

## Editorial

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# Effects of Obesity and Diabetes on Beta-Cell Mass in Japanese

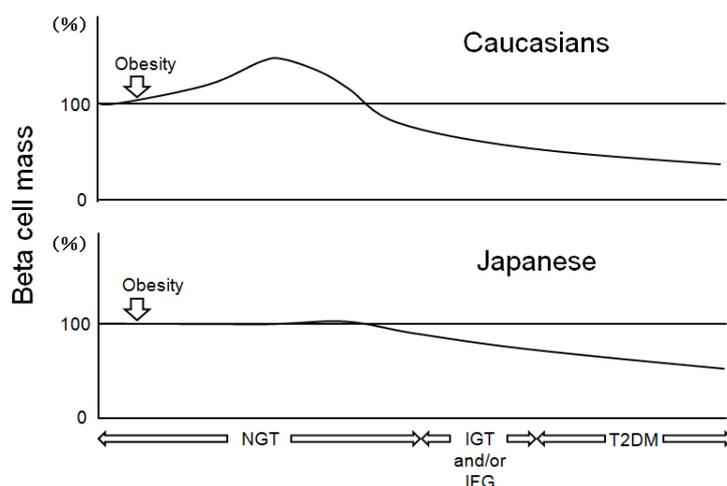
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The prevalence of type 2 diabetes mellitus (T2DM) continues to increase all over the world. T2DM is characterized by insulin resistance and  $\beta$ -cell dysfunction. Recent studies have shown that  $\beta$ -cell dysfunction, but not insulin resistance, is critical for the development of T2DM.<sup>1</sup> Since Butler et al<sup>2</sup> and other groups have reported reduced  $\beta$ -cell mass (BCM) in both lean and obese individuals with T2DM, it is now widely recognized that  $\beta$ -cell deficit is a core feature of T2DM. In adult humans, we and others have shown that BCM is increased by approximately 20-50% in obese non-diabetic individuals in the Caucasian population.<sup>3,4</sup> Increased workload of beta-cells may result in beta-cell death through various mechanisms such as hyperglycemia, dyslipidemia (glucolipotoxicity), oxidative stress, endoplasmic reticulum (ER) stress, inflammatory cytokines, and amyloid deposition. Recent rodent studies have suggested that dedifferentiation of  $\beta$ -cells to  $\alpha$ -cells is another cause of the reduction of BCM in T2DM.<sup>5</sup> However, the change in  $\alpha$ -cell mass (ACM) in patients with diabetes is controversial. ACM has been reported to increase or decrease in patients with T2DM,<sup>6,7</sup> while we and another Japanese study observed no significant increase in BCM in obese non-diabetic adults in the Japanese population.<sup>6,8</sup> The mean body mass index (BMI) of Japanese patients with T2DM is  $<25$  kg/m<sup>2</sup>, suggesting that about half of patients with T2DM are not even overweight (i.e., BMI  $\geq 25$  kg/m<sup>2</sup>, the definition of obesity in Asian countries). In contrast, most Caucasian patients with T2DM are obese, and the mean BMI of patients with T2DM is about 30 kg/m<sup>2</sup>. Considering the similar incidence of T2DM despite the lower degree of obesity in Japanese compared with Caucasians,<sup>9</sup> these findings suggest that  $\beta$ -cell regenerative capacity may differ between Japanese and Caucasians. Because of the limited capacity of  $\beta$ -cell regeneration in Japanese, excess  $\beta$ -cell workload could be induced in individuals with less obesity compared with Caucasians.

However, these studies were based on autopsy pancreas in which it was not possible to completely exclude the effects of confounding factors. We have recently examined the interaction between the effects of diabetes and obesity on BCM and ACM using surgically resected pancreas samples in 99 Japanese individuals.<sup>10</sup> Of these, 49 patients had been diagnosed with T2DM or pancreatic diabetes before operation. The questionnaire, which was conducted in 59 patients, consisted of the following categories: 1) body weight at age 20 years and every decade thereafter, and 2) maximum body weight during life, to clarify the correlation between history of obesity and BCM and ACM. The results showed that, in patients with diabetes mellitus (DM group), BCM was decreased by 46% compared with that in age- and BMI-matched non-diabetic patients (NDM group). The reduction in BCM in Japanese patients with DM was consistent with our prior report using autopsy pancreas. We observed no significant increase in ACM in the DM group, although the relative proportion of ACM to BCM was significantly increased compared with that in the NDM group. In this study, the relative increase in ACM compared with BCM in the DM group was mainly driven by reduced BCM, but not an increase in ACM. In addition, BCM, but not ACM, was associated with pre-operative and post-operative glycemic control (glycated hemoglobin (HbA1c) and glycated albumin). These findings support the concept that BCM rather than ACM has a major role in regulating blood glucose level in humans. The results concerning the effects of obesity on BCM and ACM in patients with and without diabetes showed no difference in BCM and ACM between lean and obese subjects in the NDM and DM groups (where obesity was defined as BMI  $\geq 25$  kg/m<sup>2</sup>). Similarly, there was no significant correlation between BCM or ACM and BMI, duration of obesity or maximum

BMI in the NDM and DM groups. These findings suggest that the increase in BCM in the face of insulin resistance is extremely limited in Japanese (Figure 1), and the ethnic difference in BCM could be attributable to lower maximum insulin secretory ability in Japanese compared with Caucasians. Further studies are needed to determine the genetic and environmental factors regulating BCM in humans and clarify the underlying mechanisms of the ethnic difference in  $\beta$ -cell change in response to obesity. It has also been reported that BCM was decreased by 20-40% in patients with impaired glucose tolerance (IGT) and impaired fasting glycemia (IFG),<sup>11</sup> suggesting that BCM is related to glucose intolerance even prior to the development of T2DM. A progressive decline of BCM underlies the disease progression to IGT or IFG and overt diabetes.



**Figure 1:** Proposed concept of different changes in beta cell mass between Caucasians and Japanese during the development of type 2 diabetes. BCM increases by ~50% to adapt to the increased demand in obese nondiabetic individuals in the Caucasian population, while an increase in BCM in the face of insulin resistance is extremely limited in Japanese. With progression to IGT or IFG and overt diabetes, a progressive decline of BCM underlies the disease in both populations. Difference in beta cell regenerative capacity may explain the different phenotypes of type 2 diabetes between Caucasians and Japanese.

Preservation or recovery of BCM is therefore an important therapeutic strategy for T2DM. Given the fact that Japanese have even less beta cell functional capacity compared with Caucasians, the importance of this strategy should be further emphasized in Japanese. Although no treatment strategy or medication to recover  $\beta$ -cell functional mass has been established, therapy or prevention of T2DM should focus on this point, and lifestyle modification and weight loss remain the most important therapeutic strategy.

#### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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