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Beta-cell function and insulin sensitivity at various degrees of glucose tolerance in Chinese subjects

Jiunn-Diann Lin[a], *Yen-Lin Chen*[b], *Chun-Hsien Hsu*[c], *Chung-Ze Wu*[a], *An-Tsz Hsieh*[a], *Chang-Hsun Hsieh*[d], *Jin-Biou Chang*[e], *Yao-Jen Liang*[f], *Dee Pei*[g,*]

[a] *Division of Endocrinology and Metabolism, Department of Internal Medicine, Shuang Ho Hospital, School of Medicine, College of Medicine, Taipei Medical University, Taiwan, ROC*

[b] *Department of Pathology, Cardinal Tien Hospital, Medical School, Catholic Fu-Jen University, Taipei, Taiwan, ROC*

[c] *Department of Family Medicine, Cardinal Tien Hospital, Medical School, Catholic Fu-Jen University, Taipei, Taiwan, ROC*

[d] *Division of Endocrinology and Metabolism, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical School, Taiwan, ROC*

[e] *Department of Pathology, National Defense Medical Center, Division of Clinical Pathology, Tri-Service General Hospital, Taipei, Taiwan, ROC*

[f] *Department and Institute of Life Science, Fu-Jen Catholic University, New Taipei City, Taiwan, ROC*

[g] *Department of Internal Medicine, Cardinal Tien Hospital, Medical School, Catholic Fu Jen University, Taipei, Taiwan, ROC*

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ABSTRACT

Aims: The aim of this study was to evaluate the relative importance of insulin sensitivity (S_I), and the first (1st ISEC) and second phase insulin secretion (2nd ISEC) in the development of type 2 diabetes (T2D) in Chinese subjects.

Methods: A total of 96 subjects, including 19 with normal fasting glucose, 21 with pre-diabetes, and 56 with T2D were enrolled. Subjects underwent a modified low dose graded glucose infusion (M-LDGGI; a simplified version of Polonsky's method) and frequently sampled intravenous glucose tolerance test. The results were interpreted as the slope of the changes of plasma insulin against the glucose levels. By observing the respective percentage reduction, the deterioration rate of each parameter was compared.

Results: As fasting plasma glucose (FPG) levels increased, S_I decreased mildly and non-significantly, while the 1st and 2nd ISECs decreased more dramatically and significantly. More importantly, the decrease of the 1st ISEC from baseline was greater than that of the 2nd ISEC.

Conclusions: Since the 1st ISEC decreased the most with increasing FPG levels, it is concluded that the 1st ISEC is the key trigger of T2D development. On the contrary, the 2nd ISEC remained more stable across increasing FPG levels. This latter finding may explain the effectiveness of insulin secretagogues during the early stage of T2D. The results of this study can be helpful in the development of interventions aimed at stopping the progression and/or treating T2D in Chinese populations.

* *Corresponding author at*: Dept. of Internal Medicine, Cardinal Tien Hospital, No. 362, Chung Cheng Rd., Xindian City, Taipei County 23137, Taiwan, ROC. Tel.: +886 2 22193391; fax: +886 2 22195821.

E-mail address: peidee@gmail.com (D. Pei).

Abbreviations: S_I, insulin sensitivity; 1st ISEC, first insulin secretion phase; 2nd ISEC, second insulin secretion phase; IR, insulin resistance; FPG, fasting plasma glucose; NFG, normal fasting plasma glucose; PreDM, pre-diabetes; T2D, type 2 diabetes; AIRg, acute insulin response after the glucose load; FPI, fasting plasma insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B, homeostasis model assessment of beta-cell function; M-LDGGI, modified low dose graded glucose infusion test; FSIGT, frequent sample intravenous glucose tolerance test.

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1. Introduction

Impaired insulin sensitivity (S_I) and reduced insulin secretion (ISEC) are the two major pathophysiologic abnormalities underlying type 2 diabetes (T2D) [1]. It is generally agreed that beta cell secretion increases in order to maintain normal glucose homeostasis among subjects with insulin resistance (IR) [2]. However, beta cell secretion eventually reaches a level of decompensation in many of these subjects, leading to clinically evident diabetes [1,2]. ISEC is composed of two phases: the 1st phase (1st ISEC) and 2nd phase (2nd ISEC) [3,4]. Conceptually, the 1st ISEC consists of the stored insulin within the granules of beta cells that is secreted within 10 min of an acute elevation in plasma glucose levels. On the other hand, the 2nd ISEC phase comprises the secretion of newly produced insulin from the beta-cells, which reaches a plateau within 2–3 h [4].

Whether impaired S_I or ISEC is the major contributor for diabetes or whether both factors contribute equally remains controversial. Using surrogate markers derived from an oral glucose tolerance test (OGTT), IR has been found to be the major factor determining the deterioration of plasma glucose levels in Europeans while deterioration of ISEC was the predominant factor in Asians [5–7]. The reasons behind these contradictory findings have not been fully clarified. Additionally, evidence suggests that the 2nd ISEC is maintained for a longer period than the 1st ISEC during the natural progression of diabetes. The remaining 2nd ISEC after the diagnosis of diabetes may determine the time period of the oral hypoglycemic drugs, particularly the insulin secretagogues, can effectively control glucose levels. Despite the important role of the 2nd ISEC in the pathophysiology of diabetes, most recent studies have only focused on the 1st ISEC [8].

In this study, we simultaneously measured S_I, and the 1st and 2nd ISECs in order to elucidate their respective roles in the pathogenesis of diabetes among 96 Chinese subjects with varying levels of glucose tolerance.

2. Materials and methods

2.1. Subjects

We enrolled 96 individuals between the ages of 40 and 70 years who presented at our out-patient clinic in 2011. Subjects were either self-referred or referred by health professionals for purposes of screening for diabetes and had a body mass index (BMI) between 20.0 kg/m^2 and 30.0 kg/m^2. Subjects were free of any other significant medical diseases, had no history of diabetes or diabetic ketoacidosis, nor had taken any medications known to influence S_I and/or beta-cell function (including oral hypoglycemic agents) during the study period. Subjects were categorized into three groups according to their fasting plasma glucose (FPG) as follows: normal fasting plasma glucose (NFG; FPG $<$ 5.6 mmol/l), pre-diabetes (PreDM; 5.6 $\geq$ FPG $<$ 7.0 mmol/l) and T2D (FPG $\geq$ 7 mmol/l). These FPG categories were based on the 2012 American Diabetes Association (ADA) recommendation [9]. On the first day of study, a complete routine work-up was performed to exclude the presence of cardiovascular, endocrine, renal, hepatic and respiratory disorders. The study protocol was approved by the hospital's institutional review board and ethics committee. All subjects provided written informed consent prior to participation. BMI was calculated as body weight (kg)/height (m)^2. Systolic and diastolic blood pressures were measured on the right arm with subjects seated using a standard mercury sphygmomanometer. Blood samples were drawn from the antecubital vein for biochemical analysis.

2.2. Patients and protocols

Each participant undertook 2 tests: the modified low dose graded glucose infusion test (M-LDGGI) and the frequently sampled intravenous glucose tolerance test (FSIGT). The two tests were performed in random order, separated by a minimum interval of three days. The tests were performed at 8:00 am following a 10-h overnight fast with subjects in the sitting position. An intravenous catheter was placed in each forearm: one for blood sampling and one for glucose infusion. The sampling catheters were kept patent through the slow infusion of 0.9% saline.

2.2.1. FSIGT

After the catheters were inserted, a bolus of 10% glucose water (0.3 g/kg) was given. Twenty minutes later, a bolus of regular human insulin (Novo Nordisk Pharmaceutical, Princeton) 0.05 units/kg was injected. Blood samples for plasma glucose and insulin levels were collected at 0, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100 and 180 min. Subsequently, the S_I, and acute insulin response after the glucose load (AIRg) were obtained using Bergman's Minimal Model [10]. AIRg was regarded as the 1st ISEC. Subjects with higher S_I and AIRg were considered to have better glucose metabolism.

2.2.2. M-LDGGI

This test is a simplified version of the low dose graded glucose infusion proposed by Polonsky [11], which we have used in a previously published study [8,12]. On the day of the test, catheters were placed as described above, and a stepped intravenous infusion of glucose (20% dextrose) was started at a rate of 2 mg/kg/min, followed by 6 mg/kg/min. Each infusion rate was maintained for 80 min. Blood samples were drawn every 20 min for the measurement of plasma insulin and glucose levels. The results were graphed as the slope of change of plasma insulin levels (y-axis) versus plasma glucose levels (x-axis), essentially reflecting insulin secretion in response to a certain level of plasma glucose. This slope was regarded as the 2nd ISEC.

2.2.3. Metabolic tests

Homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment of beta-cell function (HOMA-B) were calculated according to Matthew's equations [13].

Blood samples were centrifuged immediately and stored at $-30\,^{\circ}C$ until the time of analysis. Plasma insulin was measured by a commercial solid phase radioimmunoassay kit (Coat-A-Count insulin kit, Diagnostic Products Corporation, Los Angeles, CA, USA). Intra- and inter-assay coefficients