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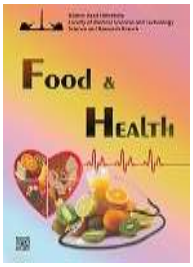

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Type 2 diabetes as a prominent global health issue: A narrative review

Asal Ansaripour [1], Behnood Abbasi [2*]

[1] School of Medicine, University of Nicosia, Nicosia, Cyprus
[2] Department of Nutrition, Electronic Health and Statistics Surveillance Research Center, Science and Research Branch. Islamic Azad University, Tehran, Iran

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ABSTRACT

Diabetes is one of the most prevalent non-communicable diseases worldwide which can lead to significant macrovascular and microvascular complications. A majority of patients with diabetes suffer from type 2 diabetes and its prevalence and incidence continue to increase globally. Its underlying pathophysiology is complicated. Both genetic predisposition and lifestyle risk factors can result in relative insulin deficiency and the development of type 2 diabetes. Patients with type 2 diabetes can present with polyuria, polydipsia, polyphagia, blurred vision, and recurrent infections. However, many patients may be initially asymptomatic, resulting in late diagnosis. Delayed diagnosis can also result in presenting with already established complications at the time of diagnosis. There are various diagnostic methods and these include measurements of glycated hemoglobin, fasting plasma glucose, or random plasma glucose together with classical signs and symptoms of hyperglycemia. Alternatively, an oral glucose tolerance test can be carried out to confirm the diagnosis. Lifestyle modification and pharmacotherapy are the backbones of type 2 diabetes treatment. Metformin is considered to be the first-line therapy of choice. However, if the desired glucose control is not achieved, then metformin is combined with other anti-diabetic medications. As type 2 diabetes is largely a preventable disease, its primary prevention is of utmost significance. The aim of primary prevention is to reduce the modifiable risk factors such as obesity, unhealthy diet, physical inactivity, and smoking.

1. Introduction

Diabetes mellitus (DM) has been known to man since antiquity. DM is a metabolic disorder that is characterized by hyperglycemia or elevated blood glucose levels. Insulin is produced by pancreatic beta cells and lack of insulin secretion or defects in its action can result in DM. There are different types of DM with types 1 and 2 being the most prevalent types (1). In fact, 90% of patients with diabetes have type 2 diabetes (T2D). Type 2 diabetes is mainly characterized by beta-cell dysfunction and the inability of peripheral tissues to have an adequate insulin response. This situation is referred to as relative insulin deficiency (2, 3). Diabetes is considered to be a growing pandemic and it has been estimated that there will be 642 million diabetic patients by 2040 (4). Diabetes was the seventh leading cause of mortality in 2016 (5). Type 2 diabetes impairs the daily lives of patients and adds socio-economic pressure on global health economics. Given that obesity is the major risk factor for T2D, the global increase in obesity, physical inactivity, and unhealthy diet have led to an unprecedented rise in type 2 diabetic cases (3). A majority of lifestyle risk factors of T2D are modifiable and this marks the significance of diabetes prevention. Raising public awareness, regular physical activity, a healthy diet, and weight loss are of paramount importance when it comes to preventing type 2 diabetes. Many types 2 diabetic patients may be asymptomatic, highlighting the need for screening and early diagnosis. There are four main diagnostic methods and hemoglobin A1C (HbA1C) measurement is the most commonly utilized method (6). Early diagnosis and a patient-centered treatment approach can lead to better health outcomes and higher patient satisfaction. The hallmark of type 2 diabetes treatment is

*Corresponding author: Department of Nutrition, Electronic Health and Statistics Surveillance Research Center, Science and Research Branch. Islamic Azad University, Tehran, Iran.

E-mail address: abbasi.b@srbiau.ac.ir (Behnood Abbasi).

taking into account individual patient characteristics, modifying their lifestyle factors, and providing pharmacotherapy. Generally, metformin is considered to be the first-line therapy. This is followed by combination therapy if there was an inadequate glucose control with metformin (1). The global burden of type 2 diabetes is rising in most countries, making it a valuable research topic. The aim of this literature review is to provide a basic understanding of type 2 diabetes, discuss different diagnostic and therapeutic approaches, address novel studies where applicable and highlight the importance of prevention.

2. Disease presentation

2.1. T2D signs and symptoms

Type 2 diabetes can present with classical signs and symptoms of hyperglycemia which include polydipsia, polyuria, polyphagia, and unintentional weight loss (7). Some patients may also experience blurred vision and frequent infections such as candidiasis. Other signs of type 2 diabetes may include delayed wound healing, foot numbness, and impotence. However, many patients are asymptomatic leaving them undiagnosed for several years (8).

2.2. Diabetes complications

Due to the asymptomatic nature of T2D, some patients may have already established complications at the time of diagnosis. Diabetic patients are at risk of macrovascular and microvascular complications. Cardiovascular disease (CVD) is the major macrovascular complication of T2D. In a study carried out by Einarson et al. (8) 57 articles were analyzed to look at the prevalence of CVD and it was shown that CVD is a major contributor to the mortality of patients with T2D (8). Moreover, diabetic patients are likely to be presented with synergistic risk factors such as hypertension, obesity, and dyslipidemia which will further contribute to increased CVD risk (9). CVD encompasses various diseases of the heart and blood vessels. Important manifestations of diabetes-related CVD are coronary artery disease (CAD), myocardial infarction (MI), stroke, and peripheral vascular disease (PVD). PVD is mainly characterized by reduced blood flow to the lower limbs (10). Microvascular complications include diabetic retinopathy, neuropathy, and nephropathy. T2D is the most common cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide. Diabetic nephropathy presents with progressive stages of an initial increased glomerular filtration rate (GFR), followed by microalbuminuria and excessive proteinuria, and finally a decreased GFR which will eventually lead to dialysis (11, 12). Diabetic retinopathy (DR) is another complication that is the most common cause of preventable blindness amongst the working-age population (13). In the early stages of T2D, diabetic retinopathy can be asymptomatic. The initial signs of DR include microaneurysms, dot and blot hemorrhages, intra-retinal microvascular anomalies and cotton wool spots. With disease progression, retinal ischemia, retinal detachment, and even vision loss can occur (14). Another microvascular complication of diabetes includes diabetic neuropathy and is characterized by autonomic and peripheral nervous system damage which can lead to pain and sensation loss. The most common form of diabetic neuropathy is distal symmetric polyneuropathy. These patients present with 'stocking and glove' distribution meaning that hands and lower limbs are more frequently affected (15).

2.3. Diagnosis

The diagnosis of diabetes can be made when the glycated hemoglobin (HbA1C) test indicates an A1C level of 6.5% or greater on two separate occasions. This is the most commonly used diagnostic test and demonstrates the average blood glucose level in the last two to three months, reflecting the lifespan of red blood cells. Alternatively, fasting plasma glucose (FPG) can be used which measures the glucose level in the blood after 8 hours of fasting and a value of ≥ 126mg/dL is indicative of diabetes. An oral glucose tolerance test (OGTT) of ≥200 mg/dL two hours following a 75-g glucose load (a standard carbohydrate load) would be another diagnostic test. Lastly, random plasma glucose (RPG) of 200 mg/dL together with classical signs and symptoms of diabetes would also confirm the diagnosis (6). A summary of the four main diagnostic methods can be found in Table 1.

Table 1. The main diagnostic methods of diabetes.

Diagnostic methods	Values in diabetes	Additional notes
HbA1C	≥ 6.5%	-
FPG	≥ 126 mg/dL (≥ 7.0 mmol/L)	Fasting for at least 8 hours prior the test
OGTT	≥200 mg/dL (≥11.1 mmol/ L)	A 75-g anhydrous glucose load should be used
RPG	≥200 mg/dL (≥11.1 mmol/ L)	Only diagnostic together with classical signs and symptoms of hyperglycemia

FPG = fasting plasma glucose
OGTT= oral glucose tolerance test.
RPG = random plasma glucose
The table has been modified from Pippitt and Li, (6).

Each diagnostic test has its own advantages and disadvantages. For instance, the A1C test does not require fasting and has lower variability than FPG as it shows the average glucose level that is bound to hemoglobin (16). However, the HbA1C levels may be falsely influenced by certain medical conditions. Diseases such as hemolytic anemias or acute blood loss can reduce the A1C levels, while, a previous splenectomy or aplastic anemias may increase it (6). Even though, type 2 diabetes is mainly diagnosed in middle-aged and older individuals, the diagnosis can also be made at young ages. Differentiating between type 1 and type 2 diabetes may be challenging for younger patients (3). Special tests such as testing for autoantibodies can help distinguish between different types of diabetes. Such autoantibodies would be present in type 1 diabetes (6).

3. Epidemiology

3.1. Prevalence and incidence

T2D is considered to be a growing pandemic as about 1 in 11 adults are globally affected with diabetes, 90% of whom have type 2 diabetes (17). The number of diabetic patients has increased from 108 million in 1980 to 422 million in 2014. Furthermore, the global prevalence rose from 4.7% in 1980 to 8.5% in 2014 for those who were older than 18 years of age (5). There was also a global increase in the incidence of diabetes from 11.3 million in 1990 to 22.9 million in 2017 (18). Unfortunately, the proportion of type 2 diabetic patients is increasing in most countries. However, there is a more rapid increase in low- and middle-income countries in comparison with high-income countries (5). 79% of patients with diabetes live in low- and middle-income countries (19). According to the Centers for Disease Control and Prevention (CDC), 34.2 million people have diabetes in the United States, 1 in 5 of whom are unaware of their condition (20). The marked regional differences in type 2 diabetes prevalence in 2019 can be seen in Fig. 1. It was shown that the Middle East and North Africa had the highest prevalence of diabetes in 2019. Diabetes is also considered to be a financial burden. In 2015 global health expenditure on diabetes was 673 billion USD and this is estimated to increase to 802 billion USD in 2040 (19).

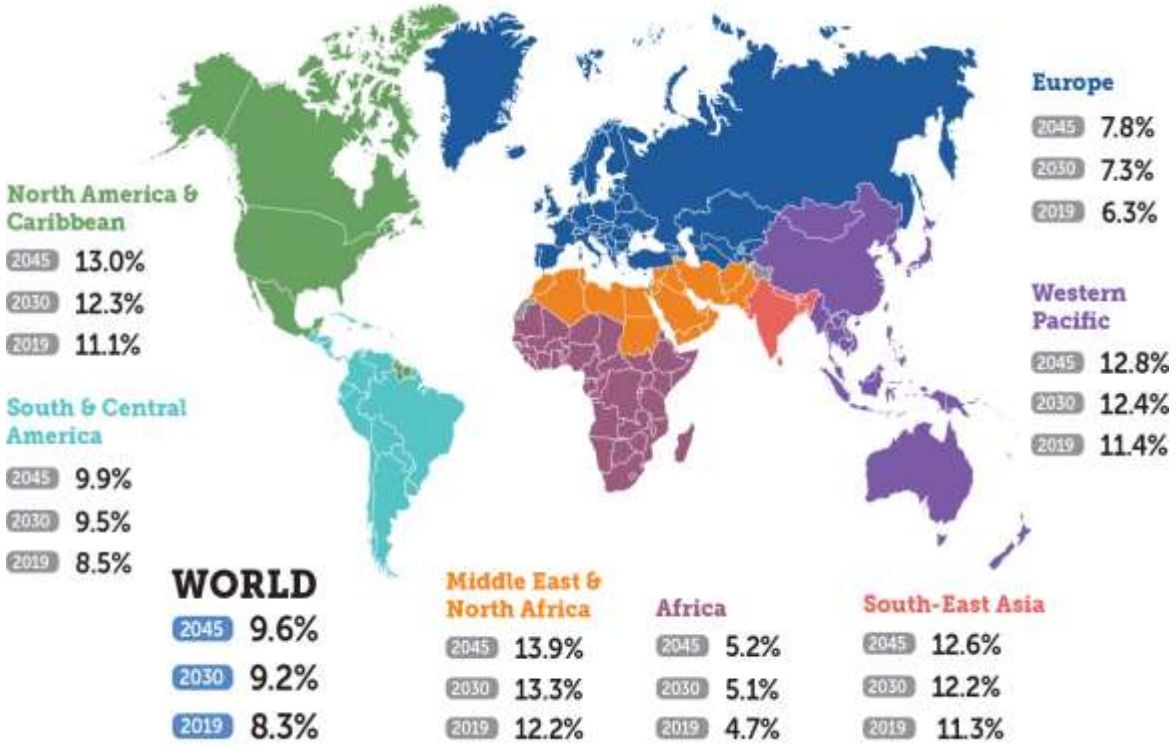

Fig. 1. The regional differences of the age-adjusted prevalence of diabetes in 2019. The estimated percentages for 2030 and 2045 are also shown. The figure is extracted from IDF Diabetes Atlas, 2019.

3.2. Mortality and survival rates

Diabetes was the seventh leading cause of death in 2016, leading to 1.6 million deaths directly. Additionally, in 2012, another 2.2 million deaths were attributable to hyperglycemia (5). Type 2 diabetic patients have a 15% increased risk of all-cause mortality. It has been shown that diabetes is associated with a greater risk of coronary heart disease and ischemic stroke. In fact, CVD is the greatest cause of morbidity and mortality in type 2 diabetic patients (3). There is less data on survival rates as it varies widely according to patients' age, treatment adherence, and lifestyle habits. However, Diabetes UK has estimated a reduction of up to 10 years in life expectancy of patients with type 2 diabetes, compared with nondiabetic subjects (21).

3.3. Differences in T2D by gender and age

When it comes to gender differences in type 2 diabetes, globally more males are affected than females. In 2017, 6219 type 2 diabetic males were diagnosed per 100000 population and this is in comparison with 5898 female cases per 100000 population (22). The explanation for gender differences can be attributed to the fact that males have a greater trunk and visceral fat. In both sexes there is an age-dependent pattern: as the age increases so does the incidence. Middle-aged

individuals made up more than half of the diabetic subjects in 2013 (23). Furthermore, the peak incidence of type 2 diabetes was about 55 years of age in 2017 (22). On the other hand, females have impaired glucose tolerance (IGT) more frequently than males irrespective of age (23).

4. Pathophysiology

4.1. Risk factors

Type 2 diabetes is a multifactorial disorder that is influenced by both lifestyle factors and genetic predisposition. Diabetogenic and obesity-related genes are linked to the development of T2D. The major risk factor for T2D is considered to be obesity. Central obesity specifically can lead to the release of hormones and cytokines that can in turn cause insulin resistance, endothelial dysfunction, and chronic inflammation, increasing the risk for both T2D and CVD (24). A meta-analysis was carried out by Bellou et al. (25). In order to identify the risk factors of T2D. In addition to obesity, other risk factors were found. These include unhealthy diet, physical inactivity, low level of education, smoking, family history of T2D, and certain medical conditions such as hypertension and gestational diabetes. On the other hand, moderate alcohol consumption seemed to be protective of T2D.

4.2. Insulin resistance and beta-cell dysfunction

T2D is a complex multisystem disease and its underlying pathophysiology can be mainly described by insulin resistance and beta-cell dysfunction. Due to insulin resistance, target tissues fail to respond appropriately to insulin and this leads to reduced glucose uptake in muscles and hence reduced glycogen synthesis. Furthermore, hepatic cells are unable to suppress gluconeogenesis which is translated into an enhanced hepatic glucose production. Under normal circumstances, insulin inhibits lipolysis. Therefore, Insulin resistance increases free fatty acid concentration which in turn recruits inflammatory cytokines that can lead to beta-cell dysfunction. Additionally, patients with T2D have a reduced incretin effect. Incretins are hormones that are normally produced by intestinal cells and activate receptors on the pancreatic beta cells. They are also responsible for delaying gastric emptying (26). As shown in Fig. 2, initially beta cells show a compensatory response to peripheral insulin resistance, maintaining normal levels of blood glucose. However, beta

Fig. 2. A simplified summary of the underlying pathophysiology of T2D. Type 2 diabetes is multifactorial and hence both genetic predisposition and lifestyle factors have an important role in its development. These risk factors lead to peripheral insulin resistance which is characterized by an inadequate response of peripheral target tissues to insulin. Initially beta cells (β-cells) show a compensatory response increasing insulin production and trying to maintain normal glucose levels. Eventually the compensatory response fails leading to beta cell dysfunction. These result in hyperglycemia and type 2 diabetes development.

cells are unable to cope with the ongoing demands of peripheral insulin resistance. This results in failure of the compensatory response and hence beta-cell dysfunction and hyperglycemia (27).

4.3. Diabetes-associated CVD

T2D can give rise to CVD. Patients with T2D are more likely to have hypertension. Both T2D and hypertension are known risk factors for atherosclerosis and CVD. Type 2 diabetic patients have stiffer arteries and are more likely to suffer from endothelial dysfunction. The coexistence of T2D and hypertension will lead to even greater arterial stiffness (28). Additionally, obesity and T2D are closely linked to each other. Obesity can lead to the build-up of atheromatous plaque in arterial walls. The underlying pathophysiology of diabetes-associated CVD is multifactorial. It is related to both plaque formation but also to damage caused by hyperglycemia and insulin resistance (9). Chronic hyperglycemia leads to the development of advanced glycation end-products (AGEs) which can cause arteriosclerosis and endothelial dysfunction. Although AGEs and atheromatous plaque can cause CVD, the exact mechanism is not completely understood (28). There are gaps in the current literature describing the underlying pathogenesis. It is suggested that microcirculatory function may also contribute to diabetes-related cardiovascular events, which requires further investigation.

5. Management:

5.1. Lifestyle modification

Lifestyle modification and pharmacotherapy are the backbones of T2D treatment. Obesity is one of the major risk factors for T2D. Hence lifestyle changes such as regular exercising, having a healthy diet, and losing weight are fundamental to T2D treatment. Moreover, educating the patients regarding diabetes, its risk factors, and complications

can lead to better treatment outcomes (1).

5.2. Metformin

Metformin belongs to biguanides and is the most commonly prescribed medication for T2D. It is considered the optimal first-line drug provided that the patient is not contraindicated to metformin (renal and hepatic failure) (1). Metformin has a complex mechanism of action that is not fully understood. It acts directly and indirectly on the liver reducing hepatic gluconeogenesis and it also acts on the gut increasing its glucose utilization (29). Metformin can lead to weight loss and reduced triglycerides and LDL levels, making it particularly beneficial for obese and overweight patients (1). It is considered to be an effective medication, decreasing the HbA1C level by 1.3-2%, and can lead to an even greater reduction for patients with very high glucose levels. Metformin also reduces the risk of diabetes-related cardiovascular events. However, vitamin B12 deficiency may develop with long-term metformin treatment (30).

5.3. Sulfonylureas

Sulfonylureas act via stimulating endogenous insulin secretion. This is achieved by inhibiting potassium channels (K_{ATP}) on beta cells and hence they require functional cells. They cannot provide a long-term protective effect and their adverse effects include hypoglycemia and weight gain (1).

5.4. Thiazolidinediones

Thiazolidinediones activate peroxisome proliferator-activated receptor γ (PPARγ), enhancing insulin sensitivity on hepatocytes and adipocytes. They can be used for treatment-resistant T2D. However, they have significant side effects and can lead to weight gain, fluid retention, and increased risk of fracture and cardiovascular events. Therefore, they are contraindicated in heart failure (31). Pioglitazone was shown to cause fluid retention leading to exacerbation of heart failure and pulmonary edema (32).

5.5. Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DPP4) inhibitors, also known as gliptins, potentiate endogenous incretins. Incretins such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) are physiological regulators of glucose homeostasis and are broken down by dipeptidyl peptidase 4. The action of this enzyme is competitively inhibited via DPP4 inhibitors. They are considered relatively safe and do not affect weight (33).

5.6. Glucagon-like peptide 1 analogues

Glucagon-like peptide 1 (GLP-1) analogs increase insulin secretion but reduce the secretion of glucagon. These lead to the suppression of hepatic glucose production. They are less well-tolerated than DPP4 inhibitors. However, they are more efficacious and have additional benefits of delaying gastric emptying, reducing blood pressure, and improving lipid profile (1).

5.7. Sodium-glucose co-transporter-2 inhibitors

Sodium-glucose co-transporter-2 (SGLT2) inhibitors block SGLT2 in the proximal tubule, suppressing reabsorption of glucose from the kidneys and hence increasing glucose excretion. They reduce systolic and diastolic blood pressure which makes them beneficial in terms of diabetes-related CVD events. They can also cause modest weight loss helping with obesity. Their adverse effects include an increased risk of urinary tract infection (UTI) and genital mycotic infections, more commonly affecting females than males (34).

5.8. Combination therapy

Metformin is considered to be the first-line therapy for T2D. This is due to its safety and beneficial effects such as lowering the A1C levels, reducing cardiovascular mortality, and causing weight loss (35). However, if adequate glucose control is not achieved then combination therapy may be initiated. One or two oral or injectable drugs can be added to metformin for combination therapy. These drugs should be chosen based on their adverse profile, their effect on cardiovascular risk reduction, and the patient's comorbidities. Metformin can be combined with a DPP-4 inhibitor, pioglitazone, or a sulfonylurea for dual therapy, provided that there are no contraindications. Eventually, insulin therapy can be used either as monotherapy or in combination with other medications to achieve the desired blood glucose control for type 2 diabetic patients. Furthermore, it is essential to have a patient-centered approach that focuses on patients' values and concerns (34).

6. Ongoing clinical trials

There are various ongoing trials for the management of T2D. For instance, a randomized interventional clinical trial is being carried out on 664 participants to check the efficacy and safety of oral semaglutide compared to placebo. Oral semaglutide is a new antidiabetic medication (a GLP-1 agonist) the clinical trial started on October 1, 2019, and the completion date is estimated to be on October 7, 2021. The investigators will measure the changes in HbA1C and several other secondary outcomes. Examples of such secondary measures include changes in FPG, BMI, lipid profile, and body weight (36). Another randomized clinical trial is comparing the effectiveness of dapagliflozin, an SGLT2 inhibitor, with metformin in early type 2 diabetes treatment. The study started in 2019 using 4300 participants and it will be complete in 2024. It will measure the time it takes for diabetes complications to occur. Examples of such complications include MI, diabetic nephropathy, heart failure, foot ulcer, or death (36).

7. Prevention

7.1. Education

Patient education is extremely crucial when it comes to diabetes prevention as it improves compliance and leads to better health outcomes. Educating individuals can enhance their understanding of lifestyle changes. There is an urgent need for health care professionals to educate diabetic patients, and encourage a healthy lifestyle and medication adherence to improve glycemic control. Patient education is particularly beneficial in low- and middle-income countries where the cases are rising more rapidly in comparison to high-income countries (37). Type 2 diabetic patients with low health literacy were shown to recall less and suffer from poor glycemic control (24). Most high-income countries are already educating the individuals through leaflets, various online platforms, and resources such as Diabetes UK or the National Diabetes Prevention Program (DPP) of the CDC. National DPP includes national-level campaigns that enhance awareness of both pre-diabetes and T2D and motivate individuals to participate in evidence-based lifestyle change programs (CDC, 2020). Education is critical for primary, secondary, and tertiary prevention of type 2 diabetes.

7.2. Primary Prevention

Primary prevention of type 2 diabetes occurs during the pre-diabetic phase which is also known as impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). The individuals have higher than normal levels of glucose but they do not meet the criteria for T2D diagnosis (38). The main aim of primary prevention is to target the modifiable risk factors of T2D and to educate individuals on ways to lower the risk of T2D development. They focus on lifestyle changes such as having a healthy diet, engaging in physical activities losing weight, and smoking cessation. Obesity is the most crucial risk factor and it has been shown that weight loss contributes to a pronounced risk reduction of T2D (39). Diet and physical activity can reduce or delay the development of T2D in individuals with IGT. Dietary patterns such as the Mediterranean diet and low carbohydrate diet can lead to weight loss, lowering the risk of T2D (40). In one clinical trial, it was shown that 58 out of 141 (41.1%) physically active participants who had IGT developed T2D. In comparison, 90 out of 133 (67.7%) control participants, who were not physically active but also had IGT, developed T2D (39). A current clinical trial is being conducted on 250 individuals with IFG and/or IGT to test metabolic outcome differences of low-carb or low-fat dietary interventions. This randomized intervention started in July 2013 and is estimated to be completed in December 2021. Changes in postprandial glycemia and hepatic fat content are the primary outcomes that will be measured during this trial (41).

7.3. Secondary Prevention

The purpose of secondary prevention is to identify the disease as early as possible and interrupt the disease process (42). Since type 2 diabetes can be asymptomatic the main focus of secondary prevention is screening. Regular measurements of HbA1C or utilization of other diagnostic methods of type 2 diabetes can result in making an early diagnosis. This allows prompt initiation of an appropriate treatment plan such as pharmacotherapy, education, and lifestyle modifications. It is recommended by the American Diabetes Association (ADA) to screen individuals with a body mass index (BMI) of ≥ 25 kg/m^2 who also have additional risk factors like IGT, hypertension, or physical inactivity. ADA also recommends screening individuals who are ≥45 years regardless of risk factors (43).

7.4. Tertiary Prevention

After the diagnosis of T2D tertiary prevention should take place in order to prevent or delay the occurrence of complications. Hence, modifying the risk factors of macrovascular and microvascular complications and good glycemic control are the main purpose of tertiary prevention. It is imperative to educate patients about diabetes, its complications, and self-monitoring of blood glucose (42). A study was carried out by Pagidipati et al. (44). which showed that the risk of diabetes-associated CVD can be lowered by addressing five prevention parameters. These parameters include the use of aspirin, improving the lipid profile of the patient (low-density lipoprotein cholesterol (LDL) <70 mg/dL or treatment with statins), having a systolic blood pressure of <140 mmHg and a diastolic pressure of <90 mmHg, taking angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) and being a non-smoker Improved lipid profile, blood pressure management, and glycemic control reduce the risk of diabetes-related complications including diabetic nephropathy, CVD, and retinopathy. However, prevention of diabetic retinopathy also includes early eye screening and regular referrals to ophthalmologists to prevent diabetes-related visual impairment (45). Diabetes-related peripheral vascular disease and diabetic neuropathy can lead to lower limb amputations. However, many of these amputations can be prevented through CVD risk factors modification, adequate foot care, early detection, and treatment of foot ulcers (46).

8. Conclusions

In conclusion, type 2 diabetes is a prominent global health issue and a significant contributor to morbidity and mortality. Primary prevention of T2D is possible and is of paramount importance. Implemented preventive measures and various treatment approaches have considerably improved diabetes care. Nevertheless, the prevalence of type 2 diabetes is increasing worldwide. The rising global burden of T2D highlights the need for better preventive measures and improved interventions for the future. There is an urgent need

to address the modifiable lifestyle risk factors of diabetes through prevention programs, education, and healthy lifestyle promotion. When it comes to T2D management, metformin is considered to be the first-line treatment of choice. However, the mechanism of action of metformin is not fully understood, suggesting the further need to explore the cellular and molecular effects of metformin. In addition, one or more medications are usually combined with metformin in order to achieve the desired therapeutic endpoints. As T2D is a huge socioeconomic burden due to its treatment costs and its complications, both patients and countries may benefit from the discovery of newer more effective pharmacological interventions. Addressing the gaps in the literature regarding the underlying pathophysiology of type 2 diabetes can aid with the detection of more novel treatment targets. Lastly, a greater emphasis should be placed on having a patient-centered approach with personalized glucose-lowering therapies.

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