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SELF-ASSESSMENT OF INSULIN SENSITIVITY

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INTRODUCTION

The ability of insulin to stimulate the body glucose disposal can be characterized by an insulin sensitivity index. Many studies have introduced several new methods from an oral glucose tolerance test (OGTT) and the euglycemic insulin clamp technique to quantify peripheral insulin sensitivity by monitoring the insulin and glucose interactions under standard glucose load and specific conditions [2]. However, 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.

In this study, we proposed a new insulin index estimated by capillary blood glucose measurements. Our approach is to evaluate the feasibility of using a mathematical compartment model proposed by Vahidi et al [1,3] to estimate the insulin sensitivity.

MATHEMATICAL MODELING OF THE TYPE II DIABETES MELLITUS

To model the glucose-insulin interactions in type II diabetic patients, we used the Vahidi model [1,3] based on the Sorensen model [4]. Vahidi model is a much more detailed dynamic model comparing with the modified minimal model (MINMOD) analysis [5]. It is able to effectively model individual abnormalities by characterizing distinct compartments as the faulty organs.

The Vahidi model consists of three main sub-models; each is divided into individual number of compartments representing a specific part or organ of a human body. Different number of compartments is considered in each sub-model. The insulin sub-model has seven compartments: brain; liver; heart and lungs; periphery; gut; kidney, and the pancreas. However, the glucose sub-model has the same six compartments excluding the pancreas compartment [6].

Later in [3], the hormonal effects of incretins on boosting pancreatic insulin secretion was included by adding two compartment models of incretin production in order to simulate the variations of incretin concentrations in the blood circulatory system as well as adding a model of gut glucose absorption in the gastrointestinal tract proposed by Dalla Man et al. [7] to modify the variations of blood glucose concentration resulted from an oral glucose intake. For more details on the Vahidi model, see [1,3].

CLINICAL DATA

In order to estimate the parameters of the Vahidi model, fifteen different available patterns of glucose and insulin concentrations during a 2-h plasma glucose (PG) in a 75-g OGTT are selected from the available literatures, and summarized in Table 1.

PARAMETER ESTIMATION RESULTS

Since different patterns of glucose and insulin concentrations result in different set of parameters in the Vahidi model, a set of parameter for each subject is estimated. To do this, an optimization problem is solved by using available clinical data presented in Table 1. All clinical data are scaled to a 70 kg body weight since the Vahidi model is based on a typical 70 kg subject. The deviation of model predictions from the measured clinical data is minimized through the following objective function:

$$\min_{\Theta} \sum_{i=1}^{n} \left(\left| {G_{PC}}_m^i - {G_{PC}}_c^i \right| + \left| {I_{PC}}_m^i - {I_{PC}}_c^i \right| \right) \quad (1)$$

Table 1: 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	[9]
2	71.10	135.90	124.92	116.10	101.34	5.72	15.58	13.67	10.48	8.03	[9]
3	75.29	125.71	129.13	108.50	84.67	8.18	30.00	33.05	33.47	16.77	[10]
4	80.00	120.40	110.40	92.10	76.50	7.00	38.40	31.10	21.90	9.30	[10]
5	71.30	130.20	145.00	122.40	91.60	9.20	23.10	34.70	41.90	21.90	[10]
6	74.00	121.00	177.00	180.00	154.00	9.00	13.00	35.00	46.00	41.00	[10]
7	71.00	125.00	134.00	103.00	80.00	7.00	62.00	58.00	36.00	20.00	[10]
8	72.00	118.00	115.00	92.00	62.00	10.00	12.00	35.00	20.00	14.00	[10]
9	89.90	160.2	134.20	-	109.00	11.30	98.90	68.40	-	43.70	[11]
10	90.90	154.80	124.70	-	130.80	11.60	109.80	53.90	-	71	[11]
11	93.30	166.20	171.40	-	122.10	11.70	66.80	103.90	-	58.30	[11]
12	95.50	171.30	193.30	-	159.10	12.70	59.60	86.70	-	118.90	[11]
13	91.30	158.10	148.50	-	144.80	14.90	96.40	74.80	-	130.20	[11]
14	153.40	238.40	292.58	278.68	239.89	6.47	18.88	22.00	20.64	14.57	[12,13]
15	97.75	164.68	154.54	110.50	87.61	5.52	37.75	42.63	19.58	7.89	[12,13]

where $G_{PC_c}^{\ i}$ and $I_{PC_c}^{\ i}$ are the corresponding clinical measurements; $G_{PC_m}^{\ i}$ and $I_{PC_m}^{\ i}$ are peripheral glucose and insulin concentrations at time *i* obtained from the model respectively; *n* is the size of clinical data set; and θ is the vector of parameters including in the glucose, insulin, and glucagon metabolic rates [1].

Figure 1 shows the estimation results of five subjects selected from Table 1. As can be seen, the model estimation results are acceptable for the model's overall trend in each subject.

QUANTITATIVE ESTIMATION OF INSULIN SENSITIVITY

In order to define a new insulin sensitivity index based on the Vahidi model, we performed a new test on fifteen subjects of Table 1 as follows: a 75-g glucose over the first 5 minutes

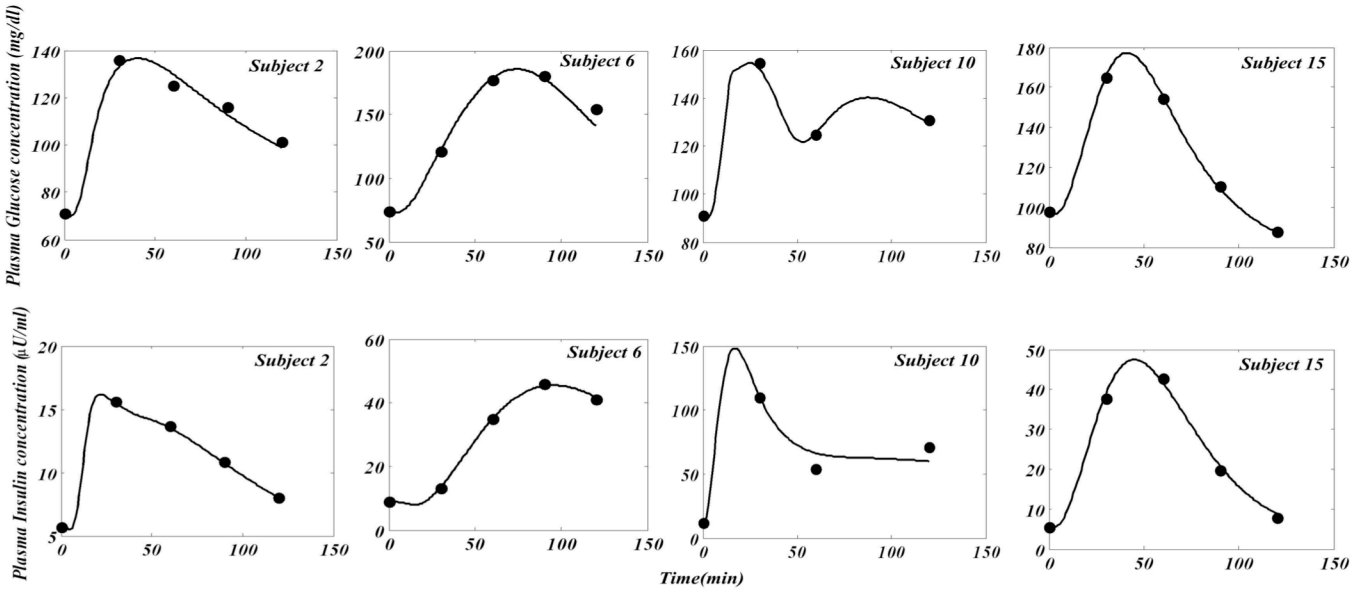

Figure 1: Peripheral glucose and insulin concentration profile for subject 2, 6, 10 and 15, the clinical data (●), the model results (-)

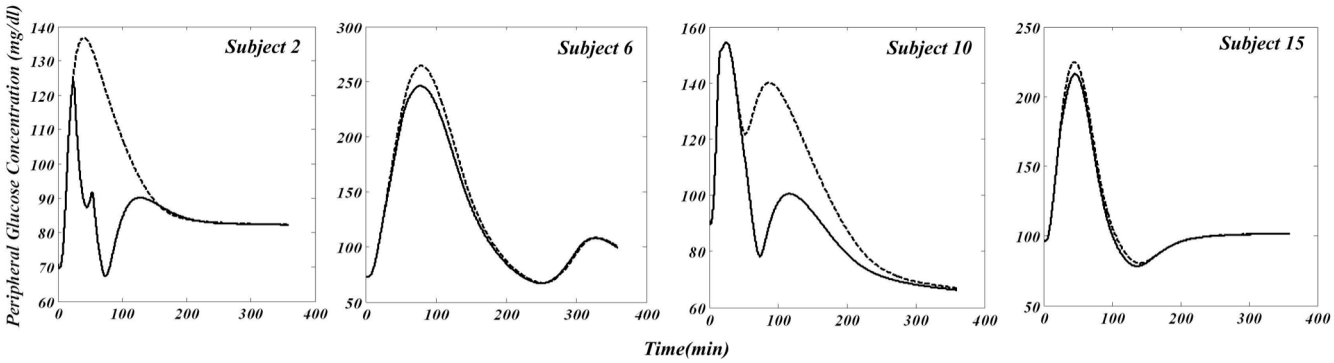

Figure 2: Effect of insulin injection in subject 2, 6, 10 and 15, twice 10 mU/kg insulin injection at 20 min and 50 min (-), no injection (--)

of the experiment is given to the fifteen subjects and 10 mU/kg insulin is injected twice intravenously into the body of the subjects after 20 min and 50 min glucose consumption. The effects of insulin injection after ingestion of a 75-g glucose are provided in Figure 2. As can be seen, the maximum differences between plasma glucose levels occur in insulin sensitive body almost at 60 min and 80 min after glucose consumption.

Thus, based on the value of peripheral glucose concentration at fasting (0 min), 60 min, and 80 min after ingestion of a 75-g glucose, Equation (2) was adopted to obtain linear regression with M-value measured by the 'gold standard' method, the euglycemic insulin clamp technique.

$$ISI = 44.071 - 0.1534 \times FPG - 0.1855 \times G_{60min} + 0.182 \times G_{80min} - (1.95 / FPG + 6.81 / G_{60\ min} - 5.88 / G_{80\ min}) \times 10^3 \quad (2)$$

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

In the euglycemic insulin clamp technique, the plasma insulin concentration is raised and maintained at a fixed level, approx. 100 mU/ml by a continuous intravenous insulin infusion. A measure of tissue insulin sensitivity labeled 'M-value' during the steady state phase is equal to the glucose infusion rate representing the total body glucose uptake rate [8].

To simulate the euglycemic insulin clamp technique in this study, the rate of insulin infusion is set to basal level for each subject, and the glucose infusion rate are obtained by trial and error to maintain the insulin concentrations at 100 mU/l and the glucose concentrations at its basal value.

Table 2 and Figure 3 present the association between the defined insulin sensitivity and M-value. It can be seen that the new defined ISI reflects the validity of insulin sensitivity measurement obtained from euglycemic clamps since the integrity of the correlation is maintained across the glycemic spectrum (r=0.927, p=0.0045) and also determines the strength of the relationship between the two measures.

Table 2: Mean plasma glucose and insulin levels during OGTT

Subject	New ISI	M-value
1	2.2794	3.2985
2	4.0260	3.9280
3	3.7202	2.6590
4	7.7888	7.0323
5	7.4029	7.2038
6	1.7746	2.6418
7	2.1649	0.5737
9	7.0903	8.0105
10	8.1858	7.0465
11	3.6569	3.8673
12	2.8845	3.4158
13	1.2569	2.3620
14	11.0334	9.4647
15	5.5294	5.3200

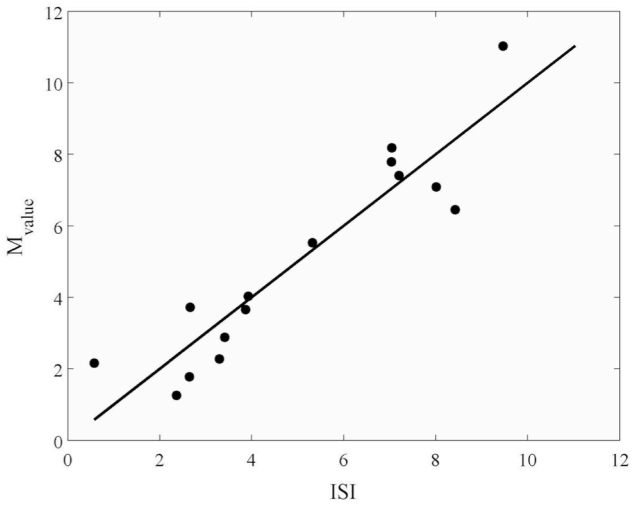

Figure 3: Correlation between IS and M-value for 15 subject, this graph shows that the correlation of ISI with M-value is significantly strong (r=0.927, p=0.0045)

Unlike the new ISI defined in Equation (2), the ISIs proposed previously from OGTT test require measuring plasma insulin levels at the specific times by laboratory equipment, which is inconvenient, time-consuming, non-self measuring and expensive. Furthermore, the new ISI can be monitored by diabetic patients daily without the need for expensive laboratory facilities.

CONCLUSION

In this study, we proposed a new ISI leading non-diabetic or diabetic subjects to self-measure the insulin sensitivity level of their body daily without refer to the diabetes laboratory. It is shown that the new ISI yielded a significant correlation with M-value obtained from the euglycemic clamp (r=0.927, p=0.0045).

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