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Clinical expert consensus on the assessment and protection of pancreatic islet β-cell function in type 2 diabetes mellitus

Jian Zhu[a], Junfeng Han[b], Liehua Liu[c], Yu Liu[d], Wen Xu[e], Xiaomu Li[f], Lin Yang[g], Yong Gu[h], Wei Tang[i], Yongquan Shi[j], Shandong Ye[k], Fei Hua[l], Guangda Xiang[m], Ming Liu[n], Zilin Sun[o], Qing Su[p], Xiaoying Li[f], Yuxiu Li[q], Yanbing Li[c], Hong Li[r], Yiming Li[s], Tao Yang[h], Jing Yang[t], Lixin Shi[u], Xuefeng Yu[v], Li Chen[w], Jiaqing Shao[x], Jun Liang[y], Xiao Han[z], Yaomin Xue[aa], Jianhua Ma[a,*], Dalong Zhu[ab,*], Yiming Mu[ac,*], On behalf of the Pancreatic Islet β-cell Expert Panel of the Chinese Diabetes Society and Endocrinology Society of Jiangsu Medical Association

[a] *Department of Endocrinology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China*
[b] *Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Clinical Center for Diabetes, Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Key Clinical Center for Metabolic Disease, Shanghai, China*
[c] *Department of Endocrinology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*
[d] *Endocrinology Department, Sir Run Run Hospital of Nanjing Medical University, Nanjing, China*
[e] *Department of Endocrinology and Metabolism, Guangdong Provincial Key Laboratory of Diabetology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*
[f] *Department of Endocrine and Metabolism, Zhongshan Hospital, Fudan University, Shanghai, China*
[g] *National Clinical Research Center for Metabolic Diseases, Key Laboratory of Diabetes Immunology, Ministry of Education, Department of Metabolism and Endocrinology, The Second Xiangya Hospital of Central South University, Changsha, China*
[h] *Department of Endocrinology and Metabolism, First Affiliated Hospital of Nanjing Medical University, Nanjing, China*
[i] *Department of Endocrinology, Geriatric Hospital of Nanjing Medical University, Nanjing, China*
[j] *Department of Endocrinology, Changzheng Hospital, The Navy Military Medical University, Shanghai, China*
[k] *Department of Endocrinology, Anhui Provincial Hospital, Hefei, China*
[l] *Department of Endocrinology, The First People's Hospital of Changzhou, Changzhou, China*
[m] *Department of Endocrinology, General Hospital of Central Theater Command of Chinese People' s Liberation Army, Wuhan, China*
[n] *Department of Endocrinology, General Hospital, Tianjin Medical University, Tianjin, China*
[o] *Department of Endocrinology, Zhongda Hospital, Institute of Diabetes, School of Medicine, Southeast University, Nanjing, China*
[p] *Department of Endocrinology, Xinhua Hospital, Shanghai Jiaotong University, Shanghai, China*
[q] *Department of Endocrinology, Peking Union Medical College Hospital, Beijing, China*
[r] *Department of Endocrinology, First Affiliated Hospital of Kunming Medical University, Kunming, China*
[s] *Department of Endocrinology, Huashan Hospital, Fudan University, Shanghai, China*
[t] *Department of Endocrinology, First Hospital of Shanxi Medical University, Taiyuan, China*
[u] *Department of Endocrinology, Guiqian International General Hospital, Guiyang 550018, China*
[v] *Department of Endocrinology, Tongji Hospital, Tongji Medical College of Huazhong University of Science & Technology, Wuhan, China*
[w] *Department of Endocrinology, Qilu Hospital of Shandong University, Jinan, China*
[x] *Department of Endocrinology, the Affiliated Jinling Hospital of Nanjing Medical University, General Hospital of Eastern Theater Command, Nanjing, China*
[y] *Department of Endocrinology, Xuzhou Central Hospital, Xuzhou, China*
[z] *Key Laboratory of Human Functional Genomics of Jiangsu Province, School of Basic Medical Science, Nanjing Medical University, Nanjing, China*
[aa] *The First Clinical Medical Institute, Southern Medical University, Guangzhou, China*
[ab] *Department of Endocrinology, Drum Tower Hospital Affiliated to Nanjing University Medical School, Nanjing, China*
[ac] *Department of Endocrinology, Chinese PLA General Hospital, Beijing, China*

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ABSTRACT

Islet β-cell dysfunction is a basic pathophysiological characteristic of type 2 diabetes mellitus (T2DM). Appropriate assessment of islet β-cell function is beneficial to better management of T2DM. Protecting islet β-cell function is vital to delay the progress of type 2 diabetes mellitus. Therefore, the Pancreatic Islet β-cell Expert Panel of the Chinese Diabetes Society and Endocrinology Society of Jiangsu Medical Association organized

* Corresponding authors.
E-mail addresses: majianhua@china.com (J. Ma), zhudalong@nju.edu.cn (D. Zhu), muyiming@301hospital.com.cn (Y. Mu).

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Weight loss
Intensive insulin therapy
Expert consensus

experts to draft the "*Clinical expert consensus on the assessment and protection of pancreatic islet β-cell function in type 2 diabetes mellitus.*" This consensus suggests that β-cell function can be clinically assessed using blood glucose-based methods or methods that combine blood glucose and endogenous insulin or C-peptide levels. Some measures, including weight loss and early and sustained euglycemia control, could effectively protect islet β-cell function, and some newly developed drugs, such as Sodium-glucose cotransporter-2 inhibitor and Glucagon-like peptide-1 receptor agonists, could improve islet β-cell function, independent of glycemic control.

The prevalence of adult diabetes mellitus in China has increased to 11.2%, and more than 90% of the cases is type 2 diabetes mellitus (T2DM) [1]. Although the precise mechanism of T2DM development has not been fully clarified, pancreatic islet β-cell dysfunction and insulin resistance are considered two major factors in the pathogenesis of T2DM. Islet β-cell function in T2DM patients decreases at an average rate of 2% yearly and considerably declines in patients with a disease duration of more than 10 years [2]. An extensive amount of time is elapsed from the full compensation of islet β-cells for glycemia control to complete decompensation, and this period may allow physicians to adopt useful measures to protect islet β-cell function. Therefore, appropriately assessing islet β-cell function and developing an optimal treatment regimen early should contribute to better delaying the progression of T2DM.

At present, there is a lack of guidance specifically documented for the assessment and protection of islet β-cell function in T2DM patients in China. To address this, the Pancreatic Islet β-cell Expert Panel of the Chinese Diabetes Society and the Endocrinology Society of Jiangsu Medical Association organized some experts to jointly draft this consensus, focusing on the mechanism of islet β-cell dysfunction, assessment methods, and treatment strategies for the protection of islet β-cell function. They searched and discussed relevant articles from PubMed, Embase, Chinese BioMedical Literature, WanFang Medicine, and China National Knowledge Infrastructure databases, ultimately reaching this consensus. The aim of the consensus is to help clinicians understand and apply assessment methods of islet β-cell function appropriately and implement effective measures to protect islet β-cell function, thus improving the clinical outcomes of T2DM patients.

1. Concept of islet β-cell function and its dysfunction mechanism

1.1. Key points

1. Islet β-cell function can be defined as the ability of β-cells to synthesize, store, and secrete insulin in appropriate amounts to maintain euglycemia.
2. Chronic nonspecific inflammatory reactions, oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction caused by glycolipid toxicity, glycemic variability, and environmental endocrine-disrupting compounds are the key factors that lead to a decline in insulin secretion ability and aging of islet β-cells.
3. β-cell apoptosis, dedifferentiation of pancreatic endocrine progenitor cells, and trans-differentiation to α-cell-like cells are the main reasons for dysregulation of functional islet β-cell mass.

Narrowly speaking, islet β-cell function can be defined as the ability of β-cells to synthesize, store, and secrete insulin in appropriate amounts to maintain euglycemia [3,4]. Pulsatile insulin secretion is an indicator of normal islet β-cell function. After glucose stimulation, islet β-cells secrete insulin in a biphasic mode, usually the first and second phases. One to two minutes after intravenous glucose stimulation, in normal individuals, insulin level in the portal vein increases, and that in the peripheral vein peaks at 3-5 min, lasting for approximately 10 min (the first phase). However, when glucose is administered orally, peak insulin level is usually attained after 20-30 min, called the early secretory phase. The amount of insulin secreted in the first or early secretory phase accounts for 2-3% of the total insulin in β-cells. After the first phase or early secretory phase (10-30 min later), insulin secretion slowly increases, reaching a plateau at 2-3 h and lasting for several hours. This is the second phase, accounting for approximately 20% of total insulin secretion in islet β-cells [3]. In term of subject with normal glucose tolerance (NGT), after glucose stimulation, the peak value of insulin can reach 5-10 times the fasting value, while the peak value of C-peptide can reach 5-8 times the fasting value and gradually returns to the fasting level within 3-4 h. For patient with type 1 diabetes mellitus (T1DM), the fasting insulin level is lower than the normal value, and blood glucose levels rise dramatically after glucose stimulation; however, insulin and C-peptide levels cannot increase simultaneously, often showing no peak and a low flat curve [5]. For T2DM patient, during the early stage of disease, fasting insulin level was often in the normal range, but insulin secretion rose slowly after glucose stimulation, and the early secretory phase subsided, reaching its peak 1-2 h after stimulation. This may be higher or lower than that of NGT subjects, and cannot fall back to the fasting level 3-4 h after stimulation in most non-overweight/obese patients. The insulin secretion curve of overweight/obesity was similar to that of non-overweight/obesity, but insulin secretion level increased significantly during fasting and after glucose stimulation. As the disease progresses, islet β-cell function gradually declines, similar to T1DM [6].

In addition to insulin, islet β-cells also secrete a variety of other hormones and peptides. Generally, islet β-cell dysfunction is believed to be first exhibited in the loss of sensitivity to glucose stimulation, especially the disappearance of the first or early secretory phase, while the non-glucose-stimulated insulin secretion (NGSIS) response may still exist. However, with prolongation of the disease course, NGSIS function also clearly decreases.

The mechanism underlying islet β-cell dysfunction is complex. Together, environmental and genetic factors lead to islet β-cell failure. Chronic nonspecific inflammatory reactions, oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction caused by glycolipid toxicity, glycemic variability, and environmental endocrine-disrupting compounds are the key factors that lead to a decline in insulin secretion ability and aging of islet β-cells [7–9]. β-cell apoptosis, dedifferentiation to pancreatic endocrine progenitor cells, and trans-differentiation to α-cell-like cells are the main reasons for the dysregulation of the islet β-cell functional mass [10]. In addition, variation in multiple susceptibility genes is closely related to islet β-cell dysfunction [11].

2. Clinical significance of assessing islet β-cell function

2.1. Key points

Appropriate assessment of islet β-cell function is beneficial to better selecting an individualized treatment regimen, and predicting the prognosis of T2DM patients.

2.2. Selecting a reasonable treatment regimen

In T2DM patients, it is necessary to analyze the severity of insulin resistance and select metformin and other insulin sensitizers to improve insulin sensitivity. Patients with insufficient insulin secretion require further analysis to determine whether islet β-cell function is temporarily inhibited by glucolipid toxicity or permanently damaged by disease

progression. These two possibilities can be briefly distinguished by combining the disease duration and NGSIS (such as arginine) response. Regarding the former, especially those with newly diagnosed T2DM and certain NGSIS, glucose toxicity should be relieved rapidly by intensive insulin therapy to restore β-cell function, and the following treatment regimen [12] can be optimized according to the reassessment results of islet β-cell function. Regarding the latter, especially for patients with a longer disease duration and poor NGSIS response, insulin supplementation or replacement therapy [13] should be reasonably performed.

2.3. Predicting the prognosis

Islet β-cell function can be used as an important parameter to predict the prognosis of patients with diabetes. There is a negative correlation

Table 1
Methods of islet β-cell function assessment based on insulin or C-peptide [4,20–27].

Appraisal procedure	Main parameters, drug required, and calculation formula	Clinical significance	Advantages	Limitations
Fasting serum insulin	–	Non-insulin-treated diabetic patients can be used to assess baseline islet function.	Simple and mature method	Testing methods and units are not uniform.
Fasting serum C-peptide	–	Diabetic patients treated with insulin or producing insulin antibodies can be used to assess islet β-cell function at baseline.	Simple method; determination is not interfered by insulin.	C-peptide level is affected by age, sex, body shape, and glucose tolerance level and has a long biological half- life.
Ratio of proinsulin to fasting serum insulin (PI/FINS)	–	The normal value was 7–9%, and the ratio progressively increased from NGT to IGT to diabetes	Simple method	Testing methods and units are not uniform, and proinsulin testing has not been commercialized and standardized.
Homeostasis model assessment-β (HOMA-β) [20,21]	HOMA-β = 20 × FINS/ (FPG − 3.5) HOMA-β (normal population) =0.27 × FCP / (FPG − 3.5) + 50; HOMA-β (diabetic population) = 0.27 × FCP / (FPG − 3.5)	It is a correction of the FINS/FPG simplification index,	Suitable for epidemiological research and assessment after clinical treatment (except for treatment with secretagogues such as insulin and sulfonylureas); if the influence of exogenous insulin is considered, C-peptide can be used instead of insulin for assessment.	The interference of insulin resistance overestimates the function of β-cells.
Modified β-cell function index (MBCI) [22]	MBCI = (FINS × FPG)/ (PG_{120} + PG_{60}–2 × FPG) 75 g oral glucose tolerance test	Represents insulin secretion stimulated by glucose	Considers the influence of blood sugar level on insulin secretion	Only represents the response of islet β-cells to glucose, which is influenced by insulin sensitivity
Ratio of peak insulin secretion to basal insulin level after stimulation (Ip/I_0)	75 g oral glucose tolerance test	After sugar loading, the peak insulin level of healthy individuals can be increased by 5–10 times compared with the basic value.	Reflects the ability of insulin secretion after stimulation	The IGT population may be compensated
Ratio of insulin increment to blood sugar increment after sugar loading [23]	($I_{30} - I_0$)/ ($G_{30} - G_0$) 75 g oral glucose tolerance test	Represents early insulin secretion	Simple calculation	Islet β-cell function of individuals with flat insulin secretion curve cannot be compared owing to interference by insulin resistance
Area under the insulin curve after glucose loading (AUCI) [23]	AUCI = ($I_0 + 2 \times I_{30} + 3 \times I_{60} + 4 \times I_{120} + 2 \times I_{180}$)/4 75 g oral glucose tolerance test	Roughly determines β-cell insulin secretion function	Comprehensively reflects the amount of insulin secretion	Cannot reflect the peak time of IGT; will misjudge β-cell hyperfunction in IGT population owing to insulin resistance
Micro-model method: insulin secretion in the first phase [24]	AIR ($I_0 + I_3 + I_4 + I_5 + I_8 + I_{10}$) The loading amount of glucose is 0.3 g/kg standard body weight, which is prepared into a 50% solution, and the intravenous injection is completed within 2–4 min.	Represents the acute reaction of islet β-cells stimulated by intravenous high glucose, which is less affected by insulin resistance	Eliminates the effects of gastrointestinal hormones and gastric emptying and is suitable for precise research with a small sample size	Was influenced by insulin clearance variability and blood sugar level. Does not consider the effects of nutrients and glucose-regulated hormones
Hyperglycemic clamp test [25]	The first and second phases of insulin secretion, maximum insulin secretion	Represents the true insulin secretion function of islet β-cell	Accurately reflects insulin secretion in each phase, including the first phase, second phase, and maximum insulin secretion, which is the golden index for evaluating islet β-cell function	The operation is complicated and time-consuming and requires professional technicians.
Arginine stimulation test [26]	($I_2 + I_4 + I_6$)/3 − I0; ($C_2 + C_4 + C_6$)/3 − C_0 Inject 50 ml of 10% arginine hydrochloride intravenously and complete the injection within 30–60 s. Start timing after the injection.	Represents the insulin secretion function of islet β-cells under non-glucose stimulation; often used to judge the reserve function of islet β-cells and whether secretagogue use is effective [25]	Simple, easy to operate, economical, safe, easy to standardize, and repeatable	For T2DM patients with blood glucose >11 mmoL/L, the results of this experiment were biased.
Glucagon stimulation test [27]	C_6-C_0 Quickly inject 1 mg glucagon intravenously and start timing after injection.	Represents residual islet β-cell function.	Islet β-cell function assessment for T1DM	Glucagon is difficult to obtain.

Abbreviations: FINS (mU/L)is fasting insulin; Ip (mU/L) is insulin peak; I_0 (mU/L) is the basic insulin value; FPG (mmoL/L) is fasting plasma glucose; FCP (pmoL/L) is fasting C-peptide; PG(n) (mmoL/L) is postprandial blood glucose at a specific time, n represents the blood drawing time (minutes); I(n) (mU/L) is insulin at a specific time, n represents the blood drawing time (minutes); G(n) (mmoL/L) is blood glucose at a specific time, n represents the blood drawing time (minutes); AIR is an acute insulin reaction; C(n) (nmoL/L) is the C-peptide at a specific time, n represents the blood drawing time (minutes); NGT is normal glucose tolerance; IGT is impaired glucose tolerance; T1DM is type 1 diabetes; T2DM is type 2 diabetes; -This item is not available.

between islet β-cell function and diabetic microvascular complications [14,15].

3. Assessment methods of islet β-cell function

3.1. Key points

Each method for assessing islet β-cell function has its own merits and drawbacks. In clinical applications, it is necessary to comprehensively consider the purpose of assessment and sensitivity and specificity of different methods during the natural course of diabetes mellitus to maximize application potential. The hyperglycemia clamp test, IVGTT, and other glucose stimulation tests are preferred among diabetes mellitus high-risk subjects with normal glucose tolerance and are helpful in evaluating diabetes risk. IVGTT, OGTT, and insulin release tests are suitable for assessing islet β-cell function in prediabetes patients. Residual β-cell function can be measured using OGTT, arginine, or glucagon stimulation in patients diagnosed with diabetes.

I. Methods for islet β-cell function assessment

(1) Blood glucose-based assessment methods

Blood glucose levels, including those of fasting blood glucose, postprandial blood glucose, and glycosylated hemoglobin A1c (HBA1c), can reflect islet β-cell function in T2DM patients. Higher blood glucose levels indicate more serious β-cell dysfunction. In addition, the mean amplitude of glycemic excursion in continuous glucose monitoring is negatively correlated with islet β-cell function; larger glycemic variability corresponds to worse islet β-cell function in T2DM patients [16,17]. The parameters of glycemic variability may serve as indirect indices for assessing islet β-cell function.

(2) Assessment methods combining blood glucose and endogenous insulin/C-peptide (Table 1)

Owing to their simplicity, fasting insulin or C-peptide level, ratio of proinsulin to fasting serum insulin and homeostasis model to assess β-cell function (HOMA-β) are generally used to represent islet β-cell function in epidemiological studies. Stimulation tests which can assess islet β-cell function both dynamically and comprehensively are commonly used in clinics. There are two types of insulin or C-peptide release test according to the stimuli: a glucose-stimulated test and a non-glucose-stimulated test. Glucose-stimulated insulin release tests mainly comprise high glucose clamp tests, intravenous glucose tolerance tests (IVGTT), and oral glucose tolerance tests (OGTT). Non-glucose-stimulated insulin release tests mainly include arginine and glucagon tests. Finally, the corresponding indices reflecting β-cell function are calculated using mathematical models and formulas.

II. Methods for measuring insulin or C-peptide

There are many methods to measure insulin in humans, including radioimmunoassay (RIA), enzyme-linked immunoassay, chemiluminescence immunoassay, and electrochemiluminescence immunoassay. RIA is a classical manual measurement method, whereas the others are automatic measurement methods. RIA recorded the lowest detection precision, while the other methods had higher precision. Manual operation may be the main factor leading to a large deviation in RIA measurement. The results of insulin measurements in non-RIA are 20-40% lower than those in RIA owing to their high antibody specificity. Although the different methods presented significantly different results, they were still highly correlated. Insulin analogs, anti-insulin antibodies, and heterophile antibodies may cross-react with insulin detection antibodies; however, if the same method is used to evaluate insulin level, this will not result in misjudgment of islet β-cell function, especially for dynamic analysis [18].

The methods for measuring C-peptides in the laboratory include RIA, enzyme-linked immunoassay, chemiluminescence immunoassay, and electrochemiluminescence immunoassay. The ratio of serum C-peptide peak value to the basic value and the time from baseline to peak values are consistent among different methods [19] and thus will not lead to misjudgments in assessing islet β-cell function in T2DM patients.

I. Assessment method of islet β-cell function based on insulin or C-peptide

Assessment method of islet β-cell function is shown in Table 1.

II. Recommendation for clinical methods for detecting islet β-cell function

Appropriate method selection is the premise for assessment of islet β-cell function. It is necessary to comprehensively consider the purpose of assessment and the sensitivity and specificity of different methods for detecting islet β-cell function during the natural course of T2DM. Hyperglycemic clamp test, IVGTT, and other OGTT can be used to determine the potential damage to β-cell function among high-risk groups whose glucose regulation is still in the normal stage, which is helpful in assessing the risk of diabetes mellitus. Prediabetic patients prefer IVGTT and OGTT combined with insulin release tests to calculate different parameters for assessment. Residual islet β-cell function can be assessed using OGTT parameters, arginine, or glucagon stimulation in patients diagnosed with diabetes mellitus.

At present, although many indices derived from different stimulation tests are used to represent the changes in the amount and phase of insulin secretion, islet β-cell function can only be “roughly” quantified. It is easy to misunderstand if we want to define a tangent point or normal range for different indices, and the dynamic assessment of islet β-cell function may be more helpful for comparative judgment. All types of assessment methods have advantages and limitations and should therefore be used reasonably. Thus, the appropriate research object and detection indicators should be selected carefully, and statistical analysis should be carefully performed to eliminate the interference of confounding factors. When one method is insufficient to reflect the profile of β-cell function, several tests can be combined according to the research purpose. Accurate, scientific, and comprehensive assessment of islet β-cell function provides a solid foundation for developing individualized treatment plans.

4. Therapeutic strategies for protecting islet β-cell function

4.1. Key points

Measures to protect islet β-cell function include the following:

1. Reducing body weight by strengthening lifestyle interventions, weight loss drugs, metabolic surgery.
2. Sustainedly near-normoglycemic control and minimization of glycemic variability via treatment with antidiabetic drugs to eliminate glucolipid toxicity over time using short-term intensive insulin therapy.
3. Paying attention to the side effects of long-term use of statins, glucocorticoids, immune checkpoint inhibitors, and other drugs on islet β-cell function.

These measures aim to eliminate glucolipid toxicity, minimize glycemic variability, control chronic low-degree inflammation, improve microcirculation of islet β-cells, and protect islet β-cell function effectively.

I. Reducing body weight

Previous studies have evaluated the metabolic effects of different degrees of weight loss (5%, 10%, and 15%) in participants with obesity. The results showed that 5% weight loss was sufficient to improve islet β-cell function and various cardiovascular risk factors, and greater weight loss corresponded to greater improvement in islet β-cell function [28]. Measures, including intensive lifestyle interventions, weight-loss drugs, and metabolic surgery, aim to reduce body weight, resulting in reduced ectopic fat deposition in the liver, muscle, and pancreas [29], optimized glycemic control [30], relieved insulin resistance, and improved islet β-cell function.

(1) Intensive lifestyle intervention.

In obese individuals with T2DM, intensive lifestyle intervention results in reduced body weight, relieving glycolipid toxicity [31]and alleviating chronic low-degree inflammation [32,33]. Basic research has shown that long-term caloric restriction reduces apoptosis, transdifferentiation, and dedifferentiation of islet β-cells and induces their redifferentiation [34]. The Diabetes Remission Clinical Trial demonstrated that 1 and 2 years after initiation of an intensive lifestyle intervention program for 3–5 months, 46% and 36% of overweight and obese T2DM patients, respectively, achieved clinical remission, compared to 4% and 3% of control participants, respectively. Further analysis showed that the complete remission rate of diabetes reached 86% in patients with weight loss >15 kg. The high glucose clamp test and arginine stimulation test demonstrated that the first phase and maximum insulin secretion rate of participants in the clinical remission group were restored to levels close to those of non-diabetic individuals [35]. A very low-calorie diet also effectively improved islet β-cell function in overweight or obese T2DM patients [36]).

Exercise improves glucose and lipid metabolism and repairs islet β-cell dysfunction [37]. Newly diagnosed obese T2DM patients demonstrated a 22% increase in HOMA-β levels compared to the baseline value by increasing exercise [38]. Moderate-intensity aerobic exercise reduces body weight and visceral fat, thus significantly improving the insulin secretion ability of patients [39].

(2) Weight loss drugs

After 52 weeks of orlistat add-on, T2DM patients who received lifestyle intervention and metformin treatment lost −5.0% body weight compared to −1.8% in the placebo group, and HOMA-β increased from 50.4% ± 38.5% at baseline to 58.2% ± 37.5% compared to a decrease from 63.5 ± 15.7% at baseline to 53.5 ± 52.3% in the placebo group [40]. A small-scale study in China also found that in obese T2DM patients, short-term (12 weeks) addition of orlistat to lifestyle intervention and metformin further reduced body weight, and the amplitude of HOMA-β improvement was 1.8 times that of the control group [41].

Glucagon-like peptide-1 receptor agonist (GLP-1RA) reduces body weight by inhibiting the feeding center, delaying gastric emptying, and promoting white adipose tissue and adipocyte browning. GLP-1RAs, including liraglutide, dulaglutide, exenatide, and meaglutide, reduced the body weight of obese patients in a dose-dependent manner. With an increase in dosage, both the proportion of weight loss >5% and the amplitude of islet β-cell function improvement increased significantly [42–47]).

(3) Metabolic surgery

According to the guidelines for the surgical treatment of type 2 diabetes in China [48], metabolic surgery is recommended as an option to treat T2DM if the patient is aged 16–65 years, with partly residual insulin secretion function and (1) BMI $\geq$ 32.5 kg/m^2 (highly recommended), (2) 27.5 kg/m^2 $\leq$ BMI $<$ 32.5 kg/m^2 (recommended), or (3) 25.0 kg/m^2 $\leq$ BMI $<$ 27.5 kg/m^2, but difficult to control hyperglycemia after lifestyle intervention and antidiabetic drug treatment, and accompanied by at least two metabolic syndrome components or complications (considered carefully). Weight loss is a major contributor to the benefits of metabolic surgery [49,50].

Metabolic surgery improves islet β-cell function in obese patients with T2DM, which is conducive to clinical remission of diabetes [51]). After gastric bypass surgery, fasting and postprandial blood glucose levels were dramatically reduced, compensatory hyperinsulinemia was relieved significantly, and the time to insulin peak was greatly shortened in obese patients with T2DM. Notably, at 3 months and 1 year after gastric bypass surgery, the glucose disposal index of patients increased 5- and 8-fold compared to the preoperational value, respectively, and the peak value of GLP-1 secretion after meals reached 10 times the baseline value [52]. The acute insulin reaction in the IVGTT increased by 770% and 93.5% [53] at 3 months and 1 year after biliopancreatic diversion with gastric bypass, respectively, in obese patients with T2DM.

II. Early and sustainedly near-normoglycemic control

Glucotoxicity and glycemic variability are important causes of islet β-cell dysfunction. Early and sustainedly near-normoglycemic control is beneficial for the long-term protection of islet β-cell function.

(1) Short-term intensive insulin therapy

Short-term intensive insulin therapy (IIT) significantly improves islet β-cell function in newly diagnosed T2DM patients, and approximately half of the participants achieved at least 1 year of clinical remission after short-term IIT [54–58]). Eliminating glucotoxicity maximally and rapidly is the main contributor to IIT improvement of islet β-cell function. Reduction in β-cell metabolic stress and endogenous insulin secretion requirements is closely related to the therapeutic effect of IIT, better glycemic control, lower average blood glucose level in the normal range, and higher inhibition of the increased amplitude of C-peptide (peak C-peptide minus fasting C-peptide) after arginine stimulation during ITT, thereby resulting in better recovery of β-cell function and a higher rate of clinical remission [57,59]).

(2) Non-insulin antidiabetic drugs

Based on the patient's age, disease course, islet β-cell function, BMI, and other characteristics, combined use of antidiabetic drugs with different mechanisms of action is key to long-term euglycemia control and an important measure to prevent islet β-cell dysfunction. Different non-insulin antidiabetic drugs, including metformin, sulfonylureas, glinides, α-glucosidase inhibitors, thiazolidinediones, and newly developed drugs, indirectly protect islet β-cell function by relieving glucotoxicity. Basic research has shown that mechanisms other than glycemia control contribute to the protection of islet β-cell function by GLP-1RA and sodium-glucose cotransporter-2 inhibitor (SGLT2i).

1. GLP-1RA: Animal experiments demonstrated that GLP-1RAs, including liraglutide, dulaglutide, and supaglutide, enhanced insulin secretion in a glucose concentration-dependent manner, promoted the conversion of proinsulin to insulin, induced β-cell proliferation and differentiation, and protected β-cells against apoptotic injury [60–62]. In vitro studies based on human islet cells found that GLP-1RA could restore the insulin secretion ability of β-cells impaired by harmful stimuli, such as palmitic acid [63]], high glucose [64] and inflammatory cytokines [65], and mildly increase the proliferation rate and number of β-cells in unsorted human islet cells [[66,67]]. It should be noted that the human ß-cell proliferation in vivo is rarely observed, in addition, the ß-cell proliferation in response to GLP-1 or GLP-1RAs has only been shown in young animals and probably is irrelevant for human type 2 diabetes occurring at older age. Nevertheless, clinical researches showed that GLP-1RAs improved first- and second-phase insulin secretion function in T2DM

patients [45–47]. They also protected islet β-cell function by reducing body weight and visceral fat and promoting brown remodeling of white fat [[68]].

2. SGLT2i: SGLT2i plays a hypoglycemic role by inhibiting the reabsorption of glucose by SGLT2 in the proximal convoluted tubule of the kidney and promoting the excretion of urine glucose. This drug indirectly protects islet β-cell function by reducing body weight, lowering blood pressure, and improving insulin sensitivity, thus relieving oxidative stress and inhibiting chronic inflammation in islet β-cells. Furthermore, SGLT2i promoted GLP-1 secretion of α cells, induced the transformation of α cells into β cells, and activated the differentiation of endocrine precursor cells into β cells [69]. A small-scale study found that the incremental area under the C-peptide curve increased by approximately 61% ± 10%, and the insulin secretion/insulin resistance index increased by 112% ± 20% in T2DM patients after two weeks of empagliflozin treatment [70]. Randomized controlled trials found that 26 weeks of canagliflozin treatment increased HOMA-β by 9.9% ± 2.0% (100 mg/d) and 20% ± 2.0% (300 mg/d) compared to baseline values, significantly decreased the ratio of proinsulin/insulin, and increased the area under the C-peptide curve in the mixed meal tolerance test [71]. Dapagliflozin treatment for 24 weeks increased HOMA-β by 17.0% (95% CI: 12.7 - 21.4%) compared to baseline values in T2DM patients [72].
3. Dipeptidyl peptidase IV inhibitor (DPP-4i): DPP-4i plays a role in regulating blood glucose by inhibiting the degradation of endogenous GLP-1, and its protection of islet β-cell function may mainly depend on GLP-1 [73]. DPP-4 is expressed in human islet β-cells, and its inhibitor MK-0626 could partially prevent the toxic effects of cytokines on nondiabetic β-cells, reduce apoptosis, and improve the ultrastructural defects of β-cells in T2DM patients [74]. Clinical studies have found that different types of DPP4i, including sitagliptin, saxagliptin, and linagliptin, reduced the ratio of proinsulin/insulin and increased HOMA-β in T2DM patients [75]. Linagliptin plus metformin treatment significantly improved β-cell function in T2DM patients compared to metformin treatment alone [76].
4. Glucokinase activator: Dorzagliatin, a novel dual-acting glucokinase activator, improved glycemic control by promoting insulin and GLP-1 secretion and inhibiting glucagon release in a glucose concentration-dependent manner. Animal experiments have shown that Dorzagliatin treatment significantly increased the number of insulin-positive cells and partially restored islet β-cell function [77]. A small-scale exploratory study reported that 28 days of Dorzagliatin treatment resulted in improvement of β-cell function as measured by HOMA-β, which increased by 36.31% and 40.59%, and by dynamic state parameter, ΔC30/ΔG30, which increased by 24.66% and 167.67%, for twice- and once-a-day groups, compared to the baseline value in T2DM patients [78]. Randomized controlled trials revealed that Dorzagliatin treatment improved the glucose disposal index and homeostasis model assessment of insulin resistance index (HOMA-IR) significantly [79]. Two registered clinical phase 3 trials have shown that Dorzagliatin treatment significantly improved the islet β-cell function index (HOMA2-β) of patients with newly diagnosed with T2DM and those with metformin treatment incapable of reaching euglycemia [80,81].
5. Peroxisome proliferator-activated receptor (PPAR) agonist: PPAR includes three subtypes, namely α, γ, and δ. PPARγ participates directly in the regulation of islet β-cell function. In vitro studies have shown that PPARγ activation could reduce the apoptosis of β-cells induced by high glucose [82], and PPARδ activation could alleviate mitochondrial swelling in β-cells induced by palmitic acid and reduce β-cell apoptosis [83]. Animal studies have reported that Chiglitazar sodium, a pan-agonist of PPAR, inhibited islet cell fibrosis, reduced lipid deposition in islets, and increased islet volume effectively [84]. The pan-agonist of PPAR was superior to the PPARγ agonist in terms of clinical efficacy because it exhibited both insulin-sensitizing and lipid-lowering effects. Two randomized controlled trials demonstrated that Chiglitazar sodium significantly reduced fasting plasma insulin, HOMA-IR, and free fatty acid levels, and increased HOMA-β compared to placebo or sitagliptin in T2DM patients [85,86].

III. Alternative protection strategies

Relieving chronic nonspecific low-level inflammation, blocking the local renin-angiotensin-aldosterone system, and improving microcirculation in the islets are helpful strategies in protecting islet β-cell function.

Short-term treatment with anakinra, a recombinant human lL-1 receptor antagonist, decreased the proinsulin/insulin ratio and significantly increased the secretion of C-peptide in T2DM patients; after 39 weeks of anakinra withdrawal, β-cell function continued to improve to some extent [87]. Another clinical study demonstrated that first-phase insulin secretion in patients with impaired glucose tolerance increased by 20% after 4 weeks of anakinra treatment [88]. A meta-analysis showed that canakinumab, an anti-IL-1β antibody, increased the 4-h postprandial C-peptide area under the curve and slightly increased HOMA-β in T2DM patients [89]. Renin-angiotensin II (Ang II) and type 1 Ang II receptor (AT1) are widely distributed in the exocrine and endocrine secretion areas of the human pancreas and play roles in maintaining the physiological function of the pancreas [90]. High levels of Ang II enhanced oxidative stress caused by hyperglycemia and lipidemia and induced apoptosis of β-cells. Aldosterone elicited β-cell dysfunction through a mineralocorticoid receptor-independent mechanism. Valsartan, an action blocker of Ang II, improved the insulin secretion ability of islet β-cells in T2DM patients [91,92]. In addition, animal experiments showed that recombinant human tissue kallikrein-1, a drug for improving microcirculation, significantly increased fasting C-peptide levels in autoimmune diabetic mice [93] and improved islet β-cell function in obese diabetic mice [94].

The possible damage to islet β-cell function due to some drugs in clinical practice should be noted, and the risk-benefit ratio of these drugs should be carefully weighed.

1. Glucocorticoid (GC): Insulin resistance induced by short-term systemic application of GC is often accompanied by the compensatory proliferation of β-cells. Long-term GC treatment may directly interfere with the expression of molecules necessary for glucose metabolism, decrease the transcription of insulin genes, enhance α-adrenergic signals to β-cells, and increase β-cell apoptosis [95].
2. Statins: Long-term use of statins is associated with an increased risk of developing diabetes mellitus. This side effect does not vary with the water or fat solubility, half-life, and metabolic enzymes of statins but is closely related to treatment intensity of statins [96–98]. Statins inhibit the influx of calcium ions induced by glucose, prevent the synthesis of coenzyme Q10 in β-cells, and decrease the intracellular concentration of isoprene, thus inducing insulin secretion dysfunction [99].
3. Immune checkpoint inhibitors (ICPis): Clinically applied ICPis mainly include programmed death receptor 1 (PD-1) inhibitors, programmed death ligand 1 (PD-L1) inhibitors, and cytotoxic T lymphocyte-associated antigen (CTLA-4) inhibitors. ICPis are used for the treatment of unresectable or metastatic melanoma, metastatic non-small cell lung cancer, metastatic small cell lung cancer, advanced renal cell carcinoma, refractory classical Hodgkin's lymphoma, and other tumors. The incidence of diabetes mellitus associated with ICPis therapy (mainly with PD-1/PD-L1 inhibitors) is approximately 1%. Most patients have one or more islet autoantibody. The onset of diabetic ketoacidosis is attributed to rapid and complete deterioration of functional islet β-cell mass caused by ICPis [100].
4. Thiazide diuretics: Thiazide diuretics cause potassium loss in cells, thus disturbing the polarization state of β-cells and leading to insulin secretion dysfunction. Low concentrations of hydrochlorothiazide

directly inhibited glucose-stimulated insulin secretion in isolated islets [101].

5. Beta receptor blockers: Beta receptor blockers can inhibit insulin secretion by blocking beta 2 receptor signal transmission in β-cells [102].

5. Summary and prospects

The onset and progression of T2DM are closely related to islet β-cell dysfunction, and accurate assessment of islet β-cell function contributes to the typing diagnosis of diabetes mellitus and development of individualized treatment regimens. Although many methods can be used to assess islet β-cell function, each method has its own merits and drawbacks, and a single method cannot be a "one size fits all" approach for different populations. Thus, these methods can be used alone or in combination depending on the purpose of β-cell function assessment and the subject's glucose tolerance stage. Antidiabetic regimens and some concomitant drugs have different effects on islet β-cell function. Early intensive insulin therapy and metabolic surgery substantially improved islet β-cell function in newly diagnosed T2DM patients and obese individuals with T2DM, respectively; however, it is still difficult to completely reverse T2DM, and the beneficial effects on islet β-cell function gradually disappear after treatment withdrawal. In the future, it will be necessary to establish a standardized assessment method for islet β-cell function and clarify the roles of related genes and signaling pathways in islet β-cell dysfunction. Precise intervention measures should be implemented for maximal restoration of islet functional β-cells by stimulating endogenous β-cell regeneration.

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Declaration of Competing Interest

All authors declare no conflict of interests.

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