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경구최소모델을 기반으로 한

포도당 대사에서의 최적화와 제어

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in glucose metabolism

based on the oral minimal model

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임 민 혁

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By

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Optimization and control in glucose metabolism based on the oral minimal model

by

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A thesis submitted to the Department of Medicine in partial fulfillment of the requirements for the Degree of Master of Science in Medicine (Biomedical Engineering) at Seoul National University College of Medicine

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Abstract

Optimization and control in glucose metabolism based on the oral minimal model

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In the mathematical models to describe physiological phenomena, optimization problem and control tactics are important. Because optimal parameters to represent status of subjects should be estimated and biological variables beyond the normal range should be recovered by using of the pertinent control or interventions. For this objective, the model is required to be validated based on clinical data and the optimal algorithm for each subject is able to be designed.

The oral minimal model is the mathematical system to understand glycemic control in vivo, which can be helpful to evaluate the beta-cell function and insulin sensitivity. In this study, 10 healthy subjects with normal glucose tolerance and 14 patients with type 2 diabetes mellitus participated.

In the results, firstly, blood glucose concentration level, C-peptide level, and Insulin response can be predicted by using of the oral minimal model. Root mean squared error (RMSE) of glucose in NGT group is 11.74 ± 1.38 (mg/dl), and RMSE of glucose in T2DM group is 24.44 ± 12.16 (mg/dl). RMSE of C-peptide in NGT group is 0.15 ± 0.04 (nmol/L), and RMSE of C-peptide in T2DM group is 0.16 ± 0.08 (nmol/L). Secondly, insulin sensitivity (13.3 ± 11.8 vs. 20.0 ± 8.2 [$\times 10^{-5}$ dl/kg/min per pmol/L], p = 0.024), beta-cell responsivity (dynamic responsivity Φ_d: 170.9 ± 138.7 vs. 661.7 ± 411.1 [$\times 10^{-9}$], p < 0.001, age-adjusted p = 0.005; static responsivity Φ_s: 13.9 ± 6.5 vs. 33.5 ± 9.4 [$\times 10^{-9}$ min^{-1}], p < 0.001, age-adjusted p < 0.001; total responsivity Φ_t: 15.5 ± 7.2 vs. 41.9 ± 13.2 [$\times 10^{-9}$ min^{-1}], p < 0.001, age-adjusted p < 0.001, respectively), and disposition indices (dynamic DI_d: 20.7 ± 19.9 vs. 114.7 ± 74.6 [$\times 10^{-12}$ dl/kg/min per pmol/L], p=0.001, age-adjusted p<0.001; static DI_s: 1.6 ± 1.0 vs. 6.4 ± 2.8 [$\times 10^{-12}$ dl/kg/min^2 per pmol/L], p <0.001, age-adjusted p < 0.001; total DI_t: 1.8 ± 1.1 vs. 7.9 ± 3.4 [$\times 10^{-12}$ dl/kg/min^2 per pmol/L], p < 0.001, age-adjusted p < 0.001, respectively) are lower in type 2 diabetes group than normal group. Thirdly, the oral minimal model indices are well correlated with pre-existing clinical indices. Therefore the oral minimal model could be applied to the Korean.

Furthermore, a proportional-integral-derivative (PID) controller and optimal control using dynamic programming can be used to establish algorithms to control blood glucose level in type 2 diabetes mellitus. PID controller showed capability to lower glucose level efficiently and the level of the glucose was continuously lowered without fluctuation. An optimal control

scheme with two simplified additional insulin loading profiles also could lower blood glucose level efficiently, and the barrier term in the cost function could prevent too low blood glucose level. Among 14 T2DM patients, immediate injections of two insulin loadings were recommended in most cases for effective control of the glucose level.

Based on this model and tactics, it is expected that latent interactions in glucose metabolism are clarified, and the models and efficient control algorithms for the artificial pancreas could be developed.

Keywords: The oral minimal model, glucose metabolism, insulin sensitivity, beta-cell responsivity, optimization, control

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1. Introduction

1.1. The mathematical modeling in glucose metabolism

Many scientists, engineers and clinicians have been endeavoring to setup physiological models to uncover the secret of nature [1-5]. Generally, mathematical models contain parameters which can be fitted to biological phenome and clinical experiments. Parameters in models can reflect the status of subjects, not only in healthy conditions but also ill conditions. If the parameters are different from being observed in normal conditions, then the parameters would be used for diagnostic purpose. For example, in the glucose metabolism, there exist a lot of indices such as Matsuda index [6], Postprandial C-peptide to glucose ratio (PCGR) [7], and homeostatic model assessment insulin resistance (HOMA) [8] to represent severity of diabetic worsening. In the same manner, insulin sensitivity and beta-cell responsivity in the oral minimal model are able to differentiate healthy people and patients in type 2 diabetes. Thus acquisition of accurate parameters is important for checking the status of the people with respect to physiological abnormality.

Otherwise, to obtain accurate parameters only is not enough to improve the condition of the subject. We should consider of some interventions to treat diseases and to care ill-conditions. Control tactics would be able to deal with the problem [9]. In diabetes, the blood glucose level should be lowered from too much high level and should

last in normal range. Since mathematical models can be viewed as non-linear system, so we can adopt mathematical algorithm from control theory such as proportional-integral-derivative (PID) controllers and model predictive control (MPC). In the oral minimal model, insulin is the simple variable for control to use these schemes to regulate blood glucose level.

Once the model is set up, the model should be validated via clinical data. East Asians have unique pathophysiology of type 2 diabetes mellitus [10]. Comparing to the Caucasian counterparts, the beta-cell is early deteriorated while the insulin sensitivity is relatively preserved. Thus it would be meaningful to check whether the oral minimal model to Korean subjects with type 2 diabetes mellitus (T2DM) and normal glucose tolerance (NGT) to evaluate beta-cell function and insulin sensitivity.

1.2. The necessity of the simulation study

The objectives in modeling of glucose metabolism are not only to clarifying the nature of human physiological system, but also to care abnormality of glycemic control in vivo. Many approaches have been proposed to regulate blood glucose level efficiently [11,12], and tested in various situations including in silico and clinical trials [13-15].

Several control algorithms can be easily evaluated using in silico models [13]. For type 1 diabetes mellitus, virtual patients based on the population distribution have been developed and became widespread to

check the singularity of the closed-loop control algorithm. The simulation can help analyses and assessments between control methodologies including proportional-integral-derivative (PID) control and model predictive control (MPC), and reduce the risk and the cost which might occur in clinical trials [15].

To care of type 2 diabetes mellitus, anti-diabetic drugs or/and insulin therapy can be applied to the patients. The glucose, C-peptide, and insulin responses can be predicted if the mathematical model is properly established. Moreover the model has the capacity to make up some tactics for regulating blood glucose levels. Insulin sensitivity and beta-cell responsivity are affected by anti-diabetic drugs, and insulin has the influence of lowering blood glucose level. To organize the combination of diverse modalities for optimal regulation of glucose metabolism, a lot of attempts to be tried and tested through the change in characteristics of patients, control algorithms, and urgent situations. An in silico environment is necessary to achieve this goal.

2. Optimization and control problems in the oral minimal model

2.1. Concepts of the oral minimal model

Patients with type 2 diabetes have defects in regulation of blood glucose level due to decreased beta-cell function, overly excited alpha-cell activity, increased hepatic glucose production, lowered glucose uptake in muscles, increased renal glucose absorption, and abnormality in neurotransmitter, which shows the disease is multifactorial [16]. This disease has complex nature, but many researches have been establishing mathematical models using biological variables to capture glucose and insulin responses in vivo. Some models can reproduce of the glucose metabolism among organs, but over-fitting problem may occur if too many parameters are related [17]. In this regard, Bergman's minimal model has its own merits to prevent this problem by requiring minimal number of parameters to estimate beta-cell function and insulin sensitivity [18].

The minimal model has the minimal number of parameters based on physiology to describe glycemic control in vivo. For finding proper paremeters in the model, clinical data has a role of input and output data. For example, the glucose minimal model, which is the one of sub-models in the oral minimal model, use clinical insulin data as input data and clinical glucose data as output data. The sub-model has parameters for constructing ordinaray differential equations, and insulin sensitivity can be obtained by estimation of those parameters through curve fitting.

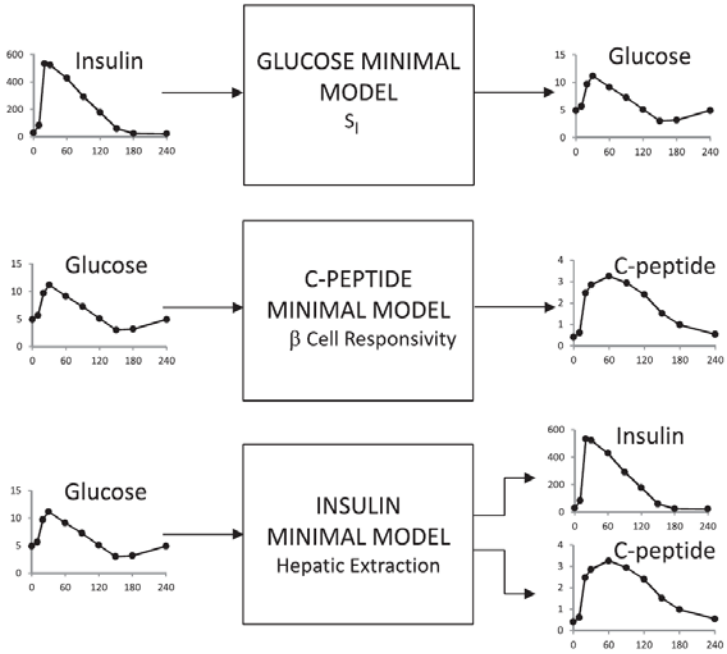


Fig.1. A schematic picture of the oral minimal model [2]

There are two types of minimal models according to the routes of glucose administration: intravenous glucose tolerance test (IVGTT)-based minimal model [18] and oral glucose tolerance test (OGTT)-based minimal model [19] are the case.

The IVGTT-based minimal model was developed prior to establishing oral minimal model. The IVGTT-based model consists of glucose and insulin subsystems, where plasma insulin passes the endothelium and reaches a remote interstitial compartment to make insulin act. But two shortcomings exist in the model. Firstly, actual insulin secretion would be underestimated via plasma level due to hepatic extraction [20], thus C-peptide based model was naturally established to calculate more accurate insulin secretion level [21, 22]. Secondly, intravenous administration of glucose is far from physiological aspects of glucose intake. In addition, IVGTT is invasive. On the contrary OGTT is the gold standard test to determine glucose tolerance status, thus OGTT have been incorporated into the pre-existing minimal models [2]. Among these models, the oral minimal model was able to be easily modified by using of OGTT and simple.

The oral minimal model has three sub-model approaches: a) the glucose minimal model assessing insulin secretion through intestinal glucose absorption and thereby increased in plasma glucose level, b) the C-peptide minimal model describing how effective insulin controls plasma glucose levels, c) the insulin and C-peptide minimal model, which is based on C-peptide minimal model, assessing the hepatic extraction of insulin. The oral minimal model has strong expandability

to be adapted in various situations and to consider several chemicals owing to its structure.

2.2. The mathematical systems in the oral minimal model

Firstly, the oral glucose minimal model and the oral C-peptide minimal model were adopted in this study. The oral glucose minimal model is the mathematical system with two ordinary differential equations that describe the changes in plasma glucose and insulin concentration levels. From previous studies [2,17,23], the following equations were derived.

$$\frac{dG(t)}{dt} = -[X(t)] \cdot G(t) - S_G \cdot [G(t) - G_b] + \frac{R_a(t)}{V} \qquad \text{(Eq.1)}$$

, $\mathrm{G}(0) = G_b$

$$\frac{dX(t)}{dt} = -p_2 \cdot X(t) + p_3 \cdot [I(t) - I_b] \ , \ \mathrm{X}(0) = 0 \qquad \text{(Eq.2)}$$

$G(t)$ is the plasma glucose concentration, *V* is the distribution volume of glucose, and S_G is the fractional glucose effectiveness for glucose disposal and altering the net hepatic glucose balance (Eq. 1). $R_a(t)$ is the glucose appearance rate in plasma via oral glucose intake. The standardized function of glucose absorption was used in this study. $X(t)$ represents effective insulin action on glucose disposal and glucose production, and the subscript of *b* denotes the basal status (Eq. 1 and Eq. 2). Time t is counted as zero when OGTT starts. Parameters of p_2 and

p_3 are rate constants for the dynamics and magnitude of insulin action. Namely, p_2 is the rate constant in the remote insulin compartment (i.e. interstitial compartment) from which insulin action is derived, and p_3 is denoted for scaling of the amplitude of insulin action [23]. $I(t)$ is the plasma insulin concentration (Eq. 2). These equations describe the glucose response to a given insulin action with the intake of glucose from the gastrointestinal tract, such as OGTT.

Secondly, the oral C-peptide minimal model consists of four ordinary differential equations [2,24]. In this model, C-peptide kinetics is used instead of plasma insulin concentrations for the purpose of using more accurate insulin secretion rates.

$$\frac{dq_1(t)}{dt} = -(k_{01} + k_{21}) \cdot q_1(t) + k_{12} \cdot q_2(t) + ISR(t) \quad \text{(Eq. 3)}$$

$$c_1(t) = \frac{q_1(t)}{V}, \; q_1(0) = 0$$

$$\frac{dq_2(t)}{dt} = -k_{12} \cdot q_2(t) + k_{21} \cdot q_1(t), \; q_2(0) = 0 \quad \text{(Eq. 4)}$$

$$\text{ISR(t)} = y(t) + K_G \cdot \frac{dG(t)}{dt} \quad \text{(Eq. 5)}$$

$$\frac{dy(t)}{dt} = -\frac{1}{T}[y(t) - \beta \cdot (G(t) - G_b)], \; \text{y(0)} = 0, \quad \text{(Eq. 6.)}$$

Briefly, in Eq. 3, q_1 and q_2 are the increased C-peptide amounts from basal amounts in the accessible and remote compartments, respectively. The variable of ISR means increased C-peptide secretion rates from basal rates. c_1 is increased C-peptide plasma concentration from basal level. k_{01}, k_{12}, and k_{21} are rate constants characterizing C-peptides

kinetics. c_1 is the increased C-peptide concentration from basal level, and y(t) is the insulin provision which is the proportion of synthesized insulin reaching the beta-cell membrane and ready to be secreted after a delay (T). K_G and β are regarded as dynamic and static parameters to correspond the time derivative of glucose level and the increased glucose level above basal value respectively.

The oral insulin and C-peptide minimal model is constructed based on the oral C-peptide minimal model, a subsystem for the hepatic extraction of insulin is combined. Insulin delivery rate (IDR) and hepatic insulin extraction ratio (HE) can be determined in this model [22].

$$\frac{dI(t)}{dt} = -\mathrm{n} \cdot \mathrm{I(t)} + IDR(t)/V_I \quad , \mathrm{I}(0) = I_b \qquad \text{(Eq. 7)}$$

$$\mathrm{IDR(t)} = ISR(t) \cdot \big(1 - HE(t)\big)/V_I \qquad \text{(Eq. 8)}$$

In this model, n is the rate constant of insulin elimination, V_I is the distribution volume of insulin, and (1–HE) means the fraction of ISR reaching C-peptide accessible compartment.

Three sub-models in the oral minimal model containing all relationships between parameters and variables are shown in Fig. 2.

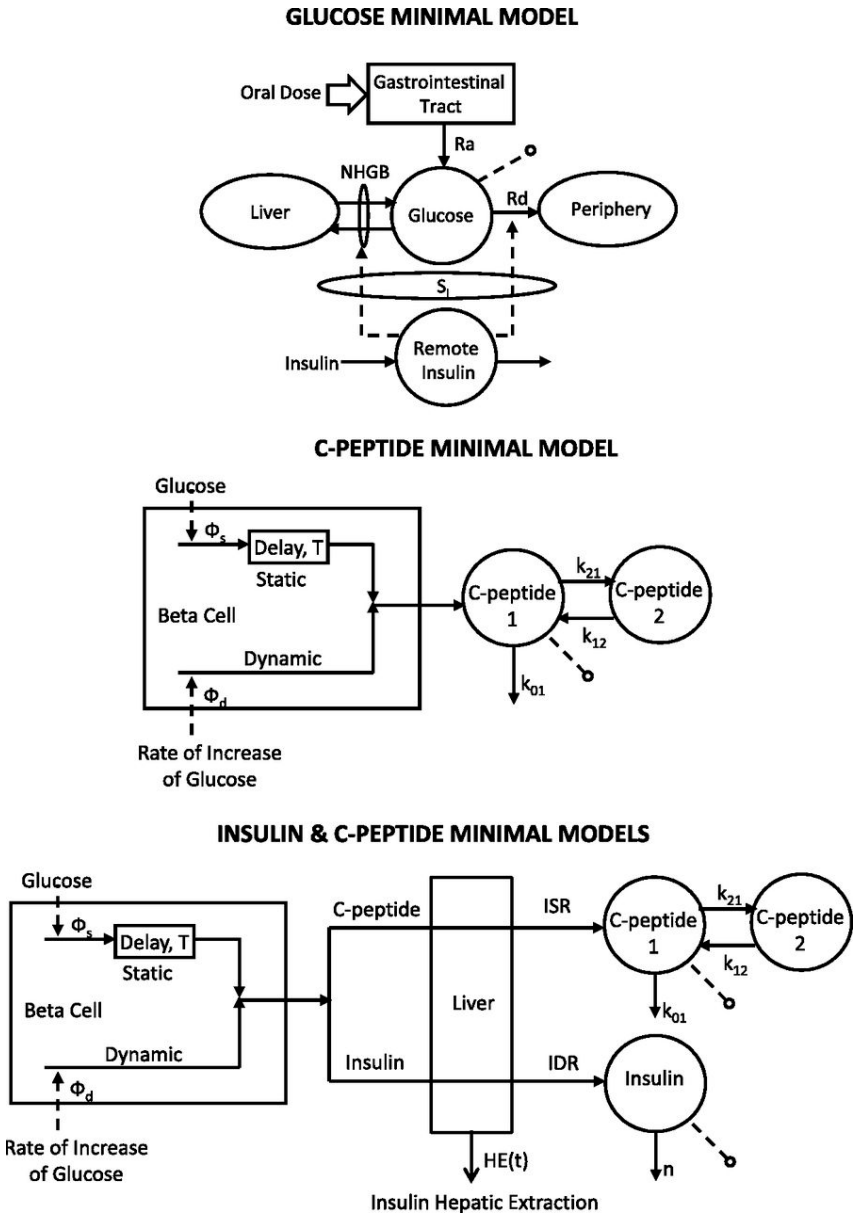


Fig.2. Three sub-models in the oral minimal model [2]

2.3. Optimization problems in the oral minimal model

In the oral minimal model, the parameter should be clarified to describe the status of subjects properly. We set the objective function as the least square function which reflecting differences between clinical data points and simulated responses [9].

$$f_{obj}(parameters) = \sum(Data_{clinical} - Data_{simulated})^2 \qquad \text{(Eq. 9)}$$

Clincal data, $Data_{clinical}$, is measured through clinical experiments. $Data_{simulated}$ is derived from simulations of the oral minimal model with estimated parameters. The cost function of f_{obj} cannot be expected as a convex function, so derived parameters may be in local optimum rather than global optimum. Thus, this problem should be dealt with the global optimization technique such as genetic algorithm or simulated annealing [25].

Simulated annealing belongs to global optimization methodologies, and uses the probability escaping local minimum based on analogy of statistical mechanics. At first, the starting point X_0 is chosen. In the next step, a random point of n-dimension is selected to establish a search direction S and a stepsize α. If the function value of new point satisfies the inequality of $f_1 = f(X_0 + \alpha S) \leq f(X_0) = f_0$, then the X_0 is updated as $X_0 + \alpha S$. But if not, the probability $p = e^{-\beta(f_0 - f_1)}$ is calculated and a random number r is generated. In that case, if $r \leq p$, then the this update is accepted, and if not the point has no change. These steps are repeated to find the minimum during β is adjusted.

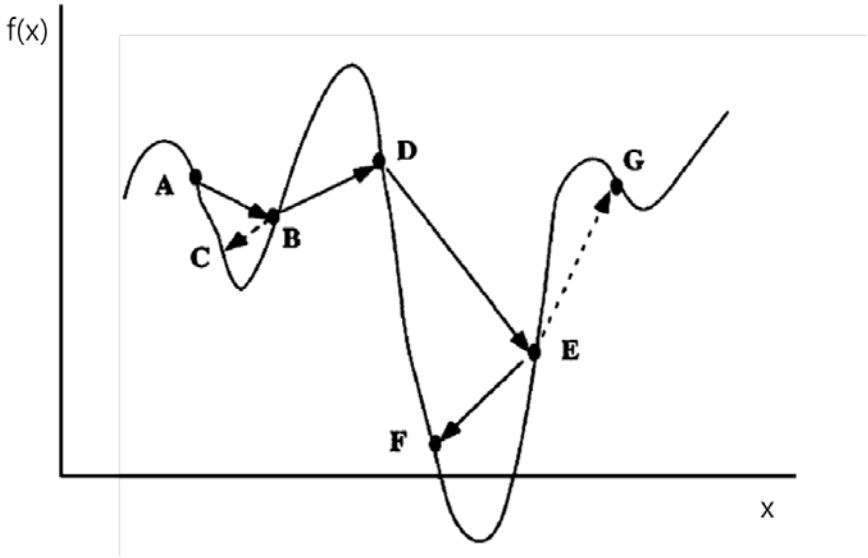


Fig. 3. Strategy for global optimum search [25]

A dashed path (E to C) can occur in simulated annealing.

2.4. Control problems in the oral minimal model

Several tactics to control mathematical systems have been developed [9]. Since insulin can lower blood glucose level, so the hormone is the one candidate of control variables. PID controller responses to glucose level change in unit time, difference between the current glucose level and the ideal level, and the accumulated effects of glucose. Additional insulin loading can be added into natural insulin secretion and be formulated by following.

$$\mathrm{AIL} = \mathrm{pid}_1 \frac{dG}{dt} + pid_2 \Delta G + pid_3 \int \Delta G dt,\ \Delta \mathrm{G} = \mathrm{G} - \mathrm{G}_{\mathrm{goal}} \qquad \text{(Eq. 10)}$$

But we cannot deliver the insulin with negative value and previous two terms can regulate the glucose level efficiently, so pid_3 is counted as zero to prevent low blood glucose level under the normal range.

The other approach, dynamic programming uses cost functions to evaluate control tactics which reflects insulin loading, gap between glucose levels and time derivatives of glucose level. Third term in the cost function is designed for glucose fluctuation. Each variable such as u, $\Delta \mathrm{G}$, $\left(\frac{\mathrm{dG}}{\mathrm{dt}}\right)$ is a vector which components are aligned according to measured time/stepping .

$$\mathrm{f}_{\mathrm{cost}}(u) = \frac{1}{2} u^T R u + \frac{1}{2} \Delta G^T R_1 \Delta G + \frac{1}{2} \left(\frac{dG}{dt}\right)^T R_2 \left(\frac{dG}{dt}\right) + \mathrm{Aexp}(\mathrm{G_p} - G) \quad \text{(Eq. 11)}$$

For optimal control, $u = [u_1\ u_2 \ldots u_{end}]$ should be determined to minimize f_{cost} and ΔG and $(\frac{dG}{dt})$ is estimated using the oral minimal model with each subject's parameters. The last term would prevent too low glucose level from control process, and G_p is the barrier level of the blood glucose.

Most of MPC algorithm use previous values of glucose, insulin, and meal information to predict the next levels of biological variables and to determine the dose of insulin for maintaining the normal range of blood glucose level, but the oral minimal model can be applied to estimate the next states and to design the optimal tactics for glycemic control. Even the parameters in the oral minimal model can be updated during the clinical setting.

3. Methods

3.1. Subjects and ethical statement

Our study had been conducted with 14 patients with type 2 diabetes and 10 subjects with normal glucose tolerance, aged 18 to 75 years. The T2DM patients were diagnosed according to the criteria by the American Diabetes Association (ADA) and had been cared by lifestyle modification or/and oral anti-diabetic drugs. Diabetic complications such as retinopathy, microalbuminuria, or cardiovascular disease were not diagnosed in the group.

The study protocol was approved by the Institutional Review Board at Seoul National University Hospital (registration number: H-1504-018-662) and was in compliance with the Declaration of Helsinki as revised in 2000. Written informed consent was obtained from all participants before any study-related procedures.

3.2. Study procedure in clinical experiments

Prior to visiting the Biomedical Research Center at Seoul National University Hospital, each subject had a one-week washout period for oral antidiabetic drugs and also fasted the night before the study day. All participants underwent a 180-min, 75-g OGTT. Venous blood was drawn at 0, 15, 30, 60, 90, 120, and 180 min for measurement of plasma glucose, insulin, and C-peptide levels. Glucose was measured by a glucose oxidase method (YSI 2300 STAT Plus analyzer, Yellow

Springs Instruments, Yellow Springs, OH, USA). Insulin (DIAsource, Nivelles, Belgium) and C-peptide (Immunotech, Prague, Czech Republic) concentrations were measured with chemiluminescence immunoassay.

3.3. Parameter estimation

In the glucose oral minimal model, three parameters, three parameters (S_G, p_2, p_3) in the equation 1 and 2 were evaluated. Their values were obtained by minimizing the nonlinear least square function reflecting differences between actual clinical data and predicted response curves. Among the three parameters in the oral glucose minimal model, glucose effectiveness S_G and the ratio of p_2 to p_3 are significant for characterizing plasma glucose and insulin responses in each subject [26]. During this estimation process, all parameters were explored based on reference values [27-29] within the parametric space using global optimization techniques such as simulated annealing. One subject in the NGT group and two subjects in the T2DM group were excluded from this calculation via outlier reduction, which the data with over than three standard deviation or attach in boundaries of parametric space are regarded as outliers. For using time derivatives of plasma glucose level, smooth curves in simulations were exploited to calculate parameters. The rate constants (k_{01}, k_{12}, k_{21}) characterizing the C-peptide kinetics were introduced from a previous study. All processes were carried out for each subject using the MATLAB 2015 system (The Mathworks, Inc., Natrick, MA, USA).

3.4. Calculation for indices

The goals of calculations were two-fold: a) to compare insulin sensitivity (S_I) and beta-cell function [the basal, dynamic, static, and total responsivity indices (Φ_b, Φ_d, Φ_s, and Φ_t)] between the NGT and T2DM groups; b) to graphically present the dynamic, static, and total disposition indices (DI_s, DI_d, and DI_t) of the subjects and the groups, using the DI metric to represent distribution of insulin sensitivity and beta-cell responsivity of the NGT and T2DM groups.

The disposition index represents the progression of type 2 diabetes mellitus. If insulin sensitivity is decreased at first, then beta-cell responsivity is increased to compensate the lowered insulin sensitivity and disposition index is maintained. But if beta-cell function is not increased enough, then the glucose tolerance changes to the impaired level. DI metric is shown in fig. 3, which can visualize the states of glucose metabolism in each subject. Disposition index is defined as production of insulin sensitivity and beta-cell responsivity. It is assumed that each group such subjects with normal glucose tolerance or patients with type 2 diabetes mellitus has different disposition indices. Additionally, therapeutic vector can show the direction of the treatment for each patient based on DI metric. It has normal direction to the curve of hyperbolae which shares the same disposition indice, the glucose tolerance can be increased optimally along this direction.

In the oral minimal model, Φ_b reflects insulin secretion at basal state which can be corresponded as fasting conditions in preparation of clinical study. Φ_d and Φ_s respectively correspond to first and second

phase insulin secretion. Φ_t combines the effects of both Φ_d and Φ_s [19].

The indices S_I and Φ_b, Φ_d, Φ_s, Φ_t of the subjects were calculated based on the derived parameters. In the glucose minimal model, S_I and S_G were calculated as follows [30].

$$S_I = \frac{P_3}{P_2}V \ (10^{-5}\ \text{dl/kg/min per pmol/l}),\ S_G = p_1 \ (\text{min}^{-1}) \quad \text{(Eq. 12)}$$

In the C-peptide minimal model, the beta-cell responsivity indices represent the capacity of the beta-cells to release insulin. They were approximated as follows [31].

$$\phi_b = \frac{k_{01}CP_b}{G_b} \quad (10^{-9}\ \text{min}^{-1}) \qquad \text{(Eq. 13)}$$

$$\phi_d = K_G \qquad (10^{-9}) \qquad \text{(Eq. 14)}$$

$$\phi_s = \beta \qquad (10^{-9}\ \text{min}^{-1}) \qquad \text{(Eq. 15)}$$

$$\phi_t = \phi_s + \frac{\phi_d\,(G_{max} - G_b)}{\int_0^{\infty}[G(t)-G_b]dt} \quad (10^{-9}\ \text{min}^{-1}) \qquad \text{(Eq. 16)}$$

The DI_d, DI_s, DI_t were calculated through multiplying respectively dynamic Φ_d, static Φ_s, and total Φ_t by S_I.

The basal hepatic insulin extraction ratio (HE_b) and post-glucose challenge hepatic insulin extraction ratio (HE_{post}) were assessed. T_0 is the time reaching the end of tests [22].

$$\mathrm{HE}_b = \frac{ISR_b - IDR_b}{ISR_b} = 1 - \frac{I_b \cdot n \cdot V_I}{ISR_b} \qquad \text{(Eq. 17)}$$

$$\mathrm{HE}_{post} = \frac{\int_o^{T0} ISR(t)dt - \int_0^{T0} IDR(t)dt}{\int_0^{T} ISR(t)dt} \qquad \text{(Eq. 18)}$$

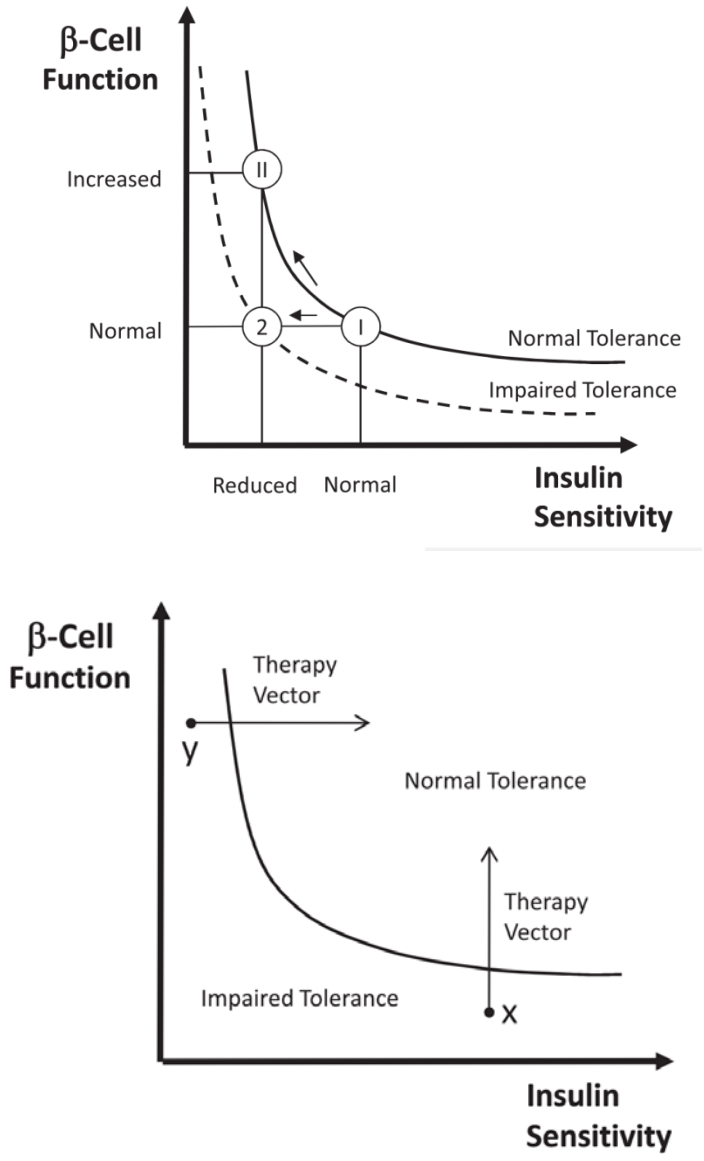


Fig. 4. A Schematic diagram of the disposition index [2]

3.5. Statistical analysis

Between the NGT and T2DM groups, the Mann-Whitney test, chi-square test, Welch's test, and analysis of covariance (ANCOVA) for adjusting differences in age were performed to compare indices. Insulin sensitivity did not satisfy the criteria of normality, so non-parametric analysis was conducted. Beta-cell responsivity and disposition indices were log transformed for analysis and back transformed to guarantee normality and equality of variances. Spearman correlation analysis was also used in non-parametrical setting.

Prism 5.0 (GraphPad, San Diego, CA, USA), R 3.1.2. (The R foundation, Vienna, Austria) and SPSS 19.0 (SPSS, Chicago, IL, US) software were used for statistical analysis. Significance level was set at 0.05 for judgment of intergroup differences.

3.6. Simulation of control procedures

With control algorithm, it is assumed that additional insulin loading is combined with natural insulin secretion. In PID control, the coefficients of pid_1 and pid_2 should be determined to minimize cost function. PID control has no assumption on the pre-existing mathematical models, so it can respond to glucose change without knowledge. But PID control needs continuous interventions, so other approaches with the small number of times being injected should be considered.

In dynamic programming to establish optimal control, two ideally simplified insulin action profiles are used. Because insulin is injected on

skin rather than continuous monitoring and injections through intravenous ways, so simplified insulin actions with trigonal shapes can be regarded in this manner. The oral minimal model can be applied to design not only closed-loop control, but also the open-loop open control for regulating blood glucose level. With this approach, personalized regimen using insulin can be proposed to each patient. This is why the open-loop style insulin loadings are introduced.

It is assumed that the first insulin profile has 30 min as the peak time and 90 min as duration and the second insulin profile has 60 min as the peat time and 180 min as duration. Both have trigonal shapes. The other assumption is that the insulin actions consisting of the therapy are regarded as additional insulin secretion rates. To establish optimal control using given insulin profiles, the optimal value of peak levels of insulin profiles and delayed time for injection to minimize cost function were searched. One patient whose data is well fitted the oral minimal model was chosen for designing control algorithm.

With the combination of two trigonal insulin profiles, it is assumed that the summation of insulin loading is added to the insulin secretion rates in the mathematical equation (Eq.5) of the oral minimal model.

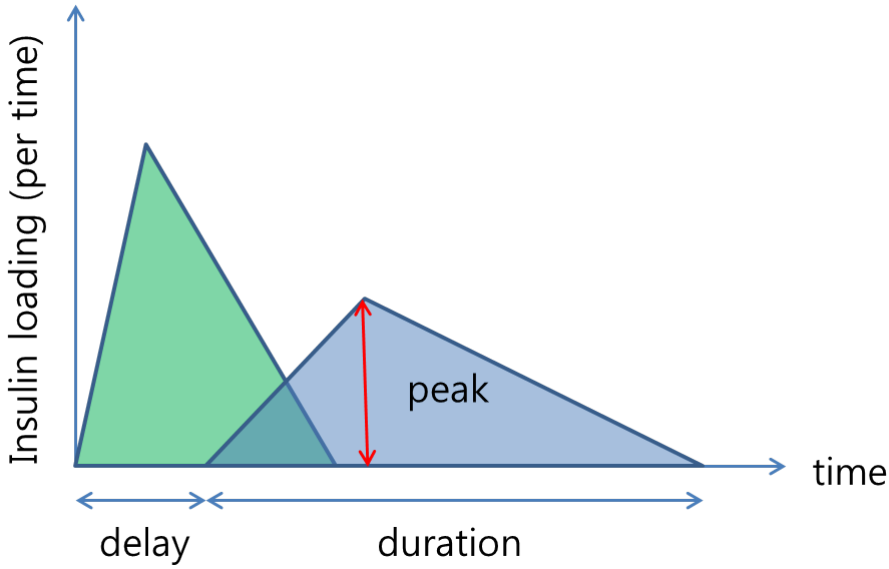


Fig. 5. Two simplified insulin profiles of trigonal shapes

4. Results

4.1. Clinical characteristics of the subjects

The clinical characteristics of the subjects are presented in Table 1. The T2DM group was older than the NGT group [mean ± standard deviation (SD), 53.8 ± 9.4 vs. 39.8 ± 13.5 years, $p < 0.019$]. Fasting glucose levels (146.2 ± 27.6 vs. 92.0 ± 4.5 mg/dl, $p < 0.001$) and peak glucose levels during the OGTT (337.0 ± 49.5 vs. 175.9 ± 17.1 mg/dl, $p < 0.001$) were higher in the T2DM group than the NGT group. The reaching peak glucose levels of T2DM group was more delayed than the NGT group (93.6 ± 18.9 vs. 49.0 ± 13.5 min, $p < 0.001$). Between the NGT and T2DM groups, body weight and body mass index were not significantly different. However the distribution of age was significantly different between the NGT group and the T2DM group (39.8 ± 13.5 vs. 53.8 ± 9.4, $p=0.019$).

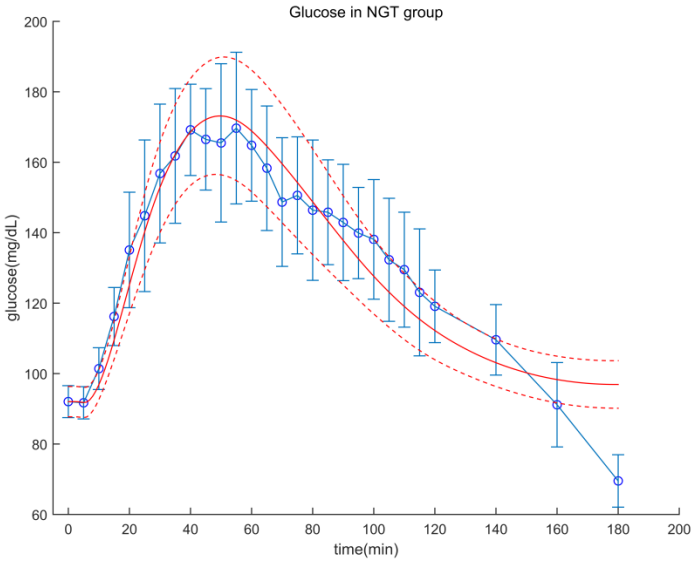
In addition, other clinical indices of insulin secretion or insulin action such as Postprandial C-peptide to glucose ratio (PCGR) [7], Matsuda index [6], and homeostatic model assessment insulin resistance (HOMA-IR) [8] were compared between the NGT and T2DM groups in Table 1. PCGR and Matsuda index were higher in the NGT group than the T2DM group (2.649 ± 0.642 vs. 1.254 ± 0.423, $p<0.001$; 8.818 ± 3.260 vs. 5.466 ± 2.814, $p=0.002$, respectively). HOMA-IR was lower in the NGT group than the T2DM group (1.2±1.1 vs. 2.3±1.3, $p=0.002$).

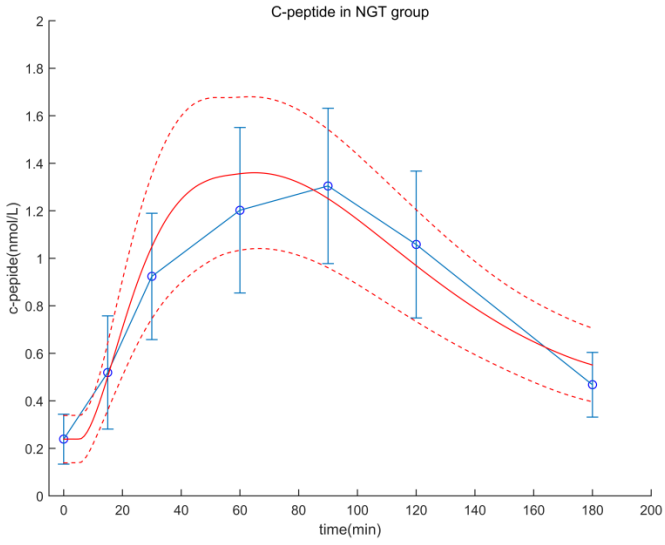
Table 1. Clinical characteristics between NGT and T2DM groups

	NGT (n = 10)	T2DM (n = 14)	P value
Gender (M:F)	8:2	9:5	0.653
Age (years)	39.8 ± 13.5	53.8 ± 9.4	0.019
Body weight (kg)	66.6 ± 15.0	67.6 ± 14.4	0.898
Body mass index (kg/m^2)	22.9 ± 3.5	24.5 ± 3.5	0.403
Duration of diabetes mellitus (years)	N/A	4.7 ± 2.4	N/A
Fasting plasma glucose (mg/dl)	92.0 ± 4.5	146.2 ± 27.6	<0.001
Peak plasma glucose (mg/dl)	175.9 ± 17.1	337.0 ± 49.5	<0.001
Time for peak glucose level (min)	49.0 ± 13.5	93.6 ± 18.9	<0.001
PCGR	2.6 ± 0.6	1.3 ± 0.4	<0.001
Matsuda Index	8.8 ± 3.3	5.5 ± 2.8	0.002
HOMA-IR	1.2 ± 1.1	2.3 ± 1.3	0.002

4.2. Simulation of plasma glucose level and C-peptide secretion

Based on the parameters in the oral minimal model, the simulated responses of plasma glucose level and C-peptide secretion are well conducted and close matched with the clinical data. Root mean squared error (RMSE) of glucose in NGT group is 11.74 ± 1.38 (mg/dl), and RMSE of glucose in T2DM group is 24.44 ± 12.16 (mg/dl). RMSE of C-peptide in NGT group is 0.15 ± 0.04 (nmol/L), and RMSE of C-peptide in T2DM group is 0.16 ± 0.08 (nmol/L).


Glucose in NGT group
glucose(mg/dL)
time(min)
200
180
160
140
120
100
80
60
0
20
40
60
80
100
120
140
160
180
200


C-peptide in NGT group
c-pepide(nmol/L)
time(min)
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
20
40
60
80
100
120
140
160
180
200

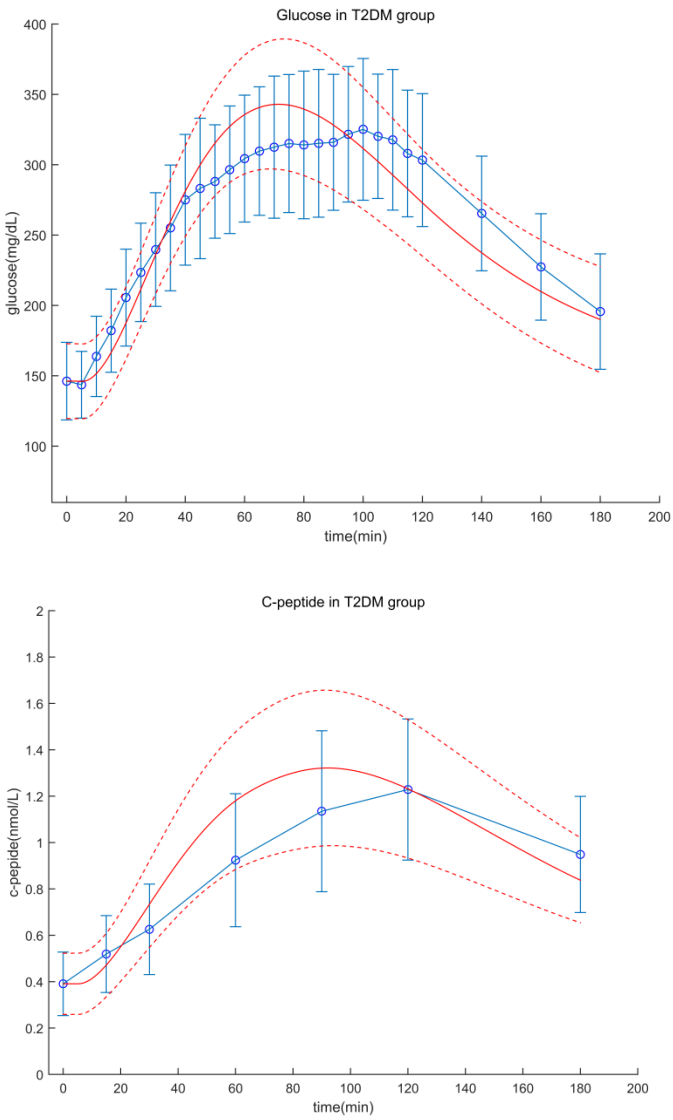


Fig. 6. Clinical data and simulation of plasma glucose level and C-peptide secretion (Red line: simulated responses – mean smooth curves and mean ± SD dashed curves, Blue lines: mean clinical data with SD)

4.3. Insulin sensitivity, beta-cell responsivity indices and hepatic insulin extraction ratios

Insulin sensitivity and beta-cell responsivity indices were compared between the NGT and T2DM groups. As shown in Fig. 6, the NGT group had a higher insulin sensitivity (S_I) than the T2DM group (20.0 ± 8.2 vs. 13.3 ± 11.8 [$\times 10^{-5}$ dl/kg/min per pmol/L], p = 0.024). The basal beta-cell responsivity index (Φ_b) was not significantly different between the NGT and T2DM groups (2.8 ± 1.2 vs. 2.9 ± 1.2 [$\times 10^{-9}$ min^{-1}], respectively, p = 0.578, age-adjusted p = 0.972). The dynamic, static, and total beta-cell responsivity indices (Φ_d, Φ_s, Φ_t) were higher in the NGT group than the T2DM group (Φ_d: 661.7 ± 411.1 vs. 170.9 ± 138.7 [$\times 10^{-9}$], p < 0.001, age-adjusted p = 0.005; Φ_s: 33.5 ± 9.4 vs. 13.9 ± 6.5 [$\times 10^{-9}$ min^{-1}], p < 0.001, age-adjusted p < 0.001; Φ_t: 41.9 ± 13.2 vs. 15.5 ± 7.2 [$\times 10^{-9}$ min^{-1}], p < 0.001, age-adjusted p < 0.001, respectively). The basal hepatic insulin extraction ratio (HE_b) was not significantly different between the NGT and T2DM groups (55.20 ± 12.91 vs. 64.26 ± 9.27 [%], p=0.064). The post-glucose challenge hepatic insulin extraction ratio (HE_{post}) appeared to be different between the NGT and T2DM groups (49.20 ± 20.79 vs. 66.99 ± 10.72 [%], p=0.028), which lost statistical significance after adjusting age difference (p=0.141).

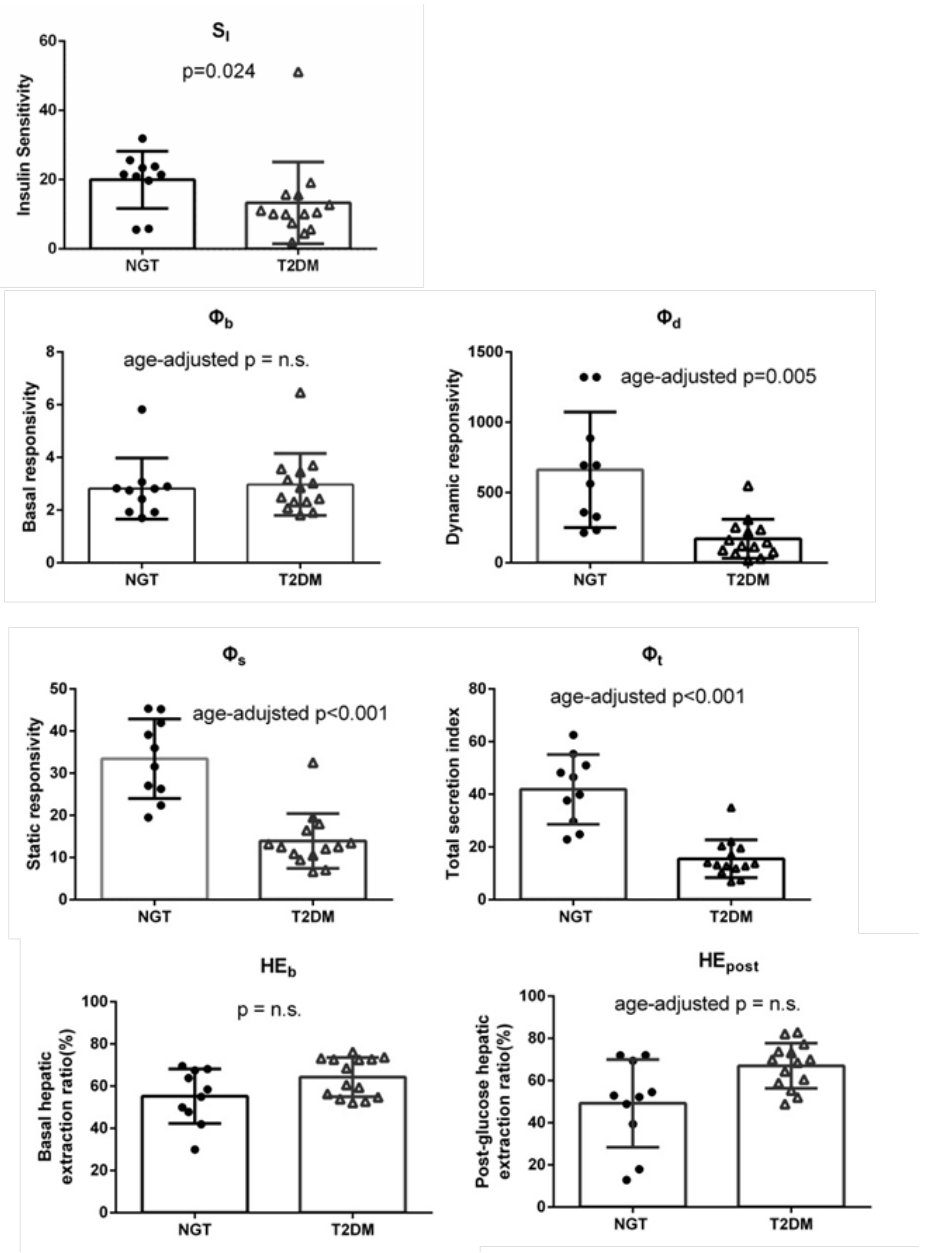


Fig. 7. Insulin sensitivity, beta-cell responsivity and hepatic extraction ratios

4.4. Disposition indices between NGT and T2DM groups

The T2DM group had significantly lower dynamic, static, and total disposition indices (DI_d, DI_s, and DI_t) than the NGT group (DI_d: 20.7 ± 19.9 vs. 114.7 ± 74.6 [$\times 10^{-12}$ dl/kg/min per pmol/L], p=0.001, age-adjusted p<0.001; DI_s: 1.6 ± 1.0 vs. 6.4 ± 2.8 [$\times 10^{-12}$ dl/kg/min^2 per pmol/L], p <0.001, age-adjusted p < 0.001; DI_t: 1.8 ± 1.1 vs. 7.9 ± 3.4 [$\times 10^{-12}$ dl/kg/min^2 per pmol/L], p < 0.001, age-adjusted p < 0.001, respectively) (Fig. 7). The hyperbolic relation is shown in the three DI metrics as shown in Fig. 8. The hyperbolic line for the T2DM group was located in the downward and leftward region of that of the NGT group.

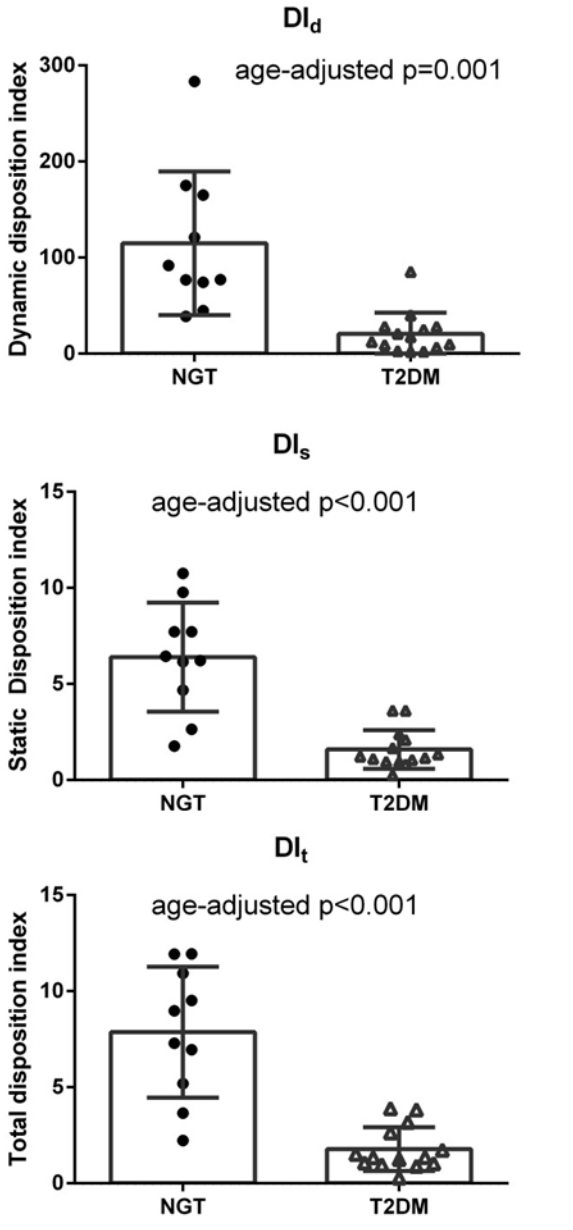
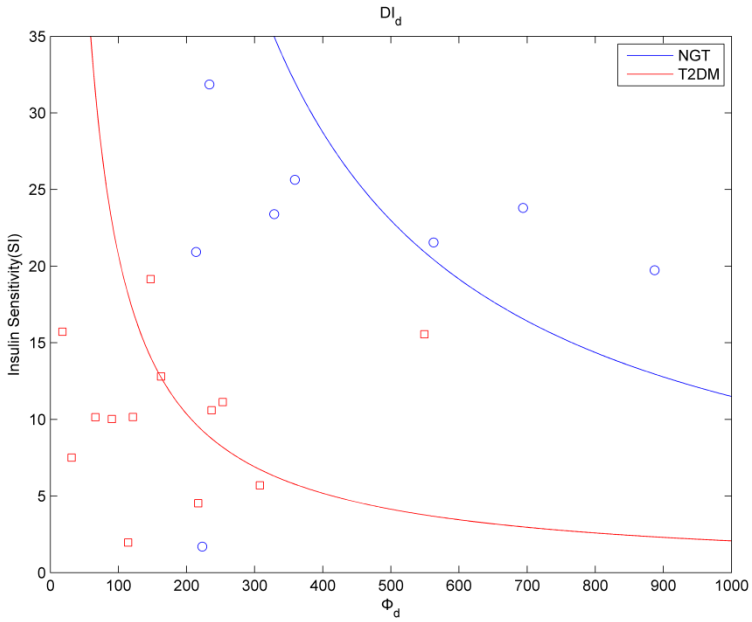
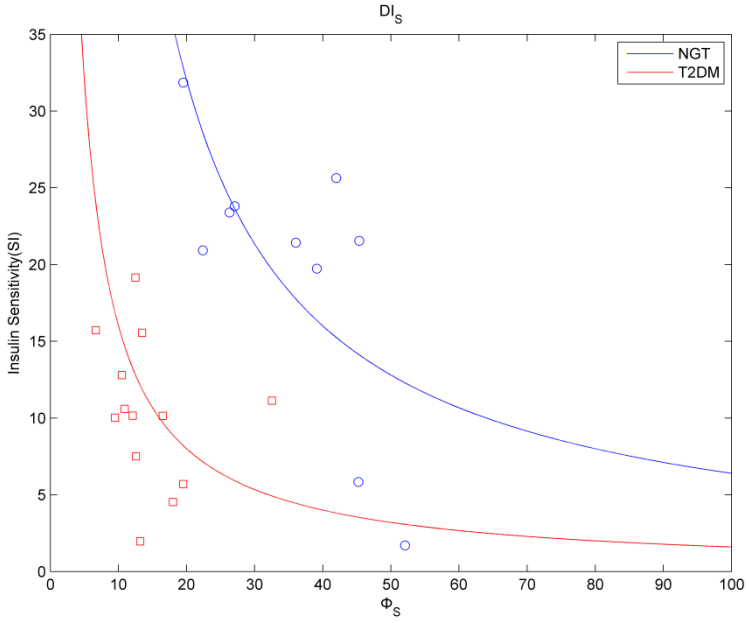


Fig. 8. Disposition indices between the NGT and T2DM groups


DI_d
NGT
T2DM
Insulin Sensitivity(SI)
Φ_d
0
5
10
15
20
25
30
35
0
100
200
300
400
500
600
700
800
900
1000


DI_S
NGT
T2DM
Insulin Sensitivity(SI)
Φ_S
0
5
10
15
20
25
30
35
0
10
20
30
40
50
60
70
80
90
100

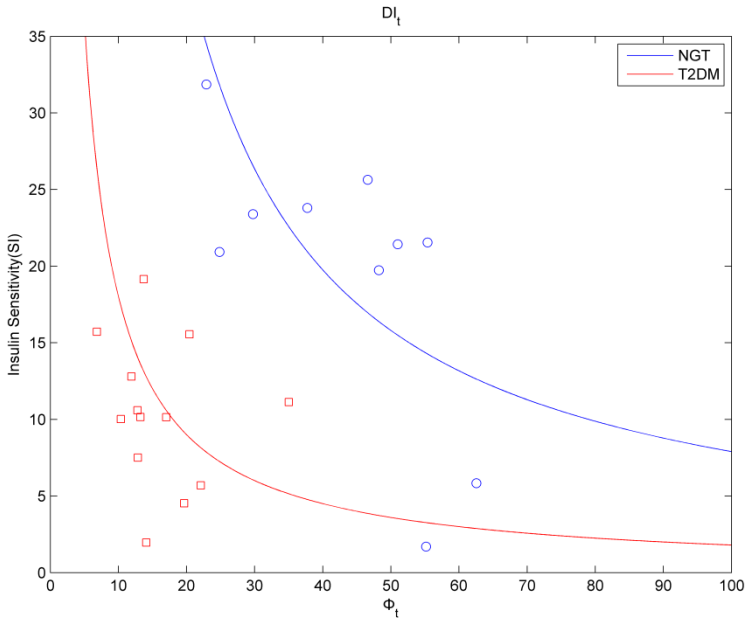


Fig. 9. Dynamic, static and total Disposition Index (DI) metrics

4.5. Correlation between other indices of insulin secretion or insulin action and the oral minimal model indices

As shown in Fig. 9, PCGR has significant positive correlation with dynamic and static responsivity indices ($r=0.77$, $p<0.001$ and $r=0.89$, $p<0.001$, respectively). Matsuda Index was significantly correlated with insulin sensitivity ($r=0.51$, $p=0.011$), whereas HOMA-IR did not show significance ($r=-0.21$, $p=0.105$).

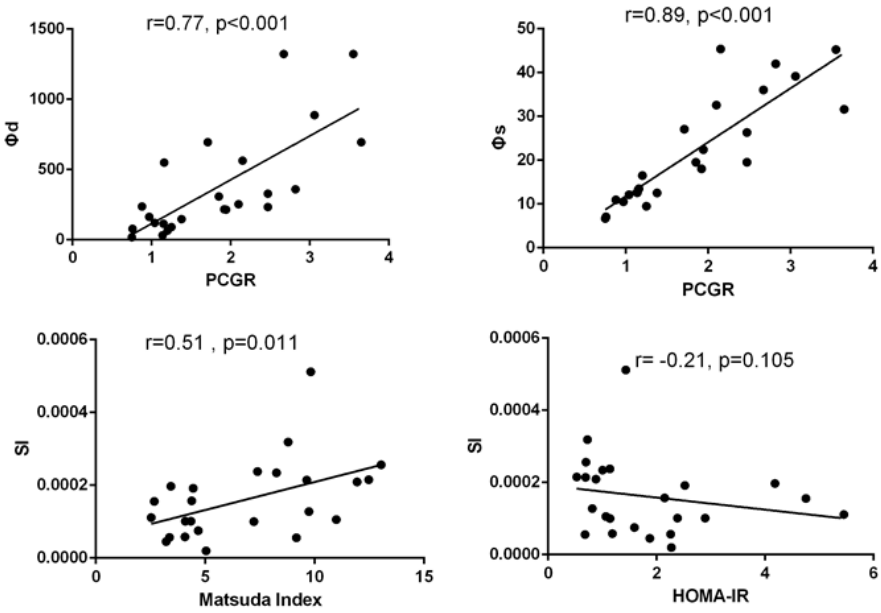


Fig. 10. Correlations with the oral minimal model indices and pre-existing indices

4.6. Correlation between glucose levels and the oral minimal model indices

Fasting blood glucose level and post-load blood glucose levels are easily measured than insulin or C-peptide levels because checking blood glucose level can be conducted with simple and non-invasive tests. In this study, insulin sensitivity was only negatively correlated with 120-min post-load glucose level ($r=-0.47$, $p=0.0194$) and other glucose levels did not show significance. But dynamic and static beta-cell responsivity represented the negative correlations with fasting and post-load glucose levels.

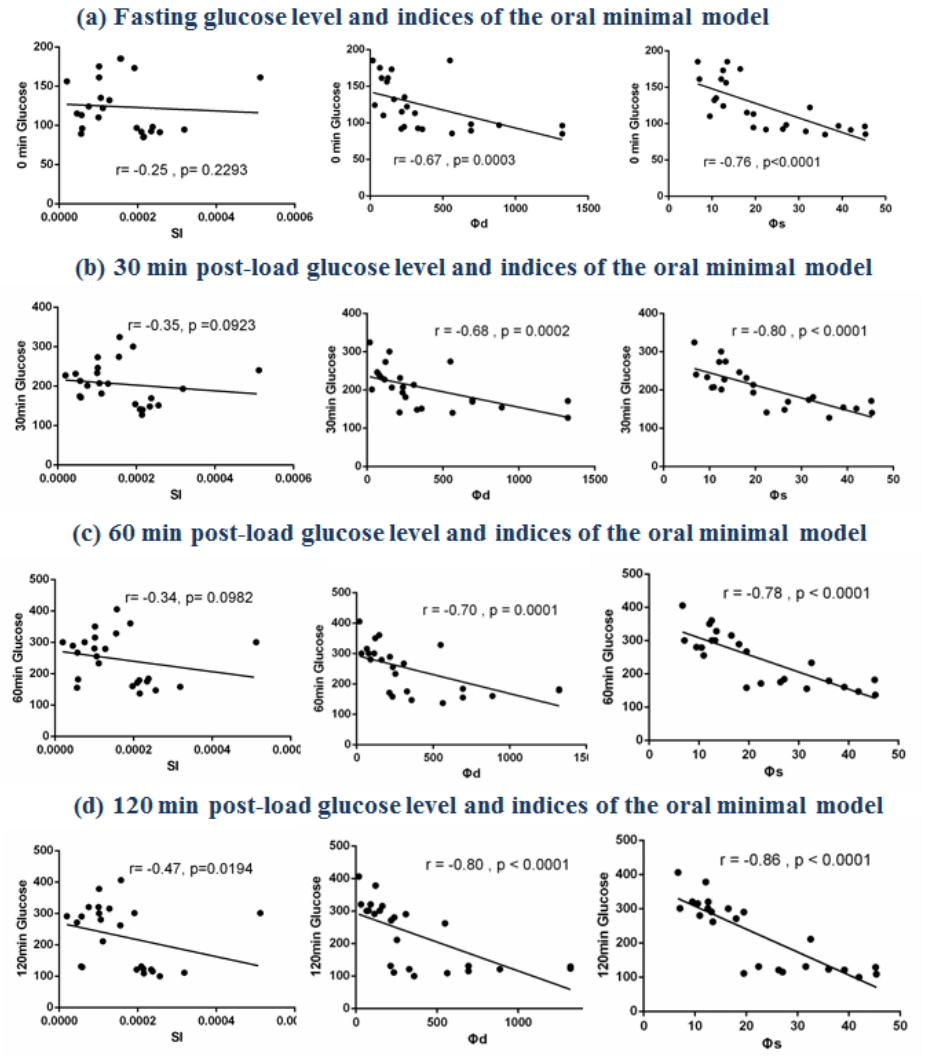


Fig. 11. Correlations with post-load glucose levels and the oral minimal model indices

4.7. Simulation of glucose control tactics via additional insulin

Firstly, the PID control to regulate the blood glucose level in one patient with diabetes was conducted. PID controller showed capability to lower glucose level efficiently and the 180-min blood glucose level reached at 88.4 (mg/dL) when the $\mathrm{pid}_1 = 0.05$ and $\mathrm{pid}_2 = 1$. The level of the glucose was continuously lowered without fluctuation.

Secondly, a simplified version of the dynamic programming with two simplified additional insulin loading profiles in triangular shapes was conducted. It was found that the first insulin action profile has 0-min delayed time and 1.7 nmol/L as a peak, while the second insulin action profile has 30-min delayed and 0.4 nmol/L as a peak. The most lowered glucose level was 64.0 (mg/dL) and the 180-min blood glucose level reached at 78.6 (mg/dL). In this simulation, a constant A was set as zero in the cost function, so the barrier cost to prevent too low blood glucose level was not contributed in this control.

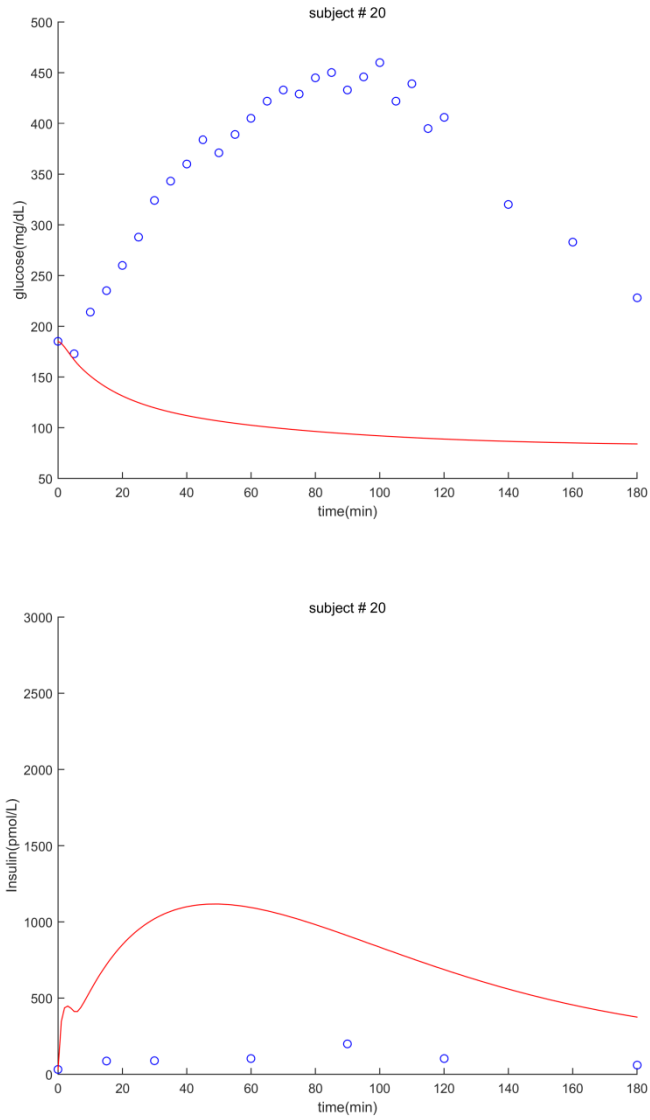


Fig. 12. Predicted responses of glucose and insulin via additional insulin loading for PID control (red lines: simulated responses, blue circle: clinical data)

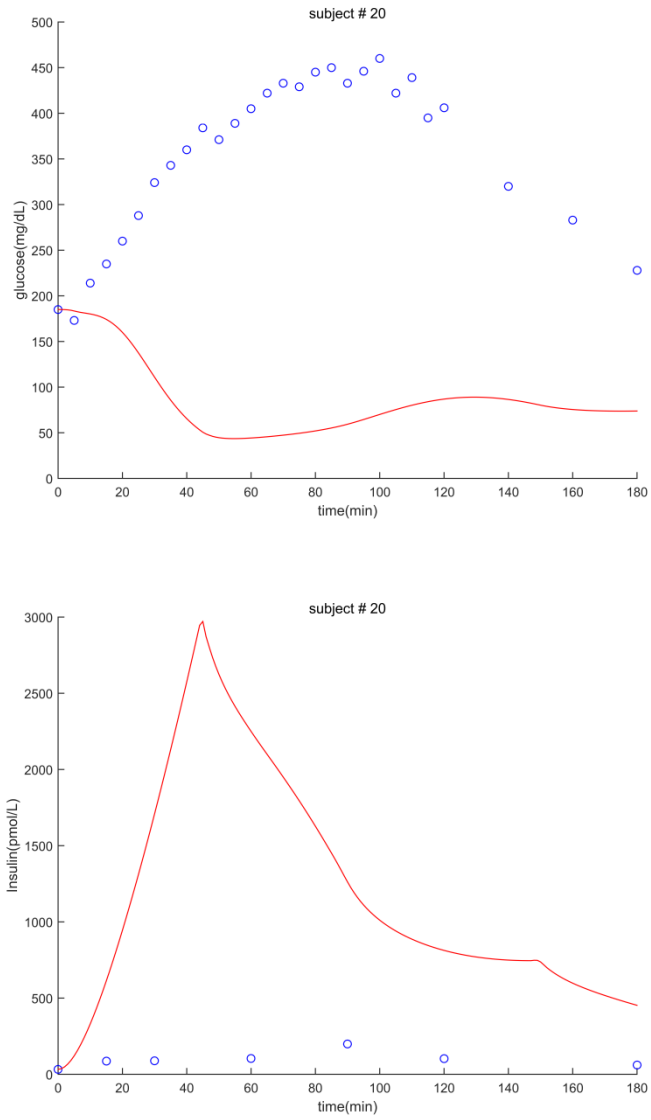


Fig. 13. Predicted responses of glucose and insulin via additional insulin loading for simplified dynamic programming without considering barrier cost (red lines: simulated responses, blue circle: clinical data)

Thirdly, the constant A was set to have a value of 100 and found optimal combination to regulate blood glucose level. For the safety, the constraint was assigned that the maximal value of insulin loading concentration per unit time is 0.6 nmol/L. Two insulin profiles have no delayed time and the peaks of insulin loading concentration per unit time were 0.6 nmol/L and 0.5 nmol/L respectively. The lowest blood glucose level was 84.2 (mg/dL) and the 180-min blood glucose level reached at 104.3 (mg/dL). In this manner, simulated glucose response with additional insulin loadings in thirteen type 2 diabetes patients are presented in Fig. 14 and table 2.

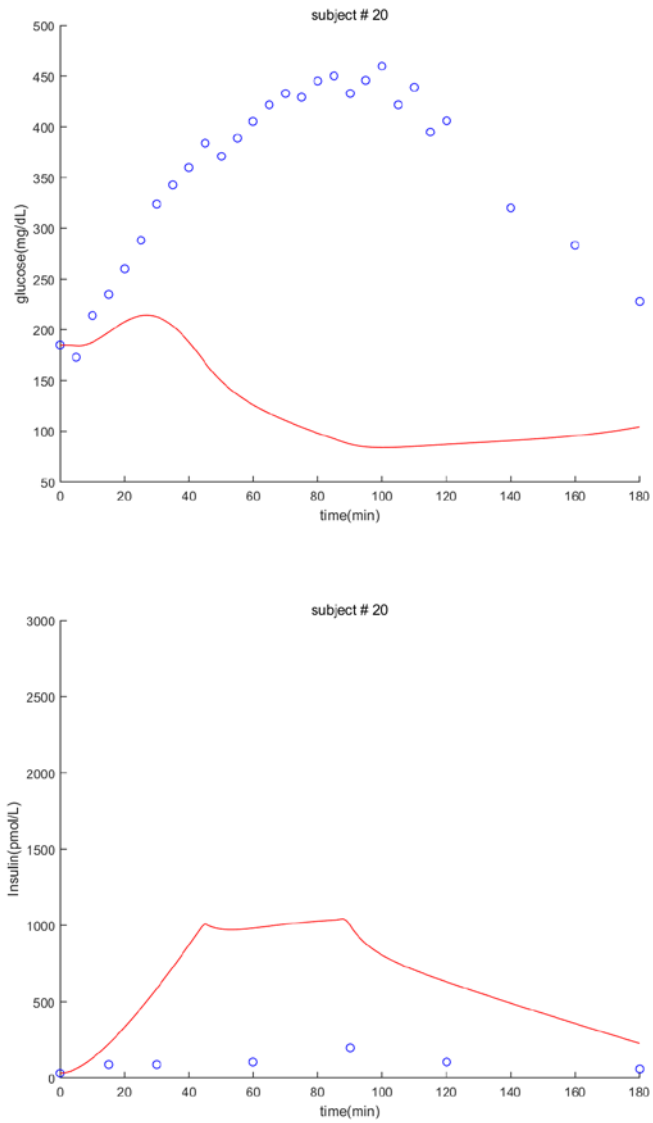


Fig. 14. Predicted responses of glucose and insulin via additional insulin loading for simplified dynamic programming with considering barrier cost (red curves: simulated response, blue circle: clinical data)

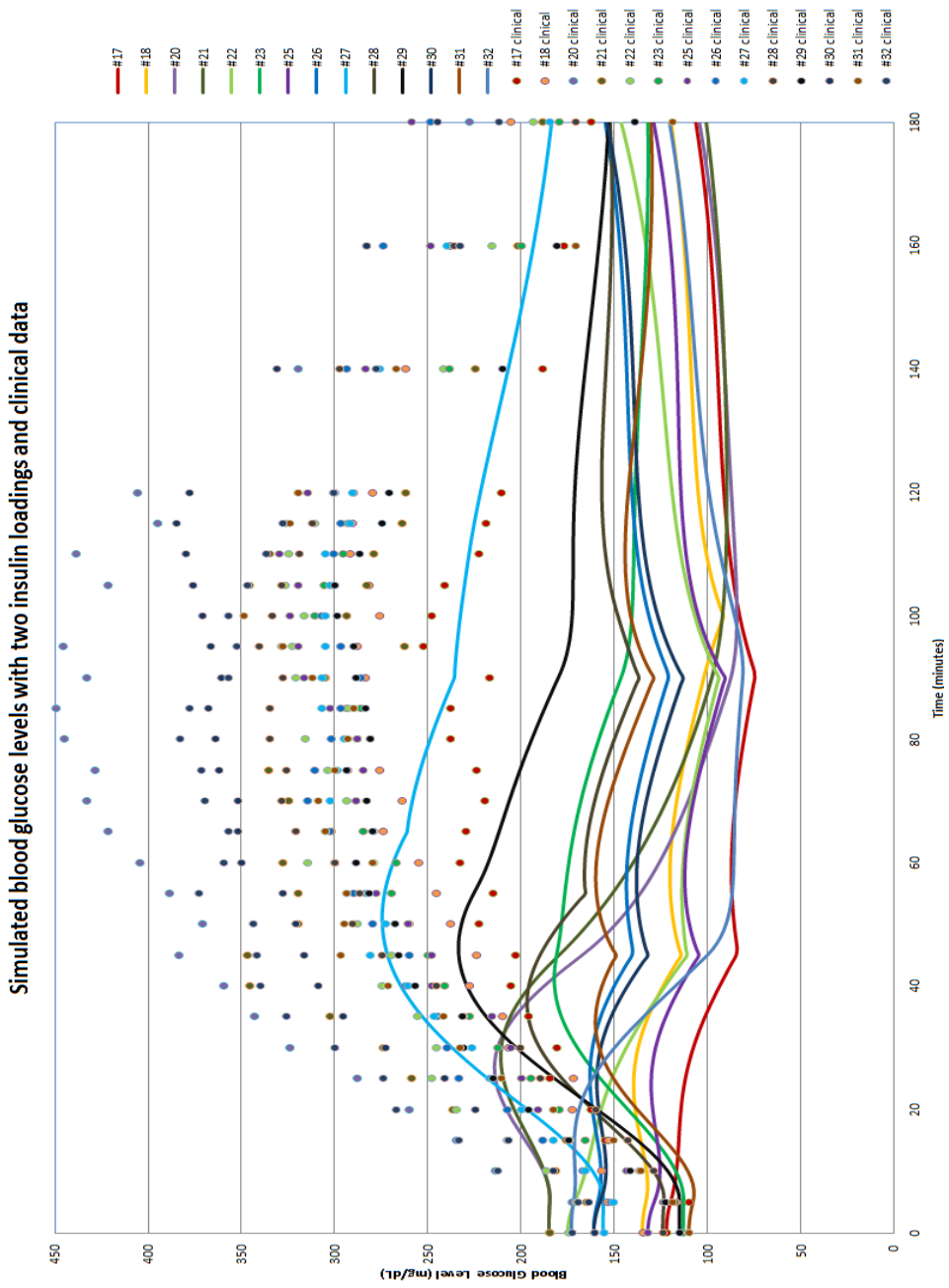


Fig. 15. Simulated blood glucose levels with additional insulin loadings and clinical data

Table 2. Characteristics of simulated blood glucose levels with insulin loading and clinical data

Patient number	Simulated peak plasma glucose (mg/dL)	Peak plasma glucose in clinical data (mg/dL)	Simulated time for peak glucose (min)	Time for peak glucose in clinical data (min)	1st insulin loading peak (nmol/L/min)	1st insulin loading delay (min)	2nd insulin loading peak (nmol/L/min)	2nd insulin loading delay (min)
#17	119.9	248	5	100	0.6	0	0.5	0
#18	139.6	292	24	110	0.6	0	0.6	10
#20	214.3	460	27	100	0.6	0	0.5	0
#21	210.9	347	29	45	0.6	0	0.3	0
#22	171.3	327	5	105	0.6	0	0.6	0
#23	182.2	329	41	95	0.6	0	0.6	0
#25	130.2	330	24	110	0.6	0	0.6	0
#26	163.0	315	25	70	0.1	0	0.1	0
#27	274.5	307	51	85	0.6	20	0.6	0
#28	196.8	341	37	95	0.6	10	0.6	0
#29	233.6	300	46	110	0.6	10	0.6	0
#30	159.4	385	24	115	0.6	0	0.6	0
#31	160.1	349	34	100	0.6	0	0.6	0
#32	171.5	383	14	80	0.6	0	0.3	0
Average (± SD)	180.5 (±42.2)	337.0 (±49.5)	27.6 (±13.7)	93.6 (±18.9)	0.6	3.1	0.5	0.7

5. Discussion

The first part of this study is to find proper parameters in the oral minimal model which can describe the characteristics of glycemic control in vivo for each patient. In most data points, clinical data and simulated curves are well matched, but the change trend of glucose level between 160 and 180 minutes in NGT group was slight different from that of clinical data. It would be due to the structure of the mathematical equations in the oral minimal model, since the linear term of $(G - G_b)$ directly affects the time derivatives of the blood glucose level. Relatively sparse measurement in last 60 minutes compared with the first 120 minutes. It means that the later part of the clinical data has lesser weights in the least square method, so that the last part of the simulated curves may be not well matched than the beginning part of that curves. However if parameters can be updated during the OGTT, then this matching problem would be resolved in the adaptive manner.

Insulin sensitivity (S_I) and beta-cell responsivity indices (Φ_d, Φ_s, Φ_t) were lower in patients with T2DM than in participants with NGT. Compared to the NGT group, insulin sensitivity was 33.9% lower and the dynamic, static, and total beta-cell responsivity indices were 74.1%, 58.3%, and 63.3% lower, respectively, in the T2DM group. This trend is shown in DI metric (Fig. 7). Our results were in line with the previous studies showing decreased insulin sensitivity and insulin secretion in Korean T2DM patients, which were evaluated with the euglycemic hyperinsulinemic clamp method [32], the hyperglycaemic clamp method [33], or the IVGTT-based minimal model [34]. Compared to

other previous methods, the oral minimal model can separately and simultaneously assess insulin sensitivity and dynamic nature of beta-cell responsivity from a single data set with simple test including OGTT.

This study observed the correlations of the oral minimal model indices with pre-existing surrogate measures for insulin sensitivity and/or beta-cell function such as homeostasis model assessment (HOMA) methods [8], Matsuda index [6] and PCGR[7]. The indices obtained from the oral minimal model and other indices of post-loading insulin secretion and insulin sensitivity were well correlated.

In those indices, fasting measures such as HOMA-insulin resistance mainly reflect hepatic insulin sensitivity rather than peripheral insulin sensitivity [35,36]. Because HOMA-beta-cell function is also derived from fasting data [8], it cannot describe the dynamics of postprandial insulin secretion. In contrast, the insulin sensitivity index calculated by the oral minimal model represents not only hepatic but also peripheral insulin sensitivity [2,37,38] based on glucose dynamics. Although Matsuda index using mean insulin and glucose responses during an OGTT well correlates with the insulin sensitivity measured by the euglycemic hyperinsulinemic clamp [32], this index would not be perfectly appropriate for a measure of beta-cell function that reflects the dynamic nature of postprandial insulin secretion. In this regard, the benefits of the oral minimal model are provision of comprehensive measures for insulin sensitivity, beta-cell function, and hepatic extraction of insulin for describing glucose metabolism in vivo.

The oral minimal model can be simpler than the IVGTT-based

minimal model [2,18] which requires much more frequent blood sampling and control for blood glucose concentrations. Therefore, it can be broadly applied for various clinical studies. Firstly, the model can be used to assess characteristics of glucose metabolism in a large number of subjects less invasively. For example, a previous study, which enrolled as many as 250 Japanese and Caucasian subjects, showed lower beta-cell function and higher insulin sensitivity in the Japanese than the Caucasians [39]. Secondly, the oral minimal model can be used to assess the effect of anti-diabetes drugs on insulin sensitivity and beta-cell function, as shown in the other study [40]. In this regards, the oral minimal model may reduce burdens of measuring physiologic parameters of glucose homeostasis in various forms of clinical research.

The oral minimal model has good expandability and can be readily modified in an engineering manner. To develop a further expanded version of the oral minimal model, the incretin effect would be a candidate component to be incorporated to the model. In addition, the gap between simulated responses and clinical data would be filled up with hidden chemicals, hormones and interactions in this manner. If equations describing the incretin effect [41] were considered to the basic form of the oral minimal model, it could become a more physiologic model. Since a glucagon adapted model also has been developed [42], it might be useful to assess glycemic responses to specific anti-diabetic regimens and to establish algorithms for the bihormonal artificial pancreas using insulin and glucagon for stability of control.

Some simulations of control tactics using PID and dynamic

programming to regulate blood glucose level were conducted. When we set the weights in cost function reflecting gaps of glucose in difference and time derivatives of glucose level curves, ratio of weights are determined as 1000:1. But this value can vary with respect to importance of glucose fluctuation and its effect to exhaust beta-cell function. Theoretically, PID control delivers optimal solutions to lower glucose with smooth curves, but always the glucose level is over than the goal of glucose level because of one directional glycemic effect of insulin. In addition, PID control is very sensitive to delayed measurement of glucose levels, so we should think of other control algorithm. Many studies have indicated that MPC algorithm has the better performance than PID control [13,43]. In the brief version of dynamic programming, this study adopted simplified insulin profiles to check feasibility of this approach, and the possibility that optimal control tactics based on the oral minimal model can be adapted in clinical environments exists. In the simulation, the additional insulin loadings with no or short delay were able to decrease blood glucose level and shorten the time for peak blood glucose level in most cases. Insulin profiles is simply added to insulin secretion rates in the oral minimal model, the insulin level may be highly over-estimated because actual external insulin is not directly contained to insulin secretion. So actual insulin profiles based on pharmacokinetics and pharmacodynamics should be combined in the future study for developing virtual patients to be used in pre-clinical tests. Also high insulin level to regulate blood glucose level may be needed because of low insulin sensitivity in type 2 diabetes mellitus. To develop more accurate models, we should consider actual insulin profiles to apply this

control tactics to care patients in reality considering pharmacodynamics, pharmacokinetics, and responses in human tissues.

This study had some limitations and room for improvements. Firstly, in this study, insulin and C-peptide were measured at 0, 15, and 30 min during the first 30 min, whereas other studies [19,26] included 0, 10, 20, and 30 min samples. Since insulin response during the first 30 min is crucial to determine dynamic beta-cell responsivity index closely related with time derivatives of glucose level, more frequent measurements in the beginning of clinical study would be helpful for more accurate estimation. Secondly, this study did not directly validate the oral minimal model indices with values of the hyperglycemic clamp and the euglycemic hyperinsulinemic clamp studies, which are considered as gold standard methods for measurement of insulin secretion and insulin sensitivity. Thirdly, subjects in prediabetes such as impaired fasting glucose or impaired glucose tolerance were not included in this study. If the characteristics of subjects of pre-diabetic conditions are evaluated via the oral minimal model, then the progression of diabetes would be clarified through observing changes of parameters and predicted responses. Lastly, adequate blood glucose level regulations should be considered. With actual characteristics of drugs and insulin, too slow or too rapid changes in blood glucose level would be useless or harmful to patients' health.

Even this study shows the potential of development of computational algorithms to lower glucose level efficiently, clinical guidelines should be well corresponded with the tactics and validation should be checked.

But it would be achievable by using of continuous glucose monitoring systems or clinical trials using OGTT. The oral minimal model can be combined with model predictive control (MPC) algorithm effectively, because previous MPC algorithms use only auto-regression and have no structure based on physiological phenomena. In this point, the oral minimal model has advantages to predict glucose, C-peptide, and insulin responses more precisely and to be applied various situations including open-loop systems. Therefore, the oral minimal models and its applications have huge potential to improve our clinical systems.

6. Conclusion

In this study, in accordance with the results of previously published studies using other physiologic methods in Koreans, the insulin sensitivity index, beta-cell responsivity indices, and disposition indices obtained in the oral minimal model were generally lower in the T2DM group than the NGT group. Based on our results, the oral minimal model can also be properly applied to Koreans to evaluate insulin sensitivity and dynamics of insulin secretion using OGTT.

Secondly, some optimization and control issues based on the oral minimal model were investigated in this study. Mathematical models to describe physiological phenomena are accompanied with optimization methodologies to find precise parameters and to establish pertinent control tactics based on clinical data and analyses of systems. With this approaches, it is expected that the complex physiology of glucose metabolism can be deeply understood and therapeutic methods including clinical protocols and artificial pancreas can be designed efficiently.

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요약 (국문초록)

생리학적 현상을 묘사하기 위한 수학적 모델에서는, 모델을 바탕으로 상태를 나타내는 최적의 파라미터를 파악하고, 이를 바탕으로 비정상적인 변수를 정상 범위로 되돌릴 수 있는 제어가 중요하다. 이를 위해서는 우선적으로 임상적 데이터를 바탕으로 모델의 유효성을 평가해야 하며, 이를 통해 각 환자에 맞는 최적 알고리듬을 설계할 수 있다.

경구최소모델은 체내의 포도당 대사를 묘사하기 위한 시스템으로 볼 수 있으며, 베타세포의 기능과 인슐린 민감도를 평가하기 위한 유용한 수학적 모델이다. 본 연구에서는 10명의 정상 내당능을 가진 자원자와 14명의 제2형 당뇨병을 지닌 자원자를 대상으로 임상 연구를 통해 베타세포의 기능과 인슐린 민감도를 평가하였다.

경구최소모델을 통해 각 자원자의 혈당, C-peptide, 인슐린 반응을 예측할 수 있었다. 정상 집단에서의 혈당에 대한 평균 제곱근 편차는 11.74 ± 1.38 (mg/dl), 제2형 당뇨 환자 집단에서는 24.44 ± 12.16 (mg/dl) 이었으며, 정상 집단에서 C-peptide에 대한 평균 제곱근 편차는 0.15 ± 0.04 (nmol/L), 제2형 당뇨 환자 집단에서는 0.16 ± 0.08 (nmol/L) 였다. 또한

인슐린 민감도 (13.3 ± 11.8 vs. 20.0 ± 8.2 [$\times 10^{-5}$ dl/kg/min per pmol/L], p = 0.024), 베타세포 반응성 (동적 반응성 Φ_d: 170.9 ± 138.7 vs. 661.7 ± 411.1 [$\times 10^{-9}$], $p < 0.001$, 나이 보정 p = 0.005; 정적 반응성 Φ_s: 13.9 ± 6.5 vs. 33.5 ± 9.4 [$\times 10^{-9}$ min^{-1}], $p < 0.001$, 나이 보정 $p < 0.001$; 전체 반응성 Φ_t: 15.5 ± 7.2 vs. 41.9 ± 13.2 [$\times 10^{-9}$ min^{-1}], $p < 0.001$, 나이 보정 $p <$ 0.001) 및 Disposition Index (동적 DI_d: 20.7 ± 19.9 vs. 114.7 ± 74.6 [$\times 10^{-12}$ dl/kg/min per pmol/L], p=0.001, 나이 보정 p<0.001; 정적 DI_s: 1.6 ± 1.0 vs. 6.4 ± 2.8 [$\times 10^{-12}$ dl/kg/min^2 per pmol/L], p <0.001, 나이 보정 $p < 0.001$; total DI_t: 1.8 ± 1.1 vs. 7.9 ± 3.4 [$\times 10^{-12}$ dl/kg/min^2 per pmol/L], $p < 0.001$, 나이 보정 $p < 0.001$)는 제2형 당뇨 그룹이 정상 집단보다 낮음을 확인하였으며, 기존에 쓰이는 임상적 지표와의 상관분석을 통해 경구최소모델의 지표도 임상적 의의와 유효성이 있음을 밝힐 수 있었다. 즉, 한국인에게도 이러한 경구최소모델이 잘 적용될 수 있음을 확인할 수 있었다.

더불어 이러한 경구최소모델을 바탕으로 PID 제어 및 간단한 동적 프로그래밍을 이용하여, 제2형 당뇨 환자에서 혈당 제어에 관한 용법과 알고리즘을 구축하였다. PID 제어의 경우, 급격한 변이 없이 혈당을 적절히 낮출 수 있음을 보여주었다. 또한 두 개의 인슐린 로딩을 통해 구성된 최적 제어의

경우에도 마찬가지로 혈당을 효율적으로 낮출 수 있었으며, 비용 함수에서 장벽을 고려한 경우 혈당이 너무 낮아지는 것을 방지할 수 있었다. 14명의 당뇨 환자를 대상으로 살펴보았을 때, 대부분의 경우 두 가지 프로필의 인슐린을 초기에 주입하는 것이 효율적인 혈당 조절을 위해 추천되었다.

이를 바탕으로 포도당 대사의 숨겨진 상호작용을 밝혀내고 인공 췌장에 적용될 수 있는 모델로서 경구최소모델이 기능할 수 있는 가능성을 확인하였다.

주제어: 경구최소모델, 포도당 대사, 인슐린 민감도,
베타세포 반응성, 최적화, 제어

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