

## Obesity, Type 2 Diabetes and Beta Cell Failure: An Asian Perspective

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### Abstract

Type 2 diabetes (T2DM) is characterized by insulin resistance and beta cell dysfunction. Although both factors are hallmarks of T2DM, evidence from recent studies has emerged showing that impaired beta cell function is always present in humans with T2DM, suggesting that beta cell dysfunction is a core factor in the pathogenesis of T2DM. Deficit of beta cell mass in humans with T2DM has also been reported, probably through an increase in beta cell apoptosis. Whether deficit of function or mass of beta cells is more important in beta cell dysfunction in T2DM remains unclear; however, collectively, functional beta cell mass is decreased in humans with T2DM. Beta cell dysfunction is not only present in T2DM but also progressively worsens with duration of the disease. Recent studies have also revealed that the functional beta cell mass is already impaired before the onset of T2DM, implying that beta cell dysfunction is essential in the development of T2DM. Finally, ethnic difference in beta cell function has also been proposed. Recent studies suggest that Asians have less beta cell functional capacity compared with Caucasians. Therefore, preservation or recovery of functional beta cell mass is an important therapeutic strategy to prevent, treat and even cure T2DM, and this seems to be further emphasized for Asians.

**Keywords:** Beta cell function; Beta cell mass; Type 2 diabetes; Ethnic difference

**Abbreviations:** T2DM: Type 2 Diabetes; IDF: International Diabetes Federation; IGT: Impaired Glucose Tolerance; IFG: Impaired Fasting Glycemia; NGT: Normal Glucose Tolerance; BMI: Body Mass Index; OGTT: 75g-Oral Glucose Tolerance test; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance

### Introduction

The number of patients with type 2 diabetes (T2DM) is continuously increasing throughout the world. According to the International Diabetes Federation (IDF), approximately 382 million people worldwide, or 8.3% of adults, were estimated to have diabetes in 2013, and approximately 592 million people, or 10% of adults, will have diabetes in 2035 [1]. Nonetheless, there is still no effective strategy to reduce this burden.

T2DM is characterized by insulin resistance and beta cell dysfunction. Since a rather higher plasma insulin level was found in patients with T2DM following the development of a radioimmunoassay for insulin, insulin resistance has been emphasized as a cause of T2DM in contrast to type 1 diabetes, and it has been often assumed that T2DM is a disease of “insulin resistance” over the last several decades.

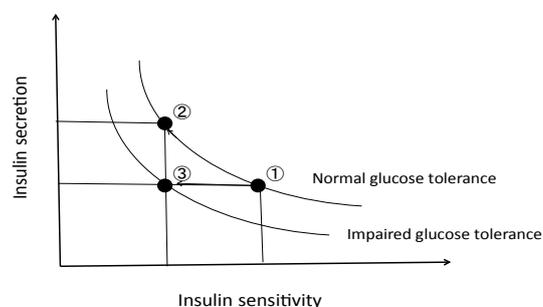
However, recent studies have consistently shown that people with T2DM have reduced beta cell function and even beta cell mass, indicating that beta cell failure is central in the pathogenesis of T2DM [2-4]. Furthermore, recent studies have suggested that beta cell failure in T2DM is more apparent in Asians than in Caucasians [5,6]. This review summarizes the current understanding of beta cell failure in T2DM and discusses its clinical implications.

### Insulin Secretion-Sensitivity Relationship

In a physiological condition, insulin secretion and insulin sensitivity are balanced. If insulin sensitivity is decreased, insulin secretion increases to maintain normoglycemia. Therefore, this relationship between insulin secretion and insulin sensitivity is expressed as a hyperbola (Figure 1). In patients with T2DM, a higher plasma insulin concentration is often found. However, based on this relationship, higher plasma insulin simply reflects greater insulin demand due to

decreased insulin sensitivity. Thus, true beta cell function needs to be assessed with adjustment for concomitant insulin sensitivity, the so-called disposition index developed by Bergman et al. [7,8].

Since the insulin secretion-insulin sensitivity relationship is hyperbolic, the disposition index, i.e., the product of insulin secretion and insulin sensitivity, is constant as long as normoglycemia is maintained. However, once the increase in insulin secretion fails to compensate the decrease in insulin sensitivity, the hyperbolic curve shifts to the left and glucose intolerance develops. As a result, the disposition index decreases (Figure 1) [9,10].



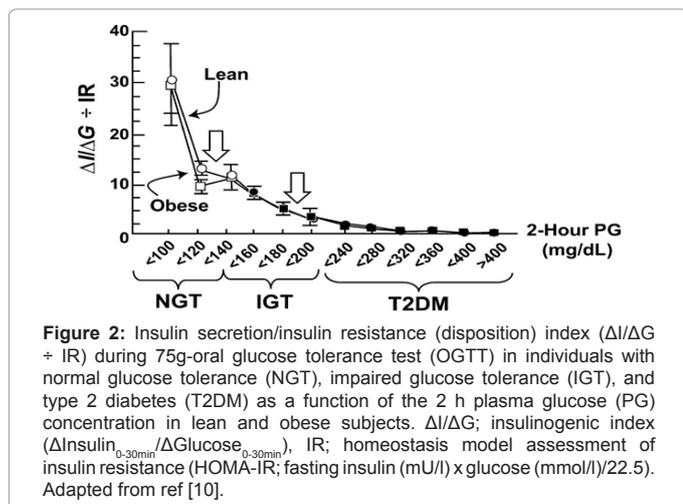
**Figure 1:** Insulin secretion-insulin sensitivity relationship. In a physiological condition, when insulin sensitivity decreases, insulin secretion increases to maintain normoglycemia (1→2), showing a hyperbolic curve. When insulin secretion fails to compensate, the hyperbolic curve shifts to the left and abnormal glucose tolerance develops (1→3).

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Therefore, even though plasma insulin concentration is often higher in patients with T2DM than in normoglycemic individuals, this does not mean that patients with T2DM have greater beta cell function. In fact, true beta cell function is consistently reported to be reduced in patients with T2DM [9-11].

### Change in Beta Cell Function in Obesity and T2DM

Since the development of the disposition index, beta cell function has been consistently reported to be reduced in patients with T2DM [9-11]. DeFronzo et al. reported that beta cell function calculated as insulin secretion/insulin resistance (disposition index) progressively decreases with deterioration of plasma glucose level (Figure 2) [10]. They reported that beta cell function is already decreased by 80% in patients with impaired glucose tolerance (IGT), and even more in patients with T2DM.

Interestingly, beta cell function starts to decline even within the normal range of glucose tolerance, as shown in Figure 2. More importantly, the decline of beta cell function with higher glucose level appears to be similar in lean and obese subjects, suggesting that the significance of beta cell function in the development of glucose intolerance is independent of the presence of obesity.

Longitudinal observation has also revealed a progressive decline of beta cell function in patients with T2DM over years [12,13]. The slope of the decline of beta cell function suggested that beta cell function starts to decline 10 years before the diagnosis of T2DM [12].

Studies have shown that the decline in beta cell function is related to treatment failure [14,15]. Less beta cell function appears to correlate with poor glycemic control, and especially greater postprandial glycemic excursion [16,17].

### Ethnic Difference in Insulin Secretion-Insulin Sensitivity Relationship

T2DM is a heterogeneous disease. It is well recognized that patients with T2DM show various combinations of beta cell dysfunction and insulin resistance. Recently, studies have suggested that heterogeneity of T2DM also exists between ethnicities.

It has been reported that Asians are less obese than Caucasians [18,19]. The definition of obesity for Asians is body mass index (BMI) of 25 kg/m<sup>2</sup> or more [20,21], which is different from that for Caucasians

of 30 kg/m<sup>2</sup> or more. The mean BMI of Japanese patients with T2DM is approximately 23 kg/m<sup>2</sup>, while that of Caucasian patients with T2DM is approximately 32 kg/m<sup>2</sup> [18]. It is of note that the mean BMI of Japanese patients is less than 25 kg/m<sup>2</sup>, the definition of obesity in Japan, implying that more than a half of Japanese patients with T2DM are not even obese.

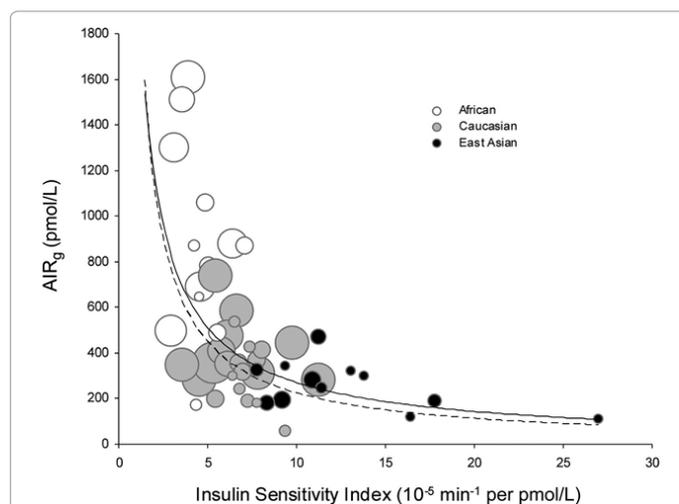
These phenotypic differences between Asians and Caucasians suggest that there is a difference in the pathophysiology of T2DM between ethnic groups. It was suggested that plasma insulin level was lower in Japanese than in Caucasians; however, a direct comparison has not been performed. Recently, Kodama et al. reported a meta-analysis of the ethnic difference in the insulin secretion-insulin sensitivity relationship (Figure 3) [22]. In their study, in the combined subjects of three ethnic groups (Caucasian, African and Asian) with normal glucose tolerance (NGT), the individual cohort of the insulin secretion-insulin sensitivity relationship was plotted on a single hyperbolic curve, showing that the disposition index is the same among ethnicities as long as subjects are normoglycemic. However, when the subjects were divided by ethnicities, Asians were characterized by higher insulin sensitivity and lower insulin secretion compared with Caucasians and Africans.

Thus, recent evidence suggests that there is a difference in the pathophysiological features of T2DM between ethnicities, and Asians seem to have less beta cell functional capacity compared to Caucasians.

### Change in Beta Cell Mass in T2DM

Beta cell function progressively declines with the progression to glucose intolerance. However, since it is not possible to measure beta cell mass in vivo in humans, the change in beta cell mass during the development of T2DM remains largely unknown.

Since the plasma insulin level is higher in patients with T2DM compared to non-diabetic subjects, it has often been believed that the beta cell mass in patients with T2DM is hyperplastic or at least normal. However, recent histological analyses have consistently shown reduced beta cell mass in patients with T2DM. In 2003, Butler et al. reported



that the beta cell mass is reduced by approximately 65% in patients with T2DM compared with age- and BMI-matched non-diabetic controls (Figure 4) [23]. Others reported a 30 to 40% decrease in beta cell mass in patients with T2DM [24-26].

If the beta cell mass is decreased in patients with T2DM, the next question is whether the beta cell dysfunction observed in T2DM is due to functional abnormality of beta cells or to a reduced number of beta cells. This issue has been repeatedly debated since 2003; however, the current consensus seems to be that there is no single mechanism for beta cell dysfunction in T2DM and it is not possible to clearly separate these two factors of beta cells. This seems true because if there is a dying cell, the function of the cell must not be normal. Thus, collectively, the expression “functional beta cell mass” has been recently used to address this issue.

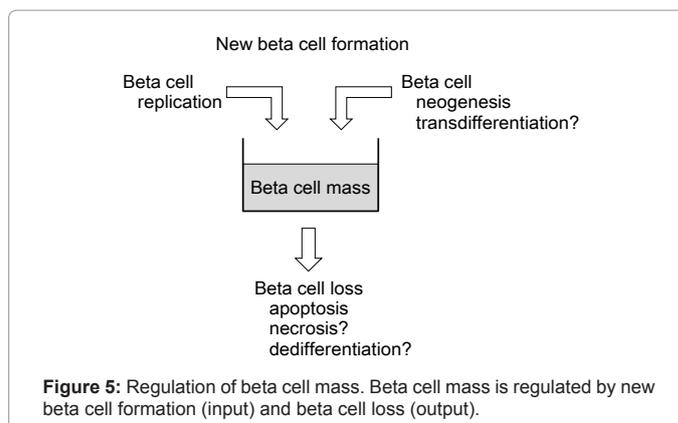
To date, there are limited data on the correlation between beta cell mass and plasma glucose level. Ritzel et al. reported a hyperbolic relationship between beta cell mass and fasting plasma glucose level in humans [27]. Their results indicated that when the beta cell mass is reduced to 50% of the normal level, fasting plasma glucose starts to rise. A similar relationship between beta cell mass and plasma glucose level was also observed in rodents and monkeys [28,29]. Meier et al. reported that beta cell mass is significantly correlated with plasma C-peptide level in humans undergoing pancreatic surgery [30].

Collectively, recent histological analyses of beta cell mass clearly showed that beta cell mass is, at least to some extent, correlated with glucose intolerance in humans [27,30].

### Mechanisms of Reduced Beta Cell Mass in T2DM

Theoretically, the amount of beta cell mass is regulated by new beta cell formation (input) and beta cell loss (output) (Figure 5). Several sources of new beta cell formation are proposed; replication of pre-existing beta cells [31,32], neogenesis from duct cells or stem cells [33,34] and transdifferentiation from acinar cells [35,36] or alpha cells [37]. Although replication of pre-existing beta cells seems to be the main source of new beta cell formation in mice [31,32] and in humans during the postnatal period [38], the source of new beta cells in adult humans remains unclear. Histological studies suggest that beta cell replication is extremely rare in adult humans [39]. In mice, beta cell replication is more frequently observed than in humans; however, most studies used juvenile mice and it has been reported that beta cell replication markedly declines in aged mice [40].

Beta cell loss seems to mostly consist of beta cell apoptosis in vivo. Several reports confirmed a significant increase in beta cell apoptosis in patients with T2DM. Various underlying mechanisms of beta cell apoptosis in T2DM have been proposed, such as glucotoxicity [41],



lipotoxicity [42], oxidative stress [43], amyloid formation [44], altered autophagy [45] and endoplasmic reticulum (ER) stress [46]. It has been suggested that necrosis of beta cells is also increased in T2DM [47].

Recently, dedifferentiation of beta cells to alpha cells has been proposed as a novel mechanism of beta cell loss in diabetes [37]. Dedifferentiation of beta cells to alpha cells may also explain the increase in alpha cell to beta cell ratio in patients with T2DM, although whether the alpha cell mass increases in patients with T2DM remains controversial [24-26].

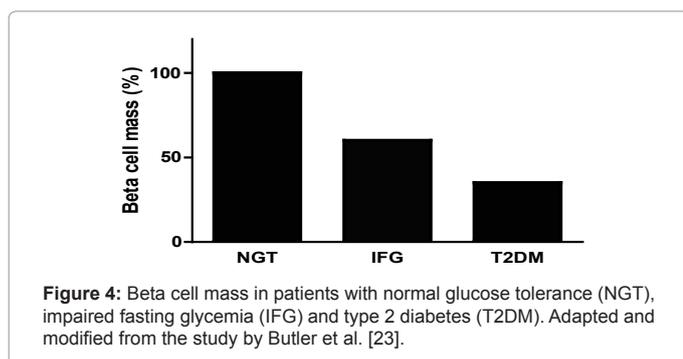
### Change in Beta Cell Mass with Obesity

Beta cell mass is decreased in patients with T2DM. However, the change in beta cell mass during the development of T2DM is largely unknown. Since the plasma insulin level is increased approximately 2 to 3-fold with obesity to compensate insulin resistance [48], called hyperinsulinemia, it is widely believed that the beta cell mass is increased with obesity. This is true in rodents; in juvenile rodents, high-fat diet induced obesity results in a 3-fold increase in beta cell mass (Figure 6), with an increase in beta cell replication [40]. In adult humans, studies have shown that the beta cell mass increases by approximately 20 to 50% in obese non-diabetic individuals [24,39]. This increase is statistically significant, but the magnitude of the increment is much less than that in rodents (Figure 6).

Since studies of beta cell mass in humans inevitably rely on postmortem histological study, the longitudinal change in beta cell mass has not been examined to date. Although an increase in beta cell mass was observed in obese humans, an increase in beta cell replication, which was observed in rodent studies, was not observed in obese humans [39]. Therefore, there is a significant difference in beta cell mass between lean and obese humans; however, the timing as well as the source of the increased beta cells in obese humans remains unclear.

Regarding the change in beta cell mass in the transition period between normoglycemia and T2DM, Butler et al. examined the beta cell mass in humans with impaired fasting glycemia (IFG) [23]. They found an approximately 40% decrease in beta cell mass in subjects with IFG compared with nondiabetic controls, suggesting that beta cell mass starts to decline before the development of T2DM. Meier et al. also reported an approximately 20% reduction in beta cell mass in patients with IGT [49].

Rahier et al. reported a significant negative association between duration of diabetes and beta cell mass in subjects with T2DM [24], consistent with the progressive decline in beta cell function with disease duration [12,13,50]. Thus, beta cell mass may progressively



decline with disease duration of T2DM; however, whether this decline in beta cell mass starts before the onset of T2DM remains controversial.

### Ethnic Difference in Beta Cell Mass with Obesity

Recently, we have examined the change in beta cell mass with obesity in Japanese non-diabetic individuals [51]. As a result, unexpectedly, we were not able to find a significant increase in beta cell mass in Japanese obese individuals compared with lean subjects (Figure 6). Another Japanese study also confirmed our findings [52]. These findings are inconsistent with the findings in the Caucasian population [24,39]. The lower degree of obesity in Japanese may be the reason for this difference. However, since the incidence of T2DM in Japanese is similar to that in Caucasians, these findings suggest that the beta cell regenerative capacity, as well as the beta cell functional capacity, may differ between Japanese and Caucasians.

### Conclusion

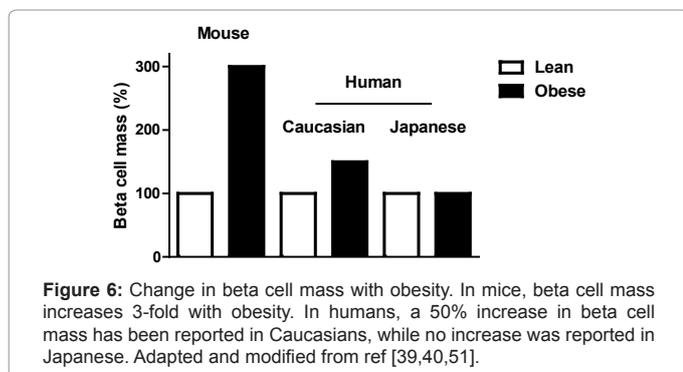
#### Implications for clinical practice

Based on the current evidence described above, a hypothesis for the changes in beta cell function and beta cell mass during the progression of T2DM is summarized in Figure 7. The Western diet and physical inactivity in modern societies increase the incidence of obesity. To compensate obesity-induced insulin resistance, insulin secretion increases approximately 2 to 3-fold to maintain normoglycemia. However, in this “normoglycemia with insulin resistance” phase, the increase in beta cell mass, if any, is 50% or less, suggesting that each beta cell secretes more insulin. Thus, beta cell workload must

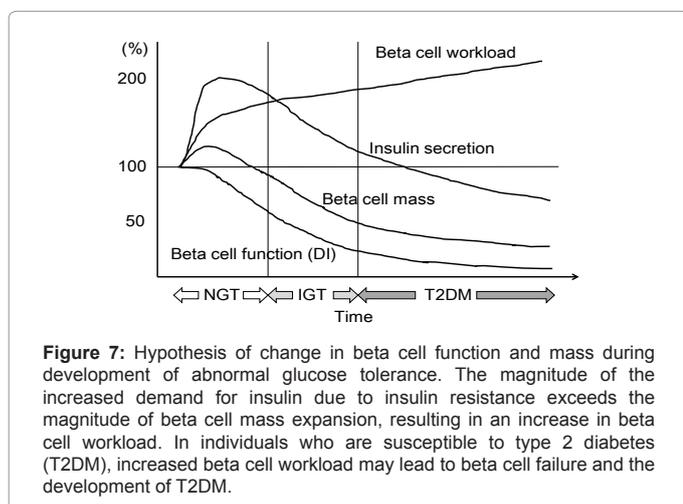
be already increased in this phase, and if the overload of beta cells persists chronically, it may cause a gradual loss of beta cell function or mass through various mechanisms such as oxidative stress, amyloid formation or ER stress. With an approximately 50% or greater reduction in beta cell function, abnormal glucose tolerance develops. At this time, beta cell mass may also already be reduced. In addition, hyperglycemia also causes beta cell dysfunction and apoptosis, which further exacerbate beta cell failure with the eventual development of T2DM. Importantly, because insulin resistance exists continuously, the beta cell workload continues to increase, with a reduction in beta cell mass. As a result, glucose metabolism progressively deteriorates in patients with T2DM.

The current perspective suggests that beta cell failure, a loss of beta cell functional mass, occurs far before the onset of T2DM and possibly even before the onset of IGT [10]. Beta cell failure in T2DM emphasizes the importance of preservation or recovery of beta cell functional mass as a treatment strategy for T2DM [4]. Clinical trials have shown that lifestyle modification and insulin sensitizers [53-58], but not insulin secretagogues [59], are effective to prevent the development of T2DM, which is probably due to a reduction in beta cell workload. Insulin therapy has also been shown to prevent the development of T2DM [60], which is also likely to be due to a reduction in beta cell workload. Thus, reducing beta cell workload seems to be the most effective treatment strategy for T2DM to date.

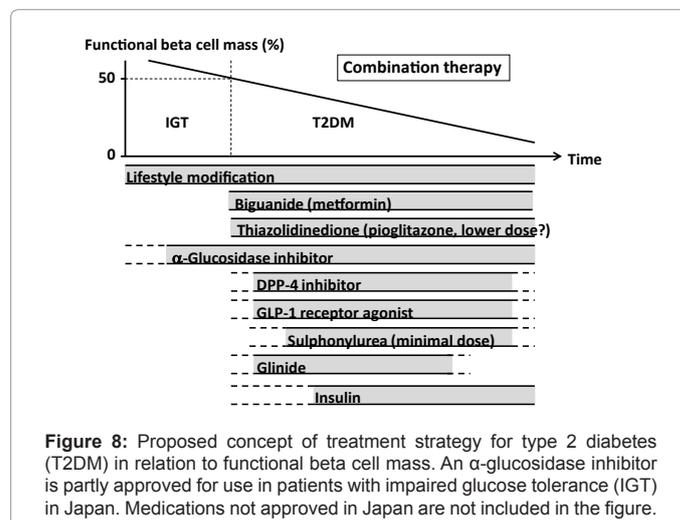
A proposed concept of a treatment strategy for type 2 diabetes in relation to functional beta cell mass is shown in Figure 8. Lifestyle modification including nutritional therapy and exercise remains the most important component of treatment of T2DM at any stage of the disease. Modest weight reduction (5-10%) by lifestyle modification has been shown to improve glycemic control and other cardiovascular risk factors, although maintained weight reduction is difficult to achieve [61,62]. Since metformin reduces insulin demand and beta cell workload through lowering hepatic glucose production, the use of metformin in addition to lifestyle modification should be considered in as early a stage of diabetes as possible, if not contraindicated. Since incretin therapy is expected to improve beta cell function in addition to its glucose-lowering effect [63], it also can be considered in a broad range of disease stage. Incretin therapy has been shown to increase beta cell mass in rodents; however, this effect has not been confirmed in humans [64,65]. In contrast, the use of insulin secretagogues, sulphonylureas, may not be considered as initial therapy but rather



**Figure 6:** Change in beta cell mass with obesity. In mice, beta cell mass increases 3-fold with obesity. In humans, a 50% increase in beta cell mass has been reported in Caucasians, while no increase was reported in Japanese. Adapted and modified from ref [39,40,51].



**Figure 7:** Hypothesis of change in beta cell function and mass during development of abnormal glucose tolerance. The magnitude of the increased demand for insulin due to insulin resistance exceeds the magnitude of beta cell mass expansion, resulting in an increase in beta cell workload. In individuals who are susceptible to type 2 diabetes (T2DM), increased beta cell workload may lead to beta cell failure and the development of T2DM.



**Figure 8:** Proposed concept of treatment strategy for type 2 diabetes (T2DM) in relation to functional beta cell mass. An  $\alpha$ -glucosidase inhibitor is partly approved for use in patients with impaired glucose tolerance (IGT) in Japan. Medications not approved in Japan are not included in the figure.

used at a lower dose aiming to support the insulinotropic effect of incretin therapy. Since to date neither drug has been shown to cure diabetes, combination therapy should be considered in most cases.

Given the fact that Asians have even less beta cell functional capacity compared with Caucasians, the importance of this strategy should be further emphasized in Asian countries. New therapeutic strategies to reduce beta cell workload, including not only novel drugs but also novel socioeconomic and psychological approaches, are warranted to prevent or treat T2DM.

#### Disclosure Statement

The author declares no conflict of interest.

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