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The first and second phase of insulin secretion in naive Chinese type 2 diabetes mellitus

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Abstract

Impaired insulin secretion (ISEC) has been recognized as one of the most important pathophysiologies of type 2 diabetes mellitus. There are 2 phases of ISEC: the first phase (first ISEC) and second phase (second ISEC). This study aimed to evaluate the 2 phases of ISEC in newly diagnosed type 2 diabetes mellitus patients. Fifty-two drug-naive type 2 diabetes mellitus patients were given 2 tests: a modified low-dose graded glucose infusion (M-LDGGI) and frequent sample intravenous glucose tolerance test. The M-LDGGI is a simplified version of the Polonsky method. Two stages of intravenous infusion of glucose with different rates were given, starting from 2 mg/(kg min) and then followed by 6 mg/(kg min). Each stage was maintained for 80 minutes. The results were interpreted as the slope of the changes of plasma insulin against the glucose levels. The slope of these curves was regarded as the second ISEC and used as the criterion for grouping-the responders and nonresponders. The responders are older and had higher body mass index and log (homeostasis model assessment of β-cell function) (log HOMA-β) but lower fasting plasma glucose and hemoglobin A_{1c} (HbA_{1c}) than the nonresponders. Significant correlations were only noted between the second ISEC and first ISEC ($r = 0.278$, $P = .046$) and between the second ISEC and log HOMA-β ($r = 0.533$, $P = .000$). Correlation between different parameters and HbA_{1c} was also evaluated. Only second ISEC and log HOMA-β were correlated significantly with HbA_{1c} ($r = -0.388$, $P = .015$ and $r = -0.357$, $P = .026$, respectively). In type 2 diabetes mellitus, subjects with higher second ISEC are older and have higher body mass index. At the same time, second ISEC is the most important factor for determining glucose levels in naive Chinese type 2 diabetes mellitus patients. The first and second ISECs were only modestly correlated, which indicated that the deterioration of these 2 phases was not synchronized. Finally, we also recommend using the M-LDGGI for quantifying second ISEC. This practical method could be done in many centers without difficulty.
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1. Introduction

Impaired insulin sensitivity (S_I), reduced β-cell mass, and insulin secretion (ISEC) have been recognized as the major pathophysiologies of type 2 diabetes mellitus [1]. Theoretically, the blood glucose will not elevate until the decompensation of β-cell function to insulin resistance occurs [2]. From the data of the United Kingdom Prospective Study, it could be noted by extrapolation that the deterioration of the ISEC should have started 10 years before the occurrence of clinical significant diabetes [3]. When considering ISEC, it is well known that there are 2 phases of ISEC: the first phase (first ISEC) and second phase (second ISEC) [4]. The first ISEC is normally secreted by β-cells within 10 minutes after they are exposed to an elevation in plasma glucose levels. The second ISEC rises gradually after the first ISEC and reaches a plateau within 2 to 3 hours [5]. In comparison with the first ISEC, the role of the second ISEC in type 2 diabetes mellitus

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remains obscure because few studies were focusing on the second ISEC in the past.

There are many different methods to measure ISEC. For instance, homeostasis model assessment of β-cell function (HOMA-β) is the easiest one and has been widely used in epidemiologic studies [6]. However, it is not accurate; and it could not be used to quantify first and second ISEC [7]. Other more sophisticated tests such as the frequent sample intravenous glucose tolerance test (FSIGT) and intravenous glucagon test are specific for first-ISEC measurement [8,9]. Meanwhile, oral glucose tolerance test [10], hyperglycemic clamp [11], low-dose graded glucose infusion [12], and arginine stimulation test [13] are regarded as the methods for second ISEC. Among them, the low-dose graded glucose infusion) was first proposed by Byrne et al [12]. During this 4-hour test, increasing the infusion rate of glucose could give β-cells a continuous, gradually increased stimulation and thus could be taken as the method for measuring second ISEC. Despite its high accuracy, this is a time-consuming and expensive test because C-peptide is measured in the study. The C-peptide is needed to calculate the "true" concentrations of insulin secretion before the hepatic extraction. This mathematical method (deconvolution) used in the calculation is quite difficult for regular research centers.

In this study, we used the FSIGT to measure S_I and first ISEC and the modified low-dose graded glucose infusion test (M-LDGGI) to measure second ISEC [14]. By these methods, we could understand the roles of these parameters in a group of newly diagnosed Chinese type 2 diabetes mellitus patients.

2. Materials and methods

2.1. Subjects

We enrolled 52 new-onset type 2 diabetes mellitus patients between 40 and 70 years old in our outpatient clinic from 2001 to 2005. The age and body mass index (BMI) are shown in Table 1. Other than diabetes, they did not have any other significant medical diseases or history of diabetic ketoacidosis; nor had they taken any medications known to have effect on S_I and/or β-cell function during the study period. The diagnostic criteria for diabetes were based on the 1997 American Diabetes Association criteria with a fasting blood glucose less than 7 mmol/dL [15].

2.2. Material and protocols

Each participant undertook the M-LDGGI and FSIGT randomly with at least 3 days of interval between the 2 tests. The tests were performed at 8:00 AM on different days with subjects in the sitting position after a 10-hour overnight fast. An intravenous catheter was placed in each forearm, one for blood sampling and one for glucose infusion. The sampling catheters were kept patent by slow infusion of 0.9% saline.

Table 1
The demographic data of nonresponders and responders

	Nonresponders	Responders	*P* value
n	26	26	
Male/Female	16/10	11/15	.165
Age (y)	47.8 ± 8.6	52.7 ± 7.2	.032
Slope	0.006 ± 0.006	0.07 ± 0.04	0
BMI (kg/m^2)	24.1 ± 2.8	25.5 ± 3.0	.033
Waist (cm)	79 ± 12	84.8 ± 8.8	.2
FPG (mmol/L)	11.8 ± 3.1	9.5 ± 1.8	.008
FPI (pmol/L)	29.7 ± 28.8	46.4 ± 55.3	.209
Log (FPI)	0.34 ± 0.63	0.62 ± 0.37	.051
HbA_{1c} (%)	11.4 ± 2.3	9.8 ± 1.2	.042
Systolic blood pressure (mm Hg)	118.5 ± 14.7	126.2 ± 18.7	.312
Diastolic blood pressure (mm Hg)	73.5 ± 8.6	79.5 ± 10.8	.076
Total cholesterol (mmol/L)	4.5 ± 1.1	4.4 ± 0.9	.376
HDL cholesterol (mmol/L)	1.1 ± 0.3	1.1 ± 0.4	.68
Triglyceride (mmol/L)	2.2 ± 1.0	1.8 ± 1.0	.236
S_I ($10^{-4} \times min^{-1} \times pmol^{-1} \times L^{-1}$)	2.1 ± 1.8	1.9 ± 1.3	.71
Log (S_I)	0.03 ± 0.54	-0.04 ± 0.54	.462
AIRg (μU/min)	3.1 ± 25.7	15.6 ± 26.0	.157
S_G (min^{-1})	0.0259 ± 0.03	0.0201 ± 0.016	.344
Log HOMA-IR	0.04 ± 0.65	0.24 ± 0.37	.189
Log HOMA-β	0.58 ± 0.62	0.95 ± 0.39	.012

HDL indicates high-density lipoprotein.

2.2.1. Frequent sample intravenous glucose tolerance test

After the catheters were placed, a bolus of 10% glucose water (0.3 g/kg) was given. Another bolus of regular human insulin (Novo Nordisk Pharmaceutical, Princeton, NJ) 0.05 U/kg was injected 20 minutes after glucose load. Blood samples for plasma glucose and insulin levels were collected at 0, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 minutes. They were put into the Bergman Minimal Model [8]; and then S_I, glucose sensitivity (S_G), and acute insulin response after the glucose load (AIRg) were obtained. The AIRg was regarded as first ISEC. the S_G is the effect of glucose itself, independent of insulin on glucose homeostasis. Subjects with higher S_I and AIRg were considered to have better glucose metabolism even though they are diabetic.

2.2.2. Modified low-dose graded glucose infusion

The catheters were placed as mentioned in the previous paragraph; a stepped intravenous infusion of glucose (20% dextrose) was then started at a rate of 2 mg/(kg min), followed by 6 mg/(kg min). Each infusion rate was maintained for 80 minutes, and blood samples were drawn at a 20-minute interval for the measurement of plasma insulin and glucose levels. The results were interpreted as the slope of the changes of plasma insulin levels (y-axis) against the plasma glucose levels (x-axis). It should be noted that the component of time is not considered in this figure. Basically, it shows the response of insulin secretion in response to certain amount of plasma glucose level. Thus, the slope of these curves was regarded as the second ISEC and used as the criterion a for grouping.

The homeostasis model assessment of insulin resistance (HOMA-IR) and HOMA-β were calculated according to the equations of Matthew et al [6].

The blood samples were centrifuged immediately and stored at −30°C until time of analysis. Plasma insulin was measured by a commercial solid-phase radioimmunoassay kit (Coat-A-Count insulin kit; Diagnostic Products, Los Angles, CA). Intra- and interassay coefficients of variance for insulin were 3.3% and 2.5%, respectively. Plasma glucose was measured by a glucose oxidase method (YSI 203 glucose analyzer; Scientific Division, Yellow Spring Instrument, Yellow spring, OH). Serum total cholesterol, triglyceride, and high-density lipoprotein cholesterol were measured by the dry, multilayer analytical Slide method in the Fuju DR-Chem 3000 analyzer (Fuji Photo Film; Minato-Ku Tokyo, Japan). The level of HbA_{1c} was evaluated by ion-exchange high-performance liquid chromatography method (Variant II; Bio-Rad, Hercules, CA).

2.3. Statistical analysis

Statistical analysis was performed by SPSS 10.0 version for Windows software (SPSS, Chicago, IL). Data are shown as mean ± standard deviation. Independent *t* test was used to evaluate the demographic data, clinical characteristics, and parameters derived from the tests between the 2 groups. Because HOMA-IR, HOMA-β, fasting plasma insulin (FPI), and S_I showed right skew, log transformation was also performed for analysis. Correlations were evaluated by Pearson correlation. All statistical tests were 2-sided, and a P value < .05 was considered to be significant.

3. Results

By using the median value of the slope during M-LDGGI as the cut point, we separated the patients into 2 equal groups arbitrarily: responders and nonresponders. Subjects with slope less than 0.019 was defined as *nonresponders*. Table 1 depicts the demographic data, fasting plasma glucose (FPG) and FPI, plasma lipids, and S_I, S_G, and AIRg derived from the FSIGT of these 2 groups. The patients in the responder

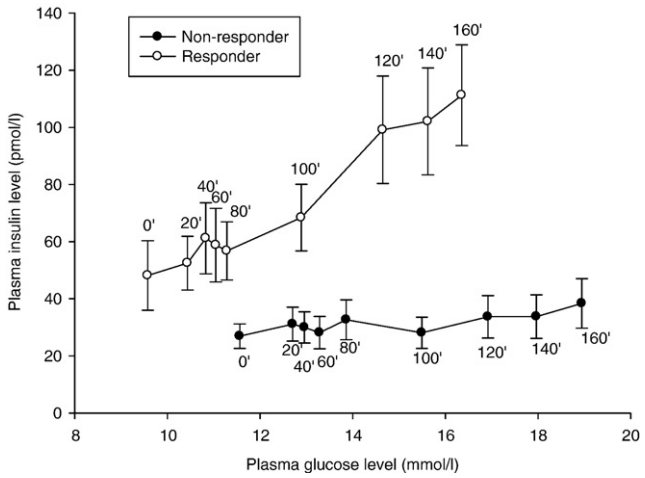

Fig. 1. Plasma glucose and insulin concentration in each time point during M-LDGGI of responder and nonresponder. Subjects with slope less than 0.019 were arbitrarily defined as *nonresponders*.

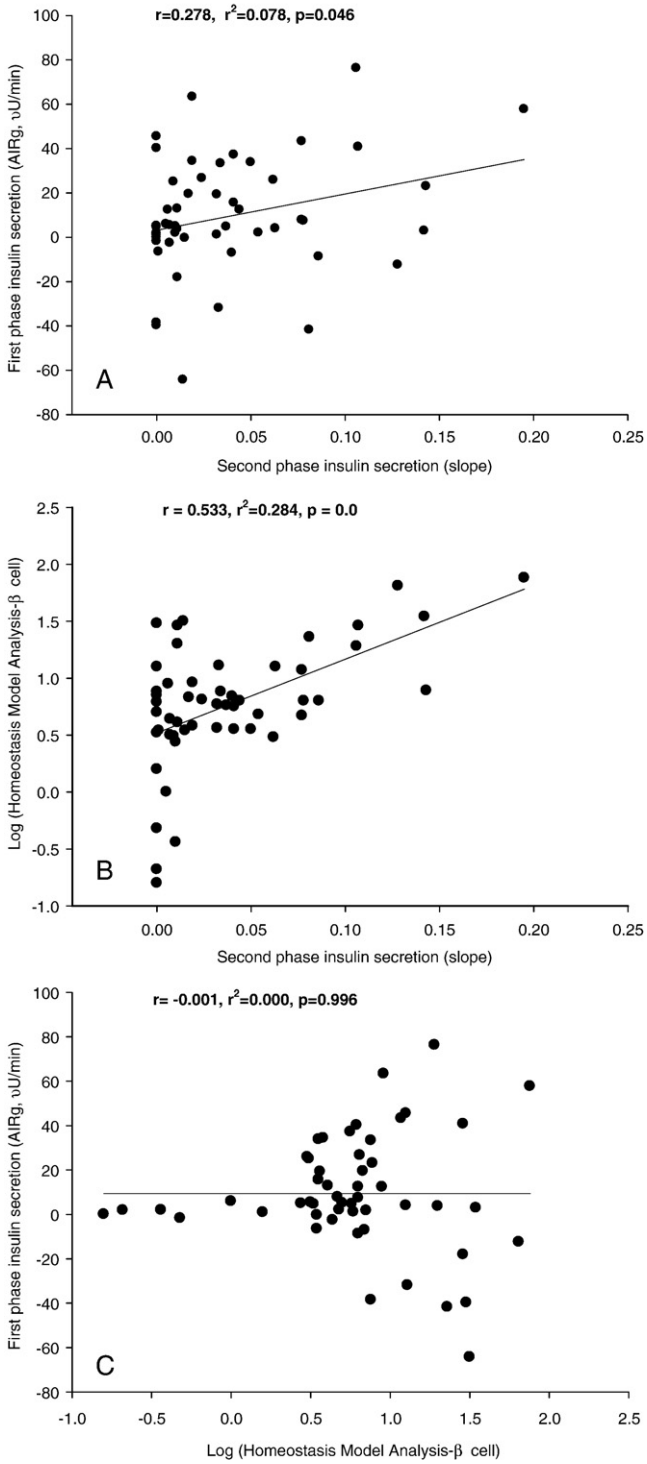

Fig. 2. The correlation between first ISEC, second ISEC (slope during M-LDGGI), and log (HOMA-β).

Table 2
The correlations between hemoglobin A_{1c} and other parameters related to glucose homeostasis

	S_I	1st ISEC	2nd ISEC	Log HOMA-IR	Log HOMA-β
HbA_{1c}	$r = -0.317$, $P = .072$	$r = -0.002$, $P = .988$	$r = -0.388$, $P = .015$	$r = -0.170$, $P = .302$	$r = -0.357$, $P = .026$

group were older and had significantly higher BMI and log HOMA-β. The mean plasma glucose and insulin levels in each time point during the M-LDGGI of the 2 groups are shown in Fig. 1. During M-LDGGI, responders had lower plasma glucose and higher insulin concentrations than nonresponders in each time point. To evaluate the relationships among 3 different methods measuring insulin secretion, that is, first ISEC, log HOMA-β, and second ISEC, Pearson correlation was performed; and Fig. 2 shows their relationships. Significant correlations are noted between the second ISEC and first ISEC ($r = 0.278$, $P = .046$), between the second ISEC and log HOMA-β ($r = 0.533$, $P = .000$), but not between log HOMA-β and first ISEC ($r = -0.001$, $P = .996$). To understand which parameters of the insulin action and secretion contribute most to the glucose control, the correlations between different parameters and HbA_{1c} were evaluated; and the results are shown in Table 2. Interestingly, in these parameters, the significances could only be noted between HbA_{1c} and second ISEC ($r = -0.388$, $P = .015$) and between HbA_{1c} and log HOMA-β ($r = -0.357$, $P = .026$). No significant correlation was noted between the HbA_{1c} and S_I, first ISEC, or log HOMA-IR.

In our study, the correlation between the BMI on second ISEC was positive but did not reach statistical significance (Fig. 3). Finally, a simple correlation between S_I and second ISEC was performed; and the graphical result is demonstrated in Fig. 4. In our study, no significant difference could be noted between S_I and second ISEC ($r = -0.182$, $P = .231$).

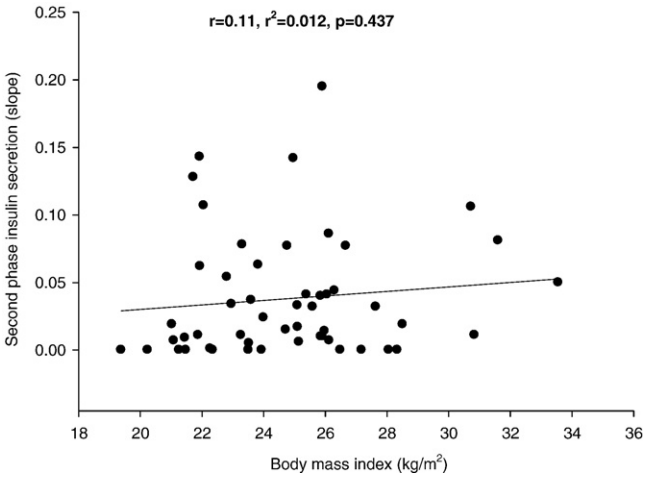

Fig. 3. Correlations between BMI and second ISEC (slope during M-LDGGI).

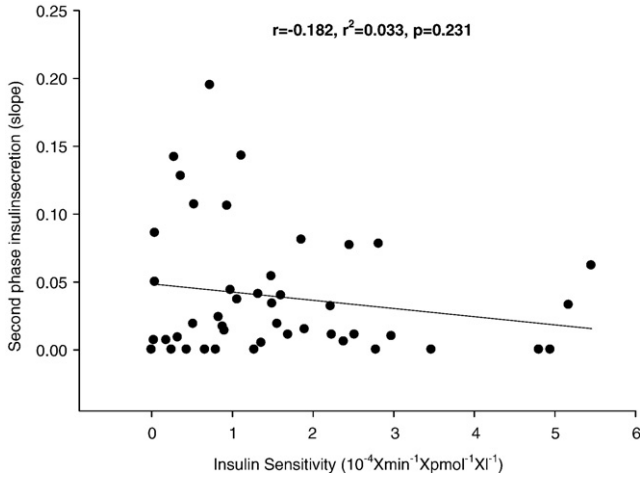

Fig. 4. The correlation between S_I and second ISEC (slope during M-LDGGI).

4. Discussion

It is a widely held belief that the underlying pathophysiologies of type 2 diabetes mellitus are decreased insulin action (insulin resistance), reduced β cell mass, and insulin secretion [1,4]. The existence of biphasic insulin secretion in response to square-wave glucose infusion was first reported by Cerasi and Luft in 1963 [16]. Because ISEC is both interesting and important, many methods were developed to measure first ISEC and second ISEC. With regard to ISEC, most of the published articles were focusing on the first ISEC; and its role in glucose metabolism is relatively more pellucid. On the contrary, few studies were done to measure second ISEC [17-22]; and its importance still remains controversial. For instance, it was shown in the study of Weiss et al [23] that first ISEC declined in IGT and disappeared in diabetic patients. This finding suggested that the deterioration of first ISEC is the most sensitive marker for the hyperglycemia to occur. Meanwhile, the defect of second ISEC is considered to be the specific hallmark of the occurrence of diabetes [23]. In other words, diabetes will not become clinically detectable unless impaired second ISEC is noted [23].

In our study, the responders had significantly higher first ISEC than nonresponders. When performing the linear regression to observe the relationships between the first and second ISEC, the r value was around 0.278 (Fig. 2A). It is interesting to note that this r value was even lower than that between log HOMA-β and second ISEC (Fig. 2B). This result is compatible with the report of Cerasi et al [24] that, in the early stage of type 2 diabetes mellitus, when the first ISEC decreases significantly, the second ISEC only begins to shift to the right. In other words, the first ISEC and second

ISEC were not "synchronized" in the pace of deterioration. Surprisingly, there was no statistical correlation between log HOMA-β and first ISEC because a positive correlation is expected. However, HOMA-β and FSIGT are basically different methods to investigate different aspects of insulin secretion. To be more specific, FSIGT is relatively more physiology because it evaluates the dynamic response after glucose challenge. Meanwhile, HOMA-β only reflects the static condition of the β-cell. In addition, as aforementioned, first ISEC has already been lost at the time diabetes is diagnosed. Both tests are less sensitive in these patients. Therefore, when comparing the results of these inaccurate data with 2 different methods, statistical insignificance could be explained.

Between the nonresponders and responders, the significant differences were age, BMI, FPG, log HOMA-β, and HbA_{1c}. From these data, 3 conclusions could be drawn: (1) Subjects with higher second ISEC are older. (2) Subjects with higher second ISEC had higher BMI. (3) Better second ISEC contributes to better glucose control. First, concerning the role of aging on ISEC, our previously published study also found young-onset type 2 diabetes mellitus had a worse first ISEC [25]. Given these corresponding results, we can intrepidly hypothesize that the relatively more severe deterioration of the ISEC in those young subjects is responsible for the early onset of diabetes in young subjects. Secondly, many evidences showed that obese subjects have better insulin secretion. Park et al [26] had found higher C-peptide levels in Korean obese type 2 diabetes mellitus patients than the lean ones. Our previous study also reported that higher first ISEC (AIRg) could be noted in obese young type 2 diabetes mellitus patients compared with the lean ones [25]. However, these data were only focusing on the first ISEC. As for the second ISEC, until now, the largest study ever done was by Kloppel et al [27]. In brief, they suggested that obesity caused a doubling of the β-cell mass and better insulin secretion; and the quantity of β-cell mass determines how much insulin could be released [28]. Their results had also been supported by some other small studies using histochemical [29,30] and immunocytochemical methods [27,31]. Considering all the above evidences, the relationship between the BMI and second ISEC should be quite confirmable. However, although there was significant difference in BMI between the responders and nonresponders, we did not find the expected correlation between BMI and second ISEC (Fig. 3). From the scatter graph, it could be seen that the trend of a positive correlation did exist. However, because these freshly diagnosed diabetes patients all had a certain severe deterioration of the β-cell function, the narrow range of the data could further decrease the power of the correlation significance. Therefore, we can postulate that if we enrolled subjects only with impaired or even normal glucose tolerance who are supposed to have better second ISEC, the correlation would have become significant because a wider range of the second ISEC is expected. Thirdly, it should be pointed out that the BMI of the responders was 25.5 kg/m^2 in our study, which was still only in the range of overweight for Chinese. Thus, it reduces the statistical power of the correlation. If the range of BMI was wider, significant correlation could be expected. Importantly, this unique nonobese characteristic delineates the fact that Chinese type 2 diabetes mellitus patients are mostly lean, which is different from the case with white people [32].

Finally, the other interesting differences were the higher HbA_{1c} and FPG in the nonresponders. To the best of our knowledge, this hypothesized relationship had not been reported in other studies. Upon further examination, we found that the second ISEC and log HOMA-β were the only factors that were significantly related to the level of HbA_{1c} among other parameters listed in Table 2. To be more specific, there was no correlation between the HbA_{1c} and S_I, first ISEC, or log HOMA-IR. According to Brunzell et al [33], the first ISEC is thought to be impaired in the early stage of glucose intolerance; the maintenance of glucose homeostasis is mainly dependent on the second ISEC [23]. Our results could be interpreted as supporting this hypothesis. In this study, we considered that our patients were only in the "early stage" of the disease course. The remaining second ISEC should be only at the stage of "shift to the right" in the responders.

We do realize that there are certain limitations in this study. First, we did not measure the proinsulin levels. It is known that its ratio to insulin increases in diabetes [34,35]. However, because all the subjects were diabetic, we would expect that the ratio increased in a similar extent in each subject. Hopefully, this could reduce the effect of noise from the proinsulin. Secondly, because approximately 50% of secreted insulin is degraded during the first pass through the liver [36], it should be more precise to use C-peptide when evaluating the insulin secretion. A mathematical method (deconvolution) could be used to overcome this problem [37]. However, this complicated method could only be done in several research centers in the world. Besides, most of the current available published data on either first ISEC or second ISEC were based on the measurement of insulin levels only. In our study, we used M-LDGGI test to measure the second ISEC, which is a relatively sensitive and easy test to use. We believed that this method could be done in many other research centers without difficulty and, in the same time, still be informative. Finally, chronic hyperglycemia might increase insulin resistance and impaired β-cell function, known as *glucotoxicity* [38,39]. One may argue that glucotoxicity might interfere with insulin concentrations and M-LDDGI results in our study. However, given the facts that the S_I is similar in the 2 groups, the only other factor that could affect glucose levels would be the ability of insulin secretion. The higher FPG and HbA_{1c} must be due to the different degree of impaired insulin secretion in these subjects. Moreover, although glucotoxicity is considered to have substantial effects on the insulin secretion, our published data did not suggest the same especially in poorly

controlled diabetes [40]. The effect of glucotoxicity might not be as significant as generally thought.

In conclusion, type 2 diabetes mellitus patients with higher second ISEC are older and have higher BMI. Among all the parameters, second ISEC is the most important factor affecting the degree of glucose levels in naive Chinese type 2 diabetes mellitus patients. In the same time, the first and second ISECs were only modestly correlated, which indicated that the deterioration of these 2 phases was not synchronized. Finally, we also recommend using the M-LDDGI for quantifying second ISEC. This practical method could be done in many centers without difficulty.

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