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Impaired insulin secretion and related factors in East Asian individuals

The main pathophysiological features of type 2 diabetes are impaired insulin secretion and insulin resistance. Impaired insulin secretion, resulting from reduced β-cell function/mass, might be more important in Asian individuals, in contrast to the relative importance of insulin resistance in white individuals. In this JDI Update, we describe the natural history of pancreatic β-cell function and related factors in East Asian individuals, and discuss recent findings regarding islet morphology, including β-cell mass.

Diabetes is characterized by gradual impairment of pancreatic β-cell function, occurring before the onset of the disease[1,2]. Fujikawa *et al.*[3] carried out a longitudinal analysis of the natural history of β-cell function in Japanese people allocated to a diabetes mellitus group and a diabetic type with glycated hemoglobin <6.5% group. The negative slope of the regression line of β-cell function for the duration, estimated using homeostasis model assessment of β-cell function, was significantly steeper in the former group. Moreover, when the participants were further subdivided into those with obesity (body mass index ≥25 kg/m^2) and those without (body mass index <25 kg/m^2), the slope of the regression line of β-cell function was significantly steeper in the participants with obesity than in those without in both groups. These results show that pancreatic β-cell function declines more rapidly in people with diabetes than in the diabetic type with glycated hemoglobin <6.5%, and in those with obesity.

Regarding the environmental factors that affect pancreatic β-cell function, Ueda *et al.*[4] evaluated the relationship between daily alcohol consumption and glucose tolerance, β-cell function, and insulin resistance in the Japanese population, and found that daily alcohol consumption caused a significant reduction in β-cell function, estimated using homeostasis model assessment of β-cell function, but not insulin resistance. This reduction in β-cell function might reflect a greater risk of diabetes in Japanese men who regularly consume alcohol. Pancreatic fat also affects glucose tolerance and β-cell function. Ishibashi *et al.*[5] evaluated the effect of pancreatic fat accumulation on glucose metabolism in Japanese people with type 2 diabetes, and found that it is associated with a longitudinal decrease in insulin secretion capacity, estimated using the increase in circulating C-peptide concentration during a glucagon stimulation test.

New gene regions involved in type 2 diabetes in East Asian individuals have been identified[6], and a family history of diabetes also has a substantial influence on the pathophysiology of diabetes. Iwata *et al.*[7] evaluated the relationships of the number and type of family history of diabetes with β-cell function, estimated using fasting C-peptide concentration and the C-peptide index (calculated using the formula: 100 × fasting C-peptide concentration / plasma glucose concentration) in Japanese patients with type 2 diabetes. In that study, the authors found that a diagnosis of diabetes in both parents was most strongly associated with impaired β-cell function. Another large Chinese population-based study showed that the risk of impaired glucose metabolism in people with a maternal family history of diabetes is significantly higher than that in people with a paternal family history of diabetes[8]. In addition, a maternal family history of diabetes, but not a paternal history, was significantly associated with impaired β-cell function, evaluated using homeostasis model assessment of β-cell function and the insulinogenic index. Thus, maternal and paternal family histories of diabetes appear to have differing influences on the pathogenesis of diabetes.

Fasting C-peptide concentration and the C-peptide index are often used to assess endogenous insulin secretory capacity in patients with diabetes. Recently, we showed that these parameters are associated with glycemic variability in Japanese patients with type 2 diabetes[9,10]. Specifically, as the fasting C-peptide concentration decreases, glycemic variability rapidly increases[10], which implies that the fasting C-peptide concentration might represent a useful marker of excessive glycemic variability in patients with type 2 diabetes.

As described above, several methods for evaluating pancreatic β-cell function in humans have been established, and each has its advantages and disadvantages. For large-scale epidemiological studies, a simple method of evaluation is required. We evaluated the relationship between glucose tolerance and β-cell function, assessed using five parameters measured in fasting blood samples, in Japanese individuals[11], and found that proinsulin concentration was the most sensitive indicator of glucose intolerance. Furthermore, it showed a positive association with fatty liver index, and a negative association with high-molecular-weight adiponectin[12,13]. Given that proinsulin is a marker of β-cell stress, fatty liver might be associated with β-cell damage, and conversely, adiponectin might protect β-cells.

Impaired insulin secretion is caused not only by a reduction in β-cell function, but also by a reduction in β-cell mass[14–18] (Table 1). Inaishi *et al.*[18] evaluated the relationship between β-cell mass and glucose tolerance using autopsy

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Table 1 | Pancreatic β-cell mass in East Asian individuals with or without diabetes

	Samples	Evaluation method	Non-diabetes	Diabetes	Reference number
Sakuraba *et al.* (2002)	Autopsy	β-cell mass	1.14 g (n = 15)	0.82 g (n = 14)	14
Yoon *et al.* (2003)	Surgically resected	Relative volume of β-cells	1.94% (n = 10)	1.37% (n = 25)	15
Mizukami *et al.* (2014)	Autopsy	β-cell mass	1.86 g (n = 30)	1.27 g (n = 47)	16
Inaishi *et al.* (2016)	Surgically resected	Fractional β-cell area	1.48% (n = 50)	0.80% (n = 49)	17
Inaishi *et al.* (2020)	Autopsy	Fractional β-cell area	1.85% (n = 40)†	1.17% (n = 32)	18

†Participants with normal glucose tolerance.

samples collected in Japan, and found that β-cell mass is approximately 14% lower in individuals with prediabetes than in those with normal glucose tolerance, and approximately 37% lower in individuals with diabetes. The key positive aspects of that study were that it involved the analysis of autopsy samples collected in a community with a high autopsy rate (the Hisayama Study), and that the glucose tolerance of the individuals had been accurately evaluated by oral glucose tolerance test. However, the authors found no correlation between β-cell mass and amyloid deposits. Recently, Takahashi *et al.*[19] made interesting findings when they evaluated the islet pathology of non-obese Japanese patients with diabetes who were categorized according to the presence or absence of acute myocardial infarction (AMI). β-Cell volume density was found to be lower and amyloid deposition was greater in the patients with AMI than in those without AMI. Furthermore, the lower β-cell volume and greater amyloid deposition were associated with islet microangiopathy, which was common in patients with AMI. This difference in the prevalence of amyloid positive islets is interesting, because it has been reported to be higher in Western than in Japanese patients.

In summary, various factors are associated with impaired insulin secretion, which is considered to be one of the central features of the pathophysiology of diabetes. It is necessary to establish more accurate methods of evaluation of β-cell function and mass in humans, and to design a therapeutic strategy to prevent the progressive impairment of insulin secretion.

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DISCLOSURE

The authors declare no conflict of interest.
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