ISSN: 2456-043X

International Journal of Engineering Science and Generic Research (IJESAR)

Available Online at www.ijesar.in

Volume 11; Issue2; 2025; Page No. 10-21

Review of Diabetes Mellitus: Prevalence, Impact, and Treatment Strategies

Sagar, Simran Kaur, Anjali, Amar Pal Singh, Ajeet Pal Singh

Department of Pharmacy, St. Soldier Institution of Pharmacy, Lidhran Campus, Behind NIT (R.E.C), Jalandhar -Amritsar By Pass Nh-1, Jalandhar, Punjab, India

Abstract

Diabetes mellitus is one of the most prevalent endocrine disorders globally, characterized by chronic high blood sugar levels due to either insulin deficiency or resistance. The two main types of diabetes, Type 1 (T1DM) and Type 2 (T2DM), pose significant health challenges. Type 1 diabetes is an autoimmune condition that primarily affects children and young adults, while Type 2 diabetes, characterized by insulin resistance, is predominantly found in adults and is increasingly common in low- and middle-income countries. This review highlights the rising global prevalence of diabetes, with projections indicating that by 2030, over 550 million people will be affected. The disease contributes to a variety of severe complications, including cardiovascular disease, kidney failure, retinopathy, nerve damage, and amputations, significantly impacting individuals' quality of life and healthcare systems. The primary objective of diabetes management is to maintain blood glucose levels within a target range to reduce the risk of long-term complications. This is achieved through a combination of lifestyle modifications, such as diet and physical activity, and pharmacological therapies. Insulin therapy remains essential for managing T1DM, while oral antidiabetic drugs (OADs) are often the first-line treatment for T2DM. Despite the availability of various treatment options, managing diabetes effectively requires a personalized approach, considering individual factors and disease progression. This review emphasizes the importance of early diagnosis, prevention strategies, and the role of both pharmacological and non-pharmacological interventions in the management of diabetes mellitus.

Keyword: Antidiabetic drug, Diabetes mellitus and types, Treatment, Side effects

Introduction

Diabetes is the most common endocrine disease. It is a combination of several conditions that frequently appear with incidents of high blood sugar and glucose intolerance. Insulin deficiency or the pancreas' insufficient synthesis of insulin is the cause of this disease.[1] It has been shown to damage several systems of the body, including the heart, kidneys, eyes, blood vessels, and nerves.[2] Diabetes mellitus increases the risk of several implications including peripheral vascular disease, cardiovascular disease, stroke, vision loss, retinopathy, loss of limbs nerve damage, kidney failure, etc.[3] According to reports, 4.6 million people died from Diabetes in 2011, whereas 366 million people had the disease.[4] In 2030, there are expected to be 552 million individuals with diabetes mellitus. In every country, the number of persons with type 2 diabetes (T2DM) is increasing, and 80% of people with DM live in countries with low or middle incomes. [5]The primary goal of antidiabetic treatment is to maintain blood glucose levels within a target range, thus reducing the risk of long-term complications. The treatment strategy often includes lifestyle changes like diet modification and regular physical activity. Pharmacological therapy is an essential component for managing diabetes, and it involves both insulin therapy and the use of oral antidiabetic drugs (OADs). Insulin therapy is a cornerstone for managing Type 1 diabetes and is also prescribed for some individuals with

Type 2 diabetes, especially when oral medications are not sufficient to control blood glucose. Insulin helps lower blood glucose by facilitating glucose uptake into cells, thereby preventing hyperglycemia. However, insulin therapy requires careful dosing and monitoring to avoid the risk of hypoglycemia.[6] The treatment of diabetes involves a combination of lifestyle changes and pharmacological interventions. While lifestyle modifications, such as maintaining a healthy diet, engaging in regular physical activity, and controlling weight, are essential in managing both types of diabetes, pharmacological treatments play a crucial role in blood glucose control, particularly in T2D. Antidiabetic drugs are used to control blood sugar levels, alleviate symptoms, and prevent long-term complications. These drugs can be categorized into various classes based on their mechanisms of action, such as oral medications and injectable agents. [7]Diabetes mellitus is divided into two categories: type 1 (insulin-dependent) and type 2 (noninsulin-dependent). As opposed to type 2 diabetes, which is defined by systemic insulin resistance and decreased insulin production, type 1 diabetes is an autoimmune illness characterized by an inflammatory response in and around islets, followed by the selective death of cells that secrete insulin. [8] Type 1 diabetes (T1DM), also known as childhood diabetes, frequently occurs in children and young people.

This type of diabetes only affects 5% of patients. T2DM is responsible for 90% to 95% of each case of diabetes and is the most frequent type of the disease. [9]

Rationale:

Type 1 (T1DM) and Type 2 (T2DM), lies in the growing global prevalence of the disease and its significant health and economic impacts. Diabetes is a leading cause of morbidity and mortality worldwide, affecting millions and resulting in complications that can severely impair an individual's quality of life. The fact that 80% of individuals with diabetes live in low- and middle-income countries underscores the need for targeted interventions in these regions, where access to healthcare and diabetes management resources may be limited. As the number of diabetes cases continues to rise—predicted to reach 552 million by 2030—the urgency for effective prevention, early detection, and treatment becomes ever more pressing. The increasing burden of diabetes is compounded by its complications, which can lead to life-threatening conditions such as cardiovascular disease, kidney failure, vision loss, and nerve damage. These complications not only threaten the health of individuals but also place a substantial strain on healthcare systems, driving up medical costs and diverting resources. Type 2 diabetes, which accounts for the majority of cases, is strongly linked to lifestyle factors such as obesity, physical inactivity, and poor diet. This makes the role of lifestyle changes, such as diet modification and regular exercise, central to both preventing and managing the disease.

- **Epidemiology and Etiology of Type 1 Diabetes (IDDM):**

About 20 million people worldwide suffering with type 1 diabetes, which is responsible for 10% of all cases of the disease. [10]All age groups are affected by type 1 diabetes; however, most people receive a diagnosis between the ages of 4 and 5 or in their teens and early maturity. [11]Type 1 diabetes is becoming more common. The incidence of asthma in children under the age of 15 has increased by 3.4% on average per year through Europe.[12] with children under the age of five having the highest increase .[13]An autoimmune response to proteins found in the pancreatic islets cells causes type 1 diabetes.[14] Family members of IDDM patients have a higher frequency of autoimmune illnesses, and there is a clear correlation between IDDM and other endocrine auto immunities, such as Addison's disease.

- **Pathogenesis of Type 1 diabetes mellitus**

Type 1 diabetes mellitus (T1DM) is an autoimmune disease where the immune system

mistakenly attacks and destroys the insulin-producing β-cells in the pancreas. The cause of T1DM is a combination of genetic and environmental factors. Genetic predisposition plays a key role, particularly involving specific variations in the HLA gene region, such as HLA-DR3 and HLA-DR4, which make individuals more susceptible to immune attacks on β-cells. However, genetics alone do not cause the disease; environmental triggers are also necessary. These may include viral infections like coxsackievirus, which can initiate an immune response against the β-cells. Early-life factors, such as diet, may also contribute to the disease, though the evidence is still not conclusive. In the immune system's response, the body produces autoantibodies that target specific components of β-cells, such as glutamic acid decarboxylase (GAD65) and insulin. Along with autoantibodies, T-cells (a type of immune cell) attack and destroy the β-cells. This leads to insulitis, an inflammatory condition where immune cells invade the pancreatic islets. Over time, as more β-cells are destroyed, the pancreas loses its ability to produce insulin, a hormone needed to regulate blood sugar. Without insulin, blood sugar levels rise, leading to symptoms like frequent urination, extreme thirst, and weight loss. The diagnosis of T1DM is confirmed by blood tests showing high blood sugar levels and the presence of specific autoantibodies. This progressive destruction of β-cells results in lifelong insulin dependency for affected individuals. [15,16,17]

- **Epidemiology of Type 2 Diabetes:**

Type 2 diabetes mellitus (T2DM) is one of the most significant global public health challenges, with its prevalence steadily rising in both developed and developing countries. According to the World Health Organization (WHO), more than 400 million people worldwide are affected by diabetes, with approximately 90-95% of these cases being type 2 diabetes. [18]The global prevalence of T2DM continues to increase, driven largely by factors such as population aging, urbanization, sedentary lifestyles, and changes in dietary patterns.

- **Global Prevalence and Trends**

The global burden of T2DM is expected to rise further, with estimates predicting that the number of people with diabetes will reach nearly 700 million by 2045. [19]This sharp increase is primarily attributed to the rapid urbanization and adoption of unhealthy lifestyle behaviours, especially in low- and middle-income countries. The highest rates of T2DM are found in regions such as the Middle East, North Africa, and the Pacific Islands, where obesity and poor dietary habits are highly prevalent. In terms of age, T2DM typically affects individuals over 45 years of age, though it is becoming increasingly common among younger populations. The age of onset has been dropping, with rising numbers of adolescents and young adults being diagnosed with T2DM, a trend strongly linked to the global obesity epidemic. [20]In the United States, the Centres for Disease Control and Prevention (CDC) reports that about 1 in 10 adults have diabetes, with a substantial proportion of these cases being undiagnosed. The rising prevalence in younger populations highlights the growing concern of early-onset diabetes, which can lead to increased morbidity and mortality if not effectively managed.

- **Ethnic and Racial Disparities**

T2DM also exhibits significant ethnic and racial disparities. In the United States, certain ethnic groups are at a higher risk of developing T2DM. Native Americans, African Americans, Hispanic/Latino populations, and Pacific Islanders have a substantially higher risk of developing diabetes compared to non-Hispanic White individuals.[19] These disparities can be attributed to a complex interplay of genetic predisposition, socioeconomic factors, and cultural lifestyle habits. Genetic factors may influence insulin sensitivity and β-cell function, which are crucial in the pathogenesis of T2DM. Environmental factors, such as socioeconomic status, access to healthcare, and lifestyle

behaviours (including diet and physical activity), also contribute to these disparities. [21]

- **Gender Differences**

While T2DM is more common in both men and women globally, gender differences exist in its clinical presentation and progression. In general, men tend to develop T2DM at a younger age and may experience more severe complications earlier. Women, on the other hand, may be more prone to developing diabetes during pregnancy (gestational diabetes), which is a known risk factor for developing T2DM later in life. [22]Additionally, postmenopausal women have an increased risk of T2DM due to hormonal changes that affect insulin sensitivity and fat distribution, particularly abdominal obesity.

- **Complications and Comorbidities**

T2DM is associated with numerous complications that can affect nearly every organ system in the body. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in individuals with T2DM. These patients are also at a higher risk of developing diabetic retinopathy, nephropathy, neuropathy, and amputations. The presence of comorbidities, such as hypertension, dyslipidaemia, and obesity, further exacerbates the risk of cardiovascular events and complications. [23]The financial burden of T2DM is also significant, as it accounts for a large portion of healthcare expenditures due to both direct medical costs and lost productivity.

- **Aetiology of Type 2 Diabetes:**

The ethology of T2DM is multifactorial, involving complex interactions between genetic predisposition, environmental factors, and lifestyle choices. Unlike type 1 diabetes, which is an autoimmune disorder, T2DM primarily involves insulin resistance and β-cell dysfunction, resulting in impaired glucose regulation and elevated blood glucose levels. The following are key factors in the pathogenesis of T2DM:

- **Genetic Factors**

Genetic susceptibility plays a crucial role in the development of T2DM. First-degree relatives of individuals with T2DM have a significantly higher risk of developing the disease themselves. Several genetic variants associated with insulin resistance, β-cell function, and glucose metabolism have been identified, although no single gene has been found to cause T2DM. The polygenic nature of the disease means that multiple genetic factors contribute to the risk, making it difficult to predict individual susceptibility based solely on genetics. The TCF7L2 gene has been particularly implicated in T2DM, as it is involved in insulin secretion and glucose metabolism. [24]Family history remains one of the strongest risk factors for T2DM, indicating that genetic predisposition is an important component of the disease. However, genetic factors alone are insufficient to cause the condition, and environmental and lifestyle factors play a significant role in its onset and progression.

- **Obesity and Insulin Resistance**

Obesity is the most significant environmental risk factor for developing T2DM, and the rising rates of obesity are directly linked to the increase in T2DM cases worldwide. Abdominal obesity is closely associated with insulin resistance, which is a hallmark of T2DM. Adipose tissue, especially visceral fat, releases pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which contribute to the development of insulin resistance by impairing insulin signalling pathways.[25] Insulin resistance occurs when the body's cells become less responsive to the effects of insulin, leading to higher insulin levels (hyperinsulinemia) as the pancreas tries to compensate for the reduced effectiveness of insulin. Over time, β-cells in the pancreas can no longer keep up with the demand for insulin, leading to β-cell dysfunction and eventual pancreatic β-cell failure.

- **Dietary Factors and Physical Inactivity**

Diet plays a central role in the development of T2DM. Diets high in refined sugars, unhealthy fats, and processed foods increase the risk of insulin resistance and metabolic syndrome, which includes obesity, hypertension, and dyslipidaemia. The consumption of sugary beverages, high-fat foods, and low-fibre diets can contribute to weight gain, abdominal obesity, and increased insulin resistance. On the other hand, a diet rich in whole grains, fruits, vegetables, and healthy fats can improve insulin sensitivity and help prevent the onset of T2DM. [26]Physical inactivity is another critical factor in the development of T2DM. Regular physical activity helps improve insulin sensitivity and aids in weight management. Sedentary lifestyles, which are increasingly common due to modern work and leisure activities, contribute significantly to the development of insulin resistance and metabolic dysfunction.

- **Age and Hormonal Changes**

Age is a significant risk factor for T2DM. As people age, there is a gradual decline in insulin sensitivity, and β-cell function may decline over time. Hormonal changes, particularly in postmenopausal women, can also affect the development of T2DM. Strogen has been shown to improve insulin sensitivity, and its decline after menopause may contribute to the increased risk of T2DM in older women. [27]

- **Other Risk Factors**

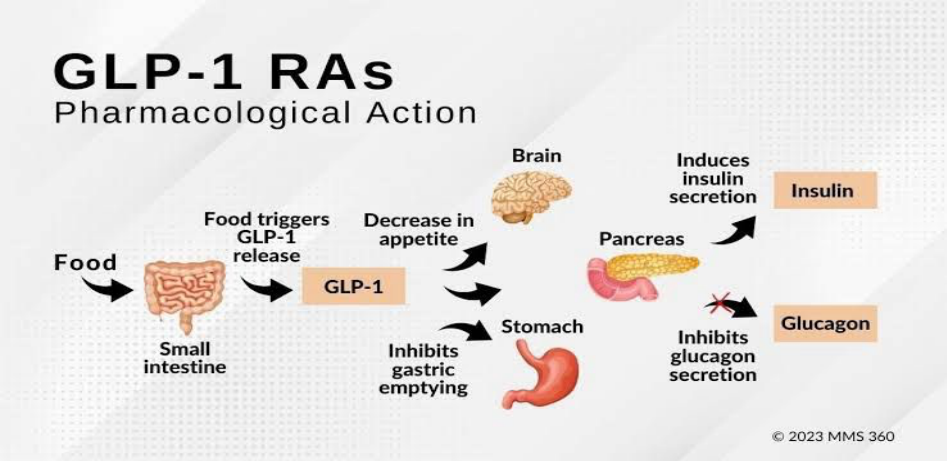
Other factors that increase the risk of T2DM include hypertension, dyslipidaemia, and gestational diabetes. Women who have had gestational diabetes during pregnancy are at a significantly higher risk of developing T2DM later in life. Additionally, individuals with metabolic syndrome, a cluster of conditions including abdominal obesity, high blood pressure, and abnormal cholesterol levels, are at an elevated risk of developing T2DM [28].

Drug Used In Treatment Of Type - 2 Diabetes mellitus: (Semaglutide)

- **Introduction:**

Semaglutide is a medication developed as a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist. It was first approved for use in 2017 by the U.S. Food and Drug Administration (FDA) for the treatment of type 2 diabetes under the brand name Ozempic. [29]It is a synthetic equivalent of the hormone that the intestinal tract naturally manufactures, glucagon-like peptide-1 (GLP-1) receptor agonist, which is essential for controlling blood sugar levels. In order to control blood glucose levels and promote satiety, semaglutide simulates the actions of GLP-1 by increasing insulin secretion in response to meals, inhibiting glucagon release, and slowing stomach evacuation. [30]

- **Mechanism of action:**



[31] Figure 1: Mechanism of action of semaglutide

- **GLP-1 Receptor Activation:**

- Semaglutide mimics the action of the naturally occurring hormone GLP-1, which is released from the intestines after food intake. By binding to GLP-1 receptors in the pancreas, semaglutide stimulates insulin secretion in a glucose-dependent manner, meaning it only stimulates insulin release when blood glucose levels are elevated. This helps lower postprandial (after-meal) blood glucose levels.

- **Inhibition of Glucagon Secretion:**

- Glucagon is a hormone produced by the pancreas that increases glucose production in the liver. Semaglutide suppresses glucagon release, which reduces hepatic glucose production, further contributing to improved glycemic control, especially during fasting states. [32]

- **Slowing of Gastric Emptying:**

- Semaglutide slows gastric emptying, which reduces the rate at which food leaves the stomach and slows the absorption of glucose into the bloodstream. This helps prevent rapid spikes in blood glucose levels after meals. [33]

- **Reduction in Appetite and Weight Loss:**

- Through its effects on the brain, semaglutide promotes satiety (feeling of fullness), which can reduce food intake and lead to weight loss. This is particularly beneficial in managing obesity, which often coexists with type 2 diabetes.

- **Potential Beta-cell Preservation:**

- GLP-1 receptor activation may also have protective effects on pancreatic beta-cells (cells that produce insulin), potentially improving or preserving insulin secretion over time, although this effect is still under investigation. [34]

- **Clinical efficacy of semaglutide:**

1. **Semaglutide for Type 2 Diabetes:**

- SUSTAIN-1 Trial (2017): In the SUSTAIN-1 trial, semaglutide was shown to significantly reduce HbA1c levels and body weight in patients with type 2 diabetes compared to placebo. The reduction in HbA1c was 1.5–1.8%, and patients lost about 4.5–6 kg of body weight on average. [35]

2. **Semaglutide for Cardiovascular Outcomes:**

- SUSTAIN-6 Trial (2016): The SUSTAIN-6 trial showed that semaglutide significantly reduced the risk of cardiovascular events, including heart attack and stroke, by 26% compared to placebo in patients with type 2 diabetes and established cardiovascular disease or at high risk.[36]

3. **Semaglutide for Obesity (STEP Trials):**

- STEP 1 Trial (2021): In the STEP 1 trial, semaglutide demonstrated significant weight loss in patients with obesity or overweight. Participants treated with 2.4 mg of semaglutide lost an average of 14.9% of their body weight compared to 2.4% in the placebo group.[37]

4. **Semaglutide for Weight Loss in Type 2 Diabetes:**

- SUSTAIN-7 Trial (2018): The SUSTAIN-7 trial demonstrated that semaglutide was more effective in reducing body weight compared to other GLP-1 receptor agonists (liraglutide) in patients with type 2 diabetes. The weight loss was significantly greater with semaglutide (about 4.5–6 kg) after 40 weeks. [38]

- **Administration and Dosage of Semaglutide:**

Semaglutide is available in two primary formulations: one for type 2 diabetes and the other for obesity management. Both are administered via subcutaneous injection.

1. **Semaglutide for Type 2 Diabetes:**

- Brand Name: Ozempic
- Dosage Form: Subcutaneous injection (SC)
- Starting Dose: 0.25 mg once weekly for 4 weeks. This is intended as a titration to minimize gastrointestinal side effects.
- Maintenance Dose: After the initial 4-week period, the dose is increased to 0.5 mg once weekly.
- Maximum Dose: If additional glycemic control is needed, the dose can be increased to 1 mg once weekly. In some patients, further increases to 2 mg may be appropriate (based on the individual's glycemic control).
- Administration: The injection is administered once a week on the same day each week, with or without food, at any time of day. It can be injected into the thigh, abdomen, or upper arm.
- Adjustment for Renal Impairment: Semaglutide is not recommended in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or end-stage renal disease.[39]

2. **Semaglutide for Weight Management in Obesity:**

- Brand Name: Wegovy
- Dosage Form: Subcutaneous injection (SC)
- Starting Dose: 0.25 mg once weekly for 4 weeks, to minimize gastrointestinal side effects.
- Titration: The dose is gradually increased every 4 weeks to allow for better tolerance:
  - Week 1-4: 0.25 mg once weekly
  - Week 5-8: 0.5 mg once weekly
  - Week 9-12: 1 mg once weekly
  - Week 13-16: 1.7 mg once weekly
  - Maintenance Dose: After week 16, the target maintenance dose is 2.4 mg once weekly.
- **Maximum Dose:** The maximum dose is 2.4 mg once weekly.
- **Administration:** Similar to Ozempic, the injection is administered once a week on the same day, at any time of day, with or without food. It can be injected in the abdomen, thigh, or upper arm. [40]

➢ **Safety and Side Effects of Semaglutide:**

Semaglutide is generally well-tolerated, but like all medications, it can cause side effects.

- **Common Side Effects:** The most common side effects of semaglutide are gastrointestinal in nature. These include:

1. **Nausea:** This is the most commonly reported side effect, especially during the initial weeks of treatment. The risk of nausea is higher at the start of the dose titration.
2. **Vomiting:** Some patients may experience vomiting, particularly when the dose is increased too rapidly.
3. **Diarrhoea:** Gastrointestinal discomfort, including diarrhoea, is common.
4. **Abdominal Pain:** Some individuals report discomfort in the stomach area.
5. **Constipation:** Although less common, constipation can occur. [41]

- **Serious Side Effects:** Some serious side effects may occur, though they are less common. These include:

1. **Pancreatitis:** Acute pancreatitis is a serious and rare side effect. Patients with a history of pancreatitis or gallstones should be monitored closely.
2. **Thyroid C-cell Tumours:** Animal studies have shown that semaglutide can cause thyroid C-cell tumours, though it is unknown whether the same effect occurs in humans. Patients with a family history of medullary thyroid carcinoma (MTC) or those with multiple endocrine neoplasia syndrome type 2 (MEN 2) should avoid semaglutide.
3. **Hypoglycemia:** While semaglutide itself does not cause hypoglycemia, it may increase the risk of low blood sugar when used in combination with other anti-diabetic medications (such as insulin or sulfonylureas). Monitoring blood glucose levels is essential, especially when adjusting doses of these medications. [42]

4. **Kidney Injury:** In some rare cases, semaglutide has been associated with acute kidney injury. Patients should be monitored for changes in renal function, particularly those with pre-existing kidney conditions.
5. **Gallbladder Disease:** There is a potential increased risk of gallbladder disease, including gallstones, in patients taking semaglutide.[43]

- **Precautions and Contraindications:**

1. **Pregnancy and Breastfeeding:** Semaglutide is not recommended during pregnancy. It is also not recommended while breastfeeding due to potential risks to the infant.
2. **Renal Impairment:** Semaglutide should be used with caution in patients with renal impairment, particularly those with severe renal dysfunction.
3. **History of Pancreatitis or Thyroid Tumors:** As mentioned, patients with a history of pancreatitis or thyroid cancers should avoid using semaglutide.
4. **Alcohol Consumption:** Excessive alcohol consumption should be avoided, as it may exacerbate certain side effects such as hypoglycemia.[44]

- **Interactions of Semaglutide with Other GLP-1 Receptor Agonists:**

1. **Additive Effects on Gastrointestinal Side Effects:**
   - Semaglutide and other GLP-1 receptor agonists (like liraglutide, dulaglutide, exenatide, etc.) share common gastrointestinal side effects such as nausea, vomiting, diarrhoea, and abdominal discomfort. Combining these medications could worsen these adverse effects without providing additional therapeutic benefit.
2. **Risk of Therapeutic Duplication:**
   - Therapeutic duplication occurs when two medications with the same mechanism of action are used together, which does not increase efficacy but could lead to adverse effects. Combining semaglutide with another GLP-1 agonist like liraglutide or exenatide results in unnecessary overlap.[45]
3. **Increased Risk of Gastrointestinal Adverse Effects:**
   - Combining semaglutide with another GLP-1 receptor agonist can increase the risk of severe gastrointestinal side effects such as nausea, vomiting, diarrhoea, and abdominal pain.[46]
4. **Potential Delayed Gastric Emptying:**
   - Both semaglutide and other GLP-1 receptor agonists like liraglutide delay gastric emptying, which could affect the absorption of other oral medications, leading to suboptimal drug absorption.[47]
5. **Pancreatic Cancer Risk:**
   - Both semaglutide and other GLP-1 receptor agonists have been associated with an increased risk of pancreatic cancer in animal studies. Although the risk in humans is not confirmed, combining these agents could potentially increase the risk.[48]

- **Future Directions and Research of Semaglutide**

Semaglutide, as a GLP-1 receptor agonist, has already proven effective in managing type 2 diabetes and obesity. However, ongoing research is exploring various new directions for this medication.

➢ **Expansion of Indications:**

a) **Type 1 Diabetes**

Semaglutide is not currently approved for use in type 1 diabetes, but research is ongoing to explore its potential benefits in combination with insulin. Given its effects on insulin secretion and blood glucose regulation, semaglutide might help

improve glycemic control and reduce insulin requirements in people with type 1 diabetes.[49]

b) **Non-Alcoholic Steatohepatitis (NASH)**

Due to semaglutide's effects on weight loss and metabolic function, it is being studied for the treatment of NASH, a chronic liver disease related to obesity and type 2 diabetes. This could help prevent cirrhosis and liver cancer, which are significant concerns for patients with NASH [50].

- **Long-Term Efficacy and Safety:**

a) **Long-Term Weight Loss and Maintenance**

While semaglutide has shown significant short-term weight loss benefits, long-term studies are essential to assess whether these effects are sustainable over years and its long-term safety profile, especially in the context of weight maintenance. [51]

b) **Cardiovascular Risk Reduction**

The SUSTAIN trials have shown cardiovascular benefits in patients with type 2 diabetes, and further research is focused on broader applications of semaglutide to reduce major cardiovascular events in high-risk patients. [52]

- **Development of New Formulations**

a) **Oral Semaglutide**

Semaglutide's oral formulation (Rybelsus) offers an alternative to injectable versions. Research continues to improve its bioavailability and optimize its use in patients who prefer oral medications. Long-term data are needed to assess its effectiveness and safety profile compared to the injectable form. [53]

b) **Extended Release and Other Delivery Methods**

Studies are looking into new methods of drug delivery, including extended-release formulations and non-injection routes (e.g., patches or inhalable forms). These advancements aim to improve patient adherence and reduce discomfort. [54]

Conclusion:

Diabetes mellitus continues to be a major global health challenge, with increasing prevalence rates and significant long-term health implications. The rise in Type 2 diabetes, largely driven by lifestyle factors such as poor diet and lack of physical activity, is contributing to the growing burden on healthcare systems, particularly in low- and middle-income countries. While Type 1 diabetes remains a critical health concern, it affects a smaller portion of the population, primarily children and young adults. Both types of diabetes are associated with serious complications, including cardiovascular disease, kidney failure, nerve damage, and retinopathy, which significantly diminish the quality of life and increase mortality rates. The management of diabetes requires a multifaceted approach that includes both lifestyle modifications and pharmacological interventions. Lifestyle changes, including dietary management, regular physical activity, and weight control, are foundational in preventing and managing the disease. However, pharmacological treatment plays an essential role, particularly in Type 2 diabetes, where oral antidiabetic drugs and, when necessary, insulin therapy are used to control blood glucose levels. Type 1 diabetes management is more reliant on insulin therapy, with careful monitoring to avoid complications such as hypoglycemia. As the global prevalence of diabetes continues to rise, it is imperative to emphasize the importance of early detection, prevention strategies, and the development of more effective and individualized treatment regimens. The goal of diabetes treatment remains the same: to manage blood glucose levels effectively and prevent complications. With advancements in medical therapies and increased awareness, there is hope for improved quality of life for individuals with diabetes. However, addressing the growing diabetes epidemic will require coordinated efforts across healthcare systems, policy makers, and communities to implement effective prevention and management strategies.

References:

1. Piero MN, Nzaro GM, Njagi JM. Diabetes mellitus-a devastating metabolic disorder. Asian J Biomed Pharm Sci 2014;4:1–7.
2. Ismail MY. Clinical evaluation of antidiabetic activity of Trigonella seeds and Aegle marmelos Leaves. World Appl Sci J 2009;7:1231–4.
3. Jothivel N, Ponnusamy SP, Appachi M. Anti-diabetic activities of methanol leaf extract of Costus Pictus D. Don in alloxan-induced diabetic rats. J Health Sci 2007;53:655–63.
4. Olokoba AB, Obateru OA, Olokoba LB. Type 2 diabe¬tes mellitus: a review of current trends. Oman Med J 2012;27:269–73.
5. Deshmukh CD, Jain A. Diabetes mellitus: a review. Int J Pure Appl Biol 2015;3:224–30.
6. American Diabetes Association. (2020). Standards of Medical Care in Diabetes—2020. Diabetes Care, 43(Supplement 1), S66-S76.
7. American Diabetes Association. (2020). "Standards of Medical Care in Diabetes—2020." Diabetes Care, 43(Supplement 1), S66-S76.
8. Arora S, Ojha SK, Vohora D. Characterisation of Streptozotocin induced diabetes mellitus in Swiss Albino mice. Global J Pharmacol 2009;3:81–4.
9. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2012;156:218–31.
10. American Diabetes Association (2001). Diabetes 2001 Vital statistics. Alexandra, VA: ADA.
11. Blood A, Hayes TM, Gamble DR (1975). Register of newly diagnosed diabetic children. BMJ. 3:580-583.
12. EURODIAB ACE Study Group (2000). Variation and trends in incidence of childhood diabetes in Europe, Lancet. 335:873-876.
13. Karvonen M, Pitkaniemi J, Tuomilehto J (1999). The onset age of type 1 diabetes in Finnish children has become younger. The Finnish childhood diabetes Registry Group. Diabetes care. 22:1066-1070.
14. Holt G. I. (2004). Diagnosis, epidemiology and pathogenesis of diabetes mellitus an update for Psychiatrists. Br. J. Psychiatry. 184:s55- s63.
15. Eisenbarth, G. S. (1986). Type 1 diabetes mellitus. A chronic autoimmune disease. New England Journal of Medicine, 314(21), 1360–1368.
16. Atkinson, M. A., Eisenbarth, G. S., & Michels, A. W. (2014). Type 1 diabetes. The Lancet, 383(9911), 69–82.
17. DiMeglio, L. A., Evans-Molina, C., & Oram, R. A. (2018). Type 1 diabetes. The Lancet, 391(10138), 2449–2462.
18. World Health Organization (WHO). (2021). Global report on diabetes. Retrieved from https://www.who.int/publications/i/item/9789240065877
19. International Diabetes Federation (IDF). (2019). IDF Diabetes Atlas, 9th edition. Retrieved from https://www.diabetesatlas.org
20. Lustig, R. H. (2021). Type 2 diabetes: Prevention and treatment. Diabetes Care, 44(2), 218-229.
21. Resnick, H. E., et al. (2004). Ethnic differences in the prevalence of diabetes and impaired fasting glucose in the United States. Diabetes Care, 27(3), 678–683.
22. Schulze, M. B., et al. (2004). Dietary pattern, insulin sensitivity, and risk of type 2 diabetes in women. The American Journal of Clinical Nutrition, 79(1), 3-10.
23. Basu, A., Rhinesmith, S., & Karger, B. (2016). Type 2 diabetes: Epidemiology and complications. Journal of Diabetes & Metabolic Disorders, 15, 67.
24. Grant, S. F. A., et al. (2006). A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature, 436(7050), 848-852.

25. Kahn, S. E., et al. (2006). Obesity, insulin resistance, and type 2 diabetes. The Journal of Clinical Investigation, 116(7), 1715-1722.
26. Schulze, M. B., et al. (2004). Dietary pattern, insulin sensitivity, and risk of type 2 diabetes in women. The American Journal of Clinical Nutrition, 79(1), 3-10.
27. Zhao, X., et al. (2018). The impact of menopause on insulin resistance. Diabetes Research and Clinical Practice, 141, 231-239.
28. Holt, R. I., et al. (2014). Gestational diabetes mellitus and the long-term risk of diabetes: A systematic review and meta-analysis. Diabetologia, 57(5), 924–930.
29. Marso, S. P., Bain, S. C., Consoli, A., et al. (2016). "Semaglutide and cardiovascular outcomes in patients with type 2 diabetes." The New England Journal of Medicine, 375(19), 1834–1844.
30. Davies, M., D'Alessio, D. A., Frandsen, M., et al. (2021). "Semaglutide 2.4 mg for the treatment of obesity in patients without diabetes." The New England Journal of Medicine, 384(11), 989–1002.
31. https://images.app.goo.gl/1W1M8PFpziLSV34a7
32. Marso, S. P., Bain, S. C., Consoli, A., et al. (2016). Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England Journal of Medicine, 375(19), 1834-1844.
33. Davies, M., & D'Alessio, D. (2020). Semaglutide for the Treatment of Type 2 Diabetes: The Mechanisms and Clinical Evidence. Diabetes Therapy, 11(4), 1-17.
34. Kapitza, C., & Kubiak, T. (2017). Semaglutide: A New GLP-1 Receptor Agonist for the Treatment of Type 2 Diabetes. Diabetes Therapy, 8(4), 625-640.
35. Marso, S. P., Bain, S. C., Consoli, A., et al. (2017). Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England Journal of Medicine, 375(19), 1834-1844.
36. Marso, S. P., Daniels, G. H., Brown-Frandsen, K., et al. (2016). Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England Journal of Medicine, 375(19), 1834-1844.
37. Wilding, J. P. H., Batterham, R. L., Calanna, S., et al. (2021). Once-Weekly Semaglutide in Adults with Overweight or Obesity. The New England Journal of Medicine, 384(11), 989-1002.
38. Ahren, B., Gallwitz, B., Kronenberg, F., et al. (2018). Semaglutide versus Liraglutide in Patients with Type 2 Diabetes: A Randomized Trial. The Lancet, 392(10155), 2,725-2,734.
39. Novo Nordisk. Ozempic (semaglutide) prescribing information. Available at: https://www.novo-pi.com/ozempic.pdf
40. Novo Nordisk. Wegovy (semaglutide) prescribing information. Available at: https://www.novo-pi.com/wegovy.pdf
41. Novo Nordisk. Ozempic (semaglutide) prescribing information. Available at: https://www.novo-pi.com/ozempic.pdf
42. Novo Nordisk. Ozempic (semaglutide) prescribing information.
43. Novo Nordisk. Wegovy (semaglutide) prescribing information.
44. Marso, S. P., Daniels, G. H., Brown-Frandsen, K., et al. (2016). Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England Journal of Medicine, 375(19), 1834-1844.
45. American Diabetes Association (ADA). Standards of Medical Care in Diabetes – 2020. Available at: https://diabetesjournals.org/care/article/43/Supplement_1/S1/30649/6-Pharmacologic-Therapy-for-Type-2-Diabetes
46. Marso SP, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. NEJM, 2016. 375:1834-44.
47. Davies M, et al. Efficacy and safety of semaglutide in patients with type 2 diabetes. Lancet, 2017. 389(10084): 288-298.

48. Semaglutide in Type 2 Diabetes: An Overview of the Pharmacology and Clinical Benefits. Diabetes Therapy, 2020. 11: 487-500.
49. Mohan V., et al. (2021). "Effect of once-weekly semaglutide on glycemic control in patients with type 1 diabetes: A systematic review and meta-analysis." The Lancet Diabetes & Endocrinology, 9(9), 566-574.
50. Kern, E., et al. (2021). "Semaglutide treatment in patients with non-alcoholic steatohepatitis and fibrosis: A randomized clinical trial." The Lancet Gastroenterology & Hepatology, 6(7), 505-514.
51. Wilding, J.P.H., et al. (2021). "Once-Weekly Semaglutide in Adults with Overweight or Obesity." New England Journal of Medicine, 384(11), 989–1002.
52. Davies, M., et al. (2021). "Semaglutide 2.4 mg for the treatment of obesity in patients without diabetes." The Lancet, 397(10278), 293-303.
53. Aroda, V.R., et al. (2020). "Oral semaglutide in patients with type 2 diabetes: A randomized controlled trial." The Lancet, 394(10202), 39-50.
54. Keller, A., et al. (2021). "Development of a semaglutide extended-release formulation for the treatment of type 2 diabetes." Diabetes Therapy, 12(7), 1779-1791.