DIET IN DIABETES MELLITUS

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INTRODUCTION

Diabetes mellitus (DM) was first recognized as a disease around 3000 years ago by the ancient Egyptians and Indians, illustrating some clinical features very similar to what we now know as diabetes. DM is a combination of two words, ―diabetes‖ Greek word derivative, means siphon - to pass through and the Latin word ―mellitus‖ means honeyed or sweet. In 1776, excess sugar in blood and urine was first confirmed in Great Britain. With the passage of time, a widespread knowledge of diabetes along with detailed etiology and pathogenesis has been achieved.

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels resulting from either insufficient insulin production, ineffective utilization of insulin, or both. This condition poses significant challenges to individuals' health and quality of life, often necessitating ongoing management and lifestyle adjustments, marking diabetes as a non-communicable lifestyle disease and a global public health problem. About 422 million people worldwide have diabetes, the majority living in low-and middle-income countries, and 1.5 million deaths are directly attributed to diabetes each year. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades.

EPIDEMIOLOGY OF DIABETES

The epidemiology of diabetes reveals its significant global burden, with prevalence rates varying across different populations.

Global Burden of Diabetes:

Diabetes mellitus is a major public health concern worldwide, with its prevalence steadily increasing over the past few decades. This rise is primarily attributed to population growth, aging, urbanization, and changes in lifestyle factors such as poor diet and sedentary behavior.

According to the International Diabetes Federation (IDF), approximately 463 million adults (20-79 years old) were living with diabetes globally in 2019. This number is projected to reach 700 million by 2045 if current trends continue. In recent decades, India has witnessed a rapidly exploding epidemic of diabetes. Indeed, India today has the second largest number of people with diabetes in the world. The International Diabetes Federation (IDF) estimates that there are 72.9 million people with diabetes in India in 2017, which is projected to rise to 134.3 million by the year 2045. The prevalence of diabetes in urban India, especially in large metropolitan cities has increased from 2% in the 1970s to over 20% at present and the rural areas are also fast catching up.

Prevalence Rates Across Different Populations:

1. **Regional Variances:** Diabetes prevalence rates vary significantly among different regions of the world. For instance, the Western Pacific region (including China and Japan) and the Middle East have some of the highest prevalence rates, while Africa has comparatively lower rates. However, even within regions, there can be considerable variation.
2. **Urban vs. Rural:** Diabetes rates tend to be higher in urban areas compared to rural areas, primarily due to lifestyle factors such as unhealthy diets, sedentary lifestyles, and higher rates of obesity in urban populations.
3. **Age and Gender:** The prevalence of diabetes increases with age, with older adults being at higher risk. However, there's also an increasing prevalence of type 2 diabetes among children and adolescents, particularly in developed countries. Historically, type 2 diabetes was more common in adults, but changing lifestyle patterns have led to an earlier onset of the disease. Additionally, men generally have slightly higher rates of diabetes compared to women, although this can vary by region and age group.

Efforts to address the global burden of diabetes include public health campaigns promoting healthy lifestyles, initiatives to improve access to healthcare and diabetes management resources, and research aimed at developing more effective prevention and treatment strategies. However, concerted efforts at both individual and population levels are essential to mitigate the impact of diabetes on public health.

CLASSIFICATION OF DIABETES

According to the American Diabetes Association and the World Health Organisation, diabetes can be classified into four main types.

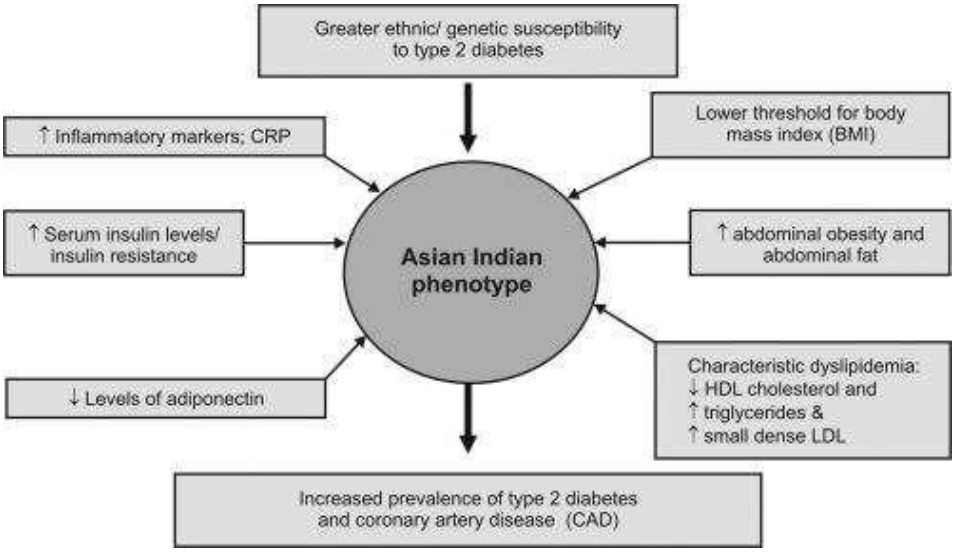
1. Type 1 diabetes
2. Type 2 diabetes
3. Gestational diabetes
4. Other types of diabetes (Monogenic diabetes, pancreatic diabetes, drug-induced diabetes etc.).

These several types of diabetes are, each with its own causes, characteristics, and treatments:

1. **Type 1 Diabetes (T1D):** Type 1 diabetes accounts for 5% to 10% of all cases of diabetes. This results from the autoimmune destruction of the insulin-producing beta cells in the pancreas, leading to an absolute deficiency of insulin. Its risk factors include autoimmune, genetic, and environmental factors. To date, there are no known ways to prevent type 1 diabetes. Type 1 diabetes typically develops during childhood or adolescence but can occur at any age. Individuals with T1D require lifelong insulin therapy for survival.
2. **Type 2 Diabetes (T2D):** Type 2 diabetes accounts for 90% to 95% of all diagnosed diabetes cases. This is characterized by insulin resistance, where the body's cells become less responsive to insulin, combined with inadequate insulin secretion. This form of diabetes generally begins as insulin resistance and, because the body is unable to produce enough insulin to address the resistance, the pancreas may reduce the production of insulin or eventually stop producing it. Type 2 diabetes is strongly associated with lifestyle factors such as obesity, physical inactivity, and poor diet. It often develops in adulthood but is increasingly diagnosed in children and

adolescents due to rising obesity rates. Initially, treatment may involve lifestyle modifications, oral medications, and eventually insulin therapy as the disease progresses. The ―Asian Indian phenotype‖ refers to a peculiar constellation of abnormalities in south Asians, whereby for any given level of body-mass index, they tend to have higher total body fat, visceral fat, insulin resistance and prevalence of diabetes diabetes compared to white Caucasians (Figure 1.1)

Figure 1. The "Asian Indian phenotype"



3. **Gestational Diabetes Mellitus (GDM):** Minority women, women who are obese, women with a family history of diabetes, and women who have had gestational diabetes in a previous pregnancy are at higher risk than other women for developing gestational diabetes. GDM increases the risk of complications for both the mother and baby during pregnancy and childbirth. Strict glycemic control and management of women with gestational diabetes is necessary to prevent birth complications in the developing infant. While blood sugar levels often return to normal after delivery, women who have had GDM have a 20% to 50% increased risk for developing type 2 diabetes later in life.
4. **Other Specific Types:** There are other specific forms of diabetes caused by genetic mutations, diseases of the pancreas, drug-induced factors, or endocrine disorders. Examples include monogenic diabetes syndromes (such as maturity-onset diabetes of the young, MODY),

pancreatic diseases, and diabetes induced by certain medications or hormonal conditions. Other types of diabetes include:

4.1. **Type 3c diabetes**: This form of diabetes happens when your pancreas experiences damage (other than autoimmune damage), which affects its ability to produce insulin. Pancreatitis, pancreatic cancer, cystic fibrosis and hemochromatosis can all lead to pancreas damage that causes diabetes. Having your pancreas removed (pancreatectomy) also results in Type 3c.

4.2. **Latent autoimmune diabetes in adults (LADA)**: Like Type 1 diabetes, LADA also results from an autoimmune reaction, but it develops much more slowly than Type 1. People diagnosed with LADA are usually over the age of 30.

4.3. **Maturity-onset diabetes of the young (MODY)**: MODY, also called monogenic diabetes, happens due to an inherited genetic mutation that affects how your body makes and uses insulin. There are currently over 10 different types of MODY. It affects up to 5% of people with diabetes and commonly runs in families.

4.4. **Neonatal diabetes**: This is a rare form of diabetes that occurs within the first six months of life. It‘s also a form of monogenic diabetes. About 50% of babies with neonatal diabetes have the lifelong form called permanent neonatal diabetes mellitus. For the other half, the condition disappears within a few months from onset, but it can come back later in life. This is called transient neonatal diabetes mellitus.

4.5. **Brittle diabetes**: Brittle diabetes is a form of Type 1 diabetes that‘s marked by frequent and severe episodes of high and low blood sugar levels. This instability often leads to hospitalization. In rare cases, a pancreas transplant may be necessary to permanently treat brittle diabetes.

Prediabetes: In addition to these main types, there's a condition called prediabetes, where blood sugar levels are higher than normal but not yet high enough to be diagnosed as diabetes. Prediabetes is a precursor condition to diabetes in which a person has elevated blood glucose levels but does not meet diagnostic criteria for diabetes. People with prediabetes can have impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), or both. Prediabetes increases the risk of developing type 2 diabetes and cardiovascular disease.

Etiology and Risk Factors of diabetes

Although the pathogenesis of diabetes is complex, a number of factors that increase the risk for the disease have been identified. Risk factors for type 1 diabetes include family history, race (with whites at higher risk than other racial or ethnic groups), and certain viral infections during childhood. Risk factors for type 2 diabetes are more diverse; some are modifiable, and others are not. Non-modifiable risk factors for type 2 diabetes include age, race or ethnicity, family history (genetic predisposition), history of gestational diabetes, and low birth weight.

Modifiable or lifestyle risk factors include increased body mass index (BMI), physical inactivity, poor nutrition, hypertension, smoking, and alcohol use, among others. Increased BMI is consistently shown to be one of the strongest risk factors for development of diabetes. In addition, distribution of body fat, and specifically an increased waist-to-hip ratio, increase a person's risk for diabetes. Consistent findings from various studies show that lower levels of physical activity increase a person's risk for diabetes. Total caloric intake, as well as specific components of diet such as refined carbohydrates and fats, have been linked to diabetes development. Moderate alcohol use may reduce the risk for developing diabetes, but smoking has been shown to be an independent risk factor for diabetes. Psychosocial factors such as depression, increased stress, lower social support, and poor mental health status also are associated with an increased risk for the development of diabetes. Recently, adverse housing conditions were found to be independently associated with the development of self-reported diabetes, although the mechanism by which housing conditions exert their risk is still unknown.

Thus the etiology of diabetes involves a complex interplay of genetic, environmental, and lifestyle factors. Understanding these factors is crucial for identifying individuals at risk and implementing effective prevention strategies.

Genetic Predisposition:

1. **Family History:** Having a family history of diabetes increases the risk of developing the condition. Type 1 diabetes is strongly influenced by genetic factors, with certain human leukocyte antigen (HLA) genotypes being associated with increased susceptibility. Recent exploration of human genomic regions associated with type 1 diabetes has identified candidate genes, gene products, and genetic loci that influence susceptibility to type 1 diabetes. Type 2 diabetes also has a genetic component, with multiple genes contributing to disease risk.
2. **Genetic Mutations:** Certain rare genetic mutations can lead to monogenic forms of diabetes, such as maturity-onset diabetes of the young (MODY) and neonatal diabetes. These mutations affect the function of genes involved in insulin production and secretion.

Environmental Factors:

1. **Obesogenic Environment:** The global rise in obesity rates is a major environmental factor contributing to the increased prevalence of type 2 diabetes. Environmental factors promoting overeating and sedentary behavior, such as easy access to high-calorie foods and reduced opportunities for physical activity, play a significant role. People who are obese, have a family history of diabetes, or belong to high-risk ethnic groups (e.g., African American, Native American, Hispanic, and Pacific Islanders) should be regularly screened for the disorder.
2. **Urbanization:** Urban environments often promote unhealthy lifestyle behaviors, including poor dietary choices and decreased physical activity, which can contribute to the development of diabetes.
3. **Infections:** Exposure to some viral infections (e.g., mumps), trauma (e.g., motor vehicle accident) and environmental factors (e.g., climate, and geographical location) could trigger the onset of type 1 diabetes.

Lifestyle Influences:

1. **Diet:** Poor dietary habits, such as consuming excessive amounts of refined carbohydrates, sugary beverages, and processed foods high in unhealthy fats, contribute to the development of obesity

and insulin resistance, increasing the risk of type 2 diabetes. A diet rich in fruits, vegetables, whole grains, and lean proteins can help reduce diabetes risk.

2. **Physical Activity:** Sedentary lifestyles are strongly associated with an increased risk of type 2 diabetes. Regular physical activity improves insulin sensitivity, helps maintain a healthy weight, and reduces diabetes risk.
3. **Stress:** Chronic stress and poor coping mechanisms can contribute to unhealthy behaviors such as overeating, physical inactivity, and disrupted sleep patterns, all of which increase the risk of diabetes.

Other Risk Factors:

1. **Age:** While gender does not appear to be a significant determinant of type 1 diabetes as incidence rates are generally similar for males and females, the risk of type 1 diabetes increases with age during childhood and adolescence. The risk of diabetes increases with age, particularly for type 2 diabetes. This is partly due to age-related changes in metabolism, decreased physical activity, and increased prevalence of obesity.
2. **Ethnicity:** Certain ethnic groups, including African Americans, Hispanics, Native Americans, and Asian Americans, have a higher risk of developing diabetes compared to Caucasians. This increased risk may be attributed to genetic predisposition, cultural factors, and socioeconomic disparities.
3. **Socioeconomic Status:** Socioeconomic factors such as low income, limited access to healthcare, and inadequate education can contribute to disparities in diabetes prevalence and outcomes. Individuals with lower socioeconomic status are more likely to experience barriers to healthy lifestyle behaviors and diabetes management.
4. **Gestational Diabetes:** Individuals of all ages diagnosed as prediabetic and pregnant mothers diagnosed with gestational diabetes are at high risk for developing type 2 diabetes.

Understanding the multifaceted nature of diabetes risk factors is essential for developing comprehensive prevention and management strategies. Efforts to address diabetes should focus

on promoting healthy lifestyles, improving access to healthcare and education, and addressing social determinants of health to reduce disparities in diabetes prevalence and outcomes.

PHYSIOLOGY OF GLUCOSE METABOLISM

Understanding the physiology of glucose metabolism is crucial for comprehending how the body regulates blood sugar levels in different metabolic states.

1. Normal Glucose Homeostasis:

Glucose Regulation in the Fed State:

- After a meal, blood glucose levels rise due to the absorption of carbohydrates from the diet.
- In response to elevated blood glucose levels, the pancreas releases insulin.
- Insulin promotes the uptake of glucose into cells, particularly muscle, liver, and adipose tissue.
- In muscle and adipose tissue, insulin stimulates glucose uptake by facilitating the translocation of glucose transporter proteins (GLUT4) to the cell membrane.
- In the liver, insulin inhibits gluconeogenesis (the synthesis of glucose from non-carbohydrate sources) and promotes glycogen synthesis, leading to storage of glucose as glycogen.

Glucose Regulation in the Fasting State:

- Between meals or during periods of fasting, blood glucose levels begin to decline.
- In response to decreased blood glucose levels, the pancreas reduces insulin secretion while increasing glucagon secretion.
- Glucagon promotes glycogen breakdown (glycogenolysis) in the liver, releasing glucose into the bloodstream.
- Glucagon also stimulates gluconeogenesis, primarily from amino acids derived from protein breakdown.
- Together, these processes help maintain blood glucose levels within a normal range during fasting.

2. Insulin Action and Secretion:

Role of Pancreatic Beta Cells:

- Insulin is synthesized and secreted by beta cells in the pancreas in response to elevated blood glucose levels.
- Beta cells sense glucose levels through glucose transporters and glucose metabolism pathways.
- Insulin secretion is tightly regulated by glucose and other factors, including incretin hormones released from the gut in response to food intake.

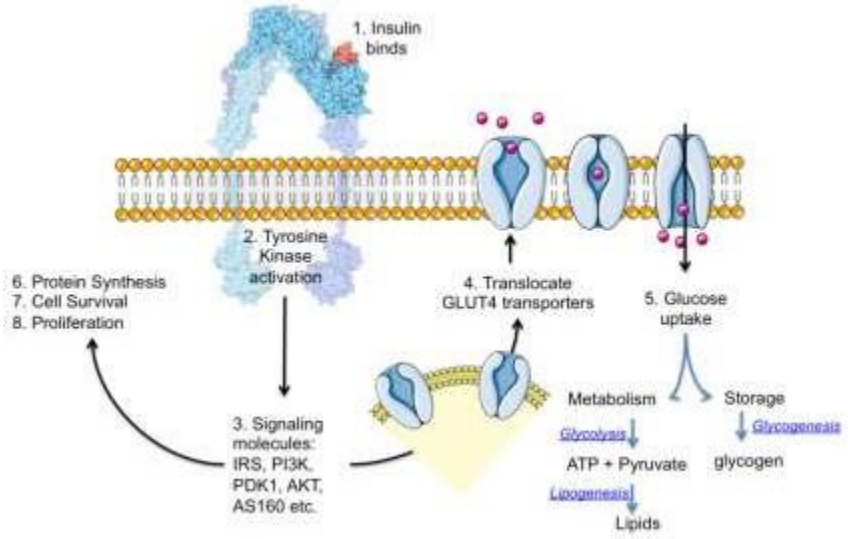
Insulin Signaling Pathways:

- Insulin binds to insulin receptors on target cells, initiating intracellular signaling pathways.
- The insulin receptor activates tyrosine kinase activity, leading to phosphorylation of downstream signaling molecules.
- These signaling cascades ultimately promote glucose uptake, glycogen synthesis, protein synthesis, and lipid storage in insulin-sensitive tissues.

Insulin Resistance: Mechanisms and Implications:

- Insulin resistance occurs when cells become less responsive to insulin's actions, leading to impaired glucose uptake and metabolism.
- It is a key feature of type 2 diabetes and is often associated with obesity, inflammation, and other metabolic abnormalities.
- Insulin resistance results in compensatory hyperinsulinemia as the pancreas secretes more insulin to overcome resistance.
- Over time, persistent insulin resistance can lead to beta cell dysfunction and impaired insulin secretion, further exacerbating hyperglycemia.
- Insulin binds to cell surface receptors to initiate a signaling cascade (Figure 2) that in turn mobilizes glucose transporter proteins to the cell surface to take up glucose. In the absence of the insulin generated signals, these transporter proteins are sequestered in the cell so the cells cannot take up glucose. Exercise activates other signals that can also translocate GLUT4 transporters to the cell surface. This is one of the mechanisms by which exercise increases insulin sensitivity.

Figure 2: Insulin Directed Glucose Uptake



Courtesy: (https://pdb101.rcsb.org/motm/182)

3. Glucagon and Counter Regulatory Hormones:

Role in Glucose Regulation:

- Glucagon is secreted by alpha cells in the pancreas and plays a crucial role in maintaining glucose homeostasis.
- It acts opposite to insulin, promoting glycogen breakdown and gluconeogenesis to increase blood glucose levels during fasting or hypoglycemia.
- Other counter regulatory hormones, such as cortisol, epinephrine, and growth hormone, also contribute to glucose regulation by promoting glycogenolysis and gluconeogenesis.

Interaction with Insulin:

- Glucagon and insulin have reciprocal effects on glucose metabolism, ensuring fine-tuned control of blood glucose levels.
- Insulin inhibits glucagon secretion and glucagon-mediated glucose production, while glucagon antagonizes insulin's actions on glucose uptake and storage.
- The balance between insulin and glucagon secretion is critical for maintaining glucose homeostasis in response to varying metabolic demands and nutrient availability.

Understanding the intricate interplay between insulin, glucagon, and other hormones is essential for maintaining normal glucose metabolism and preventing dysregulation that can lead to metabolic disorders such as diabetes mellitus.

PATHOPHYSIOLOGY OF DIABETES

Type 1 Diabetes Mellitus (T1DM):

1. **Autoimmune Destruction of Beta Cells**: In Type 1 diabetes, the immune system mistakenly targets and attacks the insulin-producing beta cells in the pancreas. This autoimmune response leads to the destruction of these cells, resulting in a significant reduction or complete absence of insulin production.
2. **Insulin Deficiency**: As a consequence of beta cell destruction, there is a severe deficiency in insulin secretion. Insulin is essential for regulating glucose levels in the blood by facilitating the uptake of glucose into cells for energy production or storage. Without sufficient insulin, glucose accumulates in the bloodstream, leading to hyperglycemia.
3. **Pathogenesis and Triggers**: The exact cause of the autoimmune response leading to T1DM is not fully understood. However, genetic predisposition, environmental factors, and potential triggers such as viral infections are believed to play a role in initiating the autoimmune attack on beta cells. Once triggered, the immune system continues to attack and destroy beta cells, progressively worsening insulin deficiency.

Type 2 Diabetes Mellitus (T2DM):

1. **Insulin Resistance and Beta Cell Dysfunction**: Type 2 diabetes is characterized by insulin resistance, where the body's cells become less responsive to the action of insulin. This resistance impairs glucose uptake by cells, leading to elevated blood sugar levels. Additionally, there is a gradual decline in beta cell function and insulin secretion over time, contributing to the progression of hyperglycemia.
2. **Role of Obesity and Adipose Tissue**: Obesity is a major risk factor for the development of insulin resistance and Type 2 diabetes. Adipose tissue, especially visceral fat, releases inflammatory cytokines and adipokines, which interfere with insulin signaling pathways and

promote insulin resistance. Excess adiposity also leads to dyslipidemia and contributes to the development of metabolic syndrome, further exacerbating insulin resistance.

3. **Inflammatory Pathways**: Chronic low-grade inflammation is associated with insulin resistance and beta cell dysfunction in Type 2 diabetes. Adipose tissue inflammation, along with increased levels of pro-inflammatory cytokines, such as TNF-alpha and IL-6, contributes to insulin resistance by impairing insulin signaling pathways in target tissues, such as liver, muscle, and adipose tissue.

Gestational Diabetes Mellitus (GDM):

1. **Pregnancy-Induced Insulin Resistance**: During pregnancy, hormonal changes lead to increased insulin resistance in women, especially in the second and third trimesters. This physiological insulin resistance ensures an adequate supply of glucose to the developing fetus. However, in some women, particularly those with pre-existing insulin resistance or impaired pancreatic function, this insulin resistance becomes exaggerated, leading to the development of gestational diabetes mellitus.
2. **Implications for Mother and Fetus**: Untreated or poorly managed gestational diabetes can result in adverse outcomes for both the mother and the fetus. Maternal complications may include an increased risk of developing Type 2 diabetes later in life, hypertension, and preeclampsia. For the fetus, GDM increases the risk of macrosomia (large birth weight), birth trauma, hypoglycemia after birth, and an increased likelihood of developing obesity and Type 2 diabetes in later life. Therefore, early detection and appropriate management of GDM are crucial to minimizing these risks.

CLINICAL PRESENTATION

The symptoms and signs of diabetes can vary depending on the type and severity of the condition. Common symptoms include:

Hyperglycemia:

The main symptoms of diabetes are described as the three polys - polyuria, polydipsia, and polyphagia.

- **Polyuria** or the need to urinate frequently helps the body remove excess glucose that is filtered from the blood by the kidneys
- **Polydipsia** or increased thirst and fluid intake compensates for the loss of fluids resulting from increased urination
- **Polyphagia** or increased appetite compensates for the loss of glucose and fluids from the body, caused by excessive urination

Individuals with high risk for developing diabetes should be alert to these symptoms and seek medical attention if they notice the above symptoms. Beyond the three "polys", other indicators for diabetes (listed by American Diabetes Association) include:

- Extreme fatigue
- Blurry vision
- Slow-healing sores or frequent infections: High blood sugar levels can impair the immune system's ability to fight infections.
- Weight loss
- Tingling, pain, or numbness in the hands/feet

In more advanced stages of diabetes, the following symptoms and diabetes complications may also be seen

- Fainting and/or dizziness (possibly due to sudden drops in blood glucose levels due to poor management or increased medication)
- Foot ulcers (resulting from inability to attend to foot injuries due to loss of sensation in the extremities. These conditions may lead to gangrene and amputation)
- Peripheral neuropathy (loss of sensation, autonomic dysfunction)
- Retinopathy (blindness, blurred vision, or eye problems)
- Nephropathy (kidney damage)

- Damage to nerves (usually affects the extremities first) and bloods vessels, exposing diabetics to risk of cardiovascular complications (e.g., high blood pressure, heart disease, heart attack, stroke)
- Increased susceptibility to infections (e.g., urinary tract infections, sepsis, gangrene), since high glycemic environment provides a favorable medium for microbes

COMPLICATIONS OF DIABETES

Uncontrolled diabetes can cause metabolic imbalance leading to acute complications that may require immediate medical attention. Hyperglycemia (high levels of glucose in blood) sets the stage for protein glycation, which in turn may lead to chronic conditions requiring constant monitoring and treatment. Individuals with diabetes may also develop high cholesterol and high blood pressure, which require medical management.

Acute Complications

Ketoacidosis

Despite high blood glucose levels, the body cells (muscle and lipid cells) may be starved for glucose due to absence or improper function of insulin. Cells may also starve for glucose if the amount of food intake is low (such as during illness) or if the dosage of insulin is too high. Under these conditions cells start using fats as a source of energy. Liver cells produce ketone bodies from fatty acids. When the glucose levels are low, brain cells can use ketone bodies, but not free fatty acids, for energy. High concentrations of ketones can make the urine acidic and cause fruity-smelling breath. If not managed, this condition can progress to coma (prolonged unconsciousness) and even death.

Hyperosmolar Hyperglycemic Nonketotic Syndrome (HHNS)

High blood glucose level triggers increased urination. If liquids are not replaced, the individual can become severely dehydrated. High blood glucose levels can lead to altered mental states, confusion, seizures, coma, and even death.

Chronic Complications

Complications of diabetes can broadly be categorized into microvascular, macrovascular, and other complications.

1. Microvascular Complications

2. Macrovascular Complications

Microvascular complications

These affect the smaller blood vessels, such as in the eyes (leading to retinopathy), kidneys (leading to nephropathy), and neurons (leading to neuropathy). Individuals with poorly managed blood glucose levels may suffer from one or more of these complications in advanced stages of the disease. Thus, besides monitoring the health of eyes and kidneys, diabetics also require foot care. Interestingly, several large population studies have shown that aggressive management of blood glucose levels (i.e., keeping blood glucose levels within a narrow range) can avoid, or at least delay, the onset of these complications (Nathan et al., 2014). Regular monitoring and management of blood glucose levels is of critical importance in maintaining metabolic balance and avoiding microvascular complications.

1. **Diabetic Retinopathy**: Damage to the blood vessels in the retina, leading to vision problems and potentially blindness if left untreated.
2. **Diabetic Nephropathy**: Kidney damage caused by prolonged high blood sugar levels, which can lead to kidney failure if not managed properly.
3. **Diabetic Neuropathy**: Nerve damage due to diabetes, which can cause numbness, tingling, pain, or weakness, commonly affecting the feet and legs.

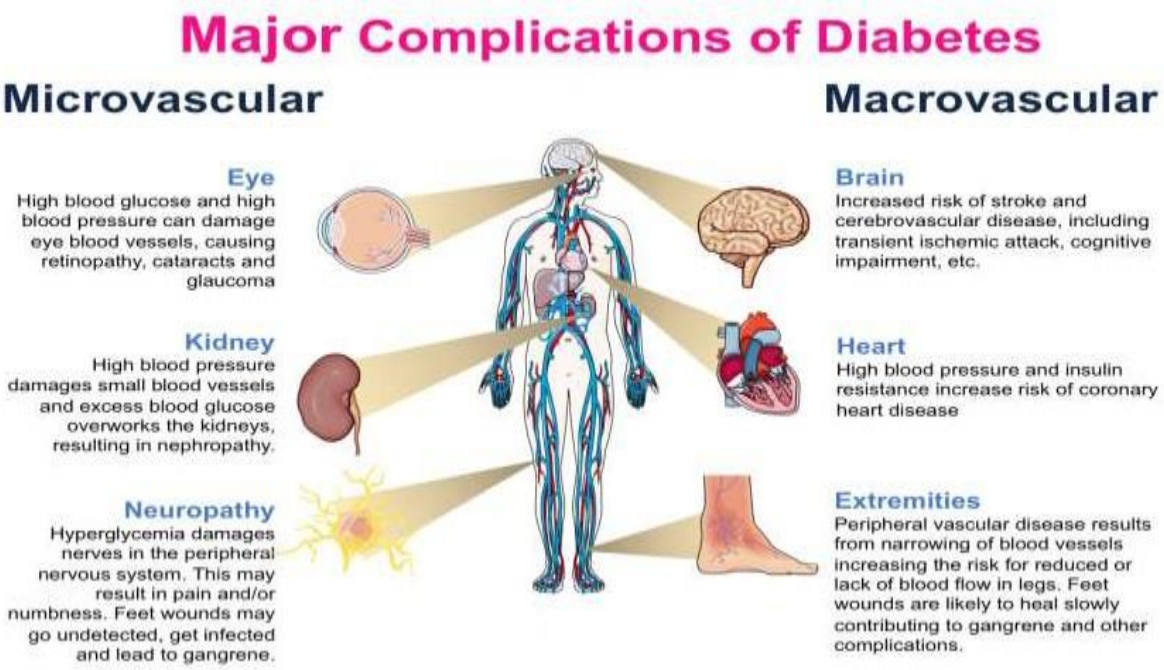
Macrovascular complications

These affect larger blood vessels, such as those supplying the heart, brain, and extremities. The causes of these complications stem from narrowing of blood vessels due to glycation, inflammation, lipid deposition and other factors. Complications resulting from large vessel damage may lead to cardiomyopathy, stroke, rheumatoid arthritis, osteoporosis, and the

degenerative process of aging (Singh et al., 2014). The major concern amongst these complications is myocardial infarction (heart attack). At present, it appears that blood glucose control does not significantly reduce the risks or delay the onset of macrovascular complications. Additional medical management is required.

1. **Cardiovascular Disease**: Diabetes increases the risk of various heart conditions, including coronary artery disease, heart attack, and heart failure.
2. **Peripheral Artery Disease (PAD)**: Narrowing or blockage of blood vessels in the legs, leading to reduced blood flow and potentially causing pain, numbness, or even tissue death (gangrene).
3. **Stroke**: Diabetes is a significant risk factor for stroke, a condition where blood supply to the brain is disrupted, leading to brain damage and potential disability or death.

Figure 3. Complications of Diabetes Mellitus



Parts of the image were adapted from Servier Medical Art.

Protein Glycation

When proteins are exposed to high levels of sugar, for long periods of time, they may covalently attach to proteins by a non-enzymatic process, called glycation (Singh et al., 2014). Note that this process differs from the post-translational glycosylation of proteins in rough endoplasmic reticulum and Golgi, where sugars are attached to proteins systematically, by specific enzymes and carrier proteins. In early stages of glycation, sugars react with free amino groups on the protein to form a Schiff base, which further undergoes rearrangements to form a more stable product called amadori product. Over time, these glycated proteins may be further modified to form advanced glycation products (AGEs). Receptors for AGEs bind to these adducts and initiate an inflammation response, which in turn lead to some of the complications of diabetes.

In poorly managed diabetes, the blood glucose levels may be high and proteins found in the blood, such as albumin, immunoglobulins, and collagen, are often glycated. A glycated product of hemoglobin (an oxygen transporting molecule present in red blood cells), called Hb A1c is used as a measure of overall glucose management in individuals with diabetes.

Diabetes and Foot Care

Diabetic foot infection (DFI) is a common and complex problem in individuals with diabetes. Due to nerve damage and numbness, individuals with diabetes may not feel any pain and foot ulcers may go undetected for long periods. Infections in these ulcers may also go untreated and even when detected may heal slowly (due to peripheral artery disease). In extreme cases, the ulcers and infections may lead to gangrene and require amputation.

Treating foot ulcers in diabetic patients is challenging. Often, multiple microorganisms infect the ulcers, some of which may be resistant to standard antimicrobial treatments. In order to effectively treat the infection, ideally the ulcer microbiome (genomes of all microorganisms found in the ulcer) should be studied. State of the art treatment protocols use molecular techniques such as polymerase chain reaction (PCR) and gene sequencing to identify key components of the ulcer microbiota and design specific treatments. However, such thorough analysis is current

Skin Complications: Diabetes can cause various skin problems, including bacterial and fungal infections, itching, and dry skin.
Dental Complications: Diabetes increases the risk of gum disease (periodontitis) and other oral health issues, which can lead to tooth loss if not treated promptly.

Complications of gestational diabetes

Most women who have gestational diabetes deliver healthy babies. However, untreated or uncontrolled blood sugar levels can cause problems for you and your baby.

Complications in your baby can be caused by gestational diabetes, including:

- **Excess growth.** Extra glucose can cross the placenta. Extra glucose triggers the baby's pancreas to make extra insulin. This can cause your baby to grow too large. It can lead to a difficult birth and sometimes the need for a C-section.
- **Low blood sugar.** Sometimes babies of mothers with gestational diabetes develop low blood sugar (hypoglycemia) shortly after birth. This is because their own insulin production is high.
- **Type 2 diabetes later in life.** Babies of mothers who have gestational diabetes have a higher risk of developing obesity and type 2 diabetes later in life.
- **Death.** Untreated gestational diabetes can lead to a baby's death either before or shortly after birth.

Complications in the mother also can be caused by gestational diabetes, including:

- **Preeclampsia.** Symptoms of this condition include high blood pressure, too much protein in the urine, and swelling in the legs and feet.

- **Gestational diabetes.** If you had gestational diabetes in one pregnancy, you're more likely to have it again with the next pregnancy.

These complications highlight the importance of proper diabetes management, including blood sugar control, regular medical check-ups, and lifestyle modifications to reduce the risk and severity of these complications.

DIAGNOSIS OF DIABETES

Diabetes is diagnosed through various tests that measure blood glucose levels. The diagnostic criteria include:

1. **Fasting Plasma Glucose (FPG) Test:**
    - A blood sample is taken after an overnight fast (typically 8 hours).
    - A fasting plasma glucose level of 126 mg/dL (7.0 mmol/L) or higher on two separate occasions indicates diabetes.

How to Determine Blood (or Plasma) Glucose Levels?

Measuring blood glucose concentrations is critical for diagnosis and monitoring of diabetes. This is usually done using a glucometer with test strips. A drop of blood is placed on the glucose test strip and exposed to a fixed quantity of an enzyme, glucose oxidase (shown in Figure 1), for a finite period of time. Glucose oxidase acts as a biosensor and oxidizes glucose to generate products (gluconic acid and hydrogen peroxide). In older models, the amount of hydrogen produced was measured by a color change reaction to indicate the glucose concentration. In modern glucometers, the hydrogen peroxide interacts with a mediator to transfer electrons to a microcircuitry included in the test strip to give a reading of blood glucose concentration. In order to get consistent glucometer readings, the test strips should be stored away from moisture and extremes of temperature so that the glucose oxidase coated on the test-strip is not denatured and rendered non-functional.

2. **Oral Glucose Tolerance Test (OGTT):**
    - This is an elaboration of the blood glucose test that reveals how the body metabolizes glucose ~2 hours after ingesting glucose. For pregnant mothers with high risk of diabetes, a glucose-screening test (OGTT) is usually performed between 24-28 weeks of pregnancy (or earlier) to identify gestational diabetes and manage the blood glucose levels for the health of mother and baby.
    - After blood is drawn, the subject is asked to drink a liquid, which contains 50, 75, or 100 grams of glucose. Normally the absorption of glucose in the body occurs rapidly, and blood glucose levels rise within 30 to 60 minutes of fluid intake. Blood work is done an hour after drinking the solution and blood glucose measurements are taken at specific intervals.
    - If the blood test shows abnormal blood glucose levels, then blood work must be repeated after three hours.
    - A blood glucose level of 200 mg/dL (11.1 mmol/L) or higher 2 hours after consuming the glucose solution confirms diabetes.
3. **Hemoglobin A1c (HbA1c) Test:**
    - This test measures the average blood glucose level over the past 2-3 months by assessing the percentage of glycated hemoglobin in the blood. Prolonged exposure to high levels of glucose leads to glycation of proteins that are exposed to blood. Red Blood Cells (or RBCs) have a 3-4 month life-span thus measuring the level of glycation of hemoglobin reflects an individual's average blood glucose control for the past 2 to 3 months. High percentage of A1c reflects poor control of blood glucose levels over the past few months.

    - Prolonged exposure to high blood glucose levels leads to glucose attaching itself to proteins including hemoglobin. Since this happens over a period of time and is irreversible - the HbA1c test is not affected by random fluctuations due to temporary alteration in diet, lifestyle, stress or illness of the subject. Maintaining an HbA1c below 5.7% is indicative of normal health. An HbA1c level of 5.7-6.4% signals prediabetes, and any values higher than 6.4% indicates a diabetic condition requiring treatment.

The diagnostic criteria for diabetes and prediabetes are summarized in Table 1.

Table 1. Diagnostic Criteria for Diabetes and Prediabetes*

Blood tests	Diabetics	Pre diabetics		Non-diabetics
		IFG	IGT	
FBS (mg/dl)	≥ 126	110 to 125	<126	<110
$2h Plasma Glucose (mg/dl)	≥ 200	<140	≥140 to <200	<140
HbA1C	≥ 6.5	5.7-6.4		<5.7

$*Venous plasma glucose 2 hours after ingestion of 75 g oral glucose load (OGTT)*

**WHO (2016) & IDF (2017)*

It is important to note that diagnosis should be based on confirmatory testing and not solely on symptoms, as some individuals may be asymptomatic despite having high blood sugar levels. Additionally, diagnosis should consider other factors such as age, risk factors, and comorbidities. Early detection and management of diabetes are essential for preventing complications and improving outcomes.

MANAGEMENT OF DIABETES

Managing diabetes involves a multifaceted approach that encompasses lifestyle modifications, pharmacotherapy, and monitoring/self-care practices. Here's a breakdown of each aspect:

Lifestyle Modifications

The cornerstone of diabetes management is tight glycemic control. The first line of action upon noticing any symptoms of type 2 diabetes should be lifestyle changes, i.e., managing blood glucose levels by regulating diet (both quality and quantity of nutritional intake) and exercise. Through these changes, individuals diagnosed as prediabetic can often check their progression to full-blown disease. Individuals diagnosed with diabetes, who are taking medications can also benefit from these lifestyle changes.

Lifestyle Goals in Diabetes:

- To improve health through optimum nutrition
- To provide energy for reasonable body weight, normal growth and development
- To maintain glycemic control
- To achieve optimum blood lipid levels
- To individualise the diet according to complications and co-morbidities
- Achieve optimal physical activity
- Advise other behavioural changes for: smoking, other tobacco products and alcohol
- Advocate stress management

Medical Nutrition Therapy (MNT) for diabetes mellitus requires application of nutritional and behavioral sciences along with physical activity.

A four-pronged approach is needed:

1. Nutritional assessment which includes metabolic, nutritional and life style parameters
2. Setting goals – practical, achievable and acceptable to the patient—individualized Nutritional Intervention, including nutrition education – individualized meal plans according to family eating patterns
3. Evaluation – to assess if the goals have been achieved and to make necessary changes.

Based on factors like age, sex, physical activity, height, weight, body mass index ICMR.

The diet should be individualized, close to the family pattern, flexible, should have variety and meal timing should be according to the patient‘s daily schedule.

1. Dietary Recommendations:

(i) Energy:

Sufficient to attain or maintain a reasonable body weight for adults, normal growth and development for children and adolescents, to meet the increased needs during pregnancy and lactation and recovery from illness. Daily physical activity and exercise needs to be considered.

Ideal Body Weight (IBW) = (Height in cm – 100) x 0.9.

Approximately, 25 kcals/kg ideal body weight/day can be given to a moderately active patient with diabetes. The change in the daily calorie should be a gradual process, and not more than 500 calories/day. (ii) Energy or Calorie Distribution: (a) Carbohydrates:

Evidence is inconclusive for an ideal amount of carbohydrate intake for people with diabetes.

Therefore, collaborative goals should be developed for individuals with diabetes. 55-60 % of energy from carbohydrates is an ideal recommendation.Carbohydrates should be complex in nature. Although different carbohydrates produce different glycemic responses, from clinical point of view it is important to manage total carbohydrate. It is recommended that carbohydrates from foods high in fi bre e.g. whole grains (unpolished cereals and millets), legumes, peas, beans, oats, barley and some fruits with low glycemic index and glycemic load are consumed. All patients with diabetes should be encouraged to take 6 small meals a day. Food exchange system can be followed to give more variety and individualization to the diet plan.

(a) Fibre:

Fibre recommendation for general population is 40 g/day (2000 Kcals). Traditional Indian diets that include whole grains along with whole pulses like grams, soy, green leafy vegetables and some fruits is the recommendation. Fruits like papaya, guava, apples, pears, oranges, mosambi can be taken in moderation. All fruit juices are best avoided.

(b) Proteins:

Proteins should provide 12-15 % of the total energy intake for people with diabetes – similar to the recommendations for the general population. Proteins from vegetable sources like pulses, soy, grams, peas, low fat milk, low fat curds, fish and lean meats are recommended.

Supplementation of foods like cereal and pulse (4:1 ratio) can improve the protein quality and also gives satiety. For e.g; Idli, dosa, Missi roti, Khichdi, Dhokla, Khandvi etc.

(c) Fats:

Fats should provide 20-30 % of total energy intake for people with diabetes. Evidence is inconclusive for an ideal amount of total fat intake for people with diabetes, therefore, goals should be individualized. Fat quality is as important as the quantity.

Fat quality:

- Saturated fats (SFA) ≤10% energy and 7% in those with raised blood lipid levels
- Polyunsaturated fats (PUFA) 10 % energy, n6: 3-7% energy, n3: >1% energy, n6/n3 ratio 5-10
- Monounsaturated Fatty Acids (MUFA) 10-15% energy + any calories left from the carbohydrate portion
- Trans fats < 1% energy – preferably totally avoided in people with type 2 diabetes, MUFA-rich cooking oil and nuts in moderation may benefit glycemic control and CVD risk factors. This can therefore be recommended as an effective alternative to a lower-fat, higher-carbohydrate eating pattern.Use of MUFA rich oils like mustard, rice bran, peanut (groundnut) and gingelly are good options. Oils rich in n6 PUFA like safflower, sunflower, cotton seed, should be mixed with oils rich in n3 like soy and mustard to maintain N6:N3 ratio between 5-10. Use of mixed oils or alternating of oils is recommended.
- (iii) Salt:Sodium intake recommendations for people with diabetes are the same as that for the general population. Added (iodized) salt should be less than 5 g/day. For persons with hypertension and diabetes, the intake should be reduced to less than 3 g/ day. In hypertensive patients or edematous patients with nephropathy, sodium restriction is required. All preserved and processed foods such as pickles, chutneys, packaged namkeens/savouries, sauces should be restricted.

(iv) Alcohol:

It is best to avoid alcohol, however if used, should be taken in moderation. If alcohol is consumed, it should not be counted as part of the meal plan. However, it should be borne in mind that alcohol does provide calories (7 kcal/ g), which are considered as ―empty calories‖. In the fasting state, alcohol may produce hypoglycaemia. Alcohol can further exacerbate fatty liver, neuropathy, dyslipidaemia, obesity and also worsen blood glucose levels.

Sweeteners:

Nutritive Sweeteners: These include fructose, honey, corn syrup, molasses, fruit juice or fruit juice concentrates dextrose, maltose, mannitol, sorbitol and xylitol. All these are best avoided.

Non-nutritive Sweeteners: Aspartame, acesulfame K, stevia, sucralose and saccharin are currently approved for use. However, they should be used in moderation and are best avoided in pregnancy.

Dietary modifications in the presence of complications of diabetes:

(i) Nephropathy:

(a) Protein: The recommended protein intake for diabetic nephropathy patients is 0.6 g/kg of the ideal body weight plus 24 hour urinary protein loss, if this is significant. However, it is recommended that the protein intake should not be less than 40 g/ day. For patients with increased creatinine, protein restriction should be advised in consultation with the nephrologist.

(b) Sodium: It could vary from 1000 mg to 2000 mg/day depending upon the fl uid status and serum sodium levels.

(c) Potassium: Potassium restriction may be required depending upon the potassium values in the blood and type of diuretic being used.

(ii) Cardiovascular Disease:

Maintaining an optimal body weight and restricting salt. Use of fruits and vegetables should be encouraged, with good quality fats in moderation.

(b) **Dyslipidaemia:** Saturated and trans fats food sources like vanaspati, butter, ghee, margarine, coconut oil, red meats like sausages, ham, bacon, egg yellow, whole milk and its products should be restricted. Use of healthy oils and fi bre rich foods is recommended. Vegetarians can take fl ax

seeds (10 g / day) in their diet as both fi sh and flax seeds are rich in omega-3 fatty acids which is protective for heart disease. Alcohol restriction will bring down the triglycerides. Dietary management should be accompanied with regular physical activity and exercise regimen.

Special situations requiring dietary modification: (i) Sick Days in the event of fever or other illness, the diabetic diet should be modified by changing the consistency and texture of foods to maintain adequate calorie intake. Semi solid foods and fluids or items like thin soups, milk, buttermilk, or fresh lime juice should be encouraged.

Lifestyle Management:

(i) Tobacco:

Smoking and tobacco chewing is totally prohibited

(ii) Stress:

Stress management is essential which could take the form of meditation, yoga, a long outdoor walk, exercise and trying out hobbies like reading, gardening, painting etc. Practice of yoga is our traditional Indian system, which has therapeutic value in controlling our physical and mental health. It should be done under the guidance of an expert.

(iii) Physical Activity and Exercise:

Regular physical activity along with regulated exercise is an essential component of management of type 2 diabetes. Complete evaluation of patients with diabetes should be performed before recommending an exercise program. The exercise programme has to be individualized according to one‘s ability and individual capacity.

Benefits of exercise:

- Improves insulin sensitivity
- reduces the risk of heart disease, high blood pressure, bone diseases, and unhealthy weight gain
- Keeps one flexible and agile
- Helps relieve stress, anxiety and prevents depression
- Increases strength and stamina

- Promotes sound sleep
- Increases metabolic rate and digestion
- Delays the process of aging
- Recommendation is about 150 minutes of aerobic activity or its equivalent /week along with some resistance training at least twice a week and flexibility exercises. People with diabetes need an extra quick acting carbohydrate snack before the exercise and during the exercise, if the exercise period extends the daily-recommended routine.

Diabetes education

Diabetes education means empowering people with diabetes with knowledge and providing tools crucial for making them active partners in the diabetes management team. These include:

- In-depth information about diabetes, its complications and treatment
- Appropriate self care skills
- Appropriate resources for self care
- A positive attitude
- Self monitoring skills

  The compliance of people with diabetes is essential for effective management of diabetes. Education programmes are intended to help people to understand why these actions are so important and thereby increase their motivation for self-management.

Table 2. Targets for Glycemic Control in Diabetes*

Blood sugar	Good	Satisfactory	Poor
FBS (mg/dl)	80 – 110	111 – 125	>125
PPBS (mg/dl)	120 – 140	141 – 180	>180
HbA1C	<6	6 – 7	>7

**ICMR guidelines (2018)*

PHARMACOTHERAPY

Insulin Therapy:

- **Insulin Administration**: Follow prescribed insulin regimen carefully, including timing, dosage, and injection technique.
- **Types of Insulin**: Depending on individual needs, use short-acting, long-acting, or intermediate-acting insulin as prescribed.
- **Blood Sugar Monitoring**: Regularly monitor blood sugar levels to adjust insulin dosage accordingly.

Oral Antidiabetic Agents:

- **Medication Adherence**: Take oral antidiabetic medications as prescribed by healthcare providers.
- **Types of Oral Agents**: Depending on the type and severity of diabetes, oral medications such as metformin, sulfonylureas, or thiazolidinediones may be prescribed.

Injectable Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists:

- **Injection Administration**: Follow healthcare provider's instructions for administering GLP-1 receptor agonists.
- **Benefits**: These medications help regulate blood sugar levels, promote weight loss, and reduce cardiovascular risk.

Monitoring and Self-Care

Blood Glucose Monitoring:

- **Regular Testing**: Monitor blood glucose levels as directed by healthcare providers, especially before and after meals and physical activity.
- **Log Keeping**: Maintain a record of blood sugar readings to track patterns and trends over time.

Hemoglobin A1c Monitoring:

- **Long-term Control**: Hemoglobin A1c provides a measure of average blood sugar levels over the past two to three months. Regular monitoring helps assess long-term diabetes management.

Complication Screening:

- **Regular Check-ups**: Undergo regular screenings for diabetes-related complications, including eye exams, foot exams, kidney function tests, and cardiovascular assessments.

- **Early Detection**: Early detection and management of complications are crucial for preventing or minimizing their impact on health.

By integrating these lifestyle modifications, pharmacotherapy, and monitoring/self-care practices into daily life, individuals with diabetes can effectively manage their condition and reduce the risk of complications. Regular communication with healthcare providers is essential for personalized diabetes management plans and adjustments as needed.

Prevention of Diabetes:

1. **Healthy Lifestyle**: Encouraging individuals to adopt a healthy lifestyle is crucial for preventing type 2 diabetes. This includes maintaining a balanced diet rich in fruits, vegetables, whole grains, and lean proteins, along with regular physical activity.
2. **Weight Management**: Obesity is a significant risk factor for type 2 diabetes. Promoting weight loss through healthy eating and exercise can reduce the risk of developing the disease.
3. **Screening and Early Detection**: Identifying individuals at risk for diabetes through screening programs can facilitate early intervention and prevent the progression to full-blown diabetes. Implementing regular screening programs for individuals at high risk of developing diabetes, such as those with a family history or obesity, can facilitate early detection and intervention. Organizing community-based screening programs in collaboration with healthcare providers and community organizations can increase access to screening services and reach underserved populations.
4. **Clinical Assessment**: Conducting routine clinical assessments, including blood glucose testing and monitoring, can help identify individuals with prediabetes or early-stage diabetes, allowing for timely intervention to prevent progression to full-blown diabetes.
5. **Education and Awareness**: Increasing awareness about the risk factors for diabetes and the importance of preventive measures can empower individuals to make healthier choices and seek appropriate medical care.
6. **Community Interventions**: Implementing community-based programs that promote healthy behaviors, such as healthy eating and regular exercise, can help prevent diabetes on a larger scale.

Research and Innovation:

Advances in Treatment Modalities:

1. **Drug Development**: Continued research into new medications and therapies for diabetes treatment, including insulin analogs, incretin-based therapies, and SGLT2 inhibitors, can improve outcomes for individuals with diabetes.
2. **Gene Therapy**: Investigating gene therapy approaches for diabetes, such as gene editing techniques and stem cell therapies, holds promise for developing novel treatments that target the underlying mechanisms of the disease.

Emerging Technologies and Therapies:

1. **Artificial Pancreas Systems**: Advancements in artificial pancreas technology, which combines continuous glucose monitoring with automated insulin delivery, can provide more precise and personalized management of blood glucose levels.
2. **Implantable Devices**: Research into implantable devices, such as glucose-responsive insulin delivery systems and bioengineered pancreatic tissues, may offer innovative solutions for diabetes management and treatment.
3. **Mobile Health Initiatives**: Leveraging mobile health technologies, such as smartphone apps and telemedicine, for diabetes screening can enhance accessibility and convenience, particularly in remote or rural areas.
4. **Artificial Intelligence (AI)**: AI algorithms can analyze large datasets to identify patterns and predict individuals at risk for diabetes, enabling early intervention and preventive measures.
5. **Technology Integration**: Integration of technology, such as wearable devices and mobile health applications, can facilitate continuous monitoring of glucose levels and lifestyle behaviors, enabling more personalized and real-time interventions for diabetes prevention and management.

Personalized Medicine Approaches:

1. **Precision Medicine**: Integrating genomic data and biomarkers into diabetes management algorithms can enable personalized prevention and treatment approaches tailored to individual patients' genetic profiles and disease characteristics.
2. **Machine Learning and AI**: Leveraging machine learning and artificial intelligence algorithms to analyze large datasets can identify patterns and predict treatment responses, facilitating personalized treatment recommendations for individuals with diabetes.
3. **Behavioral Interventions**: Further research into behavioral interventions, such as cognitive-behavioral therapy and motivational interviewing, can help address the psychological and social factors influencing diabetes prevention and management.
4. **Policy and Public Health Initiatives**: Implementing policies and public health initiatives that promote healthy environments, such as access to nutritious foods and opportunities for physical activity, can support population-wide efforts to prevent diabetes.

By focusing on primary prevention strategies, secondary prevention through early detection and intervention, and ongoing research and innovation, we can work towards reducing the burden of diabetes and improving outcomes for individuals affected by the disease.

In conclusion, diabetes remains a significant health challenge globally, with its prevalence steadily rising. This chronic condition not only affects individuals' quality of life but also imposes a substantial economic burden on healthcare systems worldwide. Effective management of diabetes requires a multifaceted approach, including lifestyle modifications, medication adherence, and regular monitoring of blood glucose levels. Patient education and empowerment play crucial roles in achieving optimal outcomes, emphasizing the importance of self-care practices and early detection of complications. Additionally, ongoing research into novel treatments, technological advancements such as continuous glucose monitoring systems and insulin pumps, and efforts to address social determinants of health offer promising avenues for improving diabetes care and outcomes in the future. By fostering collaboration among healthcare professionals, policymakers, and communities, we can work towards preventing new cases, enhancing access to care, and ultimately reducing the global impact of diabetes.

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