β-cell dysfunction: Its critical role in prevention and management of type 2 diabetes

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Abstract

Type 2 diabetes (T2DM) is characterized by insulin resistance and β-cell dysfunction. Although, in contrast to type 1 diabetes, insulin resistance is assumed to be a major pathophysiological feature of T2DM, T2DM never develops unless β-cells fail to compensate insulin resistance. Recent studies have revealed that a deficit of β-cell functional mass is an essential component of the pathophysiology of T2DM, implying that β-cell deficit is a common feature of both type 1 and type 2 diabetes. β-cell dysfunction is present at the diagnosis of T2DM and progressively worsens with disease duration. β-cell dysfunction is associated with worsening of glycemic control and treatment failure; thus, it is important to preserve or recover β-cell functional mass in the management of T2DM. Since β-cell regenerative capacity appears somewhat limited in humans, reducing β-cell workload appears to be the most effective way to preserve β-cell functional mass to date, underpinning the importance of lifestyle modification and weight loss for the treatment and prevention of T2DM. This review summarizes the current knowledge on β-cell functional mass in T2DM and discusses the treatment strategy for T2DM.

Key words: β-cell; Insulin secretion; Type 2 diabetes; Prevention; Treatment

Core tip: Recent studies have revealed that a deficit of β-cell functional mass is an essential component of the pathophysiology of type 2 diabetes (T2DM). β-cell dysfunction is present at the diagnosis of T2DM and progressively worsens with disease duration. β-cell dysfunction is associated with worsening of glycemic control and treatment failure; thus, it is important to preserve or recover β-cell functional mass in the management of T2DM. This review summarizes the current knowledge on β-cell functional mass in T2DM and discusses the treatment strategy for T2DM.

INTRODUCTION

The number of patients with diabetes is countinuously increasing all over the world. Worldwide, there were
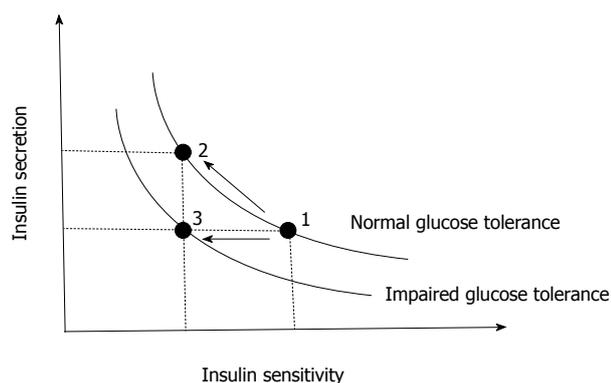
Figure 1 Insulin secretion-insulin sensitivity relationship. In a physiological condition, when insulin sensitivity decreases, insulin secretion increases to maintain normoglycemia (1→2), showing a hyperbolic curve. When insulin secretion fails to compensate, the hyperbolic curve shifts to the left and abnormal glucose tolerance develops (1→3).

382 million patients with diabetes in 2013, which will rise to 592 million in 2035[1]. Diabetes is associated not only with diabetic microangiopathy such as retinopathy, nephropathy and neuropathy, but also with a 2- to 4-fold increase in risk of cardiovascular disease[2,3]. Among the people with diabetes, more than 90% have type 2 diabetes (T2DM). Therefore, optimal treatment and prevention strategies for T2DM are urgently needed.

T2DM is characterized by insulin resistance and β-cell dysfunction. Recent evidence suggests an important role of β-cell function in the development and management of T2DM. In this review, the current knowledge regarding β-cell dysfunction in T2DM is summarized and its critical role in the prevention and treatment of T2DM is discussed.

DEFICITS OF β-CELL FUNCTION AND β-CELL MASS IN T2DM

Disposition index: A true assessment of β-cell function

T2DM is characterized by insulin resistance and β-cell dysfunction[4,5]. However, since the development of an insulin radioimmunoassay, it was found that in people with T2DM, plasma insulin concentration is rather higher than that in those with normal glucose tolerance (NGT), indicating that insulin resistance rather than insulin deficiency is central in the pathogenesis of T2DM. Therefore, in contrast to type 1 diabetes, obesity, hyperinsulinemia and insulin resistance are often emphasized as characteristics of T2DM, and β-cell function in T2DM is often less emphasized or even ignored.

However, the higher plasma insulin concentration in patients with T2DM is often confounded by a higher plasma glucose level, which itself stimulates insulin secretion. Moreover, insulin sensitivity also affects insulin secretion. In normal physiological conditions, normoglycemia is maintained under a balance between insulin sensitivity and insulin secretion, and when insulin

sensitivity decreases, insulin secretion increases to maintain normoglycemia. Thus, insulin secretion should always be assessed in relation to insulin sensitivity. Bergman and Cobelli have found that this relationship between insulin secretion and insulin sensitivity is expressed as a hyperbolic curve, and as a result the product of insulin sensitivity and insulin secretion is constant as long as normoglycemia is maintained[6,7] (Figure 1). The product of insulin sensitivity and insulin secretion, called the disposition index, refers to insulin secretion adjusted by insulin sensitivity and reflects true β-cell function *in vivo*.

Once insulin secretion is not able to sufficiently increase to compensate the decrease in insulin sensitivity, the insulin sensitivity-insulin secretion relationship is shifted to the left and abnormal glucose tolerance develops (Figure 1). In this case, the disposition index is decreased, indicating that abnormal glucose tolerance develops only when β-cells are no longer able to compensate decreased insulin sensitivity.

β-cell function in T2DM

When β-cell function is assessed using the disposition index, a number of studies have consistently shown that β-cell function is diminished in people with T2DM[4,8,9]. Using the disposition index, DeFronzo et al[9] have shown that β-cell function is decreased by -80% in patients with impaired glucose tolerance (IGT) and is even less in patients with T2DM (Figure 2). Importantly, β-cell function starts to decline with higher plasma glucose levels, even within the range of normal plasma glucose levels[9], which suggests that β-cell function is already impaired prior to the development of IGT.

β-cell mass in T2DM

If β-cell function is impaired in patients with T2DM, what about the β-cell mass? β-cells are located in the islets of Langerhans, which are scattered within the exocrine pancreas. Each islet contains -1000 β-cells together with other endocrine cells such as alpha cells, delta cells, pancreatic polypeptide (PP) cells and epsilon cells, and a total of -1 million islets exist in the pancreas. β-cell mass refers to the total mass of β-cells and is approximately 1 g in humans.

Due to the anatomical characteristics of β-cells scattered throughout the whole pancreas, it is difficult to visualize β-cells *in vivo*, and direct measurement of β-cell mass *in vivo* in humans remains to be established[10,11]. Thus, to date, the measurement of β-cell mass inevitably relies on histological analysis of the pancreas obtained surgically or at autopsy.

Since insulin resistance and hyperinsulinemia are often emphasized in people with T2DM, β-cell mass in people with T2DM is also often assumed to be increased or at least not decreased. However, based on histological analysis, Butler et al[12] have reported that β-cell mass is decreased by -40% and -65% in lean and obese people with T2DM, respectively, compared with non-diabetic controls matched for age and BMI. Other groups have
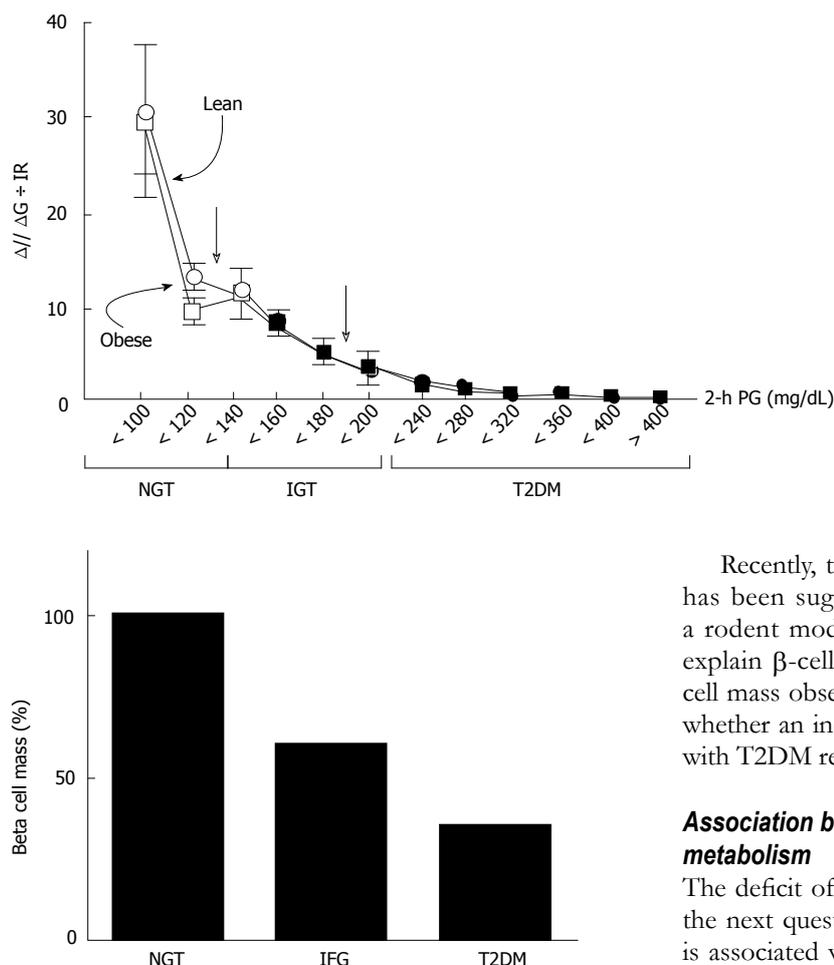
Figure 2 Insulin secretion/insulin resistance (disposition) index (I/G ÷ IR) during 75g-oral glucose tolerance test in individuals with normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes as a function of the 2 h plasma glucose concentration in lean and obese subjects. I/G: Insulinogenic index (Insulin 0-30 min/Glucose 0-30 min); IR: Homeostasis model assessment of insulin resistance [HOMA-IR; fasting insulin (mU/L) x glucose (mmol/L)/22.5]. Adapted from ref.[9]. NGT: Normal glucose tolerance; IGT: Impaired glucose tolerance; T2DM: Type 2 diabetes; PG: Plasma glucose.

Recently, transdifferentiation of β-cells to alpha cells has been suggested as a mechanism of β-cell loss in a rodent model of diabetes[32]. This mechanism could explain β-cell loss and the reciprocal increase in alpha cell mass observed in humans with T2DM[15,31], although whether an increase in alpha cell mass occurs in humans with T2DM remains controversial[33,34].

Association between β-cell mass and glucose metabolism

The deficit of β-cell mass in patients with T2DM raises the next question of whether the change in β-cell mass is associated with the severity of glucose intolerance. It has been reported that there is a reciprocal relationship between β-cell mass and fasting plasma glucose level[35], suggesting that glucose intolerance develops when the β-cell mass decreases by -50% of the normal level. A similar relationship has been observed in rodents[36], pigs[37] and monkeys[38]. An increased risk of the development of IGT or diabetes after hemipancreatectomy has been reported in dogs and humans[39-43]. It has also been reported that β-cell mass was decreased by -20%-40% in patients with IGT and impaired fasting glycemia (IFG)[12,44]. We have also reported that there was a significant negative correlation between β-cell mass and glycated hemoglobin (HbA1c) level in non-diabetic individuals[45], suggesting that β-cell mass is related to glucose intolerance even prior to the development of T2DM. A significant correlation between β-cell mass and HbA1c was also observed in patients with T2DM[31].

Association between β-cell mass and β-cell function

The relationship between β-cell mass and β-cell function is more complicated. Whether β-cell dysfunction in T2DM is mainly due to a functional defect of each β-cell or due to a defect of β-cell mass has been extensively argued[46]. A close correlation between β-cell function assessed by maximum acute insulin response (AIRmax) induced by arginine infusion under a hyperglycemic state and β-cell mass of transplanted islets has been reported[47]. On the other hand, β-cell dysfunction was markedly improved after an overnight β-cell rest by somatostatin

Figure 3 β-cell mass in patients with normal glucose tolerance, impaired fasting glycemia and type 2 diabetes. Adapted and modified from the study by Butler *et al*[12]. NGT: Normal glucose tolerance; IFG: Impaired fasting glycemia; T2DM: Type 2 diabetes.

also reported a significant (-30%-40%) decrease in β-cell mass in patients with T2DM[13-15]. These findings suggest that deficit of β-cell mass is a common pathophysiological feature of type 1 and T2DM (Figure 3), while the cause and degree of the deficit are different between type 1 and T2DM.

Mechanisms of β-cell deficit in T2DM

β-cell mass is regulated by the balance of newly formed β-cells and β-cell loss[16-18]. Butler *et al*[12] have shown that β-cell apoptosis is increased in patients with T2DM, whereas neither β-cell replication nor neogenesis is decreased, suggesting that increased β-cell loss is the main cause of reduced β-cell mass in T2DM. Various mechanisms that induce β-cell apoptosis have been proposed such as hyperglycemia (glucotoxicity)[19], fatty acids (lipotoxicity)[20], amyloid or islet amyloid polypeptide (IAPP, also called amylin)[21-24], oxidative stress[25], inflammatory cytokines[26], mitochondrial dysfunction[27], endoplasmic reticulum (ER) stress[28,29] and dysfunction of autophagy[30]. A recent study suggested that several mechanisms are simultaneously associated with β-cell failure in humans with T2DM[31].
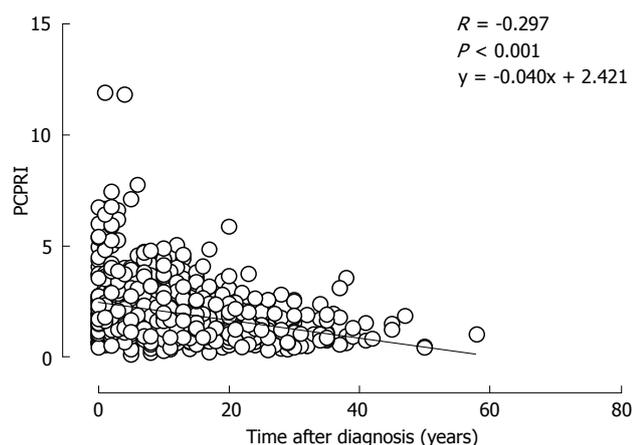
Figure 4 Relationship between postprandial C-peptide to glucose ratio (postprandial C-peptide index) and time after diagnosis in patients with Type 2 diabetes. Reproduced with permission from ref.[51]. PCPRI: Postprandial C-peptide index.
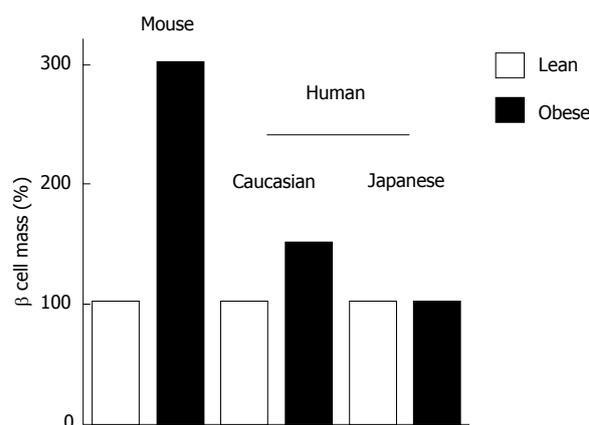

Figure 5 Change in β-cell mass with obesity. In mice, β-cell mass increases 3-fold with obesity. In humans, a 50% increase in β-cell mass has been reported in Caucasians, while no increase was reported in Japanese. Adopted and modified from ref.[54,59,85].

infusion[48]. Thus, it remains uncertain whether β-cell function *in vivo* sufficiently reflects β-cell mass in patients with T2DM.

Meier *et al*[49] assessed the relationship between β-cell mass and β-cell function in patients who had undergone pancreatic surgery and found that there was a significant positive correlation between β-cell mass and β-cell function, especially postprandial C-peptide level, suggesting that C-peptide measurement in clinical settings reflects β-cell mass.

Taken together, these results indicate that β-cell function and β-cell mass seem to be correlated with each other, although on some occasions they can be dissociated, and both β-cell function and mass seem to decrease during the development of glucose intolerance. Since β-cell function and mass are difficult to separate, currently they are referred to as "β-cell functional mass", and it is now certain that β-cell functional mass decreases during the development of T2DM.

Progressive decline in β-cell functional mass in T2DM

A deficit of β-cell functional mass is not only present in patients with T2DM, but it also progressively declines with disease duration. In the UK Prospective Diabetes Study (UKPDS), β-cell function assessed by homeostasis model assessment (HOMA) in patients with T2DM was already decreased by -50% at the time of diagnosis and progressively declined by -5% annually[50]. This also indicates that in patients with T2DM, β-cell function starts to decline -10 years prior to the onset of the disease. A gradual but significant decline in β-cell function assessed by C-peptide level has been confirmed in cross-sectional cohort studies of Japanese patients with T2DM[51,52] (Figure 4). Intriguingly, a significant negative correlation between β-cell mass and duration of T2DM has also been reported[13].

Limited β-cell regenerative capacity in humans

Since deficits of β-cell function and mass are now recognized as hallmarks of T2DM as well as type 1 diabetes, β-cell regeneration is considered to be an important therapeutic strategy for both types of diabetes.

Rodent studies show an adaptive change in β-cell mass in response to obesity or pregnancy[53-58], suggesting the presence of endogenous β-cell regenerative capacity in the postnatal period. However, recent observation of the human pancreas suggests that endogenous β-cell regenerative capacity is limited in humans.

We have reported that β-cell mass in obese non-diabetic individuals is -1.2 g compared with -0.8 g in lean non-diabetic individuals, an -50% increase[59], whereas β-cell mass increases 3- to 10-fold in response to obesity or insulin resistance in rodents[53,54] (Figure 5). This striking difference in β-cell regenerative capacity between humans and rodents suggests that the results of rodent studies are not necessarily applicable to humans[60,61].

In humans, β-cell mass increases from -37 mg to -1 g in the first five years of life, and during this period replicating β-cells are often observed[62,63]. However, after that, replicating β-cells are rarely seen and β-cell mass reaches a plateau. The β-cell mass then remains constant during adulthood[13,59,64], suggesting that β-cell turnover is limited in humans after the first five years of life. Estimation of β-cell life using either ^{14}C measurement or cellular lipofuscin body content also suggests very slow turnover of β-cells in adult humans[65,66]. Recent studies have suggested that there is an increase in β-cell neogenesis in humans with obesity, pregnancy and IGT[67-70]; however, the extent of its contribution to β-cell mass remains unclear. Limited β-cell regenerative capacity has also been observed in monkeys[71,72]. Even in rodents, β-cell regenerative capacity significantly decreases with aging[54,73,74].

A hypothetical schema of the change in β-cell functional mass during the development of T2DM is shown in Figure 6. The magnitude of the increased demand for insulin due to insulin resistance caused by excess caloric intake and physical inactivity exceeds the magnitude of β-cell mass expansion, resulting in an increase in β-cell

Figure 6 Hypothesis for change in β-cell function and mass during development of abnormal glucose tolerance. The magnitude of the increased demand for insulin due to insulin resistance caused by excess caloric intake and physical inactivity exceeds the magnitude 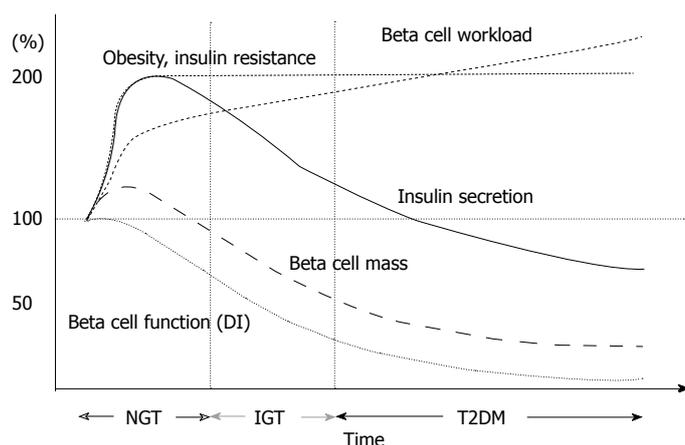of β-cell mass expansion, resulting in an increase in β-cell workload. In individuals who are susceptible to type 2 diabetes (T2DM), increased β-cell workload may lead to β-cell failure and the development of T2DM. Adopted and modified from ref.[109].

clinical outcomes.

β-cell functional mass in Asian population

T2DM is characterized by obesity, but the degree of obesity differs between ethnic groups[79,80]. In Caucasians, most patients with T2DM are obese, and the mean BMI of patients with T2DM is -30 kg/m^2. In contrast, the mean BMI of Asian patients with T2DM is -23 kg/m^2, suggesting that about half of patients with T2DM are not even overweight (*i.e.*, BMI $\geqslant$ 25 kg/m^2, the definition of obesity in Asian countries).

The difference in adiposity between Caucasians and Asians has been postulated to explain this ethnic difference. Visceral adiposity is more apparent in Asians compared to Caucasians with the same BMI[81,82], indicating that Asians have a lower capacity for subcutaneous fat deposition and are more vulnerable to visceral fat accumulation compared with Caucasians. Nonetheless, a meta-analysis of studies examining the insulin sensitivity-insulin secretion relationship in individuals with NGT clearly showed that Asians have less insulin secretion with higher insulin sensitivity compared with Caucasians[83]. Direct comparison of insulin sensitivity and insulin secretion between Japanese and Caucasians showed that most of the difference in insulin secretion between the two ethnicities can be explained by the difference in BMI between the two[84]. Since the incidence of T2DM is comparable between the two ethnicities despite the different degree of obesity[1], it is plausible that the lower degree of obesity in Asians could be attributable to the lower β-cell functional capacity in this population.

We have recently examined the change in β-cell mass in Japanese obese nondiabetic individuals (mean BMI 20.4 kg/m^2) compared to age- and sex-matched lean individuals (mean BMI 28.5 kg/m^2)[85]. As a result, in contrast to the studies in Caucasians showing a significant increase in β-cell mass with obesity[13,59], there was no significant increase in β-cell mass in Japanese obese individuals (Figure 5). Another Japanese study also confirmed our findings[86]. These studies suggest that Asians have less β-cell regenerative capacity compared with Caucasians, which is probably derived from both genetic and environmental factors, and the lower β-cell
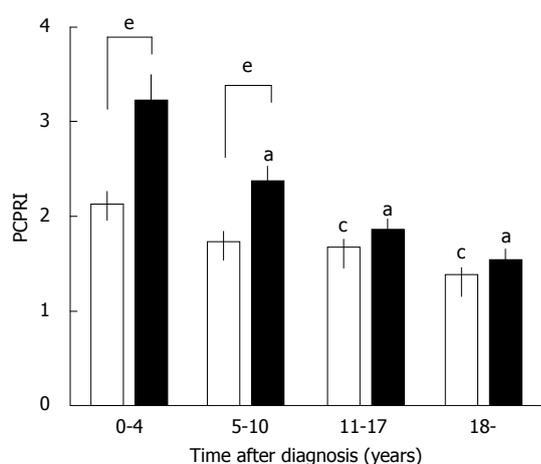

Figure 7 Postprandial C-peptide to glucose ratio (postprandial C-peptide index; PCPRI) in subjects according to obesity and time after diagnosis (0-4, 5-10, 11-17 and $\geqslant$ 18 years). There were significant differences in PCPRI between lean (open bars) and obese subjects (solid bars) in the first and second quartiles of time after diagnosis, but no significant difference was observed in the third and fourth quartiles. [a]$P < 0.05$ *vs* obese subjects $\leqslant$ 4 yr after diagnosis, [c]$P < 0.05$ *vs* lean subjects $\leqslant$ 4 yr after diagnosis, [e]$P < 0.05$ *vs* lean subjects. Reproduced with permission from ref.[51].

workload. In individuals who are susceptible to T2DM, increased β-cell workload may lead to β-cell failure and the development of T2DM. In addition, once hyperglycemia develops, it also causes β-cell dysfunction and apoptosis, which further exacerbate β-cell failure. Importantly, because insulin resistance persists, the β-cell workload continues to increase, with a reduction in β-cell mass. As a result, glucose metabolism progressively deteriorates in patients with T2DM. In our retrospective cohort, the progressive decline in β-cell function seemed to be exaggerated in the presence of obesity in Japanese patients with T2DM[51] (Figure 7). Another Japanese cohort showed a decreasing trend in fasting insulin level despite an increasing trend in BMI at the first clinic/hospital visit of patients with T2DM during the past ten years[75]. Recent studies have shown that even metabolically healthy obese individuals are at increased risk of future development of diabetes, cardiovascular events and all-cause mortality[76-78]. Thus, weight loss itself may be important to preserve β-cell function and improve
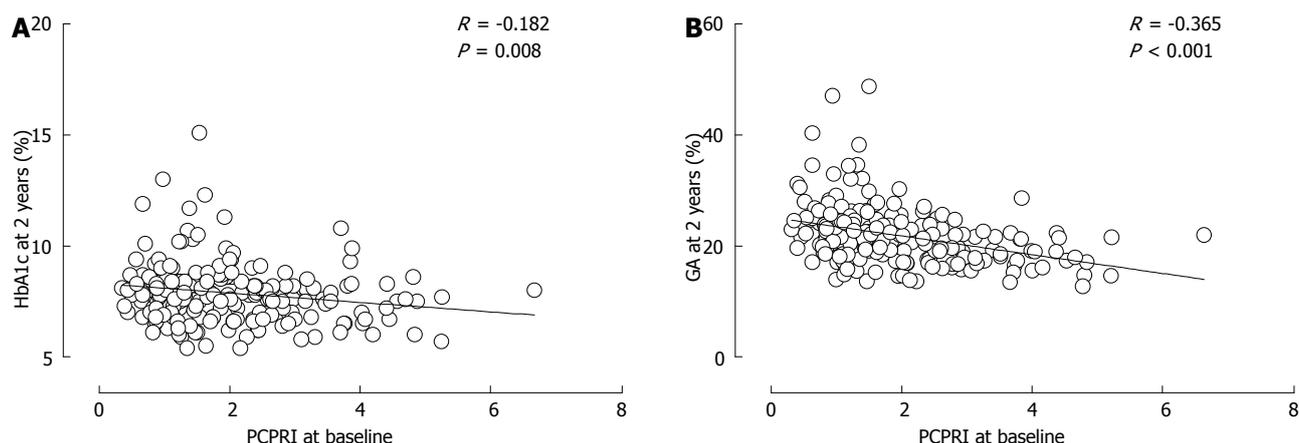
Figure 8 Correlation between baseline postprandial C-peptide index and HbA1c (A) and glycated albumin (B) after 2 years. Reproduced with permission from ref.[93]. PCPRI: Postprandial C-peptide index; GA: Glycated albumin.

functional capacity in Asians may contribute the different phenotype of T2DM between the two ethnicities. Because of the limited capacity of β-cell regeneration in Asians, excess β-cell workload could be induced in individuals with less obesity compared with Caucasians, which may lead to β-cell failure and the development of T2DM.

IMPLICATIONS FOR TREATMENT AND PREVENTION OF T2DM

β-cell function and glycemic control
If a deficit of β-cell functional mass is a hallmark of T2DM, what is the clinical consequence? In UKPDS and A Diabetes Outcome Progression Trial (ADOPT), treatment failure was associated with a progressive decline in β-cell function[50,87,88]. In the Treatment Options for T2DM Adolescents and Youth (TODAY) study, similar results were observed in adolescents with T2DM, and in this study baseline β-cell function was associated with treatment efficacy[89]. In our retrospective cohort analysis, we found that a lower baseline C-peptide level was associated with poorer glycemic control and the need for insulin therapy thereafter[90-93] (Figure 8). In these studies, postprandial C-peptide index [*i.e.,* postprandial serum C-peptide (ng/mL)/plasma glucose (mg/dL) × 100] was the best predictor of future insulin therapy among other C-peptide indices such as fasting C-peptide index and urinary C-peptide level. Since it was also significantly correlated with β-cell mass[49], postprandial C-peptide index may be a useful marker of β-cell function in clinical settings.

Thus, poorer β-cell function is associated with poorer glycemic control and treatment failure, indicating the important role of β-cell function in the treatment of T2DM.

β-cell function and glycemic variability
Furthermore, β-cell function is associated with glycemic variability. In patients with T1DM, it has been reported that lower β-cell functional capacity is associated with greater glycemic variability[94-96].

We and others have reported that serum and urinary C-peptide levels are negatively correlated with glycated albumin (GA) to HbA1c ratio in patients with T2DM[97-99] (Figure 9). Since albumin is more susceptible to glycation than is hemoglobin[100,101], GA more sensitively reflects glycemic variability than does HbA1c[97,102,103]. Thus, the inverse association between C-peptide level and GA to HbA1c ratio in patients with T2DM indicates that β-cell dysfunction is associated with greater glycemic variability in not only patients with type 1 diabetes but also those with T2DM.

Notably, we found that the relationship between postprandial C-peptide index and GA to HbA1c ratio in patients with T2DM was comparable to that in those with type 1 diabetes[97] (Figure 9B). This suggests that the impact of β-cell dysfunction on glycemic variability is irrespective of the type of diabetes, again indicating the central role of β-cell function in the pathogenesis of diabetes.

Recently, it has been reported that greater glycemic variability as well as poorer glycemic control is associated with the development of micro- and macro-angiopathy[104-107]. Thus, it should be stressed that greater glycemic variability and poorer glycemic control due to β-cell dysfunction may result in increased risk of diabetic complications.

Treatment strategy for T2DM
Since β-cell dysfunction is associated with poor glycemic control in patients with T2DM, preservation and recovery of β-cell functional mass is an important therapeutic strategy for T2DM. Moreover, the current issues in the treatment of T2DM summarized in Table 1 are, to put it simply, all associated with either excess or insufficiency of insulin supplementation[108]. Thus, the recovery of physiological insulin secretion in patients with T2DM is also a key to resolving these issues.

To preserve or recover β-cell function, a reduction in excess β-cell workload appears to be the most effective strategy to date. In ADOPT, better glycemic control was
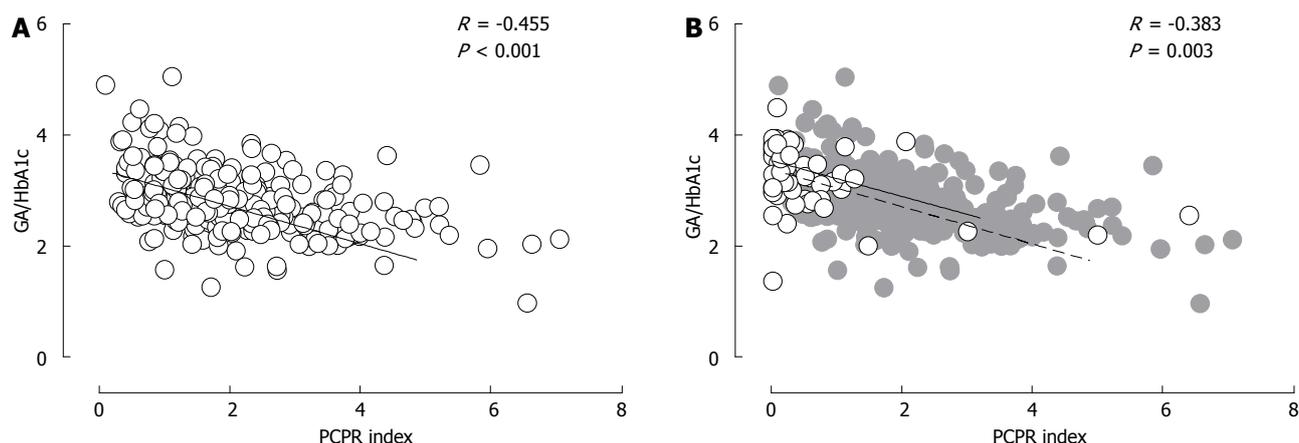
Figure 9 Correlation between postprandial C-peptide index and glycated albumin to HbA1c ratio in patients with type 2 diabetes (A) and type 1 diabetes (B). In Figure 9B, the data of patients with type 1 diabetes are superimposed on the data of those with type 2 diabetes (gray circles and dotted line). Reproduced with permission from ref.[97]. PCPRI: Postprandial C-peptide index; GA: Glycated albumin.

Table 1 Current issues in treatment of type 2 diabetes	
Issue	**Cause**
Hypoglycemia	Excess insulin
Weight gain	Excess insulin
Concern of increased risk of malignancy and/or atherosclerosis	Excess insulin, especially peripheral hyperinsulinemia
Postprandial hyperglycemia	Insufficient insulin in postprandial state, especially in portal vein

obtained with metfomin or rosiglitazone monotherapy compared with glyburide in patients with T2DM[87]. Thus, therapy should be focused on improving insulin sensitivity to reduce β-cell workload.

A proposed treatment strategy for T2DM is shown in Figure 10, as also described previously[108,109]. It is emphasized that, to reduce β-cell workload, lifestyle modification and weight reduction remain the most important therapy at any stage of T2DM. Although lifestyle modification failed to reduce the incidence of cardiovascular disease in the Action for Health in Diabetes (Look AHEAD) trial[110], it has been reported that lifestyle modification improved cardiovascular risk factors, reduced the need for and cost of medication, reduced the rate of sleep apnea and urinary incontinence, improved well-being and depression symptoms, and increased the rate of diabetes remission[111-116]. In a cohort analysis of the ADDITION-Cambridge study, it has been reported that healthy behavioral changes after the diagnosis of T2DM were associated with a significant reduction in risk of cardiovascular events[117], suggesting that early lifestyle intervention may be important to improve cardiovascular outcome.

Metformin is currently positioned as first-line therapy in most guidelines for the treatment of T2DM[118,119]. Since metformin is effective in lean patients as well as obese patients with T2DM[120,121], it should be used in both lean and obese individuals unless contraindicated.

Its efficacy in reducing HbA1c (by -1.5%), low risk of hypoglycemia, favorable effect on body weight and low cost also support metformin as a first-line drug.

Thiazolidinediones (TZDs) have also been shown to reduce β-cell workload and maintain glycemic control in the long term[87,88]. Rosiglitazone has been shown to increase low-density lipoprotein (LDL) cholesterol and the risk of coronary heart disease in patients with T2DM[122], and its use has been suspended or strictly restricted in Europe and United States[123,124], although recently the US Food and Drug Administration has lifted most of its restrictions[125]. On the other hand, pioglitazone has been shown to suppress the progression of atherosclerosis and reduce the risk of cardiovascular disease[126-129]. However, TZDs often induce weight gain and edema due to fluid retention, and are contraindicated in patients with heart failure[118]. Recent studies have also shown an increase in risk of bone fracture in women[130] and risk of bladder cancer[131-133] in patients treated with pioglitazone. The risk of bladder cancer may be dose dependent. In addition, since low-dose pioglitazone also reduces the risk of weight gain and edema, it may be preferable to use pioglitazone at lower doses, especially in women. Pioglitazone should also be used with caution in postmenopausal women with osteoporosis because of the increased fracture risk.

α-glucosidase inhibitors (AGIs) delay the absorption of carbohydrate from the small intestine, and thereby reduce postprandial hyperglycemia, resulting in reduced β-cell workload in a postprandial state. AGIs have also been reported to reduce the progression to T2DM in patients with IGT[134,135]. Improving postprandial hyperglycemia by AGIs may also improve the cardiovascular outcome[136-138]. Therefore, although the reduction in HbA1c by AGIs is relatively small (-0.5%), their use is also considered in patients with T2DM, especially those with postprandial hyperglycemia. The major side effect of AGIs is gastrointestinal disturbance such as flatulence, diarrhea and abdominal pain. In Japan, AGIs are the only medication indicated for patients with IGT.
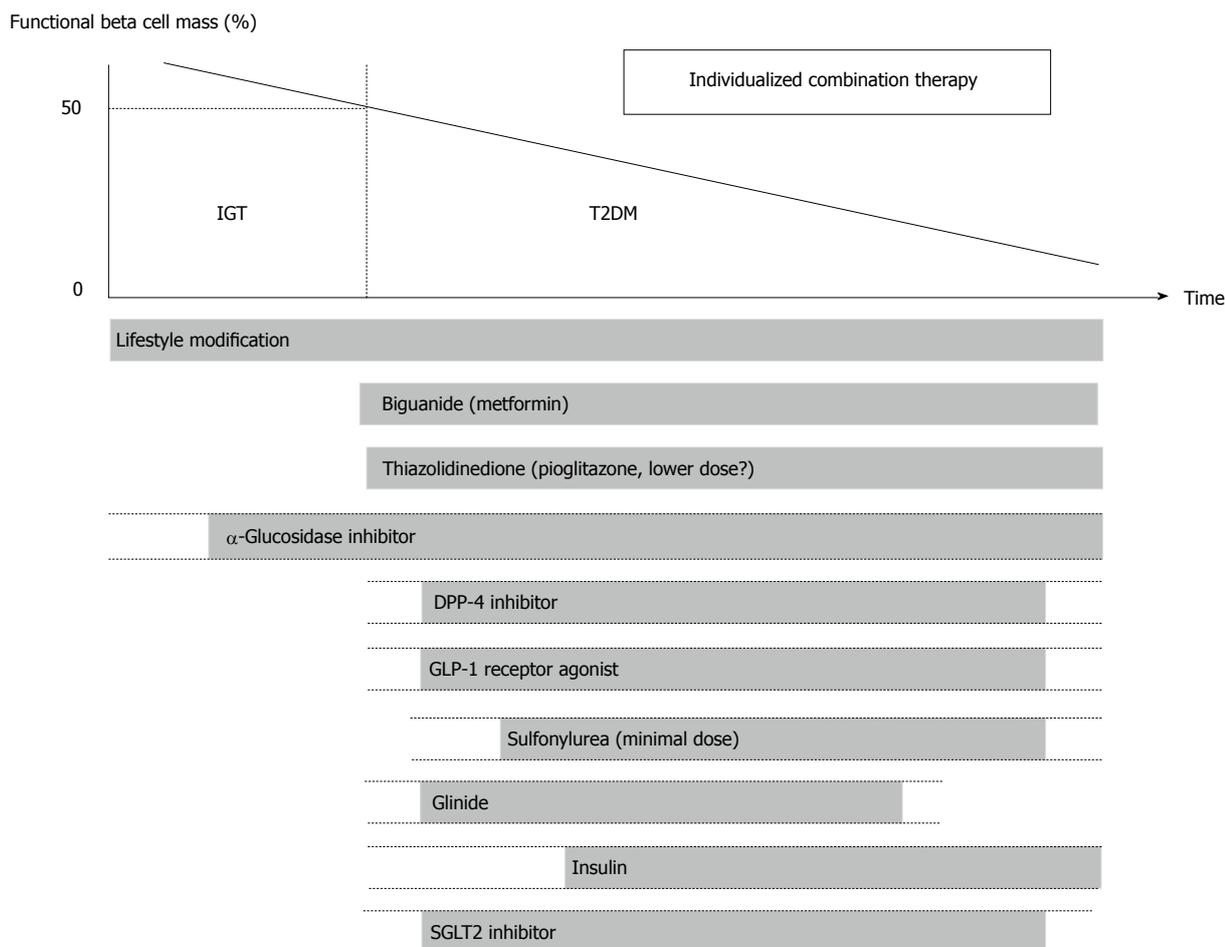
Functional beta cell mass (%)

Figure 10 Proposed concept of treatment strategy for type 2 diabetes in relation to functional β-cell mass. α-glucosidase inhibitor is partly approved for use in patients with impaired glucose tolerance 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 type 2 diabetes (T2DM), an effective combination of current medications in addition to lifestyle modification aiming at reduction in β-cell workload is important to preserve or recover β-cell function. Adopted and modified from ref.[108,109]. IGT: Impaired glucose tolerance.

Thus, AGIs are also considered for the treatment of T2DM at the early stage of the disease, if tolerated.

On the other hand, the use of insulin secretagogues, which increase β-cell workload, may be somewhat limited. Sulfonylureas (SUs), while remaining among the most highly prescribed drugs for the treatment of T2DM, increase the risk of hypoglycemia and weight gain, resulting in a high rate of treatment failure[87]. These issues of SUs may be derived from their non-physiological augmentation of insulin secretion from β-cells.

Incretin drugs include dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs). Both drug types reduce HbA1c mainly through an increase in insulin secretion, but also through suppression of glucagon secretion[139]. GLP-1RAs also slow gastric emptying and reduce appetite, resulting in weight loss. The most important characteristic of incretin drugs is probably that the enhancement of insulin secretion occurs in a glucose-dependent manner. Thus, the action of incretin drugs as insulin secretagogues is more physiological than that of SUs, thereby resulting in a low risk of hypoglycemia and weight gain with incretin

therapy[140-142]. Whether this physiological enhancement of insulin secretion results in long-term maintenance of glycemic control remains to be elucidated. Although an increase in β-cell mass with incretin therapy has been reported in rodent studies[143,144], this effect has not been confirmed in humans[145-147]. Since incretin therapy is usually well tolerated without serious adverse effects, the use of incretin drugs is rapidly increasing[148].

Glinides, short-acting insulin secretagogues, enhance early-phase insulin secretion, thereby reducing post-prandial hyperglycemia[149]. Since a defect in early-phase insulin secretion is a hallmark of glucose intolerance[150], the enhancement of early-phase insulin secretion without prolonged hyperinsulinemia by glinides is more physiological, unlike the action of SUs, and is assumed to increase β-cell workload as well as the risk of hypoglycemia to a lesser degree compared with SUs.

Thus, the use of insulin secretagogues may be limited because of an increase in β-cell workload as well as increased risk of hypoglycemia. Since incretin enhances insulin secretion in a more physiological manner and is also expected to improve β-cell function and/or mass, incretin drugs could be used at any stage of T2DM.

On the other hand, SUs may be used rather to enhance incretin action at only a minimal dose. To recover physiological insulin secretion, a combination of an incretin drug and a glinide may also be useful.

Insulin has been shown to improve β-cell function in patients with IGT and T2DM[151-153]. Since initial intensive insulin therapy has been shown to preserve β-cell function thereafter[152], insulin therapy should be considered as early as possible in patients with T2DM. Insulin therapy is also the most effective medication to reduce HbA1c[118]. However, the increased risk of hypoglycemia, weight gain and non-physiological insulin delivery (*i.e.,* systemic *vs* portal), in addition to the fear of injections, limit its use. Insulin therapy to overpower insulin resistance without eliminating excess calories may worsen ectopic lipid overload[154].

A sodium-glucose cotransporter 2 (SGLT2) inhibitor has recently been approved in several countries including United States, EU and Japan. SGLT2 inhibitors suppress reabsorption of glucose by SGLT2 in the proximal renal tubule and increase glucose excretion in urine (-60-80 g glucose/d)[155]. As a result, SGLT2 inhibitors not only decrease HbA1c, but also reduce body weight and blood pressure and improve the lipid profile. The action of SGLT2 inhibitors is independent of insulin. Thus, the efficacy of SGLT2 inhibitors seems to be regardless of β-cell function. SGLT2 inhibitors show a low risk of hypoglycemia but increase the incidence of bacterial urinary tract infections and fungal genital infections especially in women. A higher risk of hypotension has also been reported[156]. SGLT2 inhibitors may be suitable for obese patients with T2DM and metabolic syndrome; however, their longer term safety including cardiovascular and cancer risk and efficacy remain unknown[156,157].

Nonetheless, since currently no single therapy or agent can cure or even manage T2DM, an effective combination of current medications in addition to lifestyle modification aiming at reduction of β-cell workload is important to preserve or recover β-cell function.

Finally, marked weight reduction by bariatric surgery such as gastric bypass or sleeve gastrectomy has been reported to markedly improve glycemic control and even achieve remission of T2DM in severely obese T2DM patients[158,159]. This also suggests the importance of reducing β-cell workload, although change in incretin secretion has also been proposed as another mechanism by which glucose metabolism is improved after gastric bypass. On the other hand, it has been reported that gastric bypass markedly improved incretin's effect on insulin secretion, but not insulin secretion induced by intravenous glucose infusion[160], suggesting limited recovery of β-cell function even with marked weight loss. Also, the remission of T2DM after bariatric surgery is associated with residual β-cell function[161,162], indicating the importance of residual β-cell function to manage and/or cure T2DM.

Implications for prevention

The progressive decline in β-cell functional capacity during the development of glucose intolerance also implies the important role of preservation or recovery of β-cell function to prevent T2DM.

Similarly to the treatment of T2DM, prevention strategies should focus on reducing β-cell workload or inducing β-cell rest. These include lifestyle modification and/or weight reduction, and use of metformin or TZD. Lifestyle modification, *i.e.,* nutritional therapy and increase in physical activity, and weight reduction improve insulin sensitivity and thereby reduce β-cell workload. A number of studies have shown the efficacy of lifestyle intervention to prevent the development of T2DM in patients with IGT[163-166]. In the Diabetes Prevention Program (DPP), intensive lifestyle modification with more than 7% weight loss suppressed the progression to T2DM by -58% in patients with IGT[165]. In the same study, metformin therapy also reduced the progression to T2DM by -31%[165]. TZDs have also been shown to effectively suppress the progression from IGT to T2DM[167-169]. A significant reduction in the development of diabetes was also observed in patients with IGT treated with AGIs[134,135]. In the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial, adding basal insulin was also shown to suppress progression from IGT to T2DM[151], probably through inducing β-cell rest. On the other hand, in the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, nateglinide, a short-acting insulin secretagogue, failed to show a reduction in progression to T2DM in patients with IGT[170], suggesting that therapeutic strategies to increase β-cell workload may not be effective to prevent deterioration of glucose metabolism.

Importance of empowerment of patients

Although several anti-diabetic agents have been shown to effectively prevent the onset of T2DM, the importance of lifestyle modification remains unchanged, since the rapid increase in incidence of T2DM is certainly associated with the change in diet (*i.e.,* westernization) and physical inactivity, resulting in increased incidence of obesity. In the NAVIGATOR trial, it has been reported that both baseline level and change in daily ambulatory activity were associated with a reduced risk of cardiovascular events in patients with IGT[171]. A six-year lifestyle intervention program for Chinese people with IGT showed a significant reduction in the incidence of cardiovascular and all-cause mortality as well as diabetes during 23 years of follow-up[172]. A combination of diet and exercise appears more beneficial than either alone in obese older adults[173]. Lifestyle modification may improve cardiovascular outcomes even after the onset of T2DM[117].

Nonetheless, it is difficult to continue lifestyle modification in most patients. Patients' motivation is one of the most important factors in successful patient-centered management of T2DM[118]. Therefore, it is important to motivate and encourage them to improve their adherence to daily lifestyle modification. In this context,

understanding the natural history of the development of T2DM and the importance of reducing β-cell workload to prevent or manage the disease may help to motivate or encourage patients to adhere to daily lifestyle changes.

Furthermore, as a whole society, not only patients with IGT or T2DM, but the healthy, general population should also be educated to motivate or encourage them to pursue a healthy lifestyle to prevent diseases associated with obesity and physical inactivity, resulting in improvement of quality of life (QOL). Changing our understanding of T2DM and a "modern" lifestyle may be needed to overcome this pandemic burden of T2DM all over the world.

CONCLUSION

This review summarizes the current knowledge of β-cell function and β-cell mass in T2DM. Recent evidence has emerged that a deficit of β-cell function along with β-cell mass is a hallmark of T2DM. Therefore, it is now acknowledged that a deficit of β-cell functional mass is a common characteristic of both type 1 and type 2 diabetes, indicating a core pathogenesis of diabetes. Genome-wide association studies have currently detected over 60 genetic loci associated with T2DM, most of which are assumed to relate to the β-cell, also indicating the imporance of β-cells in the pathogenesis of T2DM[174-178]. It is important to stress that diabetes never develops unless β-cells fail to compensate insulin resistance. In addition, β-cell function is related to treatment failure and glycemic control, suggesting its critical role in the management of T2DM. These findings suggest that recovery of β-cell functional mass is an important therapeutic strategy to manage or even cure T2DM. Although, unfortunately, currently no treatment strategy or medication to recover β-cell functional mass has been established, current evidence suggests that reducing β-cell workload is most effective to preserve β-cell functional mass. Thus, therapy or prevention of T2DM should focus on this point, and, therefore, lifestyle modification and weight loss remain the most important therapeutic strategy. Use of medication without lifestyle modification may even result in adverse outcomes. From the point of view of prevention, we need to tackle this pandemic burden of T2DM as a whole society, and correct understanding of the pathogenesis of T2DM may help motivate people to maintain a healthy lifestyle.

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