Research Paper

A Review on Pathophysiology, Epidemiology and Current Management Strategies of Type-2 Diabetes Mellitus in Adults

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Abstract

Type 2 diabetes (T2D) is a disease characterized by heterogeneously progressive loss of islet β cell insulin secretion usually occurring after the presence of insulin resistance (IR) and it is one component of metabolic syndrome (MS), and we named it metabolic dysfunction syndrome (MDS). The pathogenesis of T2D is not fully understood, with IR and β cell dysfunction playing central roles in its pathophysiology. Dyslipidemia, hyperglycemia, along with other metabolic disorders, results in IR and/or islet β cell dysfunction via some shared pathways, such as inflammation, endoplasmic reticulum stress (ERS), oxidative stress, and ectopic lipid deposition. If prevention fails, holistic and personalized management should be taken as soon as possible through timely detection and diagnosis, considering target organ protection, comorbidities, treatment goals, and other factors in reality. In this review, we aim to summarize the underlying mechanism, screening, diagnosis, prevention, and treatment of T2D, especially regarding the personalized selection of hypoglycemic agents and holistic management based on the concept of "MDS-related TOD".

Keywords: Type 2 Diabetes Mellitus, Insulin Resistance, Epidemiology, Glycemic Control, Management

Introduction

Diabetes is a metabolic disease that results from effects in the secretion or activity of insulin within a person's body. Diabetes has many potential health complications, including coronary heart disease, stroke, peripheral vascular disease, blindness, kidney disease, and lower-extremity amputation.

There are three basic types of diabetes: Type 1 diabetes, which most often strikes children and young adults, occurs when the destruction of pancreatic cells causes insulin deficiency. Type 2 diabetes, which accounts for 85 percent to 95 percent of all cases, is usually characterized by insulin resistance when the body no longer uses insulin properly. A third type is gestational diabetes, which appears only during pregnancy[1, 2]

The rapidly escalating prevalence of diabetes is related to several factors, including the alarming increase in obesity[3] due largely to sedentary lifestyle and high-fat diets, and the aging population. More than 85% of individuals with diabetes mellitus have type 2 diabetes, and the lifetime risk of developing this disorder approaches 20% in the United States[4]. Results from the Third National Health and Nutrition Examination Survey estimated the prevalence of type 2 diabetes in adults (>20 years) at 5.1%, undiagnosed cases at 2.7%, and impaired glucose tolerance (IGT) at 6.9% (based on fasting plasma glucose values)[5]. These statistics are especially disturbing in light of the fact that diabetes is the leading cause of new cases of blindness, end-stage renal disease, and lower extremity amputation and, with nearly 50% of diabetes-related mortality being caused by cardiovascular disease, contributes substantially to cardiovascular death in the United States[6] The long-term complications associated with diabetes (including micro vascular and macro vascular diseases) have been reviewed extensively [7,8,9,10].

1.1 Pathophysiology and Natural History of Type 2 Diabetes Mellitus

Type 2 diabetes is characterized by 2 major pathophysiologic defects: insulin resistance, which results in increased hepatic glucose production (HGP) and decreased glucose disposal, and impaired β-cell secretory function (both basal and glucose stimulated) [11] Loss of the acute insulin response to a carbohydrate load, a prototypical defect that occurs early in the natural course of the disease, generally when fasting plasma glucose levels reach 115 mg/dL[12] leads to postprandial hyperglycemia. By the time fasting plasma glucose levels reach 140 mg/dL, 75% of β -cell function has been lost.

In animal models, deposition of amyloid, a product of islet-amyloid polypeptide normally produced in the βcell and secreted along with insulin, has been associated with progressive loss of β -cell function and mass[13] Whether amyloid deposition contributes to worsening β -cell function in patients with type 2 diabetes remains unclear.

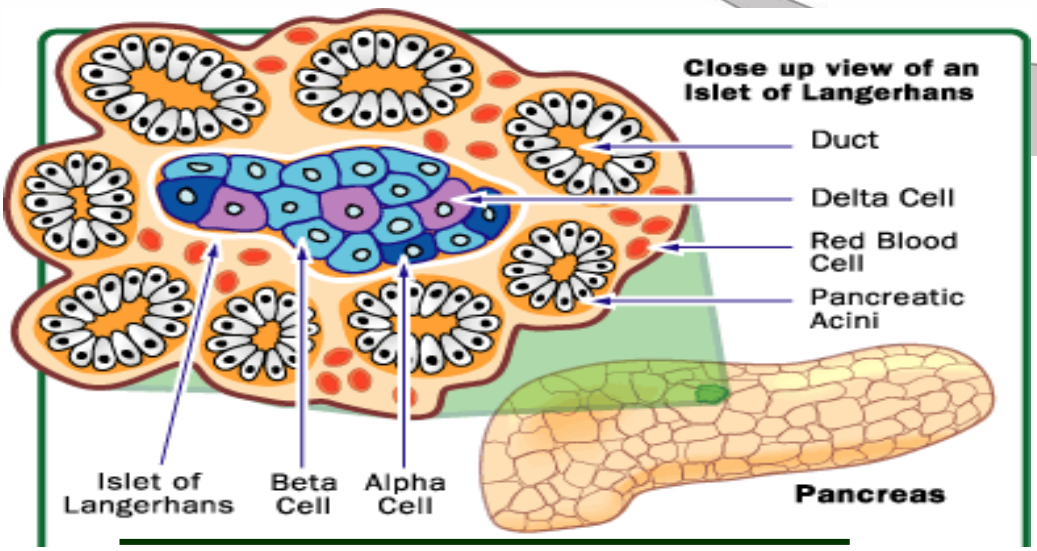


Figure 1. Histopathology of Pancreas

Insulin resistance in the hepatocyte and peripheral tissues, particularly skeletal muscle, leads to unrestrained HGP and diminished insulin-stimulated glucose uptake and utilization [14,15]. The underlying mechanism may be related to defects in insulin receptor binding, decreased numbers of insulin receptors, or post receptor attenuation of insulin action [15]

Hyperglycemia itself further impairs insulin secretion and increases insulin resistance, in part by down regulation of the glucose transport system in β-cells and insulin-sensitive tissues. These effects of chronically elevated blood glucose levels are referred to as *glucose toxicity* [15]. In addition, the high circulating free fatty acid levels associated with diabetes further aggravate insulin resistance and may adversely affect β -cell secretion, a phenomenon known as *lipotoxicity*. [16]

Table 1. Diabetes treatment goals

Parameter	Normal	ADA	ACE/AACE
Plasma glucose (mg/dL)			
Preprandial	<110	90–130	<110
Postprandial	<140+	<180	<140+
Glycosylated hemoglobin A1c (%)	<6.0	<7.0	<6.5

Note: *AACE = American Association of Clinical Endocrinology; ACE = American College of Endocrinology; ADA = American Diabetes Association.+ Two-hour postprandial.*

1.4 Increased blood-sugar levels and risk of Type-2 diabetes

Symptoms of high blood-sugar, and diabetes:

• Feeling thirsty or excessively hungry
• Feeling tired
• Low concentration
• Blurred vision
• Unexplained weight loss
• Frequent need to urinate
• Slow healing of cuts
• Tingling in hands or feet (neuropathy)
• Nausea and vomiting

1.5 Risk factors for abnormal glucose

• Liver damage or co-infection with Hep-C
• Family history of diabetes
• Overweight (BMI>30)
• Lipodystrophy or lipoatrophy
• Low exercise
• Age over 40
• High blood pressure
• High cholesterol and triglycerides and low HDL (good) cholesterol
• History of insulin resistance or high glucose

• Other meds, including niacin, glucocorticoids, megestrol and Growth Hormone and Some PIs.[17]
Type 1 DM usually develops before adulthood and the patients require exogenous insulin therapy to live. Type 2 DM typically develops later in life and in this condition normal (or even excessive) insulin secretion is insufficient to compensate for the developing insulin resistance.
Type 2 DM is a progressive disease where the symptomatic phase is preceded by a preliminary phase of impaired glucose tolerance. Type 2 DM is associated with obesity, and treatment of the obese patient should be started with changes in diet, increased exercise and weight reduction [18,19]

Table 2. American diabetes association goals for glycemic control (American Diabetes Association*; Diabetes Care.* 1998)[20, 21]

Biochemical Index	Normal	Goal	Action Suggested
Fasting preprandial plasma glucose level (mg/dL)	<110	80–120	<80 or >140
Bedtime plasma glucose level (mg/dL)	<120	100–140	<100 or >160
Hemoglobin A1c (%)	4–6	<7	>8

Management of the disease usually requires stepwise adjustment of drug therapy in addition to lifestyle changes. If treatment with one oral antidiabetic fails, then a different type of drug or a combination of different agents with complementary modes of action may improve the situation, but patients may ultimately need insulin injections as the disease advances. Tight glycemic control in type 2 DM is important in the prevention complications, but the management of dyslipidaemia (with e.g. a statin or fibrate) is also crucial for hyperlipidaemic diabetic patients.

Epidemiology

Diabetes has become a worldwide health burden due to its high incidence, disability and mortality, which is estimated to be the eighth leading cause of death combined disability.[23,24] It isestimated that the annual global health care spending on diabetes among people aged 25–75 was 537 million in 2023, and is estimated to reach more than 783 million by 2045.[25] In 2021, there were 530 million people of all ages in worldwide living with diabetes, and the global age-standardized prevalence is 6.2%, which increased by 90.5% from 3.2% in 1990, and is expected to reach 9.8%, affecting 13.1 billion people. It is noteworthy that T2D accounts for more than 96% of all.[23] T2D is a complex multifactorial polygenetic disease that can attribute to many risk factors. Preobesity/obesity are major risk factors for T2D. In 2021, high BMI contribute more than 50% of global T2D disability-adjusted life year (DALY).[23] Mounting evidence show association between T2D and gender difference.[26] The global age-standardized diabetes prevalence was higher in males than in females in 2021, with a male-to-female ratio of 1.14 despite it varied from regions.[23] Age is also an important risk factor for T2D. The global diabetes prevalence peaked in group aged 75–79 years, at 24.4% while less than 1% in group age under 20 years.[23] Other factors such as dietary risks, environmental or occupational risks, tobacco use, low physical activity alcohol use all account for part of the risk of T2D.3 In addition, genetics also play a modest but true role in T2D risk. Studies showed that the estimates of the heritability of T2D range from 30% to 70%, depending on the age of diabetes onset and the glycemic status of cases.[26] For now, more than 100 T2D susceptibility genes have been mapped in human including TCF7L2, GCK, KCNJ11, PPARG.[26] MDS-related TOD including macrovascular diseases and micro vascular complications, such as chronic kidney disease (CKD), retinopathy, neuropathy, along with diabetic foot ulcerations (DFU), are responsible for much of the burden associated with diabetes.[27] CKD, which has been recognized as primary factors contributing to elevated mortality and DALYs among diabetic patients,9 occurs in 20–40% diabetic patients and it's still rising. It is estimated approximately 50% and 34% of patients with diabetes will be affected by diabetic neuropathy (DN) and DFU over the course of their lifetime, respectively.[29,30] About 20% of people with a DFU will undergo a lower extremity amputation and the 5-year mortality rate for them is greater than 70%.10 Diabetic retinopathy (DR), occurred in 22% of diabetes patients and 6% suffer from vision threatening DR which might lead to irreversible vision impairment even blindness.[31]

Diagnosis And Screening

The diagnostic criteria for diabetes are internationally consistent. Both the ADA and the World Health Organization (WHO) have adopted fasting blood glucose (FBG) mean before meal, 2-hour postprandial blood glucose (2-h PG), and random blood glucose levels as diagnostic criteria for diabetes mellitus; later, HbA1c was included in the diagnostic criteria for expanded screening. The diagnostic cutoff points are shown in Table 1. And recently, International Diabetes Federation (IDF) state that people with 1-hour postprandial glucose (1-h PG)≥8.6mmol/L are considered to be have prediabetes while ≥11.6 mmol/L to have diabetes.[32] However, for prediabetes, which is defined as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), the diagnostic scope of the WHO and ADA for FBG and HbA1c are not completely consistent. In addition, the WHO divides individuals with prediabetes into two groups (IFG or IGT) without distinguishing between those

with both IFG and IGT (IGF +IGT), while the ADA divides those individuals into three groups (IFG, IGT, IGF+IGT). Our meta analysis revealed that patients with prediabetes and IGF + IGT have a greater risk of T2D, suggesting that it is more reasonable to classify prediabetes into three subtypes, as ADA does.[33] T2D has long been found mostly in adults, but it is increasingly common in adolescents and children due to the increase in obesity in these individuals.[34] It is important to note that we set absolute blood glucose cutoff points, but blood glucose abnormalities and the risk of developing T2D are continuous processes. A meta-analysis of 16 studies showed that for people with HbA1c between 5.5–6%, the 5-year risk of developing diabetes is 9–25%, while for people with HbA1c between 6–6.5%, the 5-year risk increases to 25–50%.[35] The Whitehall II cohort study showed a linear trend in glycemic trajectories during the natural onset of T2D, with a sharp increase in blood glucose 2 years before T2D.[36] Baseline characteristics at diagnosis of T2D might be used to predict early glycemic deterioration followed by more aggressive interventions. A study revealed that baseline characteristics such as younger age .

Prevention

In study showed that people with prediabetes are already at a steep end of the glycemia trajectory,[36] which means that blood glucose is likely to increase at an accelerated rate and progress to T2D. In addition, people with prediabetes already exhibit a loss of islet β cells and impairment of target tissues. Approximately 40–50% of islet β cell function is lost in individuals with prediabetes,[37] and approximately 10% of people with prediabetes develop DR or polyneuropathy.[38,39] Therefore, aggressive actions are necessary and important for preventing T2D in people at high risk (such as those with an HbA1c>6%). Lifestyle intervention Several major trials have shown some effective interventions to prevent the occurrence of T2D and even reduce the risk of TOD. Intensive lifestyle interventions, including physical activities and individualized medical nutrition treatment (MNT), have been proven to be highly effective at preventing diabetes. Exercise, diet or a combination of both can reduce T2D risk by 30–60% according to large-scale RCT trials (the IDPP, DPP, FDPS, and Da Qing trials), and the variation in the reduction rate may be due to differences in the population in those trials, while people with a greater BMI and older age had a greater reduction in T2D risk.[40-43]Weight loss is an important factor in intensive lifestyle intervention since both the DPP and FDPS trials set a goal for weight loss achieved by physical activities and a calorie-reduced diet. As shown in the DPP, for every kilogram of weight loss, the risk of T2D was reduced by 16%.[44] There is also evidence that physical activity and nutrition have preventive effects and metabolic improvement independent of body weight.

Conclusion And Perspective

It is hoped that this review and our idea can provide a reference for most newly diagnosed patients with T2D receiving hypogly cemic therapy. The mechanism of T2D is not fully understood, and there is no cure yet. However, as mentioned earlier, T2D and MDS related TOD are preventable, and effective measures must be taken to prevent the occurrence of diabetes, such as the prevention and treatment of preobesity and obesity and MASLD, which will greatly reduce the occurrence of T2D. If diabetes prevention fails, early detection should be emphasized. Once diabetes is diagnosed, holistic management of organ protection targeting MDS should be provided since most patients with T2D also have MDS. Due to the article layout limitation, we did not specifically address the prevention and treatment of hypergly cemic crises, DKA or the hyperosmolar hyperglycemic state (HHS). Diabetes treatment available for elderly individuals or those with gestational diabetes was not covered in this review. We also did not discuss much about the management of patients with T2D and CVD. We believe that T2D as a disease is simple, but the situation of patients with T2D is more complicated since most of them have MDS, and T2D is only one of the components that usually occurs later than preobesity, obesity and MASLD. There fore, the term “complications” should not be used arbitrarily in patients with T2D, especially for “DKD” “macrovascular complica tions”; otherwise, the management of MDS will be mistakenly guided to focus on glycemic management. Only by holistically managing MDS can we achieve our goals of improving the quality of life and prolonging the life expectancy of patients with T2D.

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