during the OGTT, the plasma glucose levels took more than 2 h to return to baseline as shown in Fig. 7 and 8 for IGT and T2DM subjects. In this complicated oral glucose bolus ingestion process during the OGTT, the measured glucose time courses in were good agreement with the calculated curve, showing an averaged R^2 value of 0.96 as listed in Table 3. The R^2 value between experimental and calculated plasma insulin time courses were 0.96 (Table 3). A lower the S_I and S_G index in IGT compared to NGT subjects was observed in both Japanese and Caucasians, although the decrease in the S_I and S_G index was more pronounced in Caucasians, resulting in higher the S_I and S_G index in Japanese than in the Caucasians at the IGT subjects. A decrease in insulin sensitivity from NGT to IGT and to T2DM had been reported both for Caucasians and Japanese (Møller *et al*., 2014).

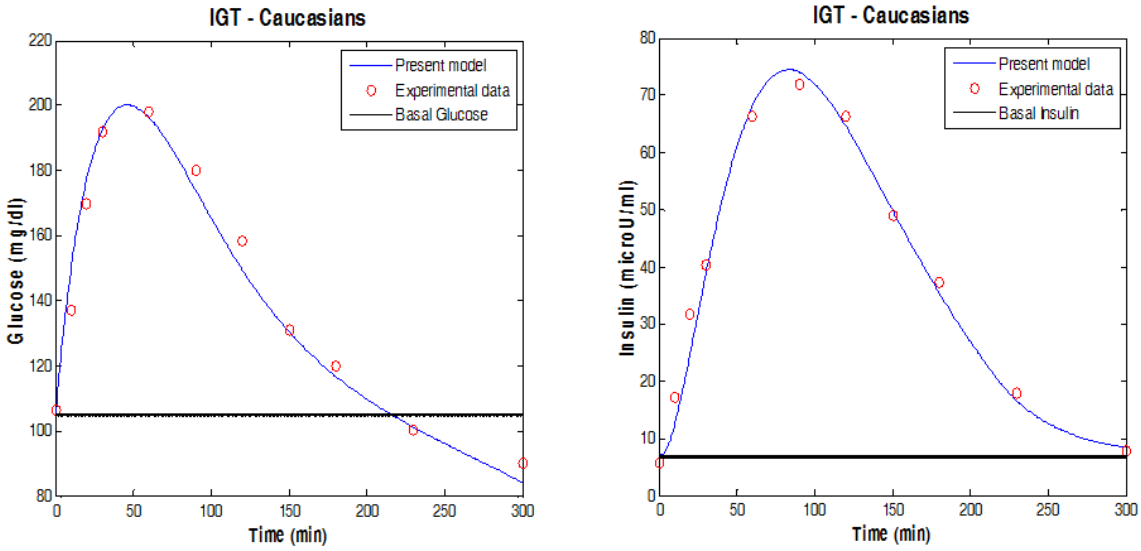

Fig. 7. Measured and calculated plasma glucose concentrations of plasma glucose and insulin level in Case 3 (IGT-Caucasians), with parameters: G_b = 105 [mg dl^{-1}], I_b = 7 [μU ml^{-1}], p_1= S_G = 0.045 [min^{-1}], p_2 = 0.0035 [min^{-1}], S_I = 6.50×10^{-4} [(μU/ml) $^{-1}$ min^{-1}], p_{I1} = 0.75 [min^{-1}], p_{I2} = 0.002 [μU ml^{-1} dl mg^{-1}], p_{I3} = 35.0 [min], p_{I4} = 0.9 [μU ml^{-1} mg^{-1} dl min^{-1}], V = 1.56 [dl/kg], n = 1.07, R^2 for glucose = 0.97 and R^2 for insulin = 0.98

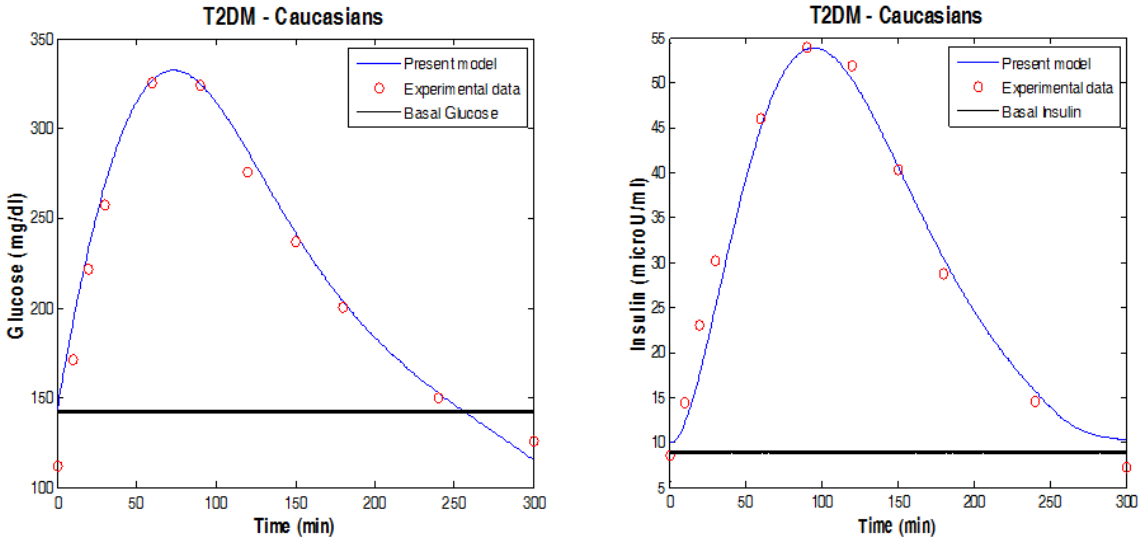

Fig. 8. Measured and calculated plasma glucose concentrations of plasma glucose and insulin level in Case 3 (T2DM-Caucasians), with parameters: G_b = 143 [mg dl^{-1}], I_b = 10 [μU ml^{-1}], p_1= S_G = 0.012 [min^{-1}], p_2 = 0.0098 [min^{-1}], S_I = 5.15×10^{-4} [(μU/ml)$^{-1}$ min^{-1}], p_{I1} = 5.0 [min^{-1}], p_{I2} = 0.002 [μU ml^{-1} dl mg^{-1}], p_{I3} = 20.0 [min], p_{I4} = 1.02 [μU ml^{-1} mg^{-1} dl min^{-1}], V = 1.56 [dl/kg], n = 0.95, R^2 for glucose = 0.97 and R^2 for insulin = 0.96

Conclusion

Insulin sensitivity and glucose effectiveness were used in diabetes diagnosis. The modified OMM model was able to optimize the S_I and S_G index in a given individual from plasma glucose and insulin concentration measured after an oral glucose ingestion, by simultaneously reconstructing also the rate of appearance of the absorbed glucose.

In this study, we had validated the modified OMM for optimizing the S_I and S_G index during a meal or an OGTT procedure. The modification included an assumption that the secretion rate of the plasma insulin from pancreas was not always a first-order process. It also indicated that the modification to the OMM improved more flexibility. The fitting process was applied between the modified model and experimental data to optimize a set of real optimal

model parameters to the glucose-insulin system as a whole dynamic integrated physiological system. An experimental data from a sampled OGTT was performed in NGT, IGT and T2DM subjects.

In summary, on the basis of measured data, the present model was developed, capable of accounting for the effect of the gastric-emptying process on glycemia in the OGTT. It was assumed that the subsequent rise and fall of the blood glucose concentration was due mainly to the production of insulin by the assumption that the insulin decay rate was not always a first-orderly process in response to hyperglycemia.

The interaction between plasma glucose and insulin concentration during the OGTT process shown a great difference between NGT, IGT and T2DM subjects. The averaged correlation between experimental and calculated time courses (R^2) was 0.96 indicating the modeling results are in good agreement. Our study showed that all NGT subjects had higher the S_I and S_G index than all IGT and T2DM subjects following an OGTT. Basal and large peak glucose were lower in all NGT subjects than in all IGT and T2DM subjects in Japanese and Caucasian glucose tolerance groups. Insulin extraction was lower in Japanese and Caucasian subjects with T2DM but was almost similar for the two ethnic groups of NGT and IGT subjects.

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Authors' Contributions

This paper evolved from the discussions of all authors.

Agus Kartono and Egha Sabila Putri: Had given major contributions and participated in the computations and paper writing.

Tony Sumaryada: Participated in the detailed discussions and paper revision (supervisor).

Ardian Arif Setiawan and Heriyanto Syafutra: Contributed to the PSO background and paper revision. All authors read and approved the final manuscript.

Ethics

This article is original. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

Competing Interests

The authors declare that they have no competing interests.

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