Early Insulin Secretory Dysfunction in Korean Prediabetic Subjects: Should We Change the Criteria for “Prediabetes?”

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Impaired insulin secretion and insulin resistance are the two main pathophysiological mechanisms that lead to type 2 diabetes. It is well-known that type 2 diabetes is preceded by a long prediabetic state characterized by mild elevation of fasting and/or postprandial glucose levels. However, previous studies on the relative contributions of insulin secretory defects and insulin resistance in the development of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) have yielded contradictory results [1-4]. Inconsistencies across the studies have been explained by differences in study populations, study designs and methods to assess insulin resistance and insulin secretion.

The nature of progressive β-cell failure occurring as normal glucose-tolerant (NGT) individuals progress to type 2 diabetes is incompletely understood. Moreover, the precise level of hyperglycemia at which β-cell function begins to decline has not yet been established. Research has shown that during the natural development of type 2 diabetes, fasting plasma insulin increases and then decreases as insulin resistance develops, displaying the typical inverted U-shaped curve that has been referred to as “Starling’s curve of the pancreas” [5]. Earlier studies reported that the plasma insulin response to glucose rises progressively until the fasting plasma glucose reaches 120 to 140 mg/dL, and further increases in fasting glucose levels are associated with a progressive decline in insulin secretion [6].

To date, several studies have examined insulin secretion as a function of glucose concentrations in various populations [7-11]. Some studies have shown that individuals with IFG and/or IGT have a pronounced defect in early insulin secretion [7,12]. Other studies demonstrated that the decline in β-cell function occurs at an earlier stage that is considered normal according to current diagnostic criteria [8,10,11]. Only limited studies have assessed early insulin secretion based on dynamic tests in Koreans [13-16]. In the studies that do exist, the numbers of participants were small; no studies have yet assessed the changes in insulin secretion in relation to the changes in fasting and postprandial glucose levels ranging from NGT to IGT and type 2 diabetes.

In this issue, Rhee et al. [17] analyzed early-phase insulin secretion during oral glucose tolerance tests (OGTT) in relation to plasma glucose levels ranging from normal to the diabetic range of hyperglycemia in 873 Korean participants. The key finding of this report was that the decline of early-phase insulin secretion according to the increase of plasma glucose concentration begins early and progresses rapidly during the period generally designated as “normal.” According to their results, early-phase insulin secretion was reduced to <50% of the control group in participants with fasting glucose levels of 100 mg/dL, postload 2-hour glucose of 145 mg/dL, and HbA1c of 5.8%. Therefore, the authors claim that the decline of early-phase insulin secretion occurs most abruptly prior to the period we currently refer to as “prediabetes.”

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Then, as Rhee and colleagues suggested, should the criteria for "prediabetes" be changed? "Prediabetes" has been defined as the period during which the risk of developing type 2 diabetes is increased and thus preventive efforts are necessary. The diagnostic criteria for IFG and IGT are not defined on the basis of any pathophysiological abnormalities. Therefore, as discussed above, it is possible that the decline in β-cell function occurs at an earlier stage that is considered normal according to current diagnostic criteria. The American Diabetes Association [18] recommended that IFG and/or IGT should not be viewed as clinical entities in their own right but rather as risk factors for diabetes as well as cardiovascular disease. In addition, defining a lower limit of a "prediabetes" category of glucose levels is somewhat arbitrary, as the risk of diabetes with any measure of glycemia is a continuum that extends well into the normal ranges [18]. Therefore, to maximize the efficiency of preventive interventions, the cut point should balance the sensitivity and specificity. Prospective intervention studies are needed to determine whether "prediabetes" criteria should be changed.

The report of Rhee et al. [17] has several strengths. To our knowledge, this study included the largest number of Korean participants to date whose insulin secretary function was evaluated by OGTT. This relatively large sample size allowed investigators to assess the changes in early-phase insulin secretion in relation to fasting and postprandial glucose levels. They also carefully adjusted for the effects of insulin resistance on individual changes in insulin secretion. Their study underscores the importance of insulin secretion defects in the pathogenesis of type 2 diabetes in Korean patients.

However, as the authors pointed out, Rhee et al.'s study [17] also has several limitations that diminish our ability to draw definitive conclusions. Most importantly, as the participants were not randomly selected from the general population, the results are difficult to generalize to the entire Korean population. In addition, the study's cross-sectional design prohibited examining time-course or causal relationships. In addition, early-phase insulin secretion indices were measured based on OGTT instead of a gold-standard method such as a glucose-clamp study or an intravenous glucose tolerance test. Another limitation would be that the participants included were "those with suspected abnormal glucose tolerance"; therefore, participants categorized as NGT based on a one-time OGTT may not be completely normal, as the poor reproducibility of OGTT is a well-known problem. Previous studies have suggested that non-diabetic participants with a positive family history of diabetes have substantially reduced insulin secretion [19,20]. This study would have been more meaningful if a family history of type 2 diabetes had been considered in the analysis.

Rhee et al.'s study also raises the question of whether Koreans really have lower β-cell capacity than do Western populations. Previous studies have suggested that Koreans have lower insulin secretory capacity than Caucasians [13,21], and an early-phase insulin secretory defect rather than insulin resistance may be a more important factor in the development of type 2 diabetes in Koreans [14-16]. Unfortunately, we do not have the definitive answer yet, as there has been no study that directly compared insulin secretion of Koreans with that of other ethnic groups in the same study setting.

The exact time-course changes of insulin secretion remain to be confirmed in longitudinal studies, although such studies are not easy to perform. While Rhee and colleagues' study provides valuable information, more questions remain unanswered including the mechanism of decline in early-phase insulin secretion. Further research is needed to address the pathogenic importance of early-phase insulin secretory dysfunction in the development of type 2 diabetes and to determine appropriate measures to prevent and treat these defects.

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