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Risk Factors and the Treatment of Type 2 Diabetes (T2D)

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Abstract: With the change in lifestyles, the incidence of diabetes is on the increase year by year, seriously affecting the quality of people's lives. Among all the types of diabetes, type 2 diabetes (T2D) is the most common. The risk of T2D increases with age and the proportion of risk trends now towards youthfulness. T2D has a complex mechanism of etiology. It is generally accepted that this is a metabolic disorder mainly due to defective insulin secretion by pancreatic β-cells, reduced responsiveness, and sensitivity of insulin-sensitive organs or tissues (liver, skeletal muscle, adipose tissue, etc.) to insulin. This article will summarize the associated risk factors of T2D, inform clinical practice work, and public health policy designation. Additionally, traditional antihyperglycemic drugs may lead to adverse reactions such as hypoglycemia and gastrointestinal reactions. To better control blood sugar, reduce the occurrence of adverse reactions, and delay or mitigate T2D complications, this article also lays out part of the new target drugs with therapeutic potential on the market, producing more drug selection to treat T2D. More studies targeting patients with all types of T2D are needed to better serve patients.

Keywords: T2D, risk factors, management.

1. Introduction

Diabetes mellitus is a metabolic chronic disease caused by the inability of the pancreas to properly secrete insulin or a decrease in the action of insulin, which leads to chronic damage and failure of various tissues and organs of the human body [1,2]. The specific characteristics of diabetic patients are unusually elevated long-term blood glucose levels (known as high blood sugar) and increased blood insulin [3]. The two main types of diabetes are type 1 diabetes and type 2 diabetes. The main visible symptoms (abnormally elevated blood glucose, increased intake, fatigue, etc.) can affect patients' wellness. Type 1 diabetes is caused by cells of the immune system attacking insulin-producing β-cells in the pancreas, type 2 diabetes is caused by impaired insulin growth and secretion in pancreatic beta cells and insulin resistance in peripheral tissues [3,4]. Of these, the most well-known and common is type 2 diabetes (T2D) since the continuous increase of the global disease rate, and is forecasted the number will reach 590 million cases by 2035. In China, T2D is also the type with the highest proportion of diabetic patients, accounting for more than 90% [1,4]. With economic development, people's lifestyles and eating habits recipes have changed, and the increasing aging population and T2D disease rates bring a huge burden and challenge to healthcare. Global healthcare spending on diabetes treatment total approximately US$1 trillion in 2021, China also spent about

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$110 billion on medical, and healthcare associated with diabetes. A stronger response should be taken to face and control these situations [5].

Numerous studies have proved the incidence of T2D can be affected by many different factors, such as genetic, metabolic, and environmental factors. These causal factors are not single, independent influences, but exist in multiple levels and dimensions that work together. Consequently, this research aims to analyze epidemiological characteristics, and risk factors of T2D, and purposely discuss disease pathogenesis, management, and treatment.

2. Epidemiological Characteristics of T2D

In 1980, there were less than 1% of diabetic patients in China, however, it increased to 10% in 2008 [4]. For the period 1990~2019, number of T2D cases in China rise sharply from 1.9 million to 3.73 million in just 30 years. Almost double the number. A significant trend in volume growth warns of the serious development situation for T2D in China, as well as a greater burden of disease [1].

Based on data from Global Burden of Disease (GBD), among the clinical data of 100,000 Chinese, it can be observed China's crude incidence rate (CIR) ascended from 160.72 per 100,000 in 1990 to 262.88/100,000 in 2019, the growth rate was 63.56%. And age-standardized incidence rate (ASIR) increased from 174.27 per 100,000 to 201.06 per 100,000, growth rate was 15.37% [1]. China's crude incidence rate (CIR) had a significant rise in 1990~1994, with trend growth slowing in 1994~2000, followed by another dramatic rise to a peak in 2005~2014, but a cliff-cutting appeared in 2014~2017 and finally became relatively stable in 2017~2019.

Local and regional studies, according to estimated trends in China's population data, analyzed the number of T2D cases in Hong Kong and Zhejiang province [6]. From 2007 to 2017, the prevalence of men with T2D in Zhejiang Province increased from 193.8 to 443.7, and from 212.9 to 370.5 for women, per 100,000 population. From 2002 to 2015, The annual incidence of T2D among males in Hong Kong increased from 75.4 to 110.8 per 100,000 youth, and 45.0 to 62.1 for females.

3. Risk factors

The common predisposition for T2D in lifestyle, including unhealthy catering, high-calorie intake, lack of exercise, as well as obesity can also significantly increase the risk of T2D. Besides, a family history of diabetes, aging, hypertension, hyperlipidemia, cardiovascular disease, and race (e.g. Asian, African, etc.) are also susceptible to diabetes.

3.1. Genetics and Family History of Diabetes

T2D is a polygenic disease, genetic factor is one of the independent risk factors. T2D has significant genetic predisposition and family aggregation, the usual heritability is 30%~70%. A family history of diabetes is an independent risk factor for diabetes. Research shows that parents who have a family history of diabetes will increase their children's risk of T2D. Children of two parents with T2D have about a 70% probability of developing the disease in their lifetime, exceeding the risk when only one parent has (40%) [4,7].

Although genetics presents an important role in T2D, the genetic model of T2D does not correspond with just a single Mendelian inheritance, but a complex genetic model. Therefore, it is difficult to study these kinds of diseases. The difficulties are: ①Since the age range of onset of patients is relatively wide (from teenagers to the elderly), some individuals who appear normal now may develop diabetes later in life. This made diagnostic of "normal people" unreliable and affected research results; ②Since there might be one or more genes participating together in leading T2D and the effects from environmental factors, different predisposing genes, and environmental factors will

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give different changes to the results between different people; ③Although several genes involved in the onset, each gene plays a very small role, it may be necessary to detect these micro efficacy genes by methods with higher test efficiency.

3.2. Obesity

Obesity (BMI≥30 kg/m^2) is the main independent risk factor in T2D development. Especially in Western countries, more than 90% of diabetic patients are overweight or obese, some research shows the risk proportion with BMI>34.9 is up to 38.8 (95%CI 31.9~47.2) [4,8]. In China, over 1/2 adults are overweight/obese and about 58.3% of diabetic patients are overweight/obese. The abnormal increase in the secretion of cytokine, for instance, tumor necrosis factor-α (TNF-α), Interleukin 6 (IL-6), and Leptin (LP), inducting insulin resistance (IR), lets the body not sensitize to the action of insulin, and finally, normal, or increased insulin does not maintain blood glucose at normal levels. Additionally, obesity also allows fat particles to accumulate in tissues such as muscle and liver, inhibiting the sensitivity of cells to blood glucose stimuli to reduce the absorption of blood sugar, resulting in the level of blood sugar in the body increasing and causing hyperglycemia, IR and induce pancreatic β-cell apoptosis. And these will further promote T2D [9].

Obesity also has a close association with genetics. By analyzing the epigenomic association of genomics of BMI, some scholars found that BMI shows a correlation with DNA methylation at 187 loci in blood and adipose tissue. These methylation changes are caused by obesity, relating to increased risk of T2D and independent from traditional risk factors [10].

3.3. Smoking

Smoking mainly consists of active smoking and passive smoking. Smokers are 30~40% more likely to develop T2D than non-smokers. Active/passive smokers in pre-diabetes have a higher risk of developing T2D than pre-diabetic non-smokers [7]. The quantity of smoking, length of smoking history, and years of smoking will present different impacts on the onset of diabetes [9]. The results show that pipe/cigar smokers are 2.15 times more likely to develop T2D than non-smokers, and cigarette smokers are 1.6 times compared to non-smokers [7]. China's smoking rate (34.17%) and incidence of diabetes (over 20.8%) are much higher than the global average [11]. Nicotine in tobacco can directly damage pancreatic β-cells and insulin receptor sensitivity, leading to T2D and exacerbation of IR.

Diabetic kidney disease (DKD) is a chronic kidney disease (CKD) caused by diabetes. The mechanisms by which smoking increases the risk of DKD are not fully understood. Smoking can promote micro-inflammation in bodies, enhance the body's oxidative stress, and cause vascular endothelial cell dysfunction might be the reasons. Some report also describes smoking as associated with deterioration of glycemic control and dyslipidemia in diabetic patients, these two factors are independently correlated with DKD [12].

Due to abnormalities of glucose-lipid metabolism (GLM), diabetic patients will experience a range of biochemical and metabolic disorders (mainly hyperglycemia) inside the body. Leading to slow wound healing after trauma and susceptibility. However, nicotine in tobacco can reduce prostacyclin, resulting in the shedding of vascular endothelial cells, increasing vascular resistance and platelet aggregation, which increases blood viscosity, slows blood flow, promotes thrombosis, and increases the risk of wound infection.

3.4. Sleep Disturbance

Various factors of sleep may be related to T2D, such as duration, quality, regularity, etc [8]. Data shows that the average sleep duration of modern people is 6.8 hours per night, reduced by 1.5 hours

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compared to the last century [7]. The one who has sleep disturbance can also develop T2D. According to Mendelian Randomization (case group = 16,761, control group = 201,194), obstructive sleep apnea has a significant correlation to the risk of T2D [OR = 2.016, 95% CI: 1.185~3.429, P<0.05] [13]. The mechanism might be sleeping disorders and increased sympathetic activity at night causing an increase in the release of catecholamines and other glucagon, leading to an increase in blood glucose, or hypoxia causes an increase in the level of adrenaline, and at the same time increases hepatic gluconeogenesis, inhibiting the uptake of glucose by the skeletal muscles, leading to an increase in blood glucose, etc. Doing blood glucose monitoring and diabetes screening actively is beneficial for OSA patients to find T2D earlier and intervene in time.

Circadian rhythm sleep disorder due to sleeping disorders can inhibit osteoclasts' functional characterization promote bone resorption and breakdown, and weaken the ability of the skeleton to repair bone microstructural damage that accumulates with age, leading to an increased risk of osteoporotic fracture in diabetic patients.

4. Management of T2D

4.1. Lifestyle Interventions

Enhancing lifestyle to intervene care is based on scientific theory. Under the guidance of care diagnosis, improving various details and processes of each link of routine care, attaching importance to diet, exercise, and mental and disease awareness. These can enhance the science and effectiveness of the nursing plan and against all kinds of complications. Every diabetic patient should take lifestyle intervention treatment. T2D patients should control the weight and let the BMI⩽24. Obese people should lose weight at least 10kg (best to lose weight by more than 15kg) or weight loss of more than 10%. Under the premise of sufficient energy provide, cut down carbohydrate intake. Increasing food intake rich in dietary fiber to slow down the speed of elevated blood sugar, reduce blood sugar fluctuations, and optimize blood lipid indicators. The order of eating can also make changes to blood sugar. Eating carbohydrates after a meal is effective in reducing postprandial blood glucose elevation. Exercise is another important component of the life intervention. Doing exercise can improve T2D patients' various metabolic indicators, blood sugar, blood lipid, blood pressure, weight, and body fat percentage, etc. And can reduce correlated risk factors of cardiovascular disease [14].

The guideline for exercise therapy of T2D in China (2024 edition) has mentioned, that it is recommended that T2D patients perform aerobic exercise for 3~7 d per week at intervals of no more than 2 d each time; walking not less than 3 d per week, 6,000 steps/d, at a frequency of not less than 60~90 steps/min according to one's situation, and preferably up to 100 steps/min; a structured exercise prescription of 3~6 months of aerobic exercise combined with resistance exercise resulted in a reduction in HbA1c of up to 0.89%, with aerobic exercise exceeding a cumulative total of 150 min/week being more effective; and also, incorporating flexibility exercises into a sport can improve physical functioning and blood glucose levels (e.g., by reducing blood glucose levels in the bloodstream) [15].

It is worth noting that for patients with longer duration of type 2 diabetes, more severe complications, and poorer pancreatic islet function, medication cannot be avoided even through measures such as lifestyle improvement and weight loss.

4.2. Medication

Sulfonylureas and biguanides were the only oral antidiabetic drugs in 1950~1990. After 1990, two new classes of oral antidiabetic drugs were introduced: α-Glucosidase inhibitor and peroxisome

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proliferator‐activated receptor gamma (PPAR‐γ). And other kinds of diabetic drugs appeared in 2005~2022 [16].

Traditional antidiabetic drugs include biguanides, thiazolidinedione, sulfonylureas, and α-Glucosidase inhibitors. Metformin has been clearly defined by several guidelines as an indispensable drug for first-line use and in combination medications. The mechanism might be activating AMPK, inhibiting hepatic adenylate cyclase or obstruction of hepatic glucose output, inhibiting hepatic gluconeogenesis and glycogenolysis, and inhibiting intestinal glucose absorption [17].If the glucose-lowering effect is not obvious enough after using it alone for a period, it can be combined with other glucose-lowering agents for treatment. Some research shows that there is better treatment effectiveness to control blood sugar by using metformin combined with saxagliptin as a treatment option. Along with continuing progress in research, more and more new antidiabetic drug is introduced, such as tirzepatide. It is a new glucose-dependent GIP and GLP-1 receptor agonist. Tirzepatide was first permitted to approve teicoplanin for improving blood sugar in adults with T2D and be used as an adjunct to diet and exercise on 13 May 2022. Compared with GLP-1RA, tirzepatide can not only improve β-cell functional characterization but also improve insulin sensitivity [18].

Dorzagliatin is a novel dual-acting systemic glucokinase agonist (GKA) that activates both pancreatic and hepatic glucokinase (GK), promotes insulin secretion and hepatic gluconeogenesis, improves pancreatic β-cell function and insulin resistance, and stimulates intestinal GK to regulate glucagon-like peptide-1 secretion, exerting multiple antihyperglycemic effects. The first marketed GKA-type diabetes drug that maintains blood glucose control for a certain period even after stopping the drug and can be used in combination with conventional hypoglycemic drugs to improve efficacy while improving the tolerability and adverse effects of conventional drugs. Approved for marketing by China's National Medicines Supervision and Administration Agency (NMPA) on 8 October 2022 [19].

5. Conclusion

Since the increased aging of the population, chronic disease prevention and treatment is urgent. Diabetes is a kind of common chronic disease, if patients do not control their blood sugar level actively, a range of complications can be caused. Especially in China, with the rapid rise in the prevalence of diabetes, how to improve glycemic management is a key point to focus on going forward. Along with the smooth progress of the human genome project and the development of molecular biotechnology, there has been a major leap forward in the study of the genetic background and causative genes of polygenic endocrine metabolic diseases such as diabetes mellitus. These studies not only provide deeper research into the mechanisms of action of drugs currently in widespread use but also lay the foundations for developing new medication. Additionally, differences in the efficacy of different novel drugs for the treatment of T2D There is still a need for more high-quality evidence from clinical studies.

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