Title: Simple Self-Administered Method for Assessing Insulin Sensitivity in Diabetic Patients

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Running title: **Self-Administered Method for Assessing Insulin Sensitivity**

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ABSTRACT

Several methods have been proposed for evaluating a person's insulin sensitivity from an oral glucose tolerance test (OGTT) and the euglycemic insulin clamp technique. However, none are easy or inexpensive to implement since the plasma insulin concentration, a key variable for assessing the insulin sensitivity index (ISI), is required to be clinically measured at specific times. Therefore, the purpose of this study is to develop a new ISI that can be easily and accurately obtained by patients themselves without costly, time-consuming, and inconvenient testing methods. This study proposes a simple self-administered testing method, simulated on a computerized model of type II diabetic patients, for estimating the ISI. The test involves a 75-g glucose ingestion and two injections of 10 mU/kg insulin. Blood glucose is measured one and two hours later. The test was evaluated by using a previously developed diabetic-patient dynamic model. Fifteen sets of OGTT data from diabetic patients published in the literature were used for the model development. A simulation of the proposed self-administered test indicates that the proposed ISI correlates well with the ISI called M-value obtained from the gold standard but elaborate euglycemic hyperinsulinemic clamp (r = 0.927, p = 0.0045). The proposed ISI is considered to be easy to perform, time-saving, inexpensive, and accurate enough for clinical assessments.

Keywords: Insulin sensitivity index, Type II diabetes mellitus, Modeling, Parameter estimation, Dynamic simulation

1. Introduction

Insulin is a key hormone secreted from β-cells in the pancreas that regulates glucose homeostasis. Type II diabetes is characterized by both insulin resistance and decreasing β-cell mass [1]. Insulin resistance happens when the sensitivity of peripheral cells to the metabolic action of insulin is decreased due to genetic or environmental factors, obesity, hypertension, dyslipidemias, and/or coronary artery diseases. The ability of insulin to stimulate body glucose disposal can be characterized by an insulin sensitivity index (ISI) [2-5].

Various methods have been developed for determining the presence and degree of insulin resistance. The hyperinsulinemic euglycemic insulin clamp technique has been widely used as a gold standard for understanding insulin resistance in vivo [6]. In this technique, the plasma insulin concentration is raised and maintained at a fixed level (approximately 100 mU/l) by a continuous intravenous insulin infusion. A measure of tissue insulin sensitivity can be reflected by the glucose infusion rate during the steady state of the euglycemic insulin clamp test. The glucose infusion rate is called the M-value. For someone with low insulin sensitivity, the M-value will be low because the person's body is less sensitive to insulin. Therefore, the body's glucose level does not drop significantly low. On the other hand, when a person is very sensitive to insulin, the M-value will be high; i.e., a high glucose infusion rate is required to maintain the euglycemic level [6]. The hyperinsulinemic euglycemic glucose clamp method is labor-intensive, expensive, and limiting for large-scale clinical studies [7].

More accurate and less labor-intensive than the glucose clamp technique is a modified minimal model (MINMOD) analysis in conjunction with the frequently sampled intravenous glucose tolerance test (FSIVGTT) [8] for the estimation of insulin sensitivity. However, the FSIVGTT is still restrictive for large studies [4,7]. Homeostasis model assessment (HOMA) of

insulin resistance (HOMA-IR) [9], fasting plasma insulin [10], and the fasting-glucose-to-insulin ratio [11] are simple indices of insulin resistance compared with the glucose clamp test. However, they produce relatively low values when the insulin secretion decreases in advanced type II diabetic patients since all are based on fasting glucose and insulin levels [12].

Recently, several methods have been investigated from oral glucose tolerance test (OGTT). Cederholm and Wibell [13] proposed a formula for ISI that uses the OGTT based on four timed samples of insulin and glucose (at 0, 30, 60, and 120 min). It has fairly good agreement with more complicated procedures, such as the clamp test and the insulin suppression test. Simple ISI were derived based on the OGTT by Matsuda and DeFronzo [14], Stumvoll et al. [15], and Gutt et al. [16]. Although these methods are relatively easy to conduct, accurate, and adaptable to both population studies and clinical settings, they are not inexpensive, self-monitoring, and convenient since the plasma insulin level must be measured at a specific time as a key variable for calculating these indices in medical labs.

The present study proposes a new ISI estimated from capillary blood glucose measurements. Our approach is to evaluate the feasibility of using the mathematical compartment model proposed by Vahidi et al. [17,18] to estimate insulin sensitivity. The Vahidi model is a much more detailed dynamic model comparing with the MINMOD approach [8]. MINMOD includes three nonlinear differential equations representing variations of plasma insulin and glucose concentrations. The Vahidi model consists of more compartments for better representation of the glucose and insulin concentrations in different parts of a human body. The application of additional compartments allows for a more accurate simulation of the physiological dynamics and individual abnormalities of type II diabetic patients. For our model development, fifteen available patterns of glucose and insulin concentrations during a 2-h 75-g

OGTT for diabetic and non-diabetic subjects were included. Then, we simulated the changes of glucose and insulin concentrations after consumption of 75-g glucose at 0 min and two injections of 10 mU/kg insulin into the bodies of fifteen subjects at 20 and 50 min. Based on the available measurements, an ISI was estimated, which is shown to correlate well with the insulin sensitivity measured by the euglycemic clamp technique described in Section 4. From the clamp method, the insulin sensitivity is reported as the body's glucose uptake rate, called the M-value [6].

2. Mathematical modeling of type II diabetes mellitus

In the present work, the detailed compartmental model of glucose-insulin interactions in a group of type II diabetic patients developed by Vahidi et al. [18] is used. This model is based on the initial work by Guyton et al. [19], which was updated by Sorensen [20]. The model contains three sub-models, which represent blood insulin, glucose, and glucagon concentrations in the body, respectively; each is divided into individual numbers of compartments representing a specific part or organ of a human body. Section 2.1 provides a summary description of the Vahidi model.

2.1 Insulin, glucose, and glucagon sub-models

In the Vahidi model, different numbers of compartments are considered in the insulin, glucose, and glucagon sub-models based on the significance of the organ's function in maintaining the respective solute concentrations. Figure 1 shows the overall structure of the insulin sub-model, which contains seven compartments: brain, liver, heart and lungs, periphery, gut, kidney, and pancreas [21]. The blocks represent different compartments and the arrows indicate the blood flow directions. Similarly, the glucose sub-model has the same compartments except for the pancreas compartment, since only insulin is secreted from the pancreas. Since the

glucagon concentration is considered to be identical in all parts of the body, only one compartment is considered in the glucagon sub-model.

In each sub-model, mass balance equations are written for all individual sub-compartments (except for the pancreas). The general form of the mass balance equation for each sub-compartment is as follows [22]:

$$V\frac{dY}{dT} = Q(Y_{in} - Y_{out}) + r_p - r_c \quad (1)$$

where V is the volume of sub-compartments, Y is the concentration of either insulin, glucose, or glucagon, t is time, Q is the blood flow rate, and r_p and r_c are metabolic production and consumption rates of the material balance substance, respectively. Since the glucagon sub-model only has one compartment, the blood flow rate is set to zero and the glucagon mass balance equation only has the metabolic production and consumption rates. The metabolic rate of different substances has the following general form [22]:

$$r = M^I(t,I)M^G(G)M^\Gamma(t,\Gamma)r^B \quad (2)$$

where I, G, and Γ represent insulin, glucose, and glucagon substances, respectively. M^I, M^G and M^Γ *are* the multipliers representing the regulatory effect of I, G, or Γ on the metabolic rate respectively. r^B is the metabolic rate at the basal condition. The general mathematical form of the multiplicative effect of each substance is [22]:

$$M^i = a + b\tanh[c(\frac{i}{i^B} - d)] \quad (3)$$

where i^B is the concentration of *I*, *G*, or *Γ* at the basal condition and *a*, *b*, *c*, and *d* are the model parameters, which are estimated from the patient's blood glucose and insulin measurements.

As described above, the Vahidi model includes mass balance equations for each sub-compartment within an individual compartment (e.g., the liver is subdivided into two sub-compartments, namely the capillary space and the interstitial space). However, due to the complex mechanism of pancreatic insulin production, a different modeling structure was used for the pancreas. In the pancreas model, insulin is exchanged between a small labile insulin unit and a large stored insulin unit. The rate of insulin secretion from the labile insulin compartment is a function of the glucose concentration, the amount of labile insulin *m*, and the instantaneous level of glucose-enhanced excitation factor *X* and its inhibitor *R*. Based on earlier data analysis, the insulin secretion rate (*S*) is calculated as follows [22]:

$$\begin{aligned} S &= [N_1 X^{1.11} + N_2 (X - R)]m \qquad X > R \\ S &= (N_1 X^{1.11})m \qquad\qquad\qquad X \leq R \end{aligned} \tag{4}$$

where constants N_1 and N_2 are the unknown model parameters, which are estimated from the patient's blood glucose and insulin measurements.

2.2 Nonlinear optimization for obtaining Vahidi sub-model parameters

The Vahidi model provides the detailed structure for the simulation of type II diabetes mellitus. For each individual patient, the Vahidi model parameters must be estimated using the patient's own glucose and insulin measurements. The modified model parameters were estimated through an iterative optimization algorithm using a sequential quadratic programming (SQP) method. In this optimization problem, the deviation of model predictions from the available

measurements of peripheral glucose, insulin, and incretin concentrations is minimized through the following objective function [23]:

$$\min_{Q} \sum_{j=1}^{n} [(G^j - \hat{G}^j)^2 + (I^j - \hat{I}^j)^2] \quad (5)$$

where G^j and I^j are the peripheral glucose and insulin concentrations at time j obtained from the model, respectively; $\hat{G}^j$ and $\hat{I}^j$ are the corresponding clinical measurements; n is the number of samples in the clinical data set; and Q is the vector of parameters containing the glucose, insulin, and glucagon metabolic rates defined in Eq. (3).

3. Clinical data used for model development

The aim of this study is to develop a simple measure of insulin sensitivity by using a self-assessment test without laboratory requirements. From a literature review of OGTT, it was found that the pattern of glucose response to insulin varies from patient to patient. To ensure that the proposed test for estimating the ISI is valid for all available patterns of glucose and insulin concentrations, different sets of blood glucose and insulin measurements must be used for the estimation of the Vahidi model parameters. Different sets of clinical data for type II diabetic patients have been published in the literature from the 2-h 75-g OGTT. Based on the Canadian Diabetes Association 2013 criteria [24], the diagnostic criteria for diabetes are summarized in Table 1.

From our literature survey, it was found that the insulin concentration profile during an OGTT can be grouped in to a few patterns. Hayashi et al. [25] derived four possible patterns of insulin profile from a study involving 400 non-diabetic Japanese Americans. They concluded that the insulin concentration pattern during an OGTT strongly predicts the development of type

II diabetes and is correlated with measures of insulin sensitivity. Bakari and Onyemelukwe [26] studied the plasma insulin pattern both in the fasting state and in response to a standard OGTT in 42 type II diabetic Nigerians and 36 healthy control subjects. They found that the type II diabetic patients demonstrated both fasting and post-OGTT hypoinsulinaemia. Therefore, for our model development, fifteen available patterns of glucose and insulin concentrations during the 2-h 75-g OGTT for diabetic and non-diabetic subjects were included. Table 2 shows the details of the fifteen patterns influenced by insulin sensitivity.

After the Vahidi model had been developed, fifteen simulated patients were used for the development and evaluation of a self-assessment method for obtaining the ISI. The next section describes the development of the proposed method for obtaining the ISI.

4. Proposed self-assessment method for estimation of insulin sensitivity

Several authors proposed various indices for measuring insulin sensitivity by using fasting state or OGTT data and correlated the indices with the data obtained from the hyperinsulinemic euglycemic clamp test. Formulas proposed for calculating the ISI are based on the intercorrelations between the concentrations of glucose and insulin and other parameters. However, they all require the measurements of plasma insulin levels sampled at specific times by laboratory equipment, which is expensive and inconvenient. Therefore, a more practical method for obtaining the ISI is the focus of this research.

A practical test for obtaining the ISI should not require plasma insulin measurements and only need capillary blood glucose measurements. Capillary blood glucose refers to the blood glucose concentration measured from capillary blood vessels. This is most commonly done by a finger prick test by a diabetic patient. The plasma insulin measurement refers to the actual insulin concentration in a person’s blood sampled and measured by a lab technician.

For type II diabetic patients, the body is suffering from some insulin resistance and it requires larger amounts of insulin either from the pancreas or from injections to lower their plasma glucose level compared to that of an insulin-sensitive body. For those with severe insulin resistance, the normal physiological response to a given amount of insulin is blunted. As a result, higher levels of insulin are needed to achieve a proper effect.

In light of this, we propose a simple testing approach, in which the simulated patients take a dose of oral glucose ingestion followed by multiple insulin injections at different times. The proposed test is considered clinically acceptable and safe as the insulin dosage can be selected with a large safety margin. We have conducted extensive simulation with different combinations of testing protocols on the fifteen simulated patients using the Vahidi model. After the extensive simulations, we have found that the ISI can be estimated by patients completing a simple testing protocol, which includes two procedures on two separate occasions.

In the first procedure, the fifteen simulated subjects were given a single dose of 75-g glucose. The plasma glucose concentrations of the fifteen subjects were sampled in order to check how their bodies suppress the plasma glucose level with no insulin injection.

In the second procedure, a single dose of 75-g glucose was given to the fifteen simulated subjects. Then, 10 mU/kg insulin was injected twice subcutaneously into the body of the simulated subjects 20 and 50 min after glucose consumption since the major response to a moderate load occurs within 15 min of glucose ingestion [30,31]. The plasma glucose concentrations of the fifteen subjects were sampled in order to check how their bodies regulate the plasma glucose level with two insulin injections.

After statistical evaluation, it was found that the differences in the plasma glucose concentration profile of each subject from the first and second procedures can be used to define a

formula for the ISI. The formula adopted for the estimation of the ISI is described in Section 5.2. This section also shows how well the proposed index correlates with the ISI (called M-value) obtained from the euglycemic insulin clamp technique.

5. Results and discussion

The Vahidi model includes a set of nonlinear ordinary differential equations and algebraic equations. The model parameters are estimated through an iterative optimization algorithm using an SQP method, as described in Section 2.2. The estimated parameters are then used to solve the Vahidi model equations. The optimization was carried out in MATLAB.

5.1 Parameter estimation results

Since different patterns of glucose and insulin concentrations result in different sets of parameters in the Vahidi model, for each subject in Table 2, a set of parameters was estimated using the nonlinear optimization algorithm described in Section 2.2. As an example, using the raw data of subject 1 in Table 2, the estimated model parameters for the glucose and insulin sub-models presented in Eq. (3) and Eq. (4) are shown in Table 3 and Table 4, respectively.

The model estimation results of the fifteen subjects from Table 2 are shown in Figs. 2 and 3. The goodness of fit between the model estimation and the available clinical data set can be calculated using different cost functions in MATLAB. In this paper, the goodness of fit is calculated using the mean square error (MSE) as a cost function:

$$MSE = \frac{\left| x - x_{ref} \right|^2}{N_s - 1} \tag{6}$$

where x is the glucose or insulin concentration matrix estimated by the model, x_{ref} is the available glucose or insulin concentration from Table 2 as the reference, and N_s is the number of

actual measured clinical data. From Eq. (6), the overall average goodness of fit for all fifteen subjects is 92%. The simulated trends are reasonably consistent with the actual clinical data from both a visual inspection and the average goodness of fit.

5.2 Quantitative estimation of insulin sensitivity

In order to validate the proposed protocol for estimating the ISI , the M-values from the euglycemic insulin clamp test were obtained for the fifteen subjects from the simulated models. To perform the euglycemic insulin clamp test on the simulated bodies of the fifteen subjects with the Vahidi model, the plasma insulin concentration was acutely raised and maintained at 100 μU/ml by a continuous infusion of insulin. Meanwhile, the plasma glucose concentration was held constant at basal levels by a variable glucose infusion in MATLAB. Then, proposed testing protocols described in Section 4 were applied to the fifteen simulated subjects.

The plasma glucose concentration profiles of each subject from the first and second procedures are plotted in Fig. 4. From Fig. 4, the plasma glucose level for insulin-sensitive subjects 2, 5, 8, 9, and 10 were suppressed significantly after the two insulin injections. However, the peripheral glucose concentration profile did not change after the two insulin injections for insulin-resistant subjects 1, 3, 4, 6, 7, 11, 12, 13, 14, and 15.

In the same figure, the maximum differences between plasma glucose levels in the insulin-sensitive subjects occur almost at 60 min and 80 min after glucose consumption because of the two insulin injections. In statistics, multiple linear regression is an approach for modeling the relationship between two or more explanatory variables denoted X and a response variable y by fitting an equation to observed data. To find a new ISI, step-wise multiple regression analysis was performed with the M-value as the dependent variable (y) and the glucose concentrations at

fasting (0 min), 60 min, and 80 min after ingestion of 75-g glucose as the three independent variables (X) in MATLAB. The obtained ISI equation from the multiple regression analysis is:

$$ISI = 44.071 - 0.1534 \times FPG - 0.1855 \times G_{60\text{min}} + 0.182 \times G_{80\text{min}} - \left(\frac{1.95}{FPG} + \frac{6.81}{G_{60\text{min}}} - \frac{5.88}{G_{80\text{min}}} \right) \times 10^3 \quad (7)$$

where FPG, $G_{60\ \text{min}}$, and $G_{80\ \text{min}}$ are the peripheral glucose concentrations in mg/dl at fasting (0 min), 60 min, and 80 min after ingestion of 75-g glucose, respectively.

The means and standard deviations were computed in MATLAB for the defined insulin sensitivity and M-values. Pearson's r coefficient was used for the calculation of correlations between these two measures. The scatter plot of the relationship between the M-value and the ISI from Eq. (7) for each subject is shown in Fig. 5. Both the Pearson's coefficient (r = 0.927) and the p-value (p = 0.0045) indicate a strong correlation between the new ISI and the M-value from the euglycemic clamp test.

Previous ISIs derived from the OGTT data require the measurements of plasma insulin levels at specific times by laboratory equipment, which is inconvenient, time-consuming, and expensive. The proposed ISI can be estimated from data collected by diabetic patients who need to frequently monitor their status without the need for expensive laboratory facilities. In the next section, other estimated ISIs calculated from the OGTT data are shown in Table 2 for comparison.

5.3 Comparison of various insulin sensitivity indices obtained from OGTT

The derivations of other indices obtained during the OGTT are briefly presented here. The index of whole-body insulin sensitivity derived by Matsuda and DeFronzo [14] calculates insulin sensitivity from plasma glucose (mg/dl) and insulin (mU/l) concentrations in the fasting

state and during the OGTT. Stumvoll et al. [15] proposed several ISI equations, which were obtained from multiple linear regression analysis. The equations calculate the insulin sensitivity from plasma glucose (mmol/l) and insulin (pmol/l) concentrations during the OGTT. The Gutt index ($ISI_{0,120}$) [16] was adopted from the ISI proposed by Cederholm and Wibell [13]. The calculation of $ISI_{0,120}$ ($mg \cdot l^2 \cdot mmol^{-1} \cdot mlU^{-1} \cdot min^{-1}$) only uses the fasting (0 min) and 120-min concentrations of glucose and insulin during the OGTT.

These three ISIs calculated from the OGTT data are shown in Table 2 to compare the correlation of each index with the M-value. Table 5 shows the Pearson's correlation of each measurement of insulin sensitivity with the M-value computed in MATLAB. As can be seen from Table 5, the correlation of the proposed ISI with the M-values is significantly stronger than those of the other indices, ($r = 0.927$, $p = 0.0045$). Although Table 5 shows a very promising and convenient ISI estimation, a proper comparison should be done by applying the proposed ISI protocol to real subjects. This will be part of our future work plan.

6. Conclusion

In this study, the feasibility of using the mathematical compartment model proposed by Vahidi et al. [17,18] to estimate insulin sensitivity has been evaluated. Fifteen sets of OGTT data from diabetic patients published in the literature have been used to estimate the Vahidi model parameters. From the estimated model parameters, a simple method for conveniently estimating insulin sensitivity by patients themselves has been developed and evaluated. It is shown that, the proposed method yields an ISI measure, which is strongly correlated with the M-value obtained from the euglycemic clamp test ($r = 0.927$, $p = 0.0045$).

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FIGURE CAPTIONS

Figure 1. Schematic diagram of insulin sub-model [18].

Figure 2. Plasma glucose concentration profile (mg/dl) for fifteen subjects (clinical data (●), model results (solid line)).

Figure 3. Plasma insulin concentration profile (μU/ml) for fifteen subjects (clinical data (●), model results (solid line)).

Figure 4. Effect of insulin injection in fifteen subjects, two 10 mU/kg insulin injections at 20 and 50 min (-), respectively, and no injection (--).

Figure 5. Correlation between proposed ISI and M-value for fifteen subjects *(r* = 0.927, *p* = 0.0045).

TABLE CAPTIONS

Table 1. Diagnosis of diabetes [24].

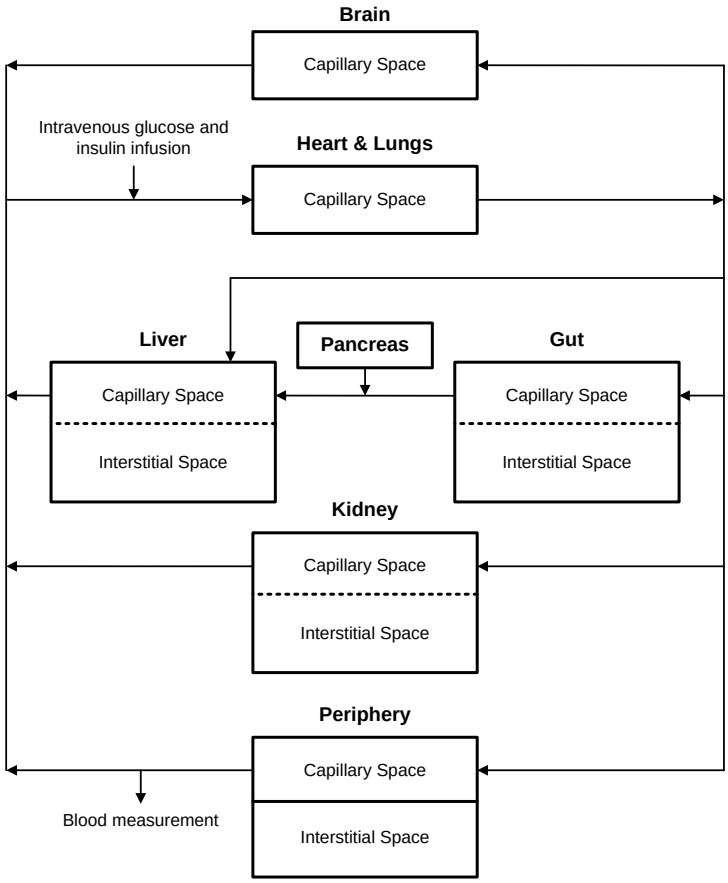
Table 2. Mean plasma glucose and insulin levels during OGTT.

Table 3. Parameter estimation results for glucose sub-model (subject 1).

Table 4. Parameter estimation results for insulin sub-model (subject 1).

Table 5. Pearson correlations with M-Value and results of correlation comparisons.

Figures:



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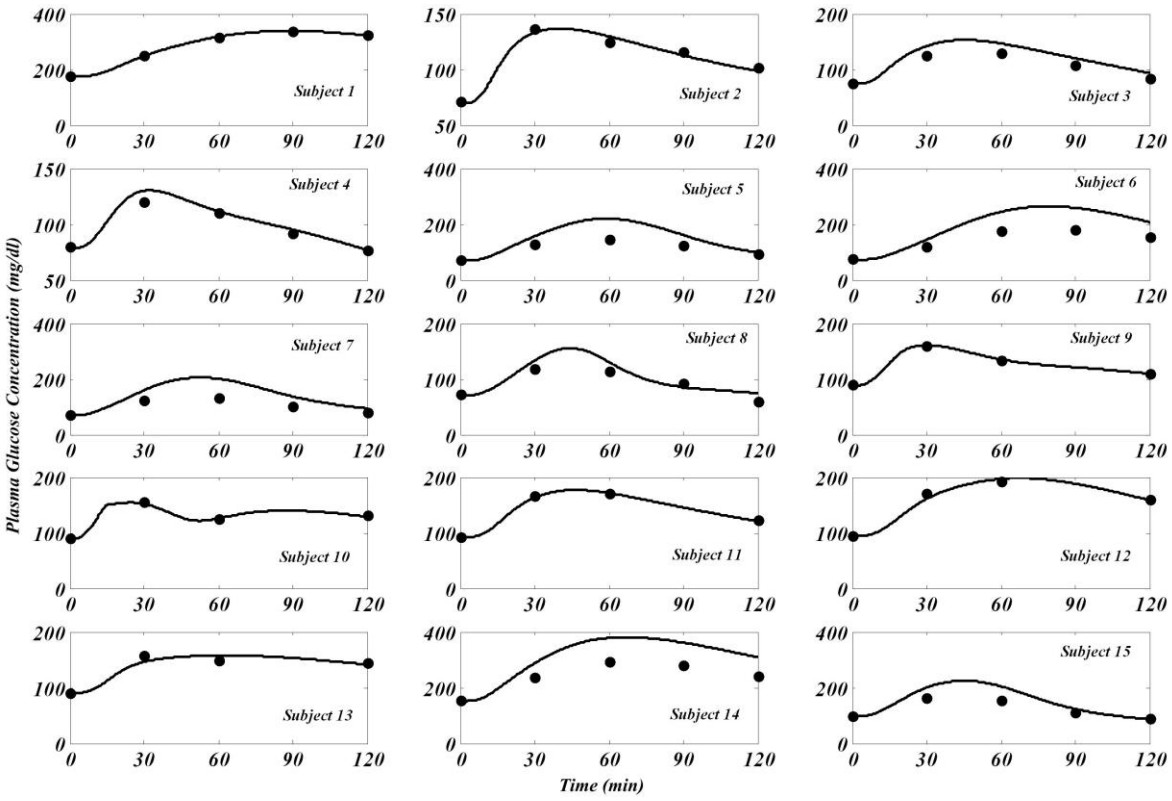

Figure 2. Plasma glucose concentration profile (mg/dl) for fifteen subjects (clinical data (●), model results (solid line)).

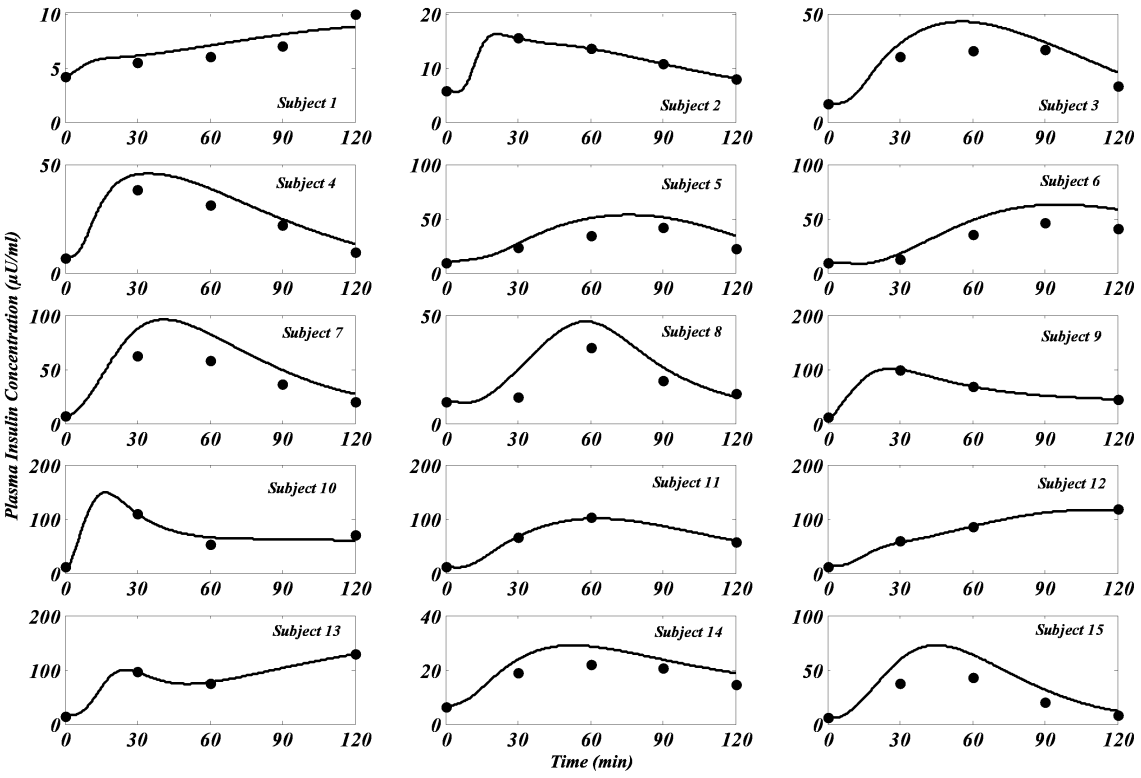

Figure 3. Plasma insulin concentration profile (μU/ml) for fifteen subjects (clinical data (●), model results (solid line)).

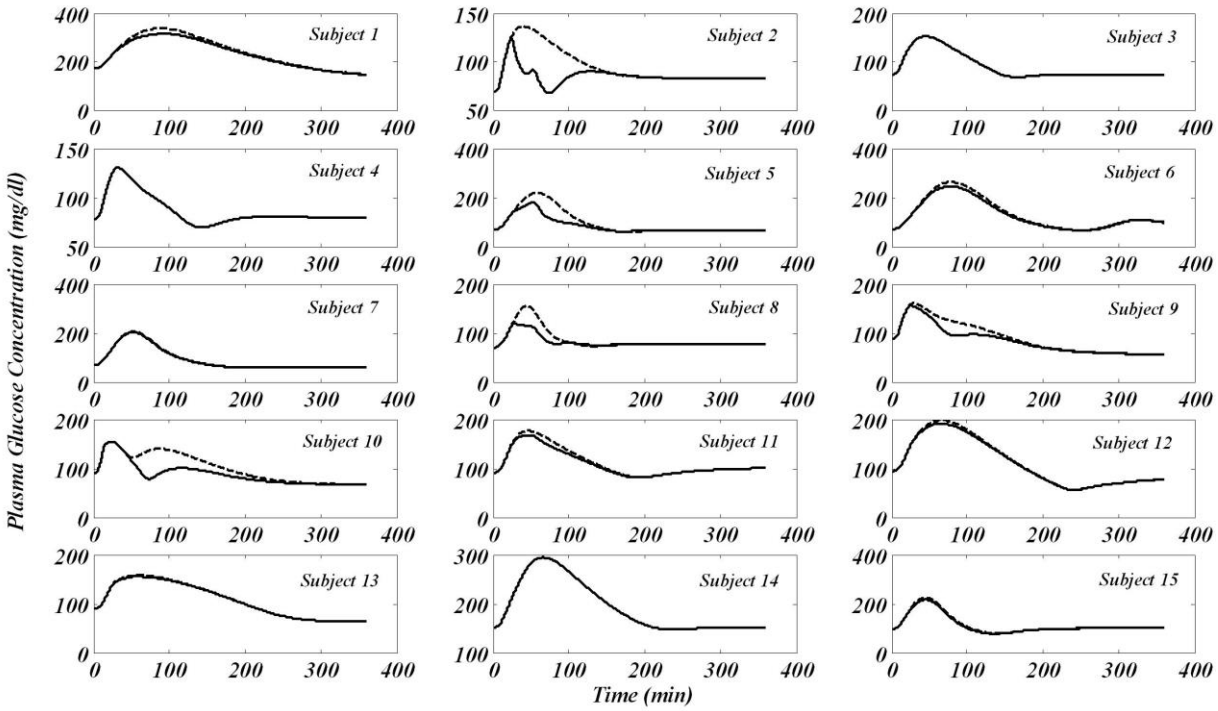

Figure 4. Effect of insulin injection in fifteen subjects, two 10 mU/kg insulin injections at 20 and 50 min (-), respectively, and no injection (--).

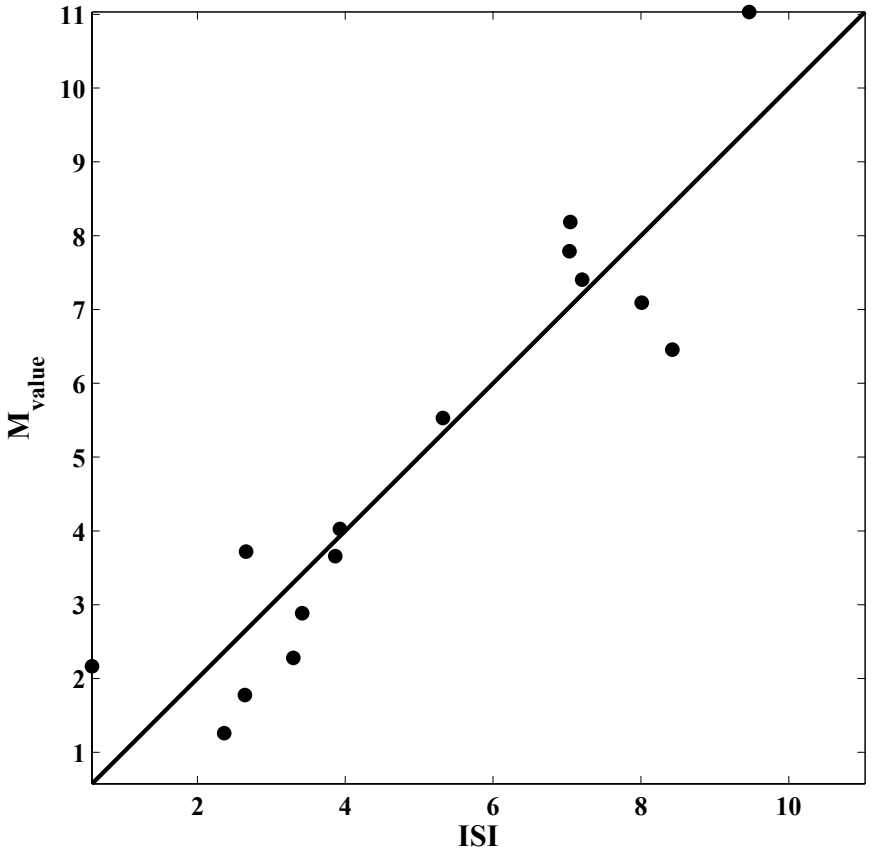

Figure 5. Correlation between proposed ISI and M-value for fifteen subjects *(r* = 0.927, *p* = 0.0045).

Tables:

Table 1. Diagnosis of diabetes [24].

Type	FPG (mg/dl)	2-h PG (mg/dl)
Normal (N)	< 110	< 140
Impaired glucose tolerance (IGT)	<110	140-199
Impaired fasting glucose (IFG)	110-125	<140
Combined IFG and IGT	110-125	140-199
Type II diabetes mellitus (TIIDM)	≥126	≥200

Table 2. Mean plasma glucose and insulin levels during OGTT.

Subject	Plasma glucose during OGTT (mg/dl)					Plasma insulin during OGTT (µU/ml)					Reference
	0 min	30 min	60 min	90 min	120 min	0 min	30 min	60 min	90 min	120 min	
1	175.86	249.84	315.00	338.40	323.64	4.20	5.50	6.01	6.98	9.92	[26]
2	71.10	135.90	124.92	116.10	101.34	5.72	15.58	13.67	10.48	8.03	[26]
3	75.29	125.71	129.13	108.50	84.67	8.18	30.00	33.05	33.47	16.77	[27]
4	80.00	120.40	110.40	92.10	76.50	7.00	38.40	31.10	21.90	9.30	[27]
5	71.30	130.20	145.00	122.40	91.60	9.20	23.10	34.70	41.90	21.90	[27]
6	74.00	121.00	177.00	180.00	154.00	9.00	13.00	35.00	46.00	41.00	[27]
7	71.00	125.00	134.00	103.00	80.00	7.00	62.00	58.00	36.00	20.00	[27]
8	72.00	118.00	115.00	92.00	62.00	10.00	12.00	35.00	20.00	14.00	[27]
9	89.90	160.2	134.20	-	109.00	11.30	98.90	68.40	-	43.70	[25]
10	90.90	154.80	124.70	-	130.80	11.60	109.80	53.90	-	71	[25]
11	93.30	166.20	171.40	-	122.10	11.70	66.80	103.90	-	58.30	[25]
12	95.50	171.30	193.30	-	159.10	12.70	59.60	86.70	-	118.90	[25]
13	91.30	158.10	148.50	-	144.80	14.90	96.40	74.80	-	130.20	[25]
14	153.40	238.40	292.58	278.68	239.89	6.47	18.88	22.00	20.64	14.57	[28,29]
15	97.75	164.68	154.54	110.50	87.61	5.52	37.75	42.63	19.58	7.89	[28,29]

Table 3. Parameter estimation results for glucose sub-model (subject 1).

Multiplier in Eq. (3)	***a***	***b***	***c***	***d***
M^{I}_{PGU}	7.035	6.516	0.150	4.000
$M^{I¥}_{HGP}$	1.425	1.406	0.607	0.241
$M^{I¥}_{HGU}$	0.001	2.000	1.500	0.001
M^{G}_{HGU}	5.664	5.658	2.013	1.678

Table 4. Parameter estimation results for insulin sub-model (subject 1).

Parameter in Eq. (4)	**Value**
N_1 ***(min^{-1})***	1.096
N_2 ***(min^{-1})***	0.654

Table 5. Pearson correlations with M-Value and results of correlation comparisons.

Measure	**Formula**	**Correlation with M-value**		**Reference**
ISI_Matsuda	$\frac{10000}{\sqrt{FPG \cdot FPI \cdot G_{mean} \cdot I_{mean}}}$	r = -0.43	p = 0.1	[14]
ISI_Stumvoll	$0.156 - 0.0000459 \cdot I_{120\min} - 0.0000321 \cdot FPI - 0.0054 \cdot G_{120\min}$	r = 0.47	p = 0.0794	[15]
ISI_Gutt	$\frac{(75000 + (FPG - G_{120\min}) \cdot 0.19 \cdot BW)}{G_{mean} \cdot \log I_{mean}}$	r = 0.2965	p = 0.28	[16]

Proposed ISI	Eq. (7)	r = 0.927	p = 0.0045	-