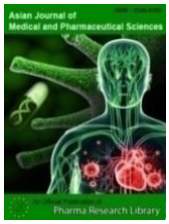

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A Review on Recent Pharmacotherapeutic Advancements in the Prevention of Diabetes Mellitus Complications

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A B S T R A C T

Diabetes is one of the largest global health emergencies of this century, ranking among the 10 leading causes of mortality together with cardiovascular disease (CVD), respiratory disease, and cancer. According to the World Health Organization (WHO), noncommunicable diseases (NCDs) accounted for 74% of deaths globally in 2019, of which, diabetes resulted in 1.6 million deaths, thus becoming the ninth leading cause of death globally. The etiology of diabetes is believed to be multifactorial. Many individual-level nonmodifiable risk factors like genetic, age, ethnicity, and family history have been prospectively associated with type 2 diabetes, but the increases in prevalence in most populations have probably been driven by a modifiable risk factors including sedentary lifestyle and/or lack of exercise, increasing prevalence of overweight/obesity, unhealthy diets and exposure to environmental pollutants, altered intrauterine environment can elevate the risk of diabetes mellitus. By the year 2035, nearly 592 million people are predicted to die of diabetes. Diabetes is a progressive disorder that leads to serious complications, which are associated with increased costs to the family, community, and healthcare system. Uncontrolled diabetes leads to increased risk of vascular disease and much of the burden of type 2 diabetes is caused by macrovascular and microvascular complications. Diabetes has already become a leading threat to public health globally and the picture becomes grimmer for the low- and middle-income countries like India, where the burden has risen significantly in recent decades and will continue to rise in the coming decades. This could have a great influence on morbidity and mortality associated with diabetes and, thus, on the overall healthcare expenditure in India. To curb the epidemic of diabetes and its associated complications, there is a need for a multipronged strategy involving early diagnosis of diabetes, screening for its complications, and offering optimal therapy at all levels of care for those who already have diabetes and primary prevention of diabetes in those with prediabetes.

Keywords: Diabetes mellitus, Macrovascular, Microvascular Complications, Global Health Emergencies, Optimal Therapy

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Diabetes mellitus is taken from the Greek word diabetes, meaning siphon - to pass through and the Latin word mellitus meaning sweet. A review of the history shows that the term "diabetes" was first used by Apollonius of Memphis around 250 to 300 BC. Ancient Greek, Indian, and Egyptian civilizations discovered the sweet nature of urine in this condition, and hence the propagation of the word Diabetes Mellitus came into being. Mering and

Minkowski, in 1889, discovered the role of the pancreas in the pathogenesis of diabetes. In 1922 Banting, Best, and Collip purified the hormone insulin from the pancreas of cows at the University of Toronto, leading to the availability of an effective treatment for diabetes in 1922. Over the years, exceptional work has taken place, and multiple discoveries, as well as management strategies, have been created to tackle this growing problem. Unfortunately, even today, diabetes is one of the most common chronic diseases in the country and worldwide. In the US, it remains as the seventh leading cause of death.

Diabetes mellitus (DM) is a metabolic disease, involving inappropriately elevated blood glucose levels. DM has several categories, including type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and secondary causes due to endocrinopathies, steroid use, etc. The main subtypes of DM are Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM), which classically result from defective insulin secretion (T1DM) and/or action (T2DM). T1DM presents in children or adolescents, while T2DM is thought to affect middle-aged and older adults who have prolonged hyperglycemia due to poor lifestyle and dietary choices. The pathogenesis for T1DM and T2DM is drastically different, and therefore each type has various etiologies, presentations, and treatments[1-3].

Etiology

In the islets of Langerhans in the pancreas, there are two main subclasses of endocrine cells: insulin-producing beta cells and glucagon secreting alpha cells. Beta and alpha cells are continually changing their levels of hormone secretions based on the glucose environment. Without the balance between insulin and glucagon, the glucose levels become inappropriately skewed. In the case of DM, insulin is either absent and/or has impaired action (insulin resistance), and thus leads to hyperglycemia. T1DM is characterized by the destruction of beta cells in the pancreas, typically secondary to an autoimmune process. The result is the absolute destruction of beta cells, and consequentially, insulin is absent or extremely low. T2DM involves a more insidious onset where an imbalance between insulin levels and insulin sensitivity causes a functional deficit of insulin. Insulin resistance is multifactorial but commonly develops from obesity and aging.

The genetic background for both types is critical as a risk factor. As the human genome gets further explored, there are different loci found that confer risk for DM. Polymorphisms have been known to influence the risk for T1DM, including major histocompatibility complex (MHC) and human leukocyte antigen (HLA). T2DM involves a more complex interplay between genetics and lifestyle. There is clear evidence suggesting that T2DM is has a stronger hereditary profile as compared to T1DM. The majority of patients with the disease have at least one parent with T2DM. Monozygotic twins with one affected twin have a 90% likelihood of the other twin developing T2DM in his/her lifetime. Approximately 50 polymorphisms to date have been described to contribute to the risk or protection for T2DM. These genes encode for proteins involved in various pathways leading to DM, including pancreatic development, insulin synthesis, secretion, and development, amyloid deposition in beta cells, insulin resistance, and impaired gluconeogenesis regulation. A genome-wide association study (GWAS) found genetic loci for transcription factor 7-like 2 gene (TCF7L2), which increases the risk for T2DM.

MODY is a heterogeneous disorder identified by non-insulin-dependent diabetes diagnosed at a young age (usually under 25 years). It carries an autosomal dominant transmission and does not involve autoantibodies as in T1DM. Several genes have implications in this disease, including mutations to hepatocyte nuclear factor-1-alpha (HNF1A) and the glucokinase (GCK) gene, which occurs in 52 to65 and 15 to 32 percent of MODY cases, respectively[4].

Gestational diabetes is essentially diabetes that manifests during pregnancy. It is still unknown why it develops; however, some speculate that HLA antigens may play a role, specifically HLA DR2, 3, and 4. Excessive proinsulin is also thought to play a role in gestational diabetes, and some suggest that proinsulin may induce beta-cell stress. Others believe that high concentrations of hormones such as progesterone, cortisol, prolactin, human placental lactogen, and estrogen may affect beta-cell function and peripheral insulin sensitivity.

Several endocrinopathies, including acromegaly, Cushing syndrome, glucagonoma, hyperthyroidism, hyperaldosteronism, and somatostatinomas, have been associated with glucose intolerance and diabetes mellitus, due to the inherent glucogenic action of the endogenous hormones excessively secreted in these conditions. Conditions like idiopathic hemochromatosis are associated with diabetes mellitus due to excessive iron deposition in the pancreas and the destruction of the beta cells.

2. Epidemiology

Globally, 1 in 11 adults has DM (90% having T2DM). The onset of T1DM gradually increases from birth and peaks at ages 4 to 6 years and then again from 10 to 14 years. Approximately 45% of children present before age ten years. The prevalence in people under age 20 is about 2.3 per 1000. While most autoimmune diseases are more common in females, there are no apparent gender differences in the incidence of childhood T1DM. In some populations, such as in older males of European origin (over 13 years), they may be more likely to develop T1DM compared to females (3:2 male to female ratio). The incidence of T1DM has been increasing worldwide. In Europe, Australia, and the Middle East, rates are rising by 2% to 5% annually. In the United States, T1DM rates rose in most age and ethnic groups by about 2% yearly, and rates are higher in Hispanic youth. The exact reason for this pattern remains unknown. However, some metrics, such as the United States Military Health System data repository, found plateauing over 2007 to 2012 with a prevalence of 1.5 per 1000 and incidence of 20.7 to 21.3 per 1000. The onset of T2DM is usually later in life, though obesity in

adolescents has led to an increase in T2DM in younger populations. T2DM has a prevalence of about 9% in the total population of the United States, but approximately 25% in those over 65 years. The International Diabetes Federation estimates that 1 in 11 adults between 20 and 79 years had DM globally in 2015. Experts expect the prevalence of DM to increase from 415 to 642 million by 2040, with the most significant increase in populations transitioning from low to middle-income levels. T2DM varies among ethnic groups and is 2 to 6 times more prevalent in Blacks, Native Americans, Pima Indians, and Hispanic Americans compared to Whites in the United States. While ethnicity alone plays a vital role in T2DM, environmental factors also greatly confer risk for the disease. For example, Pima Indians in Mexico are less likely to develop T2DM compared to Pima Indians in the United States.

Diabetes is one of the largest global health emergencies of this century, ranking among the 10 leading causes of mortality together with cardiovascular disease (CVD), respiratory disease, and cancer. According to the World Health Organization (WHO), noncommunicable diseases (NCDs) accounted for 74% of deaths globally in 2019, of which, diabetes resulted in 1.6 million deaths, thus becoming the ninth leading cause of death globally. By the year 2035, nearly 592 million people are predicted to die of diabetes. Type 2 diabetes, which constitutes 90% of all cases of diabetes, earlier considered to be a disease of the affluent "Western" countries, has now spread globally, and has become a major cause of disability and death affecting even younger age group. Diabetes has reached epidemic proportions in many developing economies, such as China and India. According to WHO, the prevalence of diabetes is growing most rapidly in low- and middle-income countries. The rapid socioeconomic change in conjunction with urbanization and industrialization are the major factors for the global increase in the diabetes epidemic, with other associated risk factors such as population growth, unhealthy eating habits, and a sedentary lifestyle also playing an important role. Diabetes is a progressive disorder that leads to serious complications, which are associated with increased costs to the family, community, and healthcare system. Uncontrolled diabetes leads to increased risk of vascular disease and much of the burden of type 2 diabetes is caused by macrovascular (cardiovascular (CV), cerebrovascular, and peripheral artery disease) and microvascular (diabetic retinopathy, nephropathy, and neuropathy) complications.

Global Burden of Diabetes

Type 2 diabetes susceptibility varies to a great extent around the globe, with Pacific Islanders, Asian Indians, and Native Americans having a significantly higher risk of developing the disorder. The number of people with type 2 diabetes began to rise globally in the 1990s, and since 2000, the world has seen a dramatic increase in the number of people with diabetes. According to the International Diabetes Federation (IDF), 8.8% of the adult population have diabetes, with men having slightly higher rates (9.6%) than women (9.0%). Current global statistics shows that 463 million and 374 million individuals have diabetes and impaired glucose tolerance (IGT), a prediabetic condition. These numbers are estimated to increase to 700 million people with diabetes and 548 million people with IGT by 2045, which represents a 51% increase compared to 2019.

Among the IDF regions, the Western Pacific has the highest number of people with diabetes (163 million), followed by the South-East Asian region (88 million), Europe (59 million), Middle East and North Africa (55 million), and North America and Caribbean (47.6 million). Currently, the lowest numbers are found in South and Central America (36.1 million) and Africa (19.4 million). According to the IDF in 2019, the top three countries with the highest number of individuals with diabetes are China (116.4 million), India (77.0 million), and the United States of America (31.0 million). This trend is expected to continue in 2030 and 2045, with China (140.5 and 147.2 million) and India (101.0 and 134.2 million) continuing to have the highest burden of diabetes. This is supported by the Global Burden of Disease Study, which reported that population growth and ageing in the world's largest countries, such as China and India, are driving the absolute increase in the number of people with diabetes[10-13].

According to prevalence estimates by IDF, the diabetes burden is growing faster in low- and middle-income countries (367.8 million) than in high-income countries (95.2 million). The Global Burden of Disease study conducted in 195 countries and territories provided a detailed overview of the numbers, rates, and rising trends in the diabetes burden between 1990 and 2025. This study also reported that the low- and middle-income regions had higher burden of diabetes, while the high-income regions had lower burden of diabetes. This study reported that the number of people with incident diabetes increased from 11.3 to 22.9 million between 1990 and 2017 (an increase by 102.9%) and the number of prevalent diabetes increased from 211.2 to 476.0 million (an increase by 129.7%), respectively. Furthermore, modifiable metabolic, environmental, and behavioral factors were found to be the major risk factors for diabetes burden.

Another cause for concern is the high percentage of individuals with undiagnosed diabetes, which is currently more than 50%. This is observed mainly in developing economies due to less developed health care systems. It is estimated that approximately 231.9 million (one in two) of adults with diabetes are undiagnosed worldwide. According to reports, nearly 59.7% of people with diabetes in Africa are unaware of their disease (the highest such proportion among all regions), while only 37.8% of people with diabetes in North America and the Caribbean are unaware of their disease (the lowest proportion among all the regions). When compared to other IDF regions, Africa and South and Central America have a lower number of individuals with undiagnosed diabetes (11.6 and 13.3 million, respectively). According to these estimates, there is an urgent need for improved diabetes screening. They also highlight the importance of identifying undiagnosed diabetes and providing appropriate and timely care as

undiagnosed diabetes can have negative consequences such as an increased risk of diabetes related complications, increased healthcare use, and associated costs.

Burden of Diabetes in India

Diabetes has steadily increased in India and around the world over the last three decades, with India accounting for a sizable portion of the global burden. India's disease patterns have shown a switch due to an epidemiological transition: thus mortality from communicable, maternal, neonatal, and nutritional diseases (CMNNDs) has decreased significantly, while NCDs and injuries have markedly increased their contribution to overall disease burden and mortality. Across India, the disease burden or DALY rate in 2016 was 4-fold for diabetes, and when looked at the leading individual causes of DALYs in India, most NCDs have risen in rank since 1990, with diabetes showing a dramatic increase, from 35th place in 1990 to 13th place in 2016.

Prevalence of diabetes and trends over time

In India, the burden of diabetes has been increasing steadily since 1990 and leaps and at a faster pace from the year 2000. The prevalence of diabetes in India has risen from 7.1% in 2009 to 8.9% in 2019. India ranks second after China in the global diabetes epidemic with 77 million people with diabetes. Of these, 12.1 million are aged >65 years, which is estimated to increase to 27.5 million in the year 2045. It is also estimated that nearly 57% of adults with diabetes are undiagnosed in India, which is approximately 43.9 million. The mean healthcare expenditure on diabetes per person is 92 US dollars, and total deaths attributable directly to diabetes account for 1 million[14-16].

Incidence of diabetes

Apart to from the rising prevalence of diabetes in India, the incidence of diabetes are also rising steadily, with a fast transition from euglycemia to prediabetes and diabetes. In India, very few longitudinal studies have been conducted to assess the incidence of diabetes and prediabetes. In the Chennai Urban Population Study cohort, diabetes and prediabetes incidence rates were reported to be 20.2 and 13.1 per 1000 person-years, respectively, while the follow-up study conducted in the Chennai Urban Rural Epidemiology Study (CURES) cohort reported the incidence rates of diabetes, prediabetes, and any dysglycemia to be 22.2, 29.5, and 51.7 per 1000 person-years, respectively.

In Kerala, participants of the Study of Life Style Diseases in Central Kerala were followed up over a 10-year period from two semiurban wards of Venmony Panchayat of Alappuzha district. The incidence rate of type 2 diabetes and impaired fasting glucose (IFG) were 24.5 per 1000 person-years and 45.01 per 1000 person-years, respectively. During the follow-up period, nearly 60% of participants with baseline IFG converted to type 2 diabetes.

Morbidity and mortality

Diabetes is well known for its systemic impact on a wide range of diabetes-related complications, including macrovascular and microvascular complications and death among the most feared outcomes. In addition, recently diabetes is also being linked to nontraditional complications such as mental health, cancer, disability, and liver disease. Diabetic retinopathy is recognized as the most specific complication of diabetes and has been used to guide diabetes diagnostic thresholds. The prevalence of diabetic retinopathy has been estimated to be 17.6% among adults with diabetes in urban South India. Spectrum of eye disorders in diabetes in India report, pan-India facility-based study, concluded that diabetic retinopathy was prevalent in one-third and sight-threatening diabetic retinopathy in one-fifth of people with type 2 diabetes presenting at 14 eye-care facilities. The relatively high prevalence of diabetic complications in developing economies like India could be due to delay in diagnosis of diabetes as well as complications, coexisting illness, inadequate health care systems, and high drug cost, particularly insulin leading to poor control of diabetes.

Diabetes, along with its complications, is a leading cause of mortality. The South East Asian region has the second highest number of deaths attributable to diabetes in adults among the IDF Regions, with 1.2 million deaths in 2019, with India contributing the lion's share with more than 1 million estimated deaths accountable to diabetes and related complications. The Prospective Urban Rural Epidemiology study which compared CV events, all-cause mortality, and CV mortality rates among 143,567 adults with and without diabetes in 21 countries including India with different income levels reported that CVD rates, all-cause mortality, and CV mortality were markedly higher among those with diabetes in low-income countries compared with middle- and high-income countries.

There are as yet no large-scale Indian studies on mortality in patients with type 2 diabetes, and most available studies are from clinical settings and therefore have shown different results. In a retrospective study from Srinagar of 234,776 inpatient admissions, 16,690 died, of whom 4.4% had diabetes. Of the top five causes of death, infections were reported by 41%, chronic renal failure by 33.6%, CAD by 16.9%, cerebrovascular disease by 13.2%, and chronic obstructive pulmonary disease by 6.9%. A follow-up of the CURES cohort reported overall mortality rate to be nearly 4-fold higher in people with diabetes compared to those without diabetes (27.9 per 1000 person-years vs. 8.0 per 1000 person-years). The study also illustrated that ischemic heart disease and diabetes had the highest population-attributable risk for all-cause mortality in the entire study cohort.

Risk Factors

The etiology of diabetes is believed to be multifactorial. Many individual-level nonmodifiable risk factors like genetic, age, ethnicity, and family history have been prospectively associated with type 2 diabetes, but the increases in prevalence in most populations have probably been driven by a modifiable risk factors including sedentary lifestyle and/or lack of exercise, increasing prevalence of overweight/obesity, unhealthy diets (increased intake of refined grains, fat, sugar, and sweetened beverages and decreased intake of fruits and vegetables) and habits (smoking and alcohol abuse), exposure to environmental pollutants, altered intrauterine environment and mental health (stress/depression), short sleep duration, and the built

environment. Tobacco use, which was accountable for 6% of the total disease burden in India in 2016, is another significant contributor to CVD and diabetes, as well as cancer and some other diseases. The Global Burden of Disease Study 2016, reported obesity, low-dietary intake of fruits, nuts and seeds, and whole grains, and tobacco use to be the most important risk factors for DALYs and deaths due to diabetes.

Strategies to tackle the Epidemic of Diabetes in India

The rising rates of prediabetes, diabetes, and associated complications in urban as well as in rural areas and among the young in India are of great concern. Addressing health issues related to diabetes in India, which is the second-most populous country and has a large and diverse population, poses many challenges. The specific challenges in diabetes prevention/management are (i) lack of strong national partnerships for multisectoral actions, (ii) lack of availability of robust surveillance and research data on diabetes, (iii) abysmally low disease awareness among the public, (iv) lack of access to basic prevention/management of diabetes in the primary health care setting, which includes access to affordable medicines leading to premature deaths, (v) disproportionate fund allocation for diabetes programs, (vi) difficulties in engaging the industry and private sector, (vii) limited human resources, and (viii) inadequate community mobilization and weak coordination among civil societies and between the civil societies and government agencies for diabetes[17-19].

Tackling diabetes calls for a fundamental change, from addressing each risk factor separately to collectively addressing a cluster of risk factors in an integrated manner, and from using a biomedical approach to a public health approach. Thus, when planning prevention/control programs, a multifaceted approach is essential for success. Diabetes prevention/control strategies include (i) reduction in exposure to lifestyle risk factors through health promotion and primary prevention, (ii) early detection and timely treatment, and (iii) surveillance to monitor trends in diabetes and associated risk factors. High levels of commitment and multisectoral actions are needed to reduce the growing burden of diabetes in India. Some of the policies that may help to slow down the epidemic of diabetes in India include (i) national food policies targeting availability and accessibility of healthy and nutritious foods, ensuring that the food industry strictly complies with norms of food safety and standards and supporting production and distribution of healthy foods (whole grains, fruit, vegetables, legumes, and nuts), (ii) health policies to reduce harmful behaviors such as smoking, alcohol misuse, use of trans fat, and consumption of junk foods and increase physical activity by the creation of amenities such as public spaces (e.g., parks) for walking, cycling, etc., (iii) prevention policies such as health information and communication to improve population awareness, and (iv) policies to reduce the cost of essential drugs and ensuring reasonable access to care. All these efforts need a healthy collaboration between health, information, education, and agriculture ministries to create awareness and to facilitate a healthy lifestyle among the Indian population.

3. Pathophysiology

A patient with DM has the potential for hyperglycemia. The pathology of DM can be unclear since several factors can often contribute to the disease. Hyperglycemia alone can impair pancreatic beta-cell function and contributes to impaired insulin secretion. Consequentially, there is a vicious cycle of hyperglycemia leading to an impaired metabolic state. Blood glucose levels above 180 mg/dL are often considered hyperglycemic in this context, though because of the variety of mechanisms, there is no clear cutoff point. Patients experience osmotic diuresis due to saturation of the glucose transporters in the nephron at higher blood glucose levels. Although the effect is variable, serum glucose levels above 250 mg/dL are likely to cause symptoms of polyuria and polydipsia.

Insulin resistance is attributable to excess fatty acids and proinflammatory cytokines, which leads to impaired glucose transport and increases fat breakdown. Since there is an inadequate response or production of insulin, the body responds by inappropriately increasing glucagon, thus further contributing to hyperglycemia. While insulin resistance is a component of T2DM, the full extent of the disease results when the patient has inadequate production of insulin to compensate for their insulin resistance. Chronic hyperglycemia also causes nonenzymatic glycation of proteins and lipids. The extent of this is measurable via the glycation hemoglobin (HbA1c) test. Glycation leads to damage in small blood vessels in the retina, kidney, and peripheral nerves. Higher glucose levels hasten the process. This damage leads to the classic diabetic complications of diabetic retinopathy, nephropathy, and neuropathy and the preventable outcomes of blindness, dialysis, and amputation, respectively.

Evaluation

The diagnosis of T1DM is usually through a characteristic history supported by elevated serum glucose levels (fasting glucose greater than 126 mg/dL, random glucose over 200 mg/dL, or hemoglobin A1C (HbA1c exceeding 6.5%) with or without antibodies to glutamic acid decarboxylase (GAD) and insulin. Fasting glucose levels and HbA1c testing are useful for the early identification of T2DM. If borderline, a glucose tolerance test is an option to evaluate both fasting glucose levels and serum response to an oral glucose tolerance test (OGTT). Prediabetes, which often precedes T2DM, presents with a fasting blood glucose level of 100 to 125 mg/dL or a 2-hour post-oral glucose tolerance test (post-OGTT) glucose level of 140 to 200 mg/dL. According to the American Diabetes Association (ADA), a diagnosis of diabetes is through any of the following: An HbA1c level of 6.5% or higher; A fasting plasma glucose level of 126 mg/dL (7.0 mmol/L) or higher (no caloric intake for at least 8 hours); A two-hour plasma glucose level of 11.1 mmol/L or 200 mg/dL or higher during a 75-g OGTT; A random plasma glucose of 11.1 mmol/L or 200 mg/dL or higher in a patient with symptoms of hyperglycemia (polyuria, polydipsia, polyphagia, weight loss) or hyperglycemic crisis. To test for gestational diabetes, all pregnant patients have screening between 24 to 28 weeks of gestation with a 1-hour fasting glucose challenge test. If blood glucose levels are over 140mg/dL,

patients have a 3-hour fasting glucose challenge test to confirm a diagnosis. A positive 3-hours OGTT test is when there is at least one abnormal value (greater than or equal to 180, 155, and 140 mg/dL for fasting one-hour, two-hour, and 3-hour plasma glucose concentration, respectively).

The HbA1c test indicates the extent of glycation due to hyperglycemia over three months (the life of the red blood cell). Urine albumin testing can identify the early stages of diabetic nephropathy. Since patients with diabetes are also prone to cardiovascular disease, serum lipid monitoring is advisable at the time of diagnosis. Similarly, some recommend monitoring thyroid status by obtaining a blood level of thyroid-stimulating hormone annually due to a higher incidence of hypothyroidism[20-21].

Management of Diabetes mellitus

The physiology and treatment of diabetes are complex and require a multitude of interventions for successful disease management. Diabetic education and patient engagement are critical in management. Patients have better outcomes if they can manage their diet (carbohydrate and overall caloric restriction), exercise regularly (more than 150 minutes weekly), and independently monitor glucose. Lifelong treatment is often necessary to prevent unwanted complications. Ideally, glucose levels should be maintained at 90 to 130 mg/dL and HbA1c at less than 7%. While glucose control is critical, excessively aggressive management may lead to hypoglycemia, which can have adverse or fatal outcomes.

Since T1DM is a disease primarily due to the absence of insulin, insulin administration through daily injections, or an insulin pump, is the mainstay of treatment. In T2DM, diet and exercise may be adequate treatments, especially initially. Other therapies may target insulin sensitivity or increase insulin secretion by the pancreas. The specific subclasses for drugs include biguanides (metformin), sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, glucagonlike-peptide-1 agonist, dipeptidyl peptidase IV inhibitors (DPP-4), selective, amylinomimetics, and sodium-glucose transporter-2 (SGLT-2) inhibitors. Metformin is the first line of the prescribed diabetic medications and works by lowering basal and postprandial plasma glucose. Insulin administration may also be necessary for T2DM patients, especially those with inadequate glucose management in the advanced stages of the disease. In morbidly obese patients, bariatric surgery is a possible means to normalize glucose levels. It is recommended for individuals who have been unresponsive to other treatments and who have significant comorbidities. The GLP-1 agonists liraglutide and semaglutide correlate with improved cardiovascular outcomes. The SGLT-2 inhibitors empagliflozin and canagliflozin have also shown to improve cardiovascular outcomes along with potential renoprotection as well as prevention for the development of heart failure.

Regular screenings are necessary since microvascular complications are a feared complication of diabetes. Regular diabetic retinal exams should be performed by qualified medical personnel to assess for diabetic retinopathy. Neurologic examination with monofilament testing can identify patients with neuropathy at risk for amputation. Clinicians can also recommend patients perform daily foot inspections to identify foot lesions that may go unnoticed due to neuropathy. Low-dose tricyclic antidepressants, duloxetine, anticonvulsants, topical capsaicin, and pain medications may be necessary to manage neuropathic pain in diabetes. Urine microalbumin testing can also assess for early renal changes from diabetes with albuminuria greater than 30mg/g creatinine along with the estimated GFR. The antiproteinuric effect of the angiotensin-converting enzyme (ACE) inhibitors and the angiotensin receptor blockers (ARBs) makes them the preferred agents to delay the progression from microalbuminuria to macroalbuminuria in patients with both Type 1 or Type 2 diabetes mellitus. The FDA has approved pregabalin and duloxetine for the treatment of diabetic peripheral neuropathy. Tricyclic antidepressants and anticonvulsants have also seen use in the management of the pain of diabetic neuropathy with variable success[26].

The ADA also recommends regular blood pressure screening for diabetics, with the goal being 130 mmHg systolic blood pressure and 85 mmHg diastolic blood pressure. Pharmacologic therapy for hypertensive diabetics typically involves angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, beta-blockers, and/or calcium channel blockers. The ADA recommends lipid monitoring for diabetics with a goal of low-density lipoprotein cholesterol (LDL-C) being less than 100 mg/dL if no cardiovascular disease (CVD) and less than 70 mg/dl if atherosclerotic cardiovascular disease (ASCVD) is present. Statins are the first-line treatment for the management of dyslipidemia in diabetics.

Diabetic complications:

Regardless of the specific type of diabetes, complications involve microvascular, macrovascular, and neuropathic issues. Microvascular and macrovascular complications vary according to the degree and the duration of poorly control diabetes and include nephropathy, retinopathy, neuropathy, and ASCVD events, especially if it is associated with other comorbidities like dyslipidemia and hypertension. DM is also a common cause of blindness in adults aged 20 to 74 years in the United States. Diabetic retinopathy contributes to 12000 to 24000 new cases of blindness annually, and treatments generally consist of laser surgery and glucose control.

Renal disease is another significant cause of morbidity and mortality in DM patients. It is the leading contributor to end-stage renal disease (ESRD) in the United States, and many patients with ESRD will need to start dialysis or receive a kidney transplant. If the albuminuria persists in the range of 30 to 300 mg/day (microalbuminuria), it seems to be a predictable earliest marker for the onset of diabetic neuropathy. Once macroalbuminuria (greater than 300 mg/24 hr) sets in, the progression to ESRD hastens up. The random spot urine specimen for measurement of the albumin-to-creatinine ratio is a quick, easy, predictable method that is the most widely used and preferred method to detect microalbuminuria. Two of three tests, done over a six month showing a persistent level greater than 30

mcg/mg creatinine, confirms the diagnosis of microalbuminuria. Diabetes mellitus is the leading cause of limb amputations in the United States; this is primarily due to vasculopathy and neuropathy associated with DM. The duration of diabetes is the most crucial risk factor for the development of diabetic retinopathy. In people with type 1 diabetes, it typically sets in about 5 years after disease onset. Hence it is recommended to start the yearly retinal exams in these patients about five years after diagnosis. Among patients with type 2 diabetes, many patients might already have retinal changes at the time of diagnosis. Approximately 10% at ten years, 40% at 15 years, and 60% at 20 years will have nonproliferative retinal disease. In these patients, the recommendation is to start the yearly retinal screening at the time of diagnosis. Study after study has shown that reasonable glycemic control favorably affected the onset and progression of diabetic retinopathy. Uncontrolled blood pressure is an added risk factor for macular edema. Lowering the blood pressure in patients with diabetes thus also affects the risk of progression of the retinopathy. Injection of antibodies vascular endothelial growth factor (anti-VEGF) agents are generally in use as the initial therapy in cases of macular edema. In cases of nonproliferative diabetic retinopathy, pan-retinal photocoagulation is being used. In cases of diabetic proliferative retinopathy, combined modalities of anti-VEGF agents and pan-retinal photocoagulation are now in use. Sudden loss of vision can occur for several reasons in patients with diabetes mellitus, the most common being vitreous hemorrhage. Less common causes that merit consideration include vascular occlusion (central retinal vein or branch vein occlusion involving the macula), retinal detachment, end-stage glaucoma, and ischemic optic neuropathy.

Those with gestational diabetes are at a higher risk for cesarean delivery and chronic hypertension. Pregnant patients with T2DM generally have a better prognosis in terms of neonatal and pregnancy complications compared to those with T1DM. Generally, neonates of DM mothers will present with hypoglycemia and macrosomia. The most acute complication of DM is diabetic ketoacidosis (DKA), which typically presents in T1DM. This condition is usually either due to inadequate dosing, missed doses, or ongoing infection. In this condition, the lack of insulin means that tissues are unable to obtain glucose from the bloodstream. Compensation for this causes the metabolism of lipids into ketones as a substitute energy source, which causes systemic acidosis, and can be calculated as a high anion-gap metabolic acidosis. The combination of hyperglycemia and ketosis causes diuresis, acidemia, and vomiting leading to dehydration and electrolyte abnormalities, which can be life-threatening. In T2DM, hyperosmolar hyperglycemic syndrome (HHS) is an emergent concern. It presents similarly to DKA with excessive thirst, elevated blood glucose, dry mouth, polyuria, tachypnea, and tachycardia. However, unlike DKA, HHS typically does not present with excessive urinary ketones since insulin still gets produced by pancreatic beta cells. Treatment for DKA or HHS involves insulin administration and aggressive intravenous hydration. Careful management of electrolytes, particularly potassium, is critical in the management of these emergent conditions.

Prevention and screening of Diabetes mellitus

Primary prevention

Randomized clinical trials in several countries have provided evidence that, in high-risk individuals with IGT, progression to type 2 diabetes can be reduced by intensive lifestyle intervention with diet or physical activity, or with drug therapy using glucose-lowering agents such as metformin.[20] In addition to their clinical effectiveness, there is now also evidence for the cost effectiveness of these interventions. The challenges that remain are to determine how high-risk individuals should be identified, and how lifestyle changes of healthier diet and regular physical activity can be sustained The evidence from randomized controlled trials that diabetes can be prevented does not prove that intervention in high-risk individuals is the most appropriate strategy for prevention in real world settings. As in many areas of primary prevention, high-risk approaches can be effective for the individuals included in the programmes but have a limited impact on the public health burden of diabetes. Complementary approaches that seek to make small shifts in the population distribution of dietary and physical activity behaviours are required. Such approaches make relatively little difference in risk at the individual level but have a major impact on the public health burden of diabetes when that risk reduction is summated across large numbers of people in the population. The future challenge involves finding ways of integrating high-risk and population approaches to prevention, and balancing relative investment in the two strategies.

Secondary prevention:

Diabetic screening

As it is estimated that the onset of type 2 diabetes occurs an average of about 4–7 years before clinical diagnosis, and as a high proportion of individuals exhibit evidence of end-organ damage by that point, screening has been proposed in the hope that early detection and early treatment would reduce long-term burden. However there is no definitive evidence that screening results in net benefit and most authorities have proposed opportunistic rather than systematic screening targeting high-risk sub-groups.

Lifestyle Changes prevention of Diabetes mellitus

After the T2D diagnosis, initial treatments usually involve altering diet and lifestyle, as well as increasing physical activity in combination with metformin.[3] Metformin decreases hepatic glycogenolysis, decreases peripheral tissue insulin resistance, increases GLP-1 postprandial secretion (which augments insulin secretion), and delays digestion.[8] Exercise and weight loss also reduce insulin resistance and reduce the risk of T2D associated post-diagnosis complications. If this treatment regime is ineffective at promoting normoglycaemia then sulfonylureas and meglitinides are usually the next treatments tried which act as insulin secretagogues. Common side effects of insulin secretagogues include weight gain and hypoglycaemia, and these drugs are only usually effective in the short term. Insulin therapy, in the form of multiple daily subcutaneous injections, is effective at lowering plasma glucose levels and is usually required in the majority of patients when the aforementioned treatment

regimens fail, but there are several side effects, such as weight gain, hypoglycaemia and increased risk of colorectal cancer.

GLP-1 analogues were also shown to confer lower hypoglycemia risk versus insulin or sulfonylureas. Additionally, GLP-1 analogues also appear to decrease the risk of cardiovascular pathology in patients, according to some studies, and preliminary data suggest they do so to a greater degree than other oral glucose-lowering drugs[27-30].

Small Molecule Agonists

Studies have demonstrated that GLP-1R has allosteric agonist binding sites and that these sites are distinct from the orthosteric agonist (GLP-1) binding site.[3] The first allosteric agonist identified for GLP-1R was compound 1, which had a low affinity and a low potency for GLP-1R.[3] Compound 2 was then produced, which has been shown to be a more potent agonist, and this molecule also increases the affinity of GLP-1R for GLP-1.

Surgical Options for T2D: Bariatric Surgery

Bariatric surgery includes a variety of procedures performed on the GIT in people who are severely obese (BMI ≥40) or in individuals with a BMI of ≥35 that have a condition that can be improved by losing weight such as T2D or high blood pressure. Weight loss is achieved by reducing the size of the stomach with a gastric band or by removing a portion of the stomach (sleeve gastrectomy or biliopancreatic diversion with duodenal switch), and resecting and re-routing the small intestine to a small stomach pouch (gastric bypass surgery) is another surgical option to promote weight loss. Reduction in the size of the stomach results in patients experiencing satiety with less food and the bypass means that fewer nutrients will be ingested as part of the intestine will no longer be involved in digestion[31-34].

4. Conclusion

Diabetes has already become a leading threat to public health globally and the picture becomes grimmer for the low- and middle-income countries like India, where the burden has risen significantly in recent decades and will continue to rise in the coming decades[35]. To curb the epidemic of diabetes and its associated complications, there is a need for a multipronged strategy involving early diagnosis of diabetes, screening for its complications, and offering optimal therapy at all levels of care for those who already have diabetes and primary prevention of diabetes in those with prediabetes. A better understanding of metabolic homeostasis in healthy individuals and the altered metabolic phenotype in diabetes mellitus will likely lead to the development of better treatments for diabetes mellitus[36-40]. The role of the nervous system, genetics, hormones involved in metabolic homeostasis, glucolipotoxicity diets and feeding behaviours, sedentary lifestyles, altered islet architecture, the immune system, altered islet-cell behaviour, UCP2, altered extrapancreatic behaviour and risk factors have in diabetes mellitus etiology and pathogenesis remains to be mechanistically understood. Given that T2D is a multifactorial disease involving an array of hormones, their receptors and subsequent intracellular activity, future therapeutic research needs to take into account how the action of all of these hormones interact synergistically in T2D to produce the altered metabolic phenotype, and also how treatments such as GLP-1R activation-based therapies can influence this hormonal synergism to produce a metabolic phenotype more similar to that of a healthy individual.

5. References

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