

Standards of care for type 2 diabetes in China

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E-mail: wpjia@yahoo.com

Received: 15 December 2015

Revised: 11 May 2016

Accepted: 9 June 2016

Epidemiology of T2DM in China

Epidemiology of T2DM

The past 30 years have witnessed significant increases in the prevalence of type 2 diabetes mellitus (T2DM) in China. A 1980 epidemiological survey that included 30 000 people from 14 provinces and cities nationwide indicated that the prevalence of diabetes was 0.67% [1]. A 1994–1995 epidemiological survey that included 210 000 people from 19 provinces and cities found that the prevalence of diabetes was 2.5% among individuals who were 25–64 years old (with a population standardized rate of 2.2%) and that the prevalence of impaired glucose tolerance was 3.2% (with a population standardized rate of 2.1%) [2]. A national nutrition survey conducted in 2002, showed that the prevalences of diabetes were 4.5% and 1.8% among people over 18 years in the urban and rural areas, respectively [3]. In 2007–2008, the Chinese Diabetes Society (CDS) performed an epidemiological survey in 14 provinces and cities nationwide. After adopting a weighted analysis that took into account factors such as gender, age, rural and urban distributions and regional differences, the estimated prevalence of diabetes was 9.7% in adults over 20 years of age in China [4], accounting for 92.4 million adults with diabetes (43.1 million rural residents and 49.3 urban residents) (Table 1).

In summary, the current epidemic of diabetes in China shows the following characteristics:

1. T2DM accounts for more than 90% of the overall population with diabetes in China; type 1 diabetes

mellitus (T1DM) accounts for approximately 5.0%, and other types of diabetes account for only 0.7% [5]. Notably, due to lack of reliable data on T1DM incidences and prevalences over the past years in China, further investigation has to be conducted to report the proportion.

2. The prevalences of diabetes appear to be correlated with degree of economic development: in the 1994 survey, the prevalence of diabetes among the high-income group was 2–3 times higher than that of the low-income group [2]. A latest study showed that the prevalence of diabetes in developed regions was still significantly higher than that in under-developed regions, and the prevalence rate in cities was higher than those in rural areas [4].
3. A large proportion of diabetes is undiagnosed: in the 2007–2008 national survey among adult population over 20 years, patient with newly diagnosed diabetes accounted for 60% of total diabetes population.
4. Male gender and low-education levels are risk factors of diabetes: in the 2007–2008 survey, after adjusting for other risk factors, the risk for men were found increased by 26% compared with that for women, and risk of diabetes among people without college education was 57% higher than those with college or higher education [4].
5. Phenotypic characteristics: the average body mass index (BMI) of China's T2DM population is approximately 25 kg/m², whereas the average BMI of Caucasian diabetes population is generally higher than 30 kg/m². In China, there is a larger proportion characterized by postprandial hyperglycaemia. Further, postprandial hyperglycaemia alone accounts for nearly 50% of the overall newly diagnosed population [6].

Table 1. Summary of five nationwide epidemiological surveys of diabetes in China

Year of survey (diagnostic criteria)	Number of surveyed people (10 000)	Age (years)	Prevalence of diabetes (%)	Prevalence of impaired glucose tolerance (%)	Screening method
1980 ^a [1] (Lanzhou standard)	30	Entire population	0.67	—	Urine glucose + 2h PG (steamed bread tolerance test) for screening the high risk subjects
1986 [49] (WHO 1985)	10	25–64	1.04	0.68	2h PG (steamed bread tolerance test) for screening the high risk subjects
1994 [2] (WHO 1985)	21	25–64	2.5	3.2	2h PG (steamed bread tolerance test) for screening the high risk subjects
2002 [3] (WHO 1999)	10	≥18	4.5 (urban) 1.8 (rural)	IFG 2.7 IFG 1.6	FPG screening of the high-risk group
2007–2008 [4] (WHO 1999)	4.6	≥20	9.7	15.5 ^b	One-step OGTT method

1 mmol/L = 18 mg/dL.

FPG: fasting plasma glucose; WHO: World Health Organization; IFG: impaired fasting glucose; OGTT: oral glucose tolerance test; 2 hPG, 2-h postprandial blood glucose; —, no data.

^aDiagnostic criteria are FPG ≥130 mg/dL and/or 2 hPG ≥200 mg/dL and/or more than three items on the OGTT curve that are above the diagnostic criteria [0' 125, 30' 190, 60' 180, 120' 140, and 180' 125 mg/dL, in which 0', 30', 60', 120' and 180' are time points (min), and 30' or 60' is one time point; the glucose measurement uses the o-toluidine method with 100 g of glucose].

^bPrediabetes, including IFG, IGT or both (IFG/IGT).

6. Cardiovascular diseases are common among diabetic patients. Because diabetes population in China shows a shorter disease duration late chronic complications such as diabetic retinopathy and diabetic nephropathy may pose great challenges in the future.

Diagnosis and classification of diabetes mellitus

Diagnosis of diabetes

This guideline recommends the World Health Organization's (WHO) (1999) the criteria for diagnosis and classification of diabetes, and classification of metabolic status (Table 2): either the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) value after a 75-g oral glucose tolerance test (OGTT) can be used alone for epidemiological investigations or mass screenings [7]. However, the data in China include only the FPG levels, resulting in a larger proportion of diabetes being missed. The ideal investigation should simultaneously check FPG and 2-h PG after the glucose load; blood glucose levels at other time points after the OGTT are not used as diagnostic criteria.

Individuals with impaired fasting glucose should undergo the OGTT to reduce the number of missed diabetes diagnoses.

The issue of using HbA_{1c} for diabetes diagnosis

The 2010 American Diabetes Association guidelines added glycated haemoglobin (HbA_{1c}) $\geq 6.5\%$ as a

diagnostic criterion for diabetes [8]. In 2011, the WHO also recommended that wherever conditions permit, countries and regions may consider adopting this cut-off point for diabetes diagnosis [9]. However, given that the HbA_{1c} test is not yet commonly applied in China, the insufficient degree of standardization, and the fact that the instruments and quality control for measuring HbA_{1c} are currently unable to meet the current diagnostic standard for diabetes, this guideline does not recommend the use of HbA_{1c} for diagnosis of diabetes in China. Nevertheless, for hospitals that use a standardized HbA_{1c} assay with a normal reference value of 4.0–6.0% and strict quality control, HbA_{1c} $\geq 6.5\%$ can be used as a reference when diagnosing diabetes.

Classification of diabetes mellitus

This guideline adopts the diabetes aetiology classification system proposed by the WHO (1999), which divides diabetes into four major categories based on aetiological evidence, that is, T1DM, T2DM, gestational diabetes mellitus (GDM) and special types of diabetes.

Primary, secondary and tertiary diabetes prevention

Primary, secondary and tertiary prevention of T2DM

The goal of primary prevention is to prevent the occurrence of T2DM. Secondary prevention aims to prevent diabetic complications in patients with T2DM. Tertiary prevention aims to delay the progression of diabetic complications, to reduce morbidity and mortality and to improve the patients' quality of life.

Strategies for the primary prevention of T2DM

Risk factors and intervention strategies for T2DM

The risk of T2DM depends primarily on the patient's number and degree of risk factors. Some of these factors cannot be changed, whereas others can (Table 3).

Diabetes screening of high-risk populations

Primary prevention efforts for T2DM should adopt hierarchical management approaches based on the differences between the high-risk population and general population. It is not feasible either to screen prediabetes in the entire Chinese population or to systematically identify high risk groups by blood glucose tests, considering the huge

Table 2. Diagnostic criteria for diabetes and prediabetes

Diagnostic methods	Venous plasma glucose level (mmol/L)
(1) Typical symptoms of diabetes (polydipsia, polyuria, polyphagia and weight loss) plus random blood glucose testing	≥ 11.1
or	
(2) Fasting plasma glucose	≥ 7.0
or	
(3) 2 h after the glucose load test Individuals who do not present diabetes symptoms should be re-tested on a separate day.	≥ 11.1

The fasting state refers to not eating for at least 8 h. Random blood glucose refers to the blood glucose level at any time of day regardless of the time of the last meal, which cannot be used to diagnose impaired fasting glucose or impaired glucose tolerance.

Table 3. Risk factors for type 2 diabetes mellitus

Unchangeable risk factors	Changeable risk factors
Age	Prediabetes (impaired glucose tolerance or combined impaired fasting glucose), the most important risk factor
Family history or genetic predisposition	Metabolic syndrome
Ethnicity	Overweight, obesity and depression
History of gestational diabetes mellitus or women with history of delivery of a baby weighing ≥ 4 kg	Excess dietary caloric intake, sedentary or physically inactive
Polycystic ovary syndrome	Use of drugs that can increase the risk of diabetes
Intrauterine growth retardation or premature birth	Social environments that can cause obesity or diabetes

population in China. Therefore, the identification of high-risk groups relies primarily on opportunistic screening (e.g. screening that occurs during routine physical examinations or during treatment for other diseases).

Screening of diabetes benefits the early diagnosis of diabetes and improves the prevention and treatment of diabetes and its complications. Therefore, when conditions permit, high-risk groups should be targeted for diabetes screening.

Definition of the high-risk diabetes group among adults are as follows: adults (>18 years) with one or more of the following diabetes risk factors: (1) age ≥ 40 years, (2) history of impaired glucose regulation, (3) overweight (BMI ≥ 24 kg/m²) or obesity (BMI ≥ 28 kg/m²) and/or central obesity (male waist circumference ≥ 90 cm and female waist circumference ≥ 85 cm), (4) sedentary lifestyle, (5) first-degree relatives with T2DM, (6) women who delivered a baby weighing ≥ 4 kg) or were diagnosed with GDM (7) hypertension [systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg (1 mmHg = 0.133 kPa)] or on therapy for hypertension, (8) dyslipidemia [high-density lipoprotein cholesterol (HDL-C) ≤ 0.91 mmol/L (≤ 35 mg/dL) and triglycerides ≥ 2.22 mmol/L (≥ 200 mg/dL)] or on therapy for hyperlipidemia, (9) atherosclerotic cardiovascular disease, (10) a transient history of steroid diabetes, (11) polycystic ovary syndrome and (12) long-term use of antipsychotics and/or antidepressant treatment. Of the aforementioned factors, impaired glucose regulation is the most important high-risk factor: approximately 5%–10.0% of patients with impaired glucose tolerance progress to T2DM annually [10].

Diabetes screening age and frequency. For adults in the high-risk group, diabetes screening should be performed as early as possible, regardless of age; for populations with no diabetes risk factors other than age, screening should begin at ≥ 40 years of age. For children and adolescents at a high risk for diabetes, screening should begin at age 10 years; however, for individuals with an earlier onset of puberty, this guideline recommends that screening

starts at puberty. Those whose initial screening results are normal are recommended to undergo screening again at least once every 3 years.

Diabetes screening strategy. At medical institutions with a qualified laboratory, diabetes screening is recommended for high-risk patients during their visits or physical examinations.

Diabetes screening method. The fasting blood glucose test is a simple diabetes screening method that should be used for routine screening, albeit there's risk of missing diagnosis. When conditions permit, the OGTT (both FPG and 2-h PG after glucose load) should be performed as often as possible. HbA_{1c} testing is not currently recommended as a routine screening method.

Diabetes screening of the general population. To improve the effectiveness of diabetes screening for the general population, targeted diabetes screening should occur according to the individual's degree of diabetes risk.

T2DM prevention through intensive lifestyle intervention Multiple randomized and controlled studies have shown that people with impaired glucose tolerance can be delayed or prevented from developing to T2DM, through appropriate lifestyle interventions, [11–13]. In a study conducted in Daqing, China, patients in the lifestyle intervention group were asked to increase vegetable intake and reduce intake of alcohol and monosaccharides, and those who were defined as overweight or obese (BMI >25 kg/m²) were encouraged to lose weight, increase intensity of physical activity by performing at least 30 min of moderately intense activity per day. After a 6-year lifestyle intervention, the cumulative incidence of T2DM risk for the subsequent 14 years decreased by 43% [14]. The lifestyle intervention groups in the Finnish Diabetes Prevention Study [15] and the American Diabetes Prevention Program [16] also demonstrated that the intervention could significantly reduce the risk of developing T2DM among patients with impaired glucose tolerance.

This guideline recommends that patients with prediabetes lower the risk of diabetes through diet control and exercise; that patients should receive regular follow-up that provides psychosocial support to ensure patients' long-term adherence to a healthy lifestyle; that blood glucose levels should be regularly tested; that the cardiovascular disease risk factors (such as smoking, hypertension and dyslipidemia) should be closely monitored; and that appropriate intervention measures should be provided. The specific objectives are (1) the BMI of overweight or obese patients should be lowered to approximately 24 kg/m² or weight loss of at least 5–10% should be achieved, (2) the patients' total daily caloric intake should be reduced by at least 400–500 kcal (1 kcal = 4.184 kJ), (3) the patients' saturated fatty acid intake should be less than 30% of their total fatty acid intake and (4) the patients should be encouraged to engage in moderate-intensity physical activity for at least 150 min/week.

T2DM prevention through medical intervention

Drug intervention trials in a pre-diabetic population showed that the oral administration of hypoglycaemic agents, such as metformin, α -glucosidase inhibitors, thiazolidinediones (TZDs), metformin combined with TZDs, the diet pill orlistat and traditional Chinese herbal medicine (Tianqi capsules), reduced the risk of diabetes [13,17–21]. However, because there is no sufficient evidence showing that drug interventions have long-term efficacy and/or health economics benefits, the clinical guidelines developed by various countries have not widely recommended medical interventions as the primary prevention for diabetes. Given that economic development in China is still in the preliminary stage and significant regional imbalances exist and that diabetes prevention-related health care is currently unsophisticated and imperfect, this guideline currently does not recommend the use of drug interventions to prevent diabetes.

Strategies for the secondary prevention of T2DM

Blood glucose control

The clinical trials on intensive glucose control, such as the Diabetes Control and Complications Trial (DCCT) [22], the United Kingdom Prospective Diabetes Study (UKPDS) [23] and the Kumamoto Study in Japan [24], found that among patients in the early stage of diabetes, intensive glucose control can significantly reduce the risk of diabetic microvascular diseases. The UKPDS study also showed that in obese or overweight populations, the use of metformin was correlated with a significant decrease in the risk of myocardial infarction and death [25]. The long-term follow-up studies of the DCCT and UKPDS patient populations indicated that early intensive glycaemic control was correlated with a reduction in diabetic microvascular diseases and a significant

decrease in the risks of myocardial infarction and death [26,27]. These results provide evidence that intensive blood glucose control during the early stages of T2DM can reduce the risks of diabetic macrovascular and microvascular diseases.

This guideline recommends that for newly diagnosed diabetes patients and early T2DM patients, strict glycaemic control strategies should be adopted to reduce the risk of diabetic complications.

Blood pressure control, lipid control and aspirin use

The UKPDS study showed that in patients newly diagnosed with diabetes, intensive blood pressure control not only significantly reduced the risk of diabetic vascular diseases but also the risk of microvascular diseases [28]. An analysis of a subgroup in a trial of hypertensive optimization therapy and other clinical trials of anti-hypertensive therapy also showed that intensive blood pressure control reduced the risk of cardiovascular diseases in diabetic patients without significant vascular complications [28,29]. The British Heart Protection Study–subgroup analysis of diabetic patients [30], the Collaborative Atorvastatin Diabetes Study [31] and other large-scale clinical studies [32] indicated that the use of statins to lower low-density lipoprotein cholesterol (LDL-C) could reduce the risk of cardiovascular diseases in diabetic patients without causing significant vascular complications. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study showed that the combination of statins and lipid-lowering drug did not achieve additional cardiovascular benefits, as compared with statins alone [32]. The results of clinical trials using aspirin for the primary prevention of cardiovascular diseases in diabetic patients varied [33,34]; therefore, whether aspirin has a protective effect in the primary prevention of cardiovascular diseases in diabetes patients remains unclear. Nevertheless, a systematic review of multiple clinical trials demonstrated that among patients with T2DM and cardiovascular disease risk factors, aspirin showed a certain cardiovascular protective effect [35].

This guideline recommends that for T2DM patients without significant diabetic vascular complications but with risk factors for cardiovascular diseases, controlling blood glucose, lowering blood pressure and adjusting lipids (mainly to reduce LDL-C) and aspirin therapy are all useful methods to prevent cardiovascular diseases and diabetic microvascular diseases.

Strategies for the tertiary prevention of T2DM

Blood glucose control

The clinical findings in intensive glucose control trials such as DCCT, UKPDS, Kumamoto, The Action in Diabetes

and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT) suggest that intensive glucose control reduced the progression of diabetic microvascular diseases (e.g. background diabetic retinopathy and microalbuminuria) [22,24,28,36,37].

Among patients who have already developed severe diabetic microvascular diseases, relevant clinical evidence is still necessary to verify whether intensive glucose control measures can reduce the risks of blindness, kidney failure and amputation.

The results of clinical trials such as ADVANCE, ACCORD and VADT all suggest that for patients with a longer duration of diabetes, who are older in age and who have multiple cardiovascular risk factors or cardiovascular diseases, the use of intensive glucose control measures does not reduce the risks of cardiovascular diseases and death. Conversely, the ACCORD study showed that in the aforementioned described population, intensive glucose control was correlated with an increased risk of all-cause mortality [38].

This guideline recommends that for patients who are older and who have a longer diabetes duration and cardiovascular diseases, the pros and cons of adopting intensive glucose control must be cautiously evaluated. In addition, an individualized strategy should be used and, a patient-centred diabetes management system should be developed to determine glycaemic control targets.

Blood pressure control, lipid control and aspirin use

There is sufficient clinical evidence that in patients with T2DM who have had cardiovascular diseases, lowering blood pressure, lowering lipids, or the proper use of aspirin therapy alone or in combination can reduce the risk of cardiovascular disease recurrence and death [35,39–43]. In patients with diabetic nephropathy, the use of blood pressure-lowering agents, particularly the use of angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist drugs, significantly reduced the risk of diabetic nephropathy progression [43].

This guideline recommends that for older patients who have had a long diabetes duration and cardiovascular disease, in terms of individualized glycaemic control, measures such as lowering blood pressure, adjusting lipids (mainly to reduce LDL-C) and taking aspirin should be used to reduce the risk of recurrent cardiovascular diseases and death and to reduce the risk of diabetic microangiopathy.

Diabetes education and management

The risks of microvascular and macrovascular diseases in diabetic patients are significantly higher than in non-

diabetic patients, and reducing these risks in diabetic patients depends not only on controlling high blood glucose but also on addressing other cardiovascular disease risk factors and improving lifestyle. In addition to drug therapy, diabetes control must also monitor blood glucose and other cardiovascular risk factors so as to determine whether the control reaches the target or whether the treatment must be adjusted. Moreover, as diabetes is a lifelong disease, the patient behaviour and self-management ability are keys to successful diabetes control; further, diabetes control is not a treatment in the traditional sense but a management approach in nature.

Objectives of integrated T2DM control and treatment options for high blood glucose

Objectives for comprehensive T2DM control

The ideal comprehensive control of T2DM varies according to the age, comorbidities and complications of patients (Table 4). A treatment that does not achieve the control targets should not be viewed as a failure because any improvement in the control indicators confers benefits to the patient and reduces the risks associated with complications; for example, reductions in HbA_{1c} are closely

Table 4. Targets for the integrated control of type 2 diabetes mellitus in China

Indicator	Target value
Blood glucose (mmol/L) ^a	
Fasting	4.4–7.0
Non-fasting	<10.0
Glycated haemoglobin (%)	<7.0
Blood pressure (mmHg)	<140/80
Total cholesterol (mmol/L)	<4.5
High-density lipoprotein cholesterol (mmol/L)	
Male	>1.0
Female	>1.3
Triglycerides (mmol/L)	<1.7
Low-density lipoprotein cholesterol (mmol/L)	
Not complicated with coronary heart disease	<2.6
Complicated with coronary heart disease	<1.8
Body mass index (kg/m ²)	<24.0
Urinary albumin/creatinine ratio [mg/mmol (mg/g)]	
Male	<2.5 (22.0)
Female	<3.5 (31.0)
Urinary albumin excretion rate [μg/min (mg/dL)]	<20.0 (30.0)
Active aerobic activity (min/week)	≥150.0

^aCapillary blood glucose.

correlated with reductions in microvascular complications and neuropathy.

The primary principle for determining the targets for integrated T2DM control is individualization management, which should comprehensively consider age, disease duration, life expectancy, severity of complications or comorbidities and other relevant factors of patients.

Hypertension is a common complication of diabetes. Younger patients and those with a shorter disease duration may not require much treatment to reduce blood pressure to 130/80 mmHg or less. The target blood pressure value for elderly patients may be adjusted to 150/90 mmHg.

T2DM blood glucose control strategy and treatment options

T2DM is a progressive disease. The blood glucose tends to increase gradually as the disease duration increases; therefore, the intensity of hyperglycaemia control treatment should be increased accordingly. Lifestyle intervention is the basis for T2DM treatment and should be applied throughout the diabetes treatment process. When lifestyle change alone is unable to reach blood glucose target, drug treatment should be initiated. The preferred first-line drug for T2DM is metformin. If no contraindications are present, metformin should remain part of the

diabetes treatment regimen. Patients who could not take metformin may use α -glucosidase inhibitors or insulin secretagogues. When metformin alone is unable to achieve blood glucose target, insulin secretagogues, α -glucosidase inhibitors, dipeptidyl peptidase IV (DPP-4) inhibitors or TZDs (a second-line treatment) can be added. Patients who could not take metformin may undergo combination therapy with other oral medicines. When a combination therapy of two types of oral medicines still unable to achieve blood glucose target, insulin may be added (once-daily basal insulin or once-daily or twice-daily premixed insulin), or a combination of three types of oral medicines may be initiated. Glucagon-like peptide-1 (GLP-1) receptor agonists can be used as a third-line treatment. When basal insulin or premixed insulin combined with other oral medications is still unable to achieve blood glucose target, the regimen should be adjusted to include multiple daily injections of insulin (basal insulin plus prandial insulin or thrice-daily premixed insulin analogues). When treating with premixed insulin and multiple insulin injections, insulin secretagogue use should be discontinued.

Based on the principles mentioned above, and the recommendations of International Diabetes Federation (IDF) [44], the American Diabetes Association (ADA) [45] and National Institute for Health and Clinical Excellence (NICE) [46], the treatment pathways for hyperglycaemia in T2DM are proposed and shown in Figure 1.

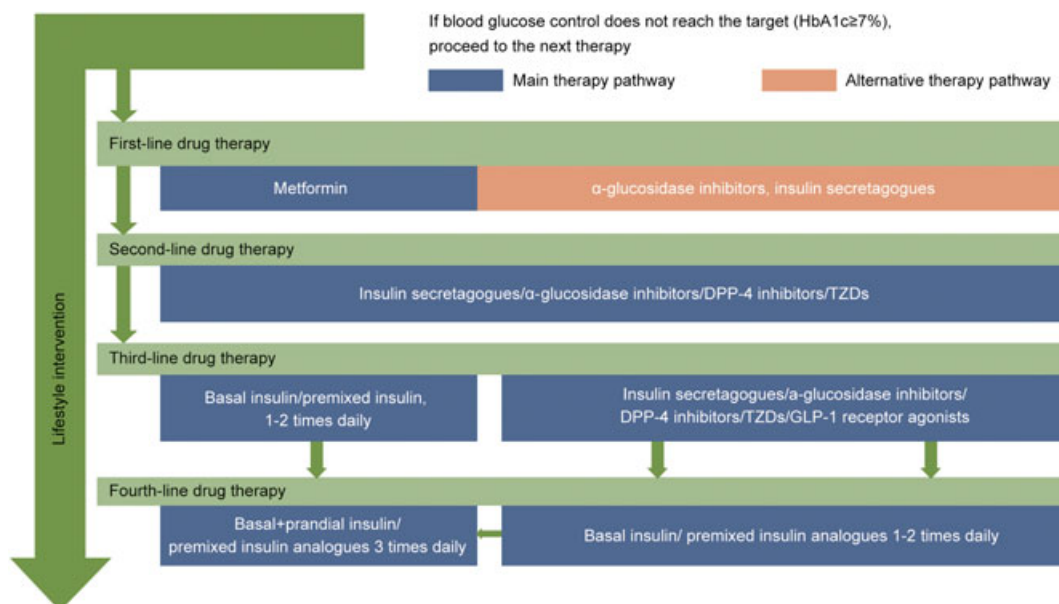


Figure 1. The treatment algorithm for high blood glucose in T2DM. The blue paths are the recommended primary drug treatment paths based on comprehensive considerations, including clinical evidence of the drug's health economics, efficacy and safety and China's national conditions. These paths are similar to the drug treatment pathways recommended by most international diabetes guidelines. The orange paths are alternative paths for the corresponding blue paths. HbA_{1c}, glycated haemoglobin; DPP-4, dipeptidyl peptidase IV; TZD, thiazolidinedione; GLP-1, glucagon-like peptide-1

Medical nutrition therapy for T2DM

Principles of nutrition therapy

Patients with diabetes or prediabetes require individualized medical nutrition therapy. Such treatment should be provided under the guidance of a dietician or an integrated management team (including a diabetes educator) who is familiar with diabetes treatment. To achieve the metabolic control objective for patients and satisfy his or her dietary preference, reasonable quality objects should be established. In order to control the total energy intake and distribute various nutrients in a reasonable and balanced manner, the nutrition status should be evaluated before setting reasonable quality objectives. For overweight or obese patients, this guideline recommends moderate weight loss measures combined with physical exercise and behavioural changes to maintain weight loss outcomes.

Objectives of medical nutrition therapy

- 1 Maintaining a proper body weight: the weight loss goal for overweight/obese patients is 5–10% of body weight in 3–6 months. People who are underweight should recover and maintain an ideal body weight over the long term via a sound nutrition plan.
- 2 Providing balanced nutritious meals.
- 3 Achieving and maintaining an ideal blood glucose level and reducing the HbA_{1c} level.
- 4 Reducing the risk factors for cardiovascular disease, dyslipidemia and hypertension.
- 5 Reducing insulin resistance and pancreatic β -cell load.

Exercise therapy for T2DM

Exercise plays an important role in the comprehensive management of T2DM. Regular exercise increases insulin sensitivity, helps control blood glucose, reduces cardiovascular risk factors, reduces weight and improves overall well-being [47,48]. Moreover, exercise has a remarkable primary preventive effect on populations at high risk of diabetes [49]. Epidemiological studies have shown that the regular exercise of more than 8 weeks reduced the HbA_{1c} level by 0.66% and that the mortality of diabetes patients who adhered to regular exercise for 12–14 years significantly decreases [47].

Smoking cessation

Every diabetic smoker should be advised to stop smoking or using tobacco products. Patients' smoking status and

the extent of nicotine dependence should be assessed. Brief consultations and hotlines for quitting should be provided, and if necessary, medications should be prescribed to help patients quit smoking.

Drug treatments for hyperglycaemia

Oral antihyperglycaemic medications

Medical nutrition therapy and exercise treatment are basic for controlling high blood glucose in T2DM. When diet and exercise cannot effectively control the blood glucose level, medication therapy, including oral medications, should be provided in a timely manner.

T2DM is a progressive disease. During the natural course of T2DM, pancreatic β -cell function gradually decreases, meanwhile insulin resistance undergoes less change. Thus, as T2DM progresses, the reliance on exogenous glycaemic control measures gradually increases. Clinical treatment often requires the use of oral medication and a combination of oral medication and injectable anti-diabetic medications (e.g. insulin and GLP-1 receptor agonists).

Metformin

Metformin hydrochloride is the primary biguanide medication currently used in medical practice. The major pharmacological effect of biguanides is lowering blood glucose by reducing the hepatic glucose output and improving peripheral insulin resistance. The diabetes treatment guidelines of many countries and international organizations recommend metformin as the basic medication among the first-line medications and combinations for control of hyperglycaemia in T2DM [44,45,50]. Systematic reviews of clinical trials have shown that metformin can reduce HbA_{1c} by 1.0–1.5% and can also reduce body weight [51]. The efficacy of metformin has been shown to be separate from the body weight reduction. The UKPDS study results showed that metformin also decreased the likelihood of cardiovascular events and death in obese patients with T2DM [25]. In China, randomized controlled clinical trials have been conducted to investigate the effect of metformin and sulfonylureas on recurrent cardiovascular events in patients with T2DM combined with coronary heart disease, and the results showed that metformin treatment was correlated with a significant reduction of major cardiovascular events. Metformin alone did not cause hypoglycaemia, but the combination of metformin and insulin or insulin secretagogues increased the risk of hypoglycaemia. The main side effect of metformin was gastrointestinal reactions. Starting with a small dose and gradually increasing the dosage was an effective way to reduce adverse

reactions. The efficacy of metformin was unaffected by body weight [52]. The relationship between biguanides and lactic acidosis risk is uncertain [53].

Biguanides are contraindicated in patients with renal insufficiency [serum creatinine >132.6 $\mu\text{mol/L}$ (1.5 mg/dL) for men, >123.8 $\mu\text{mol/L}$ (1.4 mg/dL) for women or estimated glomerular filtration rate (eGFR) <45 mL/min], liver dysfunction, serious infections, hypoxia or those undergoing major surgery. Metformin should be temporarily discontinued for patients undergoing angiography with iodinated contrast agents.

Sulfonylureas

Sulfonylureas are insulin secretagogues, and their main pharmacological effect is increasing the insulin level by stimulating insulin secretion from pancreatic β -cells, therefore lowers the blood glucose level [54]. Clinical trials have shown that sulfonylureas can reduce HbA_{1c} by 1.0–1.5% [55]. At present, sulfonylureas are the primary medications recommended in the diabetes treatment guidelines of many countries and international organizations. Prospective and randomized clinical studies have shown that the use of sulfonylureas was correlated with reduced risks of diabetic microvascular and macrovascular diseases [28]. Currently, the main commercially available sulfonylureas in China are glyburide, glimepiride, gliclazide, glipizide and gliquidone. Sulfonylureas, if used improperly, can lead to hypoglycaemia, particularly in elderly patients and in those with liver and kidney dysfunctions; sulfonylureas may also cause weight gain. Patients with mild renal insufficiency should use gliquidone. Patients who exhibit poor compliance can take sulfonylurea drugs once a day. Xiao Ke Wan is a fixed dose combination drug containing glibenclamide and various traditional Chinese medicines (TCM) that have an antihyperglycaemic effect similar to that of glyburide. Compared with glyburide, Xiao Ke Wan carries a lower risk of hypoglycaemia and yields a more pronounced improvement of diabetes-related TCM symptoms [56].

TZDs

Thiazolidinediones decrease blood glucose primarily by increasing the target cells' sensitivity to the action of insulin. Currently, the main commercially available TZDs in China are rosiglitazone and pioglitazone. Clinical trials have shown that TZDs can decrease HbA_{1c} by 1.0–1.5% [55].

Thiazolidinediones do not cause hypoglycaemia when used alone, but they may increase the risk of hypoglycaemia when used in combination with insulin or insulin secretagogues. Weight gain and oedema are common side effects of TZDs, and these side effects are more remarkable when TZDs are used in combination with insulin. TZD use has been correlated with increase risk of fractures and heart failure [57]. Patients with heart failure (New York Heart

Association heart function classification class II and above), active liver disease, transaminase elevations exceeding 2.5 times the upper limit of normal, and severe osteoporosis and fractures should not take TZDs.

Glinides

Glinides are non-sulfonylurea insulin secretagogues. The currently available glinides in China are repaglinide, nateglinide and mitiglinide. This class of medications reduces postprandial blood glucose by stimulating insulin secretion in the early phase, and they can lower HbA_{1c} by 0.5–1.5% [55]. These medications must be taken immediately before a meal and can be used separately or in combination with other anti-diabetic medications (except sulfonylurea). The systematic reviews of clinical studies conducted on T2DM patients in China showed that in terms of reducing HbA_{1c}, repaglinide was superior to placebo and sulfonylureas and was equivalent to α -glucosidase inhibitors, nateglinide, metformin and TZDs. A systematic review of clinical studies of Asian populations with T2DM, including Chinese people, showed that in terms of reducing HbA_{1c}, nateglinide worked better than α -glucosidase inhibitors and was similar to sulfonylureas, repaglinide and mitiglinide [58]. For newly diagnosed T2DM patients, combination therapy using repaglinide with metformin reduced HbA_{1c} more significantly than repaglinide alone but with a significantly increased risk of hypoglycaemia [59].

Common side effects of glinides are hypoglycaemia and weight gain, but the risk and degree of hypoglycaemia are lower with glinides than with sulfonylureas. Glinides can be used in patients with renal insufficiency.

α -Glucosidase inhibitors

α -Glucosidase inhibitors reduce postprandial blood glucose by inhibiting carbohydrate absorption in the upper small intestine. They are suitable for patients who consume carbohydrates as their main food ingredient and experience postprandial hyperglycaemia. In China, commercially listed α -glucosidase inhibitors include acarbose, voglibose and miglitol. Systematic reviews of clinical studies conducted on the T2DM population, including Chinese patients, showed that α -glucosidase inhibitors could reduce HbA_{1c} by 0.50% and cause weight loss [60]. Clinical studies of Chinese people with T2DM showed that the hypoglycaemic effect of a daily dose of 300 mg of acarbose was equivalent to that of a daily dose of 1500 mg of metformin [61]. α -Glucosidase inhibitors can be combined with biguanides, sulfonylureas, TZDs or insulin.

Common adverse reactions to α -glucosidase inhibitors are gastrointestinal reactions, such as abdominal distension and flatulence. Starting with a small dose and gradually increasing the dosage are effective way to reduce adverse effects. The use of this class alone usually does

not lead to hypoglycaemia and may reduce the risk of preprandial reactive hypoglycaemia; no adjustments in medication dosage and frequency are necessary for elderly patients, no increase in the incidence of hypoglycaemia occurs and this medication is well tolerated. When patients using combination therapy with α -glucosidase inhibitors manifest hypoglycaemia, glucose or honey can be used as treatments; dietary sucrose and starchy foods have a poor ability to correct hypoglycaemia.

DPP-4 inhibitors

Dipeptidyl peptidase IV (DPP-4) inhibitors enhance endogenous levels of GLP-1 by reducing the deactivation of GLP-1 *in vivo* through inhibition of DPP-4. GLP-1 enhances insulin secretion in a glucose concentration-dependent manner and inhibits glucagon secretion. Currently, the commercially available DPP-4 inhibitors in China include sitagliptin, saxagliptin, vildagliptin, linagliptin and alogliptin. Clinical trials in T2DM patients in China showed that sitagliptin, saxagliptin and vildagliptin can reduce HbA_{1c} by 0.70–0.90%, 0.40–0.50% and 0.50%, respectively [62–64]; a comparison study showed that the HbA_{1c}-lowering effect of vildagliptin was similar to that of acarbose [64] and that linagliptin and alogliptin can reduce HbA_{1c} by 0.68% and 0.57–0.68%, respectively. Notably, the HbA_{1c}-lowering extent of DPP-4 inhibitors is related to the patient's baseline HbA_{1c} level, that is, the higher the baseline HbA_{1c} level, the much it will be reduced by DPP-4 inhibitors. The use of DPP-4 inhibitors alone does not increase the risk of hypoglycaemia. DPP-4 inhibitors have a neutral effect on body weight or may increase it. Saxagliptin, alogliptin and sitagliptin do not increase the risk of cardiovascular disease, pancreatitis and pancreatic cancer. When sitagliptin, saxagliptin, alogliptin or vildagliptin is prescribed for patients with renal dysfunction, the dosage must be reduced according to the instructions of medication. When using linagliptin in patients with liver or renal insufficiency, dosage adjustments are unnecessary.

GLP-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists reduce blood glucose by activating GLP-1 receptors. They enhance insulin secretion and inhibit glucagon secretion in a glucose concentration-dependent manner and can delay gastric emptying, thus reducing food intake via central appetite suppression. Currently, in the Chinese domestic market, the available GLP-1 receptor agonists are exenatide and liraglutide, both require subcutaneous injection. GLP-1 receptor agonists effectively lower blood glucose; and also significantly reduce body weight and improve triglycerides and blood pressure. GLP-1 receptor

agonists alone do not significantly increase the risk of hypoglycaemia. Clinical trials of patients with T2DM, including Chinese patients, showed that the HbA_{1c}-lowering effect of liraglutide was similar to that of glimepiride, leading to a body weight loss of 1.8–2.4 kg and a decrease in systolic blood pressure of approximately 3 mmHg [65]; additionally, exenatide reduced HbA_{1c} by 0.8% and body weight by 1.6–3.6 kg [66]. GLP-1 receptor agonists may be used alone or in combination with other oral antihyperglycaemic agents. A number of clinical studies have shown that when used after the failure of an oral antihyperglycaemic agent (metformin or sulfonylurea), GLP-1 receptor agonists showed better efficacy than the active control drug [67]. Common side effects of GLP-1 receptor agonists are gastrointestinal symptoms (e.g. nausea and vomiting), which occur mainly in the initial stage of treatment and gradually diminish with treatment time increased.

Insulin

Initial treatment with insulin

Basal insulin or premixed insulin can be used to initiate insulin therapy.

Short-term intensive insulin therapy programme for newly diagnosed T2DM patients.

For newly diagnosed T2DM patients with HbA_{1c} >9.0% or FPG >11.1 mmol/L and with hyperglycaemic symptoms, short-term intensive insulin therapy may be implemented [68–71]. The appropriate treatment duration is 2 weeks–3 months, with a therapeutic target of 3.9–7.2 mmol/L for fasting blood glucose and \leq 10.0 mmol/L for non-fasting blood glucose, without considering the HbA_{1c} target as treatment objective. Intensive insulin therapy should be combined with medical nutrition, exercise therapy and diabetes education. Intensive insulin treatment regimen include a basal-prandial insulin regimen [multiple subcutaneous insulin injections or continuous subcutaneous insulin infusion (CSII)] or premixed insulin injections two or three times a day.

For patients who fail to achieve treatment goals after short-term intensive insulin therapy, the decision to continue insulin therapy or to switch to another medication should be based on the patient-specific conditions as determined by a diabetes specialist. For patients have reached the therapy target, regular (e.g. every 3 months) follow-up monitoring should be planned; if blood glucose increases again (i.e. FPG >7.0 mmol/L or 2-h PG >10.0 mmol/L), the medication should be re-initiated.

Intensive insulin therapy programme

Multiple subcutaneous insulin injections.

CSII. CSII is a form of intensive insulin therapy delivered via an insulin pump. The main appropriate populations

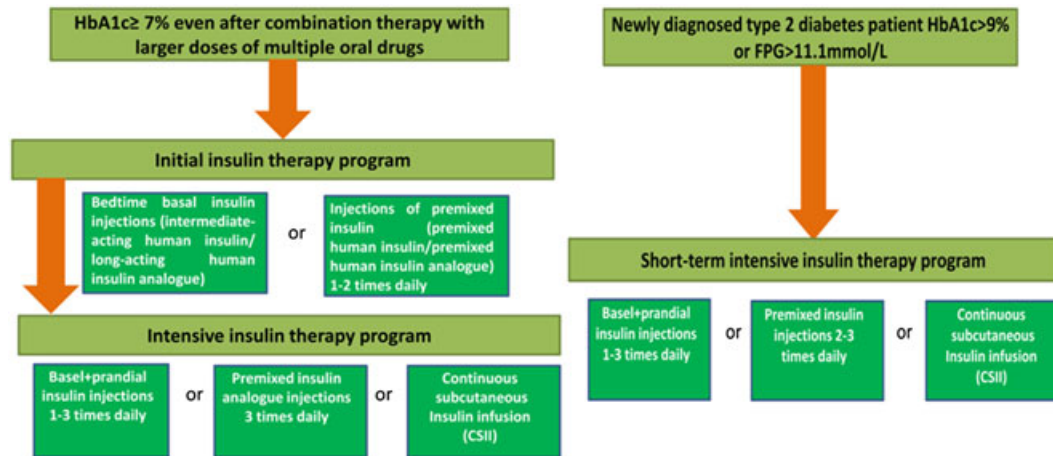


Figure 2. Insulin treatment paths for T2DM. HbA_{1c}, glycated haemoglobin; FPG, fasting plasma glucose; CSII, continuous subcutaneous insulin infusion

are T1DM patients, women with diabetes who are pregnant or expect to become pregnant, pregnant women who require insulin therapy and patients with T2DM who require intensive insulin therapy.

The insulin treatment paths are shown in Figure 2.

Hypoglycaemia

During treatment, patients may experience hypoglycaemia, which may cause discomfort and can be life-threatening. Hypoglycaemia poses a major obstacle to reaching the blood glucose target and warrants special attention.

Bariatric surgery to treat T2DM

Indications for bariatric surgery

Patients with T2DM who are 18 to 60 years old are generally in good condition, have a low surgical risk and are difficult to control the disease or concomitant diseases (HbA_{1c} > 7.0%) after lifestyle interventions and various drug treatments and who meet the following conditions may consider bariatric surgery.

1. Indications: gastrointestinal bariatric surgery is feasible if the patient has a BMI ≥ 32 kg/m² with or without diabetic complications.
2. Precautions: bariatric surgery could be considered with caution for T2DM patients with a BMI of 28–32 kg/m², particularly in the presence of other cardiovascular risk factors.

3. Not recommended: patients with a BMI 25–28 kg/m², with diabetic complications and central obesity (waist circumference >90 cm in men and >85 cm in women) and at least two additional metabolic syndrome components: high triglycerides, low HDL-C and high blood pressure. Surgery should be conducted in strict accordance with study protocol with the patient's informed consent. The operation should be regarded as pure for clinical research and must be approved by the Medical Ethics Committee in advance; currently, evidence is insufficient, and surgery is not recommended as a clinical routine treatment.

Contraindications for bariatric surgery

- 1 Patients abuse drugs, addict to alcohol or have a mental illness that is difficult to control, and who are lack the ability to understand the risks, benefits and expected consequences of bariatric surgery.
- 2 Patients with confirmed, diagnosed T1DM.
- 3 T2DM patients who have a clear failure of pancreatic β -cell function.
- 4 Contraindications for surgery.
- 5 BMI < 25 kg/m².
- 6 GDM and other specific types of diabetes.

Chronic complications of diabetes

Diabetic nephropathy

Approximately 20–40% of diabetic patients suffer from diabetic nephropathy, which is the main cause of renal failure in diabetes patients [72,73].

Diagnosis

Diagnosis of diabetic nephropathy: T1DM-induced renal damage is divided into five stages, which are also used for T2DM-induced renal damage: stage I, elevated glomerular filtration rate and increased renal size; stage II, intermittent microalbuminuria; stage III, early diabetic nephropathy with persistent microalbuminuria; stage IV, clinical diabetic nephropathy with overt albuminuria; and stage V, renal failure. Diabetic nephropathy is an important type of chronic kidney disease; for diabetic nephropathy patients, the eGFR should be calculated using the Modification of Diet in Renal Disease Study equation or the Cockcroft–Gault formula (Table 5) [74–77].

Treatment

1. Lifestyle changes: reasonable weight control, diabetic diet, smoking cessation, proper exercise and so on
2. Low-protein diet.
3. Control blood glucose.
4. Control blood pressure.
5. Correct dyslipidemia.
6. Control proteinuria: starting from the early stages of diabetic nephropathy (microalbuminuria) with or without hypertension, renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist drugs) are the preferred drugs for reducing urinary albumin [78–80]. Because these drugs may also lead to a short-term decline in the GFR in the first 1–2 weeks, serum creatinine and potassium concentrations must be monitored. Renin-angiotensin system inhibitors are not recommended for patients with serum creatinine levels $>265.2 \mu\text{mol/L}$ (3 mg/dL).
7. Dialysis therapy and transplantation: when the eGFR is less than $60 \text{ mL}/(\text{min} \cdot 1.73 \text{ m}^2)$, the potential complications of chronic kidney disease should be assessed and treated. Diabetic patients with kidney failure who require dialysis or transplant treatments should

Table 5. Stages of renal function in CKD

CKD stage	Feature description	eGFR [mL/(min · 1.73 m ²)]
1	Increased GFR or normal GFR with kidney damage ^a	≥ 90
2	Slightly decreased GFR with kidney damage ^a	60–89
3	3a Mild to moderate GFR decrease	45–59
	3b Moderate to severe GFR decrease	30–44
4	Severe GFR decrease	15–29
5	Kidney failure	<15 or dialysis

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.

^aKidney injury is defined as an abnormality in pathological, urine, blood or imaging examinations.

undergo these procedures as soon as possible. Generally, when the GFR drops to 15–20 mL/min or the serum creatinine level is higher than $442 \mu\text{mol/L}$ (5 mg/dL), dialysis, either peritoneal dialysis or haemodialysis, should be prepared. When conditions permit, a kidney or pancreas-kidney transplant could be performed.

Diabetic retinopathy

Diabetic retinopathy is the most common cause of new onset blindness among adults aged 20–74 years.

Screening

Patients with non-proliferative diabetic retinopathy and macular oedema may have no obvious clinical symptoms; therefore, in terms of preventive treatment, regular fundus examinations are particularly important.

Follow-up frequency: diabetic patients without retinopathy are recommended to undergo follow-up check-up once every 1–2 years; patients with mild retinopathy should be checked once a year, and patients with severe retinopathy should be checked once every 3–6 months. The frequency of check-up should be increased for pregnant women.

Diagnosis

Diabetic retinopathy is graded according to the observable indicators after dilation under ophthalmoscope. The international clinical grading standard for diabetic retinopathy is shown in Table 6.

Table 6. International clinical grading standard for diabetic retinopathy (2002)

Disease severity	Observation after dilation under ophthalmoscope
No obvious diabetic retinopathy	No abnormality
NPDR	
Mild	Diabetic microaneurysm only
Moderate	Diabetic microaneurysm with mild or moderate NPDR
Severe	Any of the following, but without PDR
	1. More than 20 intraretinal haemorrhages in any one quadrant
	2. Retinal venous beading in two or more quadrants
	3. Intraretinal microvascular abnormalities in one or more quadrants
Proliferative diabetic retinopathy	One or more of the following: new vessels at the optic disc, vitreous haemorrhage or preretinal haemorrhage

NPDR, non-proliferative diabetic retinopathy.

Treatment

Good control of blood glucose, blood pressure and lipids may prevent or delay the progression of diabetic retinopathy [81,82].

1. Patients with sudden blindness or retinal detachment require an immediate referral to an ophthalmologist; diabetic patients with any degree of macular oedema, severe non-proliferative diabetic retinopathy or any proliferative diabetic retinopathy should be referred to an ophthalmologist with extensive experience in diagnosing and treating diabetic retinopathy.
2. Laser photocoagulation therapy may reduce high-risk proliferative diabetic retinopathy, clinically significant macular oedema and the risk of blindness in some patients with severe non-proliferative diabetic retinopathy [83].
3. Anti-vascular endothelial growth factor therapy may be used to treat patients with diabetic macular oedema [84].
4. Retinopathy is not a contraindication for aspirin therapy; aspirin therapy does not increase the risk of retinal haemorrhage.
5. Fenofibrate may slow the progression of diabetic retinopathy and decrease the need for laser treatment.

Diabetic neuropathy

Diabetic neuropathy is one of the most common chronic complications of diabetes. Neuropathy may affect the central nervous system or, more commonly, the peripheral nerves [85].

Diabetic peripheral neuropathy refers to peripheral nerve dysfunction-related symptoms or signs in diabetic patients that cannot be attributed to other causes. Distal symmetric polyneuropathy is a typical diabetic neuropathy. The diagnosis of other asymptomatic diabetic neuropathies relies on the screening of clinical signs or electrophysiological examination [86].

Prevention

(1) General treatment: good blood glucose control, correction of dyslipidemia and hypertension control. (2) Regular disease screening and evaluation: all patients should undergo screening for diabetic peripheral neuropathy at least once a year after the diagnosis of diabetes. For patients with a long course of diabetes or microvascular complications, such as retinopathy and nephropathy, check-up should occur every 3–6 months. (3) Increased foot care: patients suffering from peripheral neuropathy should receive education about foot care to reduce the incidence of foot ulcers [87].

Etiological therapy

(1) Glycaemic control. (2) Nerve repair: commonly used medications, such as methylcobalamin and growth

factors, may be useful. (3) Anti-oxidative stress: commonly used medications, such as lipoic acid, may be useful. (4) Improved microcirculation: commonly used medications include prostaglandin E1, beraprost natriuretic peptide, cilostazol, pentoxifylline, pancreatic kallikrein, calcium antagonists and blood circulation-promoting TCM [88].

Symptomatic treatment

Medications for the treatment of painful diabetic neuropathy include anticonvulsants (pregabalin, gabapentin, valproate and carbamazepine), antidepressants (duloxetine, amitriptyline, imipramine and citalopram), opioids (tramadol and oxycodone) and capsaicin [87,88].

Lower extremity vascular disease

Lower extremity vascular disease mainly refers to peripheral artery disease; although it is not a complication specific to diabetes, the risk of peripheral artery disease in patients with diabetes significantly increases compared with patients without diabetes. In addition, patients with diabetes also have an earlier age of onset and increased severity of lower extremity vascular disease, as well as more extensive pathology and worse prognoses [82].

Lower extremity arterial disease

Lower extremity arterial disease (LEAD) is a component of peripheral artery disease that manifests as lower extremity arterial stenosis or occlusion.

Screening for diabetic LEAD

For diabetes patients over age of 50 years, LEAD screening should be conducted routinely [89,90]. For diabetes patients with LEAD-associated risk factors (e.g. cardiovascular disease, dyslipidemia, hypertension, smoking or a diabetes duration of more than 5 years) should be screened at least once a year.

For diabetes patients with foot ulcers and gangrene, regardless of their age, a comprehensive examination and evaluation of arterial disease should be conducted.

Diagnosis of diabetic LEAD

(1) If the patient has a resting ABI ≤ 0.90 , regardless of the presence of lower limb discomfort, a LEAD diagnosis should be considered. (2) For a patient who experiences discomfort upon moving and has a resting ABI ≥ 0.90 : if ABI decreases by 15–20% after a treadmill test, a LEAD diagnosis should be considered; (3) if the patient has a resting ABI < 0.40 , or ankle arterial pressure < 50 mmHg or toe arterial pressure < 30 mmHg, a critical limb ischaemia diagnosis should be considered.

Treatment of diabetic LEAD

The therapeutic approach to LEAD includes the prevention of systemic atherosclerotic disease progression, the

prevention of cardiovascular events, the prevention of ischaemic-induced ulcers and gangrene, the prevention of amputation or the reduction of the amputation level and the improvement of the functional status of patients with intermittent claudication. Therefore, the standard treatment for diabetic LEAD consists of three parts: primary prevention (to prevent or delay the occurrence of LEAD), secondary prevention (to relieve symptoms and delay LEAD progression) and tertiary prevention (to promote revascularization and reduce amputation and cardiovascular events).

Prevention and treatment of cardiovascular and cerebrovascular diseases in patients with T2DM

Diabetes is an independent risk factor for cardiovascular and cerebrovascular diseases. Patients with diabetes have

2–4 times higher risk of cardiovascular and cerebrovascular diseases [91–93] compared with patients without diabetes. FPG and postprandial hyperglycaemia are correlated with an increased risk of cardiovascular and cerebrovascular diseases, even when they do not reach the diagnostic criteria for diabetes. Diabetic patients often present important risk factors for cardiovascular and cerebrovascular diseases, such as dyslipidemia and hypertension [94,95].

Clinical evidence suggests that strict glycaemic control in patients with T2DM has a limited effect on reducing the risks of cardiovascular and cerebrovascular diseases and death from those causes, particularly among patients with a longer disease duration, who are older, and who have a history of cardiovascular diseases or multiple cardiovascular risk factors [38]. However, the comprehensive management of multiple risk factors can significantly decrease the risk of cardiovascular and cerebrovascular diseases and death from those

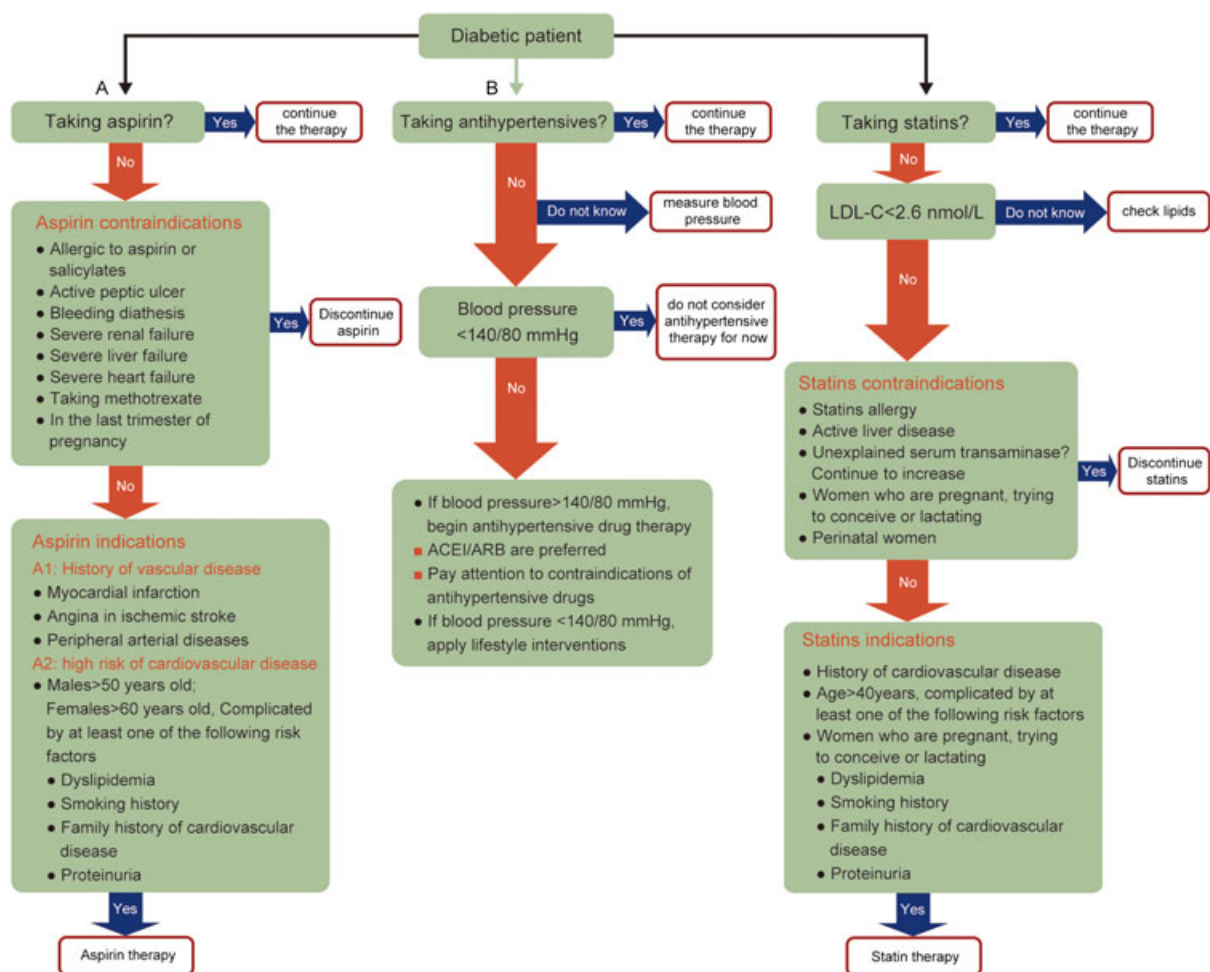


Figure 3. The clinical decision-making paths for screening and the standard lipid-lowering, antihypertensive and antiplatelet treatments for patients with T2DM. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; LDL-C, low-density lipoprotein cholesterol

causes in patients with diabetes. Therefore, the prevention of diabetic vascular diseases requires the comprehensive assessment and control of cardiovascular disease risk factors (e.g. high blood glucose, hypertension and dyslipidemia) and appropriate antiplatelet therapy.

At present, the incidence of cardiovascular risk factors is high among T2DM patients in China, and they are insufficiently controlled. Among outpatients with T2DM, only 5.6% achieved all triple therapeutic goals for HbA_{1c}, blood pressure, and total cholesterol [96]. The use of aspirin has also been low. Clinically, more active screening and treatment of cardiovascular risk factors and an increased rate of aspirin therapy are recommended.

The clinical decision-making paths for screening and the lipid-lowering, antihypertensive and antiplatelet treatments for patients with T2DM are shown in Figure 3.

Metabolic syndrome

Diagnostic criteria for metabolic syndrome

According to an epidemiological analysis of metabolic syndrome in the current Chinese population, this guideline has revised the quantitative indicators of the metabolic syndrome components based on the CDS's 2004 recommendations [97]. The diagnostic criteria are as follows: (1) abdominal obesity: waist circumference: men ≥ 90 cm and women ≥ 85 cm, (2) high blood glucose: fasting blood glucose ≥ 6.1 mmol/L or glucose at 2 h after glucose load ≥ 7.8 mmol/L and/or diabetes diagnosis and treatment, (3) high blood pressure: blood pressure $\geq 130/85$ mmHg and/or diagnosed and on antihypertension therapy, (4) fasting TG ≥ 1.70 mmol/L and (5) fasting HDL-C < 1.04 mmol/L. Patients with three or more of the aforementioned characteristics are diagnosed with metabolic syndrome.

References

- National Diabetes Study Group. A mass survey of diabetes mellitus in a population of 300,000 in 14 provinces and municipalities in China. *Zhonghua Nei Ke Za Zhi* 1981; **20**(11): 678–683.
- Pan XR, Yang WY, Li GW, *et al.*, Prevalence of diabetes and its risk factors in China, 1994. National Diabetes Prevention and Control Cooperative Group. *Diabetes Care* 1997; **20**(11): 1664–1669.
- Li LM, Rao KQ, Kong LZ, *et al.* A description on the Chinese national nutrition and health survey in 2002. *Zhonghua Liu Xing Bing Xue Za Zhi* 2005; **26**(7): 478–484.
- Yang W, Lu J, Weng J, *et al.* Prevalence of diabetes among men and women in China. *N Engl J Med* 2010; **362**(12): 1090–1101.
- Chinese Diabetes Society. China guideline for type 2 diabetes (2010). *Chin J Diabetes* 2012; **20**(1): S1–S36.
- Jia WP, Pang C, Chen L, *et al.* Epidemiological characteristics of diabetes mellitus and impaired glucose regulation in a Chinese adult population: the Shanghai Diabetes Studies, a cross-sectional 3-year follow-up study in Shanghai urban communities. *Diabetologia* 2007; **50**(2): 286–292.
- Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; **15**(7): 539–553.
- Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010; **33**(Suppl 1): S62–S69.
- World Health Organization. Use of glycated haemoglobin (HbA_{1c}) in the diagnosis of diabetes mellitus: abbreviated report of a WHO consultation. 2011.
- Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet Med* 2002; **19**: 708–723.
- Knowler WC, Barrett-Connor E, Fowler SE, *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**(6): 393–403.
- Tuomilehto J, Lindstrom J, Eriksson JG, *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; **344**(18): 1343–1350.
- Chiasson JL, Josse RG, Gomis R, *et al.* Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002; **359**(9323): 2072–2077.
- Li G, Zhang P, Wang J, *et al.* The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 2008; **371**(9626): 1783–1789.
- Lindstrom J, Ilanne-Parikka P, Peltonen M, *et al.* Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 2006; **368**(9548): 1673–1679.
- Knowler WC, Fowler SE, Hamman RF, *et al.* 10-Year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009; **374**(9702): 1677–1686.
- Lian F, Li G, Chen X, *et al.* Chinese herbal medicine Tianqi reduces progression from impaired glucose tolerance to diabetes: a double-blind, randomized, placebo-controlled, multicenter trial. *J Clin Endocrinol Metab* 2014; **99**(2): 648–655.
- Torgerson JS, Hauptman J, Boldrin MN, *et al.* XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004; **27**(1): 155–161.
- Gerstein HC, Yusuf S, Bosch J, *et al.* Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006; **368**(9541): 1096–1105.
- DeFronzo RA, Tripathy D, Schwenke DC, *et al.* Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med* 2011; **364**(12): 1104–1115.
- Zinman B, Harris SB, Neuman J, *et al.* Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study. *Lancet* 2010; **376**(9735): 103–111.
- The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus.

- The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; **329**(14): 977–986.
23. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. *Diabetes* 1995; **44**(11): 1249–1258.
 24. Shichiri M, Kishikawa H, Ohkubo Y, et al. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care* 2000; **23**(Suppl 2): B21–B29.
 25. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; **352**(9131): 854–865.
 26. Holman RR, Paul SK, Bethel MA, et al. 10-Year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359**(15): 1577–1589.
 27. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; **353**(25): 2643–2653.
 28. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; **317**(7160): 703–713.
 29. Snow V, Weiss KB, Mottur-Pilson C. The evidence base for tight blood pressure control in the management of type 2 diabetes mellitus. *Ann Intern Med* 2003; **138**(7): 587–592.
 30. Collins R, Armitage J, Parish S, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; **361**(9374): 2005–2016.
 31. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364**(9435): 685–696.
 32. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**(17): 1563–1574.
 33. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008; **300**(18): 2134–2141.
 34. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; **373**(9678): 1849–1860.
 35. Zhang C, Sun A, Zhang P, et al. Aspirin for primary prevention of cardiovascular events in patients with diabetes: a meta-analysis. *Diabetes Res Clin Pract* 2010; **87**(2): 211–218.
 36. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**(24): 2560–2572.
 37. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360**(2): 129–139.
 38. Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes Trials: a position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association. *J Am Coll Cardiol* 2009; **53**(3): 298–304.
 39. Pignone M, Alberts MJ, Colwell JA, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. *Diabetes Care* 2010; **33**(6): 1395–1402.
 40. Sever PS, Poulter NR, Dahlof B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm (ASCOT-LLA). *Diabetes Care* 2005; **28**(5): 1151–1157.
 41. Shepherd J, Barter P, Carmena R, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. *Diabetes Care* 2006; **29**(6): 1220–1226.
 42. Cooper-DeHoff RM, Gong Y, Handberg EM, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA* 2010; **304**(1): 61–68.
 43. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**(19): 2560–2572.
 44. IDF Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes: recommendations for standard, comprehensive, and minimal care. *Diabet Med* 2006; **23**(6): 579–593.
 45. American Diabetes Association. Standards of medical care in diabetes – 2010. *Diabetes Care* 2010; **33**(Suppl 1): S11–S61.
 46. CG NIFH. National Institute for Health and Clinical Excellence. Type 2 diabetes: the management of type 2 diabetes. NICE clinical guideline 66[DB/OL]. (2008-05-12)[2013-11-12].
 47. Boule NG, Haddad E, Kenny GP, et al. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* 2001; **286**(10): 1218–1227.
 48. Snowling NJ, Hopkins WG. Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. *Diabetes Care* 2006; **29**(11): 2518–2527.
 49. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 1997; **20**(4): 537–544.
 50. Shimizu T, Nathan DM, Buse JB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Nihon Rinsho* 2012; **70**(Suppl 3): 591–601.
 51. Saenz A, Fernandez-Esteban I, Mataix A, et al. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2005; **3**: D2966.
 52. Ji L, Li H, Guo X, et al. Impact of baseline BMI on glycemic control and weight change with metformin monotherapy in Chinese type 2 diabetes patients: phase IV open-label trial. *PLoS One* 2013; **8**(2): e57222.
 53. Salpeter SR, Greyber E, Pasternak GA, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2010; **4**: D2967.
 54. Groop LC. Sulfonylureas in NIDDM. *Diabetes Care* 1992; **15**(6): 737–754.
 55. Sherifali D, Nerenberg K, Pullenayegum E, et al. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. *Diabetes Care* 2010; **33**(8): 1859–1864.
 56. Ji L, Tong X, Wang H, et al. Efficacy and safety of traditional Chinese medicine for diabetes: a double-blind, randomised, controlled trial. *PLoS One* 2013; **8**(2): e56703.
 57. Hernandez AV, Usmani A, Rajamanickam A, et al. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. *Am J Cardiovasc Drugs* 2011; **11**(2): 115–128.
 58. Cai X, Luo Y, Han X, et al. Meta-analysis of efficacy and safety of nateglinide in Asian type 2 diabetes. *Chin J Diabetes* 2013; **21**(10): 913–917.
 59. Wang W, Bu R, Su Q, et al. Randomized study of repaglinide alone and in combination with metformin in Chinese subjects with type 2 diabetes naive to oral antidiabetes therapy. *Expert Opin Pharmacother* 2011; **12**(18): 2791–2799.
 60. Cai X, Han X, Luo Y, et al. Comparisons of the efficacy of alpha glucosidase

- inhibitors on type 2 diabetes patients between Asian and Caucasian. *PLoS One* 2013; **8**(11): e79421.
61. Yang W, Liu J, Shan Z, *et al.* Acarbose compared with metformin as initial therapy in patients with newly diagnosed type 2 diabetes: an open-label, non-inferiority randomised trial. *Lancet Diabetes Endocrinol* 2014; **2**(1): 46–55.
 62. Mohan V, Yang W, Son HY, *et al.* Efficacy and safety of sitagliptin in the treatment of patients with type 2 diabetes in China, India and Korea. *Diabetes Res Clin Pract* 2009; **83**: 106–116.
 63. Dhillon S, Weber J. Saxagliptin. *Drugs* 2009; **69**: 2103–2114.
 64. Pan C, Yang W, Barona JP, *et al.* Comparison of vildagliptin and acarbose monotherapy in patients with type 2 diabetes: a 24-week, double-blind, randomized trial. *Diabet Med* 2008; **25**(4): 435–441.
 65. Yang W, Chen L, Ji Q, *et al.* Liraglutide provides similar glycaemic control as glimepiride (both in combination with metformin) and reduces body weight and systolic blood pressure in Asian population with type 2 diabetes from China, South Korea and India: a 16-week, randomized, double-blind, active control trial(*). *Diabetes Obes Metab* 2011; **13**(1): 81–88.
 66. DeFronzo RA, Ratner RE, Han J, *et al.* Effects of exenatide (exendin-4) on glycaemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005; **28**(5): 1092–1100.
 67. Gao Y, Yoon KH, Chuang LM, *et al.* Efficacy and safety of exenatide in patients of Asian descent with type 2 diabetes inadequately controlled with metformin or metformin and a sulphonylurea. *Diabetes Res Clin Pract* 2009; **83**(1): 69–76.
 68. Weng J, Li Y, Xu W, *et al.* Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet* 2008; **371**(9626): 1753–1760.
 69. Li Y, Xu W, Liao Z, *et al.* Induction of long-term glycaemic control in newly diagnosed type 2 diabetic patients is associated with improvement of beta-cell function. *Diabetes Care* 2004; **27**(11): 2597–2602.
 70. Zhu F, Ji L, Han X, *et al.* Induction of long-term good glycaemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. *Chin J Diabetes* 2003; **11**(1): 5–9.
 71. Weng J, Li Y, Xu W, *et al.* The effects of short-term continuous subcutaneous insulin infusion treatment on beta-cell function in newly diagnosed type 2 diabetic patients. *Chin J Diabetes* 2003; **11**(1): 10–15.
 72. Lu B, Song X, Dong X, *et al.* High prevalence of chronic kidney disease in population-based patients diagnosed with type 2 diabetes in downtown Shanghai. *J Diabetes Complications* 2008; **22**(2): 96–103.
 73. Kramer H, Molitch ME. Screening for kidney disease in adults with diabetes. *Diabetes Care* 2005; **28**(7): 1813–1816.
 74. Tervaert TW, Mooyaart AL, Amann K, *et al.* Pathologic classification of diabetic nephropathy. *J Am Soc Nephrol* 2010; **21**(4): 556–563.
 75. Lu B, Gong W, Yang Z, *et al.* An evaluation of the diabetic kidney disease definition in Chinese patients diagnosed with type 2 diabetes mellitus. *J Int Med Res* 2009; **37**(5): 1493–1500.
 76. Ma YC, Zuo L, Chen JH, *et al.* Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006; **17**(10): 2937–2944.
 77. Dong X, He M, Song X, *et al.* Performance and comparison of the Cockcroft–Gault and simplified modification of diet in renal disease formulae in estimating glomerular filtration rate in a Chinese type 2 diabetic population. *Diabet Med* 2007; **24**(12): 1482–1486.
 78. Lindholm LH, Ibsen H, Dahlof B, *et al.* Cardiovascular morbidity and mortality in patients with diabetes in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**(9311): 1004–1010.
 79. Lewis EJ, Hunsicker LG, Clarke WR, *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345**(12): 851–860.
 80. Parving HH, Lehnert H, Brochner-Mortensen J, *et al.* The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001; **345**(12): 870–878.
 81. Chew EY, Ambrosius WT. Update of the ACCORD eye study. *N Engl J Med* 2011; **364**(2): 188–189.
 82. Standards of medical care in diabetes – 2012. *Diabetes Care* 2012; **35**(Suppl 1): S11–S63.
 83. Keech AC, Mitchell P, Summanen PA, *et al.* Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 2007; **370**(9600): 1687–1697.
 84. Wilkinson CP, Ferris FR, Klein RE, *et al.* Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology* 2003; **110**(9): 1677–1682.
 85. Veves A, Backonja M, Malik RA. Painful diabetic neuropathy: epidemiology, natural history, early diagnosis, and treatment options. *Pain Med* 2008; **9**(6): 660–674.
 86. Jia WP, Shen Q, Bao YQ, *et al.* Evaluation of the four simple methods in the diagnosis of diabetic peripheral neuropathy. *Zhonghua Yi Xue Za Zhi* 2006; **86**(38): 2707–2710.
 87. Boulton AJ, Vinik AI, Arezzo JC, *et al.* Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 2005; **28**(4): 956–962.
 88. Zin CS, Nissen LM, Smith MT, *et al.* An update on the pharmacological management of post-herpetic neuralgia and painful diabetic neuropathy. *CNS Drugs* 2008; **22**(5): 417–442.
 89. Lange S, Diehm C, Darius H, *et al.* High prevalence of peripheral arterial disease and low treatment rates in elderly primary care patients with diabetes. *Exp Clin Endocrinol Diabetes* 2004; **112**(10): 566–573.
 90. Guan H, Li YJ, Xu ZR, *et al.* Prevalence and risk factors of peripheral arterial disease in diabetic patients over 50 years old in China. *Chin Med Sci J* 2007; **22**(2): 83–88.
 91. Buse JB, Ginsberg HN, Bakris GL, *et al.* Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 2007; **30**(1): 162–172.
 92. Morrish NJ, Wang SL, Stevens LK, *et al.* Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 2001; **44**(Suppl 2): S14–S21.
 93. Nakagami T. Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin. *Diabetologia* 2004; **47**(3): 385–394.
 94. Lawes CM, Parag V, Bennett DA, *et al.* Blood glucose and risk of cardiovascular disease in the Asia Pacific region. *Diabetes Care* 2004; **27**(12): 2836–2842.
 95. Hypertension in Diabetes Study (HDS): I. Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. *J Hypertens* 1993; **11**(3): 309–317.
 96. Ji L, Hu D, Pan C, *et al.* Primacy of the 3B approach to control risk factors for cardiovascular disease in type 2 diabetes patients. *Am J Med* 2013; **126**(10): 911–925.
 97. Chinese Diabetes Society: Metabolic Syndrome Cooperative Study Group. The suggestion about metabolic syndrome from Chinese diabetes society. *Chin J Diabetes Mellitus* 2004; **12**(3): 156–161.