Prevention of beta cell “karoshi”: a new paradigm for prevention and management of type 2 diabetes

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"It is better to try to avoid problems in the first place, rather than trying to fix them once they arise."

Benjamin Franklin

Diabetes is a pandemic disease. According to the International Diabetes Federation, the number of people with diabetes throughout the world is projected to reach 415 million in 2015 and to rise to 642 million in 2040 (1). Every 6 seconds, a person dies from diabetes (5.0 million deaths in 2015). The cost of diabetes treatment is estimated to be 12% of global health expenditure (673 billion dollars in 2015). Diabetes is not only a medical problem but also one of the biggest socioeconomic problems in the world.

Most patients with diabetes are classified as having type 2 diabetes (T2DM). T2DM is characterized by insulin resistance and beta cell dysfunction (2). Since people with T2DM are typically characterized by obesity, insulin resistance and hyperinsulinemia, T2DM is often assumed to contrast to type 1 diabetes (T1DM) in which beta cells are destroyed by autoimmune attack, and the significance of beta cell dysfunction in T2DM is often underestimated or even ignored.

However, recent studies have shown that beta cell mass is decreased in both T1DM and T2DM (Figure 1) (3, 4), suggesting the presence of beta cell deficit in T2DM. The deficit of beta cells in patients with T2DM is observed across

ethnic groups (5-9), suggesting that a deficit of beta cells is a universal pathological feature of T2DM. Thus, the concept of diabetes is now changing to a new one in which deficit of beta cells is a common pathological feature of both T1DM and T2DM (10). The distinctions between the two are the cause (autoimmune vs. insulin resistance) and the extent of deficit (almost complete vs. partial) (Figure 2).

Recent studies have also shown that diabetes is a progressive disease. Progressive loss of beta cell function as well as beta cell mass has been reported, while insulin resistance remains unchanged with the disease duration (6, 10, 11), suggesting that the progressive nature of T2DM is mainly due to progressive loss of functional beta cell mass. The UK Prospective Diabetes Study (UKPDS) showed that beta cell function assessed by homeostasis model assessment (HOMA) was decreased by ~50% at the time of diagnosis of T2DM, and progressively decreased by ~5% a year (12). This also suggests that loss of functional beta cell mass begins ~10 years before the onset of T2DM. A reduction in beta cell mass in individuals with prediabetes has also been reported (Figure 1) (3, 13). These findings highlight that beta cell loss has already started far before the onset of hyperglycemia (Figure 3).

This new concept indicates that T2DM does not develop in the absence of beta cell dysfunction. That is, although

T2DM is characterized by insulin resistance and beta cell dysfunction, beta cell deficit is necessary for the development of T2DM (Figure 4). In obese non-diabetic individuals, insulin secretion increases two to three fold to compensate insulin resistance (14). However, it has been shown that, unlike in rodents, compensatory beta cell mass expansion in response to insulin resistance is very limited in humans (Figure 5) (8, 9, 15, 16), suggesting that an increase in insulin secretion per beta cell rather than an increase in the number of beta cells is the major compensatory mechanism against obesity and insulin resistance in humans. Based on these findings, we here propose the beta cell workload hypothesis (Figure 6) (10). That is, in the face of insulin resistance, beta cells work harder to secrete more insulin to maintain normoglycemia. If excess workload on beta cells continues, stress-induced beta cell death (apoptosis) may eventually occur and beta cell mass is reduced. Plausible mechanisms by which beta cell death is induced have been proposed, such as oxidative stress (17), endoplasmic reticulum (ER) stress (18, 19), mitochondrial dysfunction (20), amyloid toxicity (21, 22), inflammatory cytokines (23) and autophagy dysfunction (24). A recent rodent study has also suggested beta cell dedifferentiation as a mechanism of beta cell loss in diabetes (25). Once beta cell mass is reduced, each residual beta cell will be exposed to an even greater workload, which results in a

vicious cycle fostering further beta cell loss. When functional beta cell mass eventually fails to compensate insulin resistance, hyperglycemia develops. Hyperglycemia further augments beta cell workload and beta cell toxicity, so-called gluco(lipo)toxicity (26), which leads to further loss of beta cells, reflecting the progressive nature of this disease (Figure 7). Since, unfortunately, the current therapy for T2DM does not reverse or cure the disease, this concept emphasizes the importance of beta cell preservation for the prevention of T2DM.

This change in the concept of diabetes is important because current therapy for diabetes cannot reverse or cure the deficit of beta cells. From knowledge obtained from a number of clinical studies in patients with T2DM and prediabetes, we now appreciate that reduction of beta cell workload is a key strategy to preserve residual beta cell function (10, 27). Proposed treatment strategies for type 2 diabetes aiming at reducing beta cell workload are shown in Figure 8.

Elimination of insulin resistance by metabolic surgery is expected to be a potential therapy leading to a cure for diabetes (28). However, even if drastic weight loss can be achieved after surgery, remission of diabetes occurs only in a small proportion of subjects (29). This suggests that even if insulin resistance can be eliminated, beta cell deficit remains in patients with T2DM.

So what should we learn from these facts? We really need to focus on

protection of beta cells even prior to the development of diabetes, emphasizing education not only of people with diabetes but also those without diabetes. We need to share this new and important concept of diabetes with the general population all over the world and recognize that most of the functional beta cell mass is already lost when hyperglycemia develops. The development of hyperglycemia in the diabetic range may indicate that the person has already crossed the point of no-return in terms of beta cell reserve.

A key to the prevention of T2DM is lifestyle modification, including a healthy diet and increased physical activity (30, 31). Lifestyle modification is indeed the most fundamental and effective therapy for patients with T2DM as well (32, 33), presumably reducing beta cell workload through the improvement of obesity and insulin resistance. Considering the fact that one in eleven adults throughout the world are assumed to have diabetes (1), lifestyle modification for patients with T2DM should apply to most adults (and children) all over the world.

Lifestyle modification requires self-management. It is therefore important for not only patients with T2DM but also the general population to correctly understand diabetes in order to empower them. Our mindset should change from saying that a bad lifestyle is not good for your health to saying that your beta cells should be protected through a healthy lifestyle, to prevent the development of T2DM. There is a limited source of beta

cells in the human body, which weigh only ~1 g. Having a healthy lifestyle is a consequence of individual choice. To maintain individuals’ motivation to continue making healthy choices in their daily life, it is important to correctly understand the nature of the disease. “Karoshi” is a Japanese term which can be translated literally as “death from overwork” (34) causing occupational sudden mortality. Here we propose that we should call beta cell death due to excess workload under insulin resistance, beta cell “karoshi”, which may be more easily understandable for the general population of our society. The concept of beta cell “karoshi” may help people to imagine protecting their own beta cells from overwork that leads to beta cell death or “karoshi”, and could empower and motivate them to make better choices.

So, diabetes is now a serious social problem throughout the world. Patients with T2DM provide an important message to our society. Lifestyle modification is the most fundamental treatment for T2DM as well as its prevention. A huge body of work has revealed that protection of beta cells is undoubtedly a key message in order to achieve this goal. We should learn from patients with T2DM and fight with them to prevent this pandemic disease. The concept of beta cell “karoshi” not only empowers people to adhere to a healthy lifestyle, but also may foster a policy change to improve our “toxic” environment which increases obesity and stresses our beta cells.

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Conflict of interest

The author has no conflict of interest regarding this manuscript.

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Figures

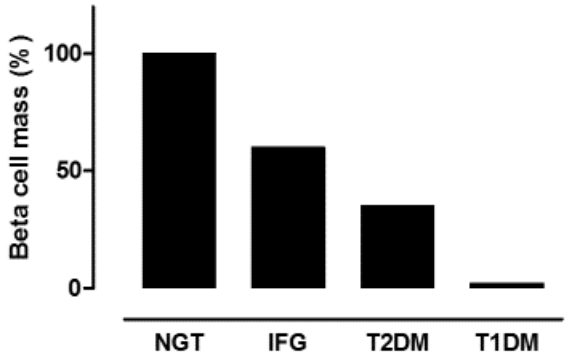

Figure 1. Beta cell mass in patients with normal glucose tolerance (NGT), impaired fasting glycemia (IFG), type 2 diabetes (T2DM) and long-standing type 1 diabetes (T1DM). Adapted and modified from the study by Butler et al. (3) and (4).

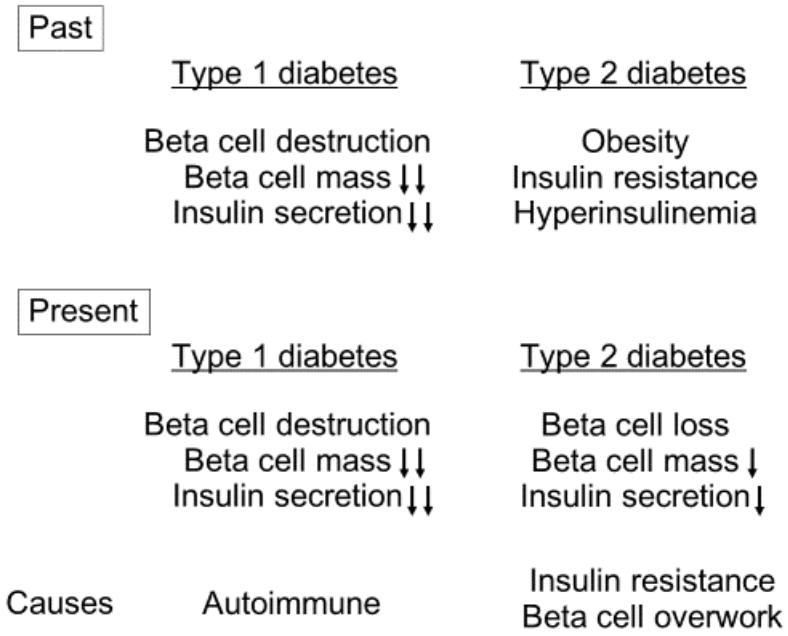

Figure 2. Changing concepts of pathogenesis of type 1 and type 2 diabetes in the past and present.

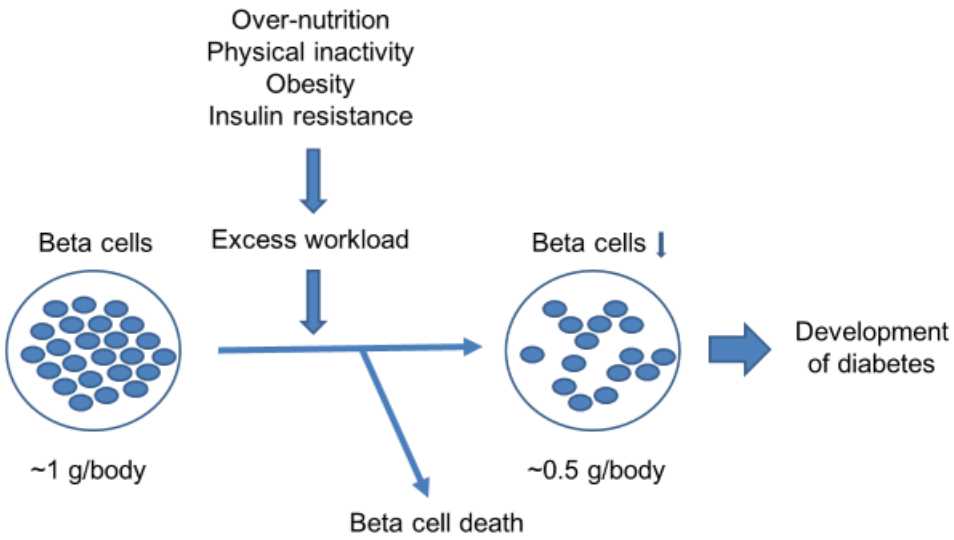

Figure 3. Conceptual schema of beta cell change during development of type 2 diabetes.

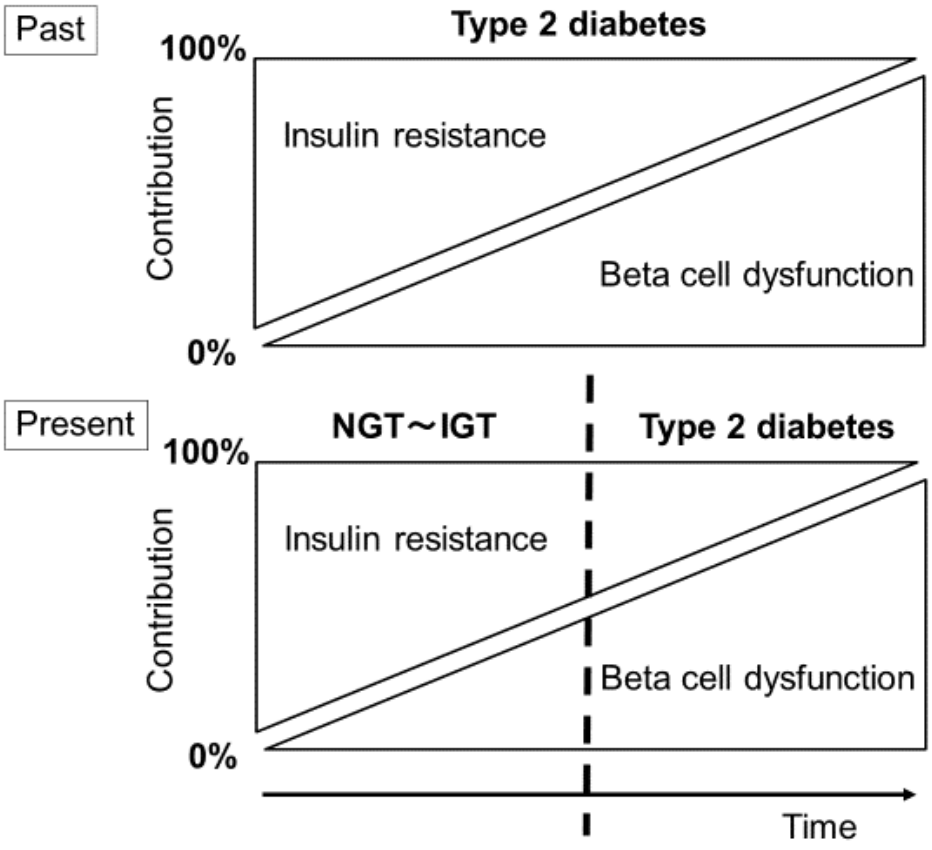

Figure 4. New concept of relative contributions of insulin resistance and beta cell dysfunction in type 2 diabetes. Type 2 diabetes never develops without beta cell dysfunction. This new concept indicates the need for beta cell protection before the onset of T2DM. NGT; normal glucose tolerance. IGT; impaired glucose tolerance.

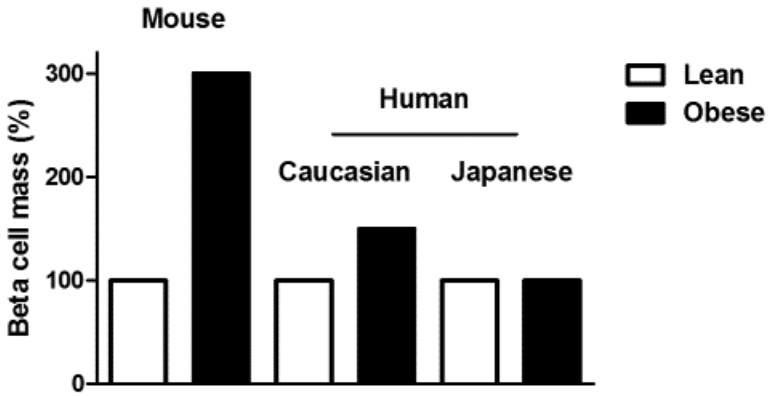

Figure 5. Change in beta cell mass with obesity. In mice, beta cell mass increases 3-fold with obesity. In humans, a 50% increase in beta cell mass has been reported in Caucasians, while no increase was reported in Japanese. Adopted and modified from ref. (15, 16, 35).

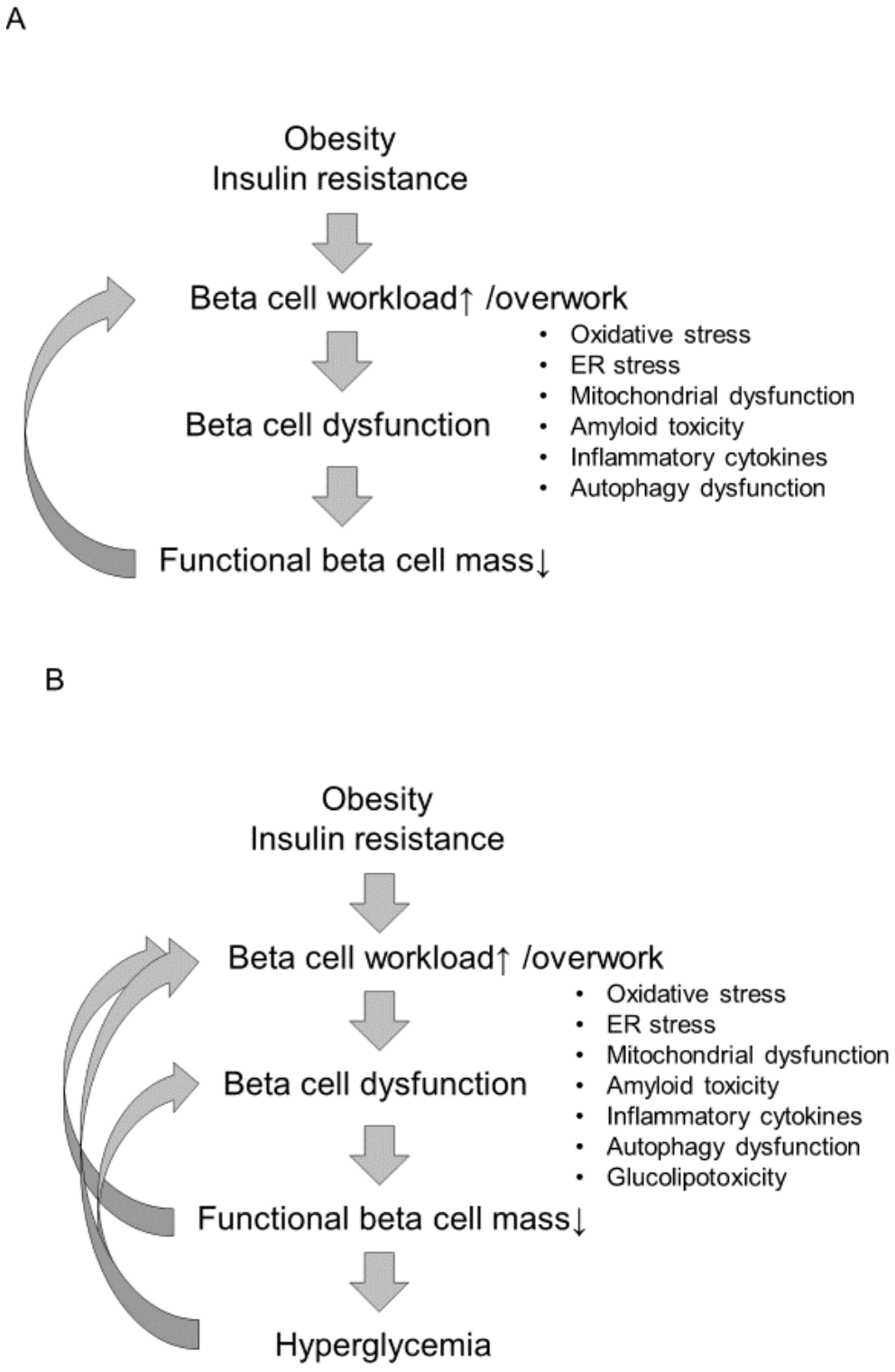

Figure 6. Proposed mechanisms of beta cell death before (A) and after (B) the development of type 2 diabetes (hyperglycemia). Increased beta cell workload induces beta cell loss through various mechanisms and once hyperglycemia develops, gluco(lipo)toxicity causes further beta cell loss.

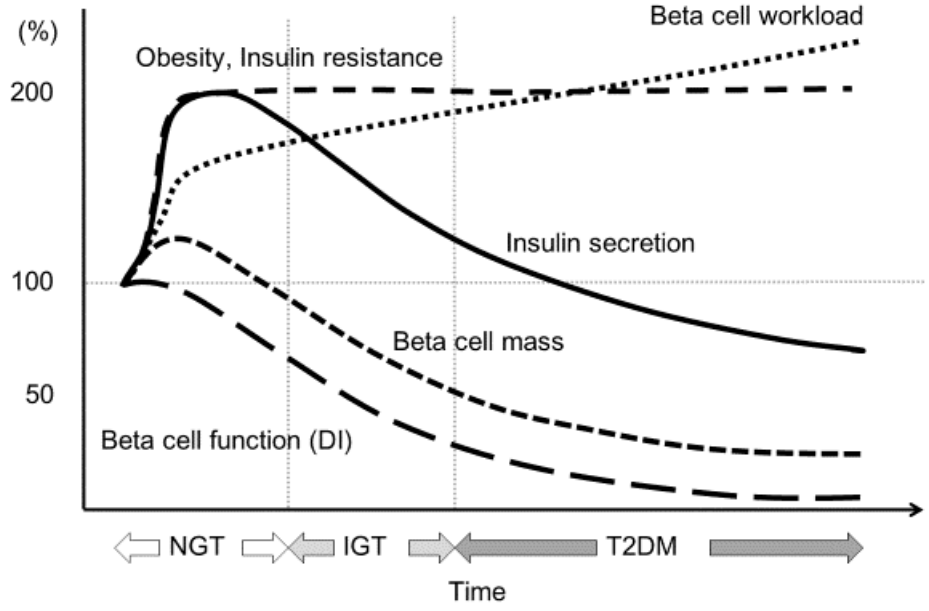

Figure 7. Chronological change in functional beta cell mass in relation to beta cell workload during the development of T2DM. Adopted from ref(10). Recent studies have suggested that functional beta cell mass is already reduced at the onset of T2DM. Excess workload on beta cells induced by insulin resistance continues, stress-induced beta cell death, "karoshi", may eventually occur, and beta cell mass is reduced even before the onset of diabetes. Once beta cell mass is reduced, the workload on residual beta cell is further exaggerated, reflecting the progressive nature of the disease.

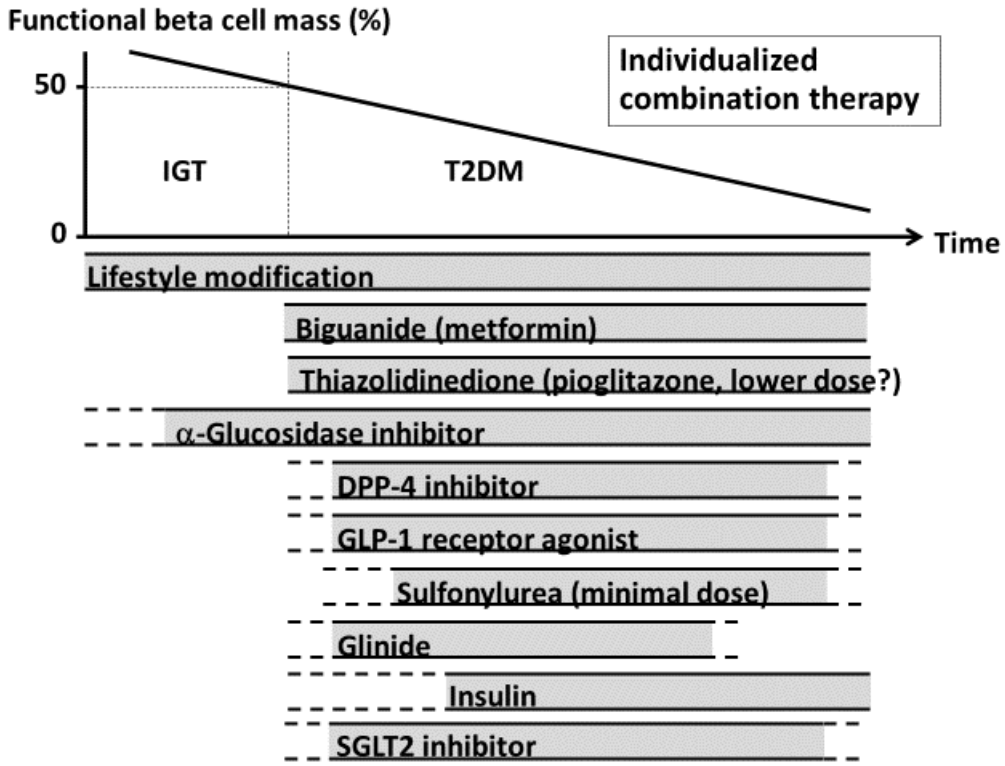

Figure 8. Proposed concept of treatment strategy for type 2 diabetes (T2DM) in relation to functional beta cell mass. Adopted and modified from ref(2, 36). An α-glucosidase inhibitor is partly approved for use in patients with impaired glucose tolerance (IGT) in Japan. Medications not approved in Japan are not included in the figure. Since currently no single therapy or agent can cure and even manage T2DM, an effective combination of current medications in addition to lifestyle modification aiming at reduction in beta cell workload is important to preserve or recover beta cell function. SGLT2 inhibitors, the most recently marketed anti-diabetic drug class, show a glucose-lowering effect through an increase in urinary glucose excretion. This effect is insulin-independent, and thus SGLT2 inhibitors reduce beta cell workload.

