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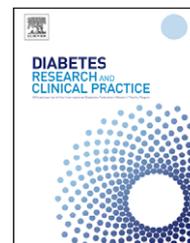**ScienceDirect**

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New insulin sensitivity index from the oral glucose tolerance test

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ABSTRACT

A new insulin sensitivity index was devised on the basis of an autoregressive model and its validity was investigated.

Using data from the 75-g oral glucose tolerance test (OGTT), 115 subjects were divided into 3 groups: 40 with normal glucose tolerance, 34 with impaired glucose tolerance, and 41 with type 2 diabetes mellitus. The new insulin sensitivity index: oral glucose insulin sensitivity index (GSI) was calculated from five sets of plasma glucose and insulin levels obtained at 0, 30, 60, 90 and 120 min during OGTT using a formula based on an autoregressive model. Forty-three of the 115 subjects were examined for insulin sensitivity index (ISI) by euglycemic hyperinsulinemic clamp.

GSI decreased in the order of normal glucose tolerance group > impaired glucose tolerance group > diabetic group. There was a significant correlation between GSI and the ISI derived from euglycemic hyperinsulinemic clamp study data in all 43 subjects who underwent both tests ($r = 0.72$; $P < 0.0001$). The ISI calculated by previous methods poorly correlated with the ISIs obtained by euglycemic hyperinsulinemic clamp study.

In conclusion, this new insulin sensitivity index based on the data obtained from OGTT using an autoregressive model is comparable to an insulin sensitivity index by euglycemic hyperinsulinemic clamp technique and may be superior to previous indexes that have been devised to determine insulin sensitivity from OGTT data.

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1. Introduction

The euglycemic hyperinsulinemic clamp method is generally regarded as one of the standard for assessment of insulin sensitivity, it only measures the influence of exogenously administered insulin on glucose utilization under steady-state conditions during fasting state representing peripheral glucose disposal [1–3]. The oral glucose tolerance test (OGTT) has

the potential to be employed for evaluation of postprandial or post-glucose loaded insulin resistance or insulin sensitivity.

Some attempts have been made to assess insulin sensitivity by using OGTT, all of these indices were calculated from empirical formulae not from glucose disposal model [4–9]. Here, we propose a new insulin sensitivity index based on an autoregressive model that is based on individual data of both glucose and insulin concentrations obtained from OGTT. The autoregressive model approach, which was invented by Akaike [11], has been commonly used in the field of system engineering and has been employed by Wada et al. [12] in the field of medicine.

2. Materials and methods

2.1. Subjects

One hundred and fifteen subjects with various levels of glucose tolerance underwent a 75-g OGTT, and then were divided into a normal glucose tolerance group ($n = 40$), an impaired glucose tolerance group ($n = 34$), and a type 2 diabetes group ($n = 41$) according to the criteria of the American Diabetes Association [10]. The subjects showed wide variation of physique, with a body mass index (BMI) ranging from 16.4 to 39.4 kg/m^2. None of the subjects was receiving treatment with insulin, oral hypoglycemic agents, or any other drugs known to affect glucose tolerance at the time of testing.

2.2. OGTT

After an overnight fast (10–12 h), the 75-g OGTT was performed at 8:30 a.m. Blood samples were taken at 0, 30, 60, 90, and 120 min after the glucose load to measure the plasma glucose and insulin concentrations.

Evaluation of initial β-cell response was performed by determining the insulinogenic index (II), which was calculated as the increment of insulin above the basal level at 30 min divided by the increment of glucose above the basal level at 30 min.

2.3. Euglycemic hyperinsulinemic clamp test

Forty-three of the 115 subjects also underwent a glucose clamp study, which was carried out as described by DeFronzo et al. [1]. The subjects were studied while resting in the recumbent position at 9:00 after a 10-h overnight fast. After 10 min of priming with insulin, constant infusion of insulin was performed at a rate of 3 μU/kg/min for 120 min to suppress hepatic glucose production. During the clamp period, the serum glucose concentration was maintained at 73–112 mg/dL by monitoring the glucose level at 1-min intervals and adjusting the infusion rate of a 20% glucose solution. The glucose infusion rate was calculated every 1 min and was averaged over the last 30 min of the clamp study.

2.4. Principle of the autoregressive model

Consider a simple feedback system in which i regulates g and g regulates i (Fig. 1). In such a system, the output signal emitted from i is transmitted to g and then returns to i, so a signal originating from i affects both g and i in the same way. Based on this principle, we can quantitatively express the extent of transmission (with time lag) of the fluctuation of one variable to another in a bivariate feedback system, such as that regulating plasma insulin and glucose levels.

To construct an autoregressive model for plasma insulin or glucose, data should be obtained frequently at short intervals (e.g., every 1–5 mm) and processing with complex software is required. To construct a "conventional" autoregressive model that uses ordinary OGTT data, the following method can be employed.

2.5. Calculation of autoregressive coefficients and new insulin sensitivity index: oral glucose insulin sensitivity index (GSI)

For a bivariate feedback system, the values of g (plasma glucose) and i (plasma insulin) at any discrete time, s, can be denoted by $g(s)$ (the plasma glucose level at time s) and $i(s)$ (the plasma insulin level at time s). The basic equation describing an autoregressive process variable is as follows [11,12]:

$$x_j(s) = \sum_{m=0}^{M} [\alpha_{j1}(m)x_1(s-m) + \alpha_{j2}(m)x_2(s-m)] + \varepsilon_j(s) \tag{1}$$

where $g(s)$ is $x_1(s)$ and $i(s)$ is $x_2(s)$, m is the time lag between the present time (s) and a previous time, M is the maximal time lag for which the feedback contributions are optimal, $a_{j1}(m)$ and $a_{j2}(m)$ are autoregressive coefficients, and $\varepsilon_1(s)$ and $\varepsilon_2(s)$ are white noises.

The autoregressive coefficients were determined by the least squares method so that the sum of the squared residual terms, $\varepsilon_j(s)$, was as small as possible. To simplify the mathematical processes, we assumed that the maximal time lag M was 2, which meant that the model included up to two time points in the past. Based on these assumptions, Eq. (1) can be written as follows (see Appendix A).
If $x_1(s) = g(s) = g_s$ and $x_2(s) = i(s) = i_s$ then:

$$\begin{aligned}
g_0 &= ai_0 + bg_{-30} + ci_{-30} + dg_{-60} + ei_{-60} + \varepsilon_0 \\
g_{30} &= ai_{30} + bg_0 + ci_0 + dg_{-30} + ei_{-30} + \varepsilon_{30} \\
g_{60} &= ai_{60} + bg_{30} + ci_{30} + dg_0 + ei_0 + \varepsilon_{60} \\
g_{90} &= ai_{90} + bg_{60} + ci_{60} + dg_{30} + ei_{30} + \varepsilon_{90} \\
g_{120} &= ai_{120} + bg_{90} + ci_{90} + dg_{60} + ei_{60} + \varepsilon_{120}
\end{aligned} \tag{2}$$

Here,

$$a = \alpha_{12}(0), \quad b = \alpha_{11}(1), \quad c = \alpha_{12}(1), \quad d = \alpha_{11}(2),$$
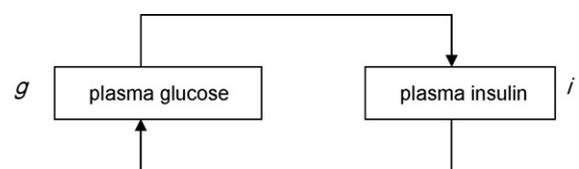$$e = \alpha_{12}(2), \quad g_0 = g_{-30} = g_{-60}, \quad i_0 = i_{-30} = i_{-60}$$

Fig. 1 – A simple feedback system composed of two variables, i.e., the plasma glucose level (g) and the plasma insulin (i) level.

Next, the coefficients a to e were determined to solve this simultaneous linear equation by Cramer's formula, with the residual term as $\varepsilon_n = 0$.

$$
c = \begin{bmatrix} i_0 & g_0 & g_0 & g_0 & i_0 \\ i_{30} & g_0 & g_{30} & g_0 & i_0 \\ i_{60} & g_{30} & g_{60} & g_0 & i_0 \\ i_{90} & g_{60} & g_{90} & g_{30} & i_{30} \\ i_{120} & g_{90} & g_{120} & g_{60} & i_{60} \end{bmatrix} \bigg/ \begin{bmatrix} i_0 & g_0 & i_0 & g_0 & i_0 \\ i_{30} & g_0 & i_0 & g_0 & i_0 \\ i_{60} & g_{30} & i_{30} & g_0 & i_0 \\ i_{90} & g_{60} & i_{60} & g_{30} & i_{30} \\ i_{120} & g_{90} & i_{90} & g_{60} & i_{60} \end{bmatrix}
$$

$$
g_0 = ai_0 + bg_{-30} + ci_{-30} + dg_{-60} + ei_{-60} \tag{2'}
$$

If we assume unit insulin release of $(i_0, i_{-30}, i_{-60}, g_{-30}, g_{-60}) = (0, 1, 0, 0, 0)$ in Eq. (2'), then:

Eq. $(2') = g_0 = c < 0$

The decrease of plasma glucose in response to the release of one unit of insulin ($i = 1$) is given by $-g_0 = -c$.

The state represented by Eq. (2') can be converted to the basal state, in which $g_0 \times i_0/405 = 1$ (i.e., homa-R = 1), and successively to the state of $g_{60} = 100$. Here, $g_{60} = g(60)$ and this is defined as the representative plasma glucose level during the OGTT (see Appendix A).

The decrease of plasma glucose in response to one unit of insulin release is then represented by modified $-c$ ($-c'$) as follows:

$$
-c' = -\frac{100}{g_{60}} \left(\frac{405}{g_0 \times i_0} c \right)
$$

We defined $-c'$ as the oral glucose insulin sensitivity index.

$$
-c'[\text{GSI}] = -\frac{40,500}{g_0 \times i_0 \times g_{60}}
$$
$$
\times \begin{bmatrix} i_0 & g_0 & g_0 & g_0 & i_0 \\ i_{30} & g_0 & g_{30} & g_0 & i_0 \\ i_{60} & g_{30} & g_{60} & g_0 & i_0 \\ i_{90} & g_{60} & g_{90} & g_{30} & i_{30} \\ i_{120} & g_{90} & g_{120} & g_{60} & i_{60} \end{bmatrix} \bigg/ \begin{bmatrix} i_0 & g_0 & i_0 & g_0 & i_0 \\ i_{30} & g_0 & i_0 & g_0 & i_0 \\ i_{60} & g_{30} & i_{30} & g_0 & i_0 \\ i_{90} & g_{60} & i_{60} & g_{30} & i_{30} \\ i_{120} & g_{90} & i_{90} & g_{60} & i_{60} \end{bmatrix} \tag{3}
$$

2.6. Simulation of plasma glucose response to the increment of insulin

Utilizing the matrix of AR coefficients, a "state equation" that is specific to the subject under study can be written as follows (the details are shown in Appendix B):

$$
Z_{2n+1} = \Theta Z_{2n} + V_{2n} \tag{4}
$$

In this equation, the matrix Θ is a so-called transitional matrix, and is composed of the matrices of AR coefficients such as

$$
\Theta = \begin{pmatrix} a & b & c & d & e \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix}
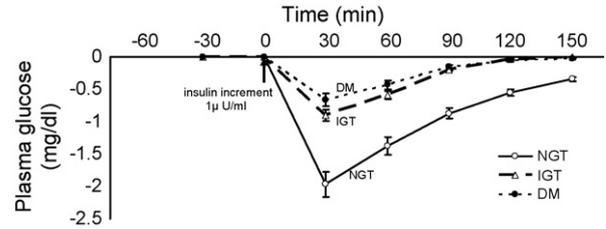$$

Fig. 2 – Simulated response of glucose to an increment of plasma insulin by 1 μU/mL in response to oral glucose based on impulse response function for a feedback system (Fig. 1 and Appendix B). Curves were simulated for subjects with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and type 2 diabetes (DM). Insulin increment causes the glucose level to fall in each group and the decrease at 30 min corresponds to the insulin sensitivity index ($-c'$ (GSI) in Eq. (3)). The arrow shows the timing of the insulin increment. Mean ± S.E.M.

while Z_n is the state variable, and V_n is the matrix of the noise terms.

$$
Z_{2(n+2)+1} = \begin{pmatrix} g_{n+2} \\ i_{n+2} \\ g_{n+1} \\ i_{n+1} \\ g_n \end{pmatrix}, \quad Z_{2(n+2)} = \begin{pmatrix} i_{n+2} \\ g_{n+1} \\ i_{n+1} \\ g_n \\ i_n \end{pmatrix},
$$

$$
V_{2(n+2) \neq 2} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \quad V_2 = \begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 0 \end{pmatrix} \quad \text{(insulin impulse)}
$$

Using Eq. (4) the insulin response in a feedback system can be simulated by a curve, which we called the insulin response curve (Fig. 2).

2.7. Insulin sensitivity index from clamp data

The insulin sensitivity index based on clamp study data (ISI (clamp)) was calculated as the ratio of the glucose infusion rate to the steady-state glucose concentration, based on the
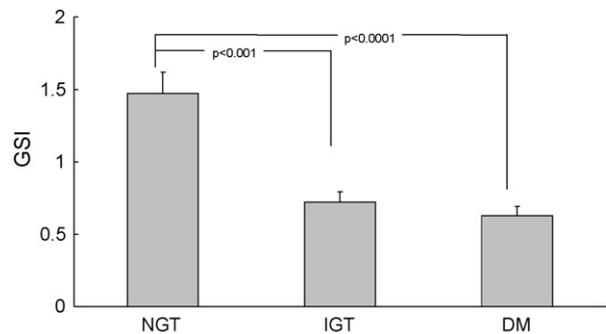

Fig. 3 – Mean (±S.E.M.) oral glucose insulin sensitivity index (GSI) calculated for each group. The GSI was derived from OGTT data in subjects with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and type 2 diabetes (DM).

assumption that glucose production represents only a small fraction of the total glucose turnover.

2.8. Ethics

All subjects gave informed consents for this study. The institutional review board approved the protocol.

2.9. Statistical analysis

Results were expressed as the mean ± S.D. Student's *t*-test was used to compare differences between various parameters. Pearson's correlation coefficients were calculated to determine the strength of associations. In all analyses, $P < 0.05$ was considered statistically significant.

3. Results

The simulated plasma glucose response to an increment of plasma insulin (1 μU/mL) in each of the three groups was expressed in Fig. 2. These curves were created by using Eq. (4) (see Appendix B) and the clinical data were obtained during the OGTT. After the insulin spike, the plasma glucose level declined in each group and the decrease at 30 min corresponded to $-c'$ in Eq. (3), that is GSI.

The GSI was significantly lower in the impaired glucose tolerance group than in the normal glucose tolerance group (1.47 ± 0.16 vs. 0.72 ± 0.08, Fig. 3), and tended to be lower in the diabetic group than in the impaired glucose tolerance group (0.72 ± 0.08 vs. 0.62 ± 0.08, P = ns, Fig. 3).

There was a significant correlation between our new GSI and the ISI (clamp) ($r = 0.72$, $P < 0.0001$, $n = 43$) (Fig. 4). There was also a significant correlation between the two indexes in each of the groups (normal glucose tolerance group: $r = 0.73$, $P = 0.001$, $n = 15$; impaired glucose tolerance group: $r = 0.71$, $P < 0.01$, $n = 12$; and diabetic group: $r = 0.78$, $P < 0.0001$, $n = 16$). Insulin sensitivity indexes that are based on OGTT data and published by other [4,8] were poorly correlated with the ISI (clamp) (Fig. 5). The r values were significantly lower than that of our GSI ($P < 0.0001$).
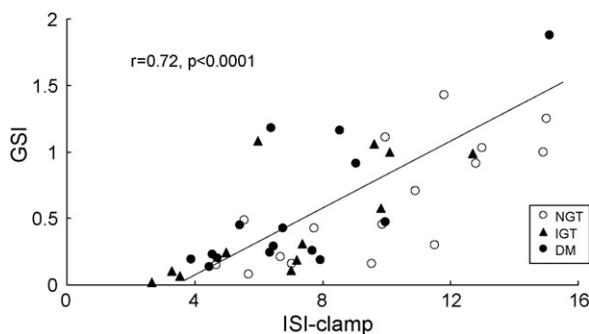

Fig. 4 – Relationship between indexes of insulin sensitivity index derived from glucose clamp data (ISI-clamp) and our GSI. The correlation obtained from all 43 subjects undergoing both tests is shown. (○) Normal glucose tolerance (NGT); (▲) impaired glucose tolerance (IGT); (●) diabetes mellitus (DM).
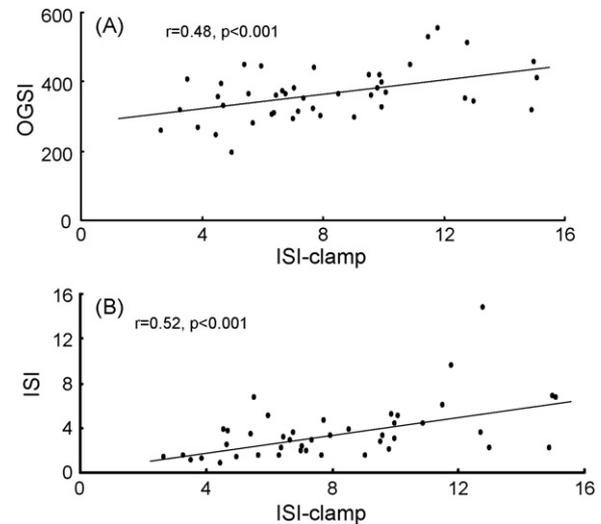

Fig. 5 – Correlation between the insulin sensitivity index derived from glucose clamp data (ISI-clamp) and the index by Matsuda and DeFronzo [4] (A) and that by Mari et al. [8] (B). (A) The correlation between ISI (clamp) and OGIS [8] was significant (r = 0.48, P < 0.001). (B) The correlation between ISI (clamp) and ISI [4] was also significant (r = 0.52, P < 0.001). These r values were significantly lower than that of our GSI (r = 0.72, P < 0.0001).

4. Discussion

Insulin resistance not only plays an important pathophysiological role in the development of type 2 diabetes mellitus from IGT, but is also a common component of the metabolic abnormalities, which lead to the coronary heart disease, obesity, hyperlipidemia, and hypertension [13]. Therefore, there has been widespread interest in the development of techniques to assess insulin resistance or sensitivity in non-diabetic, pre-diabetic and diabetic state. To evaluate insulin resistance or insulin sensitivity, investigators have reported various methods such as the glucose clamp technique [1], the minimal model approach [14], and insulin sensitivity indexes from OGTT [4–9]. The euglycemic hyperinsulinemic clamp method is widely used measures to investigate the insulin sensitivity as gold standard. It directly measures the influence of exogenous insulin on glucose utilization under fasting steady-state conditions. However, in this method insulin is infused intravenously and represents the sensitivity of exogenously administered insulin. In addition, this method is laborious, expensive, and not routinely available for clinicians. In contrast, the OGTT is simple, safe, and less expensive. Assessment of insulin sensitivity based on OGTT data principally represents insulin sensitivity to endogenously secreted insulin to the portal system. So several formulae have been proposed for calculating insulin sensitivity indexes from OGTT data [4–9].

In the present study, we attained higher correlation between our OGTT-based ISI (named GSI) and ISI (clamp) (Fig. 4). In contrast, the correlation between ISI calculated by other OGTT-based formula ISI [4,8] and the ISI (clamp) is poor with the correlation values (r) of 0.48 and 0.52 (Fig. 5). The first

possible reason for the poor relationship between other OGTT-based ISI may be explained by the fact that the indexes proposed by Cederholm and Wibell [7], Stumvoll et al. [5], and Matsuda and DeFronzo [4] incorporate only post-loading glucose and insulin concentrations. These authors either employed mean values or only performed blood sampling a few times during OGTT. Second, the glucose clamp method is designed to measure peripheral glucose utilization suppressing hepatic glucose production by administrating exogenous insulin, whereas the plasma glucose response during OGTT represents the net effect of both peripheral glucose utilization and hepatic glucose production. To overcome such problems in previous OGTT-based measurement of insulin sensitivity [4–9], we at first obtained data from blood samples at 0, 30, 60, 90, and 120 min during the OGTT and then used a linear equation (Eq. (2′)) to calculate the coefficient c, simulated decrease of blood glucose level based on the data of blood glucose and plasma insulin at 0, 30, 60, 90, and 120 min. After that, the modified value of $-c$, that is oral glucose insulin sensitivity index: $-c'$, was obtained from Eq. (3). GSI was calculated by dividing c with fasting plasma insulin multiply fasting blood glucose dividing by 60-min blood glucose value to calibrate the c value to the value in steady-state condition. GSI represents the decrease of plasma glucose in response to the release of one unit of insulin in a posturated state in normal insulin sensitivity.

We consider that our GSI most adequately represents insulin sensitivity for the following reasons. First, incorporation of the impulse response is considered to be a basic function because it is a characteristic of the feedback system regulating glucose and insulin levels. Second, the value of the new index decreased seemingly in the order of NGT, IGT, and type 2 diabetes (Fig. 3), and insulin sensitivity is generally considered to decrease in the same order [15].

In conclusion, our new index calculated from the data during OGTT on the basis of an autoregressive model may represent well the insulin sensitivity, being comparable with that calculated by euglycemic hyperinsulinemic clamp study.

We present a website to calculate our new glucose sensitivity index on the following Web named GSI calculator: http://www18.ocn.ne.jp/~ogsi/.

Appendix A. Calculation of autoregressive coefficients

For a bivariate feedback system, the values of g (plasma glucose) and i (plasma insulin) at any discrete time, s, can be denoted by $g(s)$ (the plasma glucose level at time s) and $i(s)$ (the plasma insulin level at time s). The basic equation describing an autoregressive process variable is as follows [12]:

$$x_j(s) = \sum_{m=0}^{M} [\alpha_{j1}(m)x_1(s-m) + \alpha_{j2}(m)x_2(s-m)] + \varepsilon_j(s)$$

Let $g(s)$ and $i(s)$ be $x_1(s)$ and $x_2(s)$, respectively. Putting $\alpha_{11}(0) = 0$, $\alpha_{12}(0) = a$, $\alpha_{11}(1) = b$, $\alpha_{12}(1) = c$, $\alpha_{11}(2) = d$, $\alpha_{12}(2) = e$, the following equation is derived:

$$g(s) = ai(s) + bg(s-1) + ci(s-1) + dg(s-2) + ei(s-2) + \varepsilon_1(s)$$

If the specific time (s) is indicated by a subscript, e.g., 30 min is represented by the subscript ''30s'', then when s equals 30 min:

$$g(s) = g_{30s}, \quad i(s) = i_{30s}$$

$$g_{30s} = ai_{30s} + bg_{30(s-1)} + ci_{30(s-1)} + dg_{30(s-2)} + ei_{30(s-2)} + \varepsilon_{30s}$$

When 120 min (duration of the OGTT) is divided into 30-min periods, s takes a value from 0 to 4.

$$
\begin{aligned}
g_0 &= ai_0 + bg_{-30} + ci_{-30} + dg_{-60} + ei_{-60} + \varepsilon_0 \\
g_{30} &= ai_{30} + bg_0 + ci_0 + dg_{-30} + ei_{-30} + \varepsilon_{30} \\
g_{60} &= ai_{60} + bg_{30} + ci_{30} + dg_0 + ei_0 + \varepsilon_{60} \\
g_{90} &= ai_{90} + bg_{60} + ci_{60} + dg_{30} + ei_{30} + \varepsilon_{90} \\
g_{120} &= ai_{120} + bg_{90} + ci_{90} + dg_{60} + ei_{60} + \varepsilon_{120}
\end{aligned}
\tag{2}
$$

Next, the coefficients a to e were determined to solve this simultaneous linear equation using Cramer's formula, with the residual term $\varepsilon_n = 0$.

$$
c = \begin{bmatrix}
i_0 & g_0 & g_0 & g_0 & i_0 \\
i_{30} & g_0 & g_0 & g_0 & i_0 \\
i_{60} & g_{30} & g_{30} & g_0 & i_0 \\
i_{90} & g_{60} & g_{60} & g_{30} & i_{30} \\
i_{120} & g_{90} & g_{90} & g_{60} & i_{60}
\end{bmatrix}
\Big/
\begin{bmatrix}
i_0 & g_0 & i_0 & g_0 & i_0 \\
i_{30} & g_0 & i_0 & g_0 & i_0 \\
i_{60} & g_{30} & i_{30} & g_0 & i_0 \\
i_{90} & g_{60} & i_{60} & g_{30} & i_{30} \\
i_{120} & g_{90} & i_{90} & g_{60} & i_{60}
\end{bmatrix}
$$

$$g_0 = ai_0 + bg_{-30} + ci_{-30} + dg_{-60} + ei_{-60} \tag{2′}$$

The insulin response can be assessed using this equation.

If Eq. (2′) is converted as follows:

$$g_0 = \frac{g_0 \times i_0}{405} g_{B0}, \quad g_{-30} = \frac{g_0 \times i_0}{405} g_{B-30}, \quad g_{-60} = \frac{g_0 \times i_0}{405} g_{B-60}, \tag{a}$$

then the following equation (i_0, i_{-30}, i_{-60}, g_{B-30}, g_{B-60}) represents a new state of insulin and glucose responses.

$$
\begin{aligned}
g_{B0} &= \frac{1}{(g_0 \times i_0)/405} ai_0 + bg_{B-30} + \frac{1}{(g_0 \times i_0)/405} ci_{-30} + dg_{B-60} \\
&\quad + \frac{1}{(g_0 \times i_0)/405} ei_{-60}
\end{aligned}
\tag{5}
$$

If $g_{B0} = g_{B-30} = g_{B-60}$, and $i_0 = i_{-30} = i_{-60}$ (i.e., a steady state), then

$$
\begin{aligned}
g_{B0} &= \frac{1}{(g_0 \times i_0)/405} ai_0 + bg_{B0} + \frac{1}{(g_0 \times i_0)/405} ci_0 + dg_{B0} \\
&\quad + \frac{1}{(g_0 \times i_0)/405} ei_0
\end{aligned}
\tag{5′}
$$

$$\frac{g_{B0} \times i_0}{405} = 1$$

This corresponds to the basal state where homa-R = 1.

If we assume unit insulin release of (i_0, i_{-30}, i_{-60}, g_{B-30}, g_{B-60}) = (0, 1, 0, 0, 0) in Eq. (5), then

$$\text{Eq. (5)} = g_B = \frac{405}{g_0 \times i_0} c$$

Namely, the state represented by Eq. (2) can be converted by (a) to the basal state represented by Eq. (5′), in which $g_0 \times i_0/405 = 1$ (i.e., homa-R = 1). The decrease of plasma glucose

relative to this basal state in response to the release of one unit of insulin ($i = 1$) is given by

$$-g_B = -\frac{405}{g_0 \times i_0} c.$$

Similarly, if Eq. (2) is converted as follows:

$$g'_{30} = \frac{100}{g_{60}} g_{30}, \quad g'_{60} = \frac{100}{g_{60}} g_{60} = 100, \tag{b}$$

then the equation for a new state is obtained:

$$g'_{30s} = a \frac{100}{g_{60}} i_{30s} + b g'_{30(s-1)} + c \frac{100}{g_{60}} i_{30(s-1)} + d g'_{30(s-2)} + e$$
$$\times \frac{100}{g_{60}} i_{30(s-2)} \tag{6}$$

This equation represents the state where $g_{60} = 100$. Here, $g_{60} = g(60)$ is defined as the representative plasma glucose value during the OGTT. If we assume unit insulin release of $(i_0, i_{-30}, i_{-60}, g'_{-30}, g'_{-60}) = (0, 1, 0, 0, 0)$ in Eq. (6), then we obtain

Eq. (4) $= g' = \dfrac{100}{g_{60}} c$

The decrease of plasma glucose relative to this basal state in response to the release of one unit of insulin ($i = 1$) is given by $-g' = -(100/g_{60})c$. If conversion of Eq. (2) is performed by (a) and (b) successively, the decrease of plasma glucose in response to release of one unit of insulin ($i = 1$) can be given by $-c'$.

The value of $-c'$ is calculated as follows:

$$-c'[GSI] = -\frac{100}{g_{60}} \left(\frac{405}{g_0 \times i_0} c \right) = -\frac{40,500}{g_0 \times i_0 \times g_{60}}$$

$$\times \begin{bmatrix} i_0 & g_0 & g_0 & g_0 & i_0 \\ i_{30} & g_0 & g_{30} & g_0 & i_0 \\ i_{60} & g_{30} & g_{60} & g_0 & i_0 \\ i_{90} & g_{60} & g_{90} & g_{30} & i_{30} \\ i_{120} & g_{90} & g_{120} & g_{60} & i_{60} \end{bmatrix} \Big/ \begin{bmatrix} i_0 & g_0 & i_0 & g_0 & i_0 \\ i_{30} & g_0 & i_0 & g_0 & i_0 \\ i_{60} & g_{30} & i_{30} & g_0 & i_0 \\ i_{90} & g_{60} & i_{60} & g_{30} & i_{30} \\ i_{120} & g_{90} & i_{90} & g_{60} & i_{60} \end{bmatrix} \tag{3}$$

We defined $-c'$ as the insulin sensitivity index (GSI).

Appendix B

The "state equation" expressed in the text is
$$Z_{2n+1} = \Theta Z_{2n} + V_{2n} \tag{4}$$

where Z_n is the state variable, Θ is the transitional matrix, and V_n is the matrix of the noise term.

$$Z_{2(n+2)+1} = \begin{pmatrix} g_{n+2} \\ i_{n+2} \\ g_{n+1} \\ i_{n+1} \\ g_n \end{pmatrix}, \quad Z_{2(n+2)} = \begin{pmatrix} i_{n+2} \\ g_{n+1} \\ i_{n+1} \\ g_n \\ i_n \end{pmatrix},$$

$$V_{2(n+2) \neq 2} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \quad V_2 = \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad \text{(insulin impulse)}$$

$$\Theta = \begin{pmatrix} a & b & c & d & e \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix}$$

$$\begin{pmatrix} a & b & c & d & e \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix} \times \begin{pmatrix} i_{n+2} \\ g_{n+1} \\ i_{n+1} \\ g_n \\ i_n \end{pmatrix} + V_{2(n+2)} = \begin{pmatrix} g_{n+2} \\ i_{n+2} \\ g_{n+1} \\ i_{n+1} \\ g_n \end{pmatrix} \tag{4'}$$

Using Eqs. (4) and (4') successively, it is possible to simulate the impulse response function for a feedback system, which we call the impulse response curve.

As the first step in the stimulation, process the state variable is initialized as a zero state, which is expressed as $n = -2$,

$$Z_0 = \begin{pmatrix} i_0 \\ g_{-1} \\ i_{-1} \\ g_{-2} \\ i_{-2} \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

Since no impulse exists at this time, the matrix of the noise term V should be

$$V_0 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

$$Z_1 = \Theta Z_0 + V_0 = \begin{pmatrix} g_0 \\ i_0 \\ g_{-1} \\ i_{-1} \\ g_{-2} \end{pmatrix} = \begin{pmatrix} a & b & c & d & e \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix} \times \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

$$= \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

Since no impulse has occurred, Z_2 is the zero state ($n = -1$).

$$Z_2 = \begin{pmatrix} i_1 \\ g_0 \\ i_0 \\ g_{-1} \\ i_{-1} \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

Now, let us provide an impulse to the noise term of variable V_2, with the system going ahead one step from Z_2 to Z_3.

$$Z_3 = \Theta Z_2 + V_2 = \begin{pmatrix} g_1 \\ i_1 \\ g_0 \\ i_0 \\ g_{-1} \end{pmatrix} = \begin{pmatrix} a & b & c & d & e \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix} \times \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} + \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

$$= \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \quad V_2 = \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

In a similar manner, for $n = 0$:

$$Z_4 = \begin{pmatrix} i_2 \\ g_1 \\ i_1 \\ g_0 \\ i_0 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 0 \end{pmatrix}$$

$$Z_5 = \Theta Z_4 + V_4 = \begin{pmatrix} g_2 \\ i_2 \\ g_1 \\ i_1 \\ g_0 \end{pmatrix} = \begin{pmatrix} a & b & c & d & e \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix} \times \begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 0 \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

$$= \begin{pmatrix} c \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix}, \quad V_4 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

Likewise, for $n = 1$:

$$Z_6 = \begin{pmatrix} i_3 \\ g_2 \\ i_2 \\ g_1 \\ i_1 \end{pmatrix} = \begin{pmatrix} 0 \\ c \\ 0 \\ 1 \\ 0 \end{pmatrix}$$

$$Z_7 = \Theta Z_6 + V_6 = \begin{pmatrix} g_3 \\ i_3 \\ g_2 \\ i_2 \\ g_1 \end{pmatrix} = \begin{pmatrix} a & b & c & d & e \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix} \times \begin{pmatrix} 0 \\ c \\ 0 \\ 0 \\ 1 \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

$$= \begin{pmatrix} bc + e \\ 0 \\ c \\ 0 \\ 0 \end{pmatrix}, \quad V_6 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

And for $n = 2$:

$$Z_8 = \begin{pmatrix} i_4 \\ g_3 \\ i_3 \\ g_2 \\ i_2 \end{pmatrix} = \begin{pmatrix} 0 \\ bc + e \\ 0 \\ c \\ 0 \end{pmatrix}$$

$$Z_9 = \Theta Z_8 + V_8 = \begin{pmatrix} g_3 \\ i_3 \\ g_2 \\ i_2 \\ g_1 \end{pmatrix} = \begin{pmatrix} a & b & c & d & e \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix} \times \begin{pmatrix} 0 \\ bc + e \\ 0 \\ c \\ 0 \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

$$= \begin{pmatrix} b(bc + e) + cd \\ 0 \\ bc + e \\ 0 \\ c \end{pmatrix}, \quad V_8 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

And so on for $n = 3, 4, \dots$.

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