International Journal of Pharmaceutical Drug Design
IJPDD (April, 2024)
ISSN: 2584-2897
Website: https://ijpdd.org/

Review

A REVIEW ON USE OF NANOPARTICLES IN THE TREATMENT OF DIABETES MELLITUS

Naina*[1], Maninderjeet Kaur[1], Tichakunda Xavier Mharazanye[2]

[1]*GHG Khalsa College of Pharmacy, Gurusar Sudhar*

[2]*RIMT University, Mandi Gobindgarh*

Article History
Received: 15/03/2024
Revised : 12/04/2024
Accepted : 29/04/2024
DOI:
10.62896/ijpdd.1.5.17

Abstract:

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. This essay provides a comprehensive overview of diabetes mellitus, exploring its types, etiology, pathophysiology, diagnosis, and treatment and management strategies. Additionally, it discusses the emerging field of nanoparticle-based therapies and their potential use in diabetes mellitus management. A thorough understanding of these aspects is essential for effectively managing diabetes and improving patient outcomes.

Keywords: *Diabetes mellitus, chronic metabolic disorder, hyperglycemia, diabetes mellitus management*

***Corresponding Author**

Naina

GHG Khalsa College of Pharmacy, Gurusar Sudhar

Email: nainapuri121@gmail.com

Introduction:

Diabetes mellitus (DM) is a significant public health issue affecting over 400 million people worldwide, causing chronic microvascular, macrovascular, and neuropathic complications. Diabetes is a condition resulting from high blood sugar levels, caused by inadequate insulin production or inadequate body response to insulin. It affects people of all ages and is typically chronic, but can be managed with medication and lifestyle changes.Glucose, primarily derived from carbohydrates, is the body's primary energy source. When glucose is in the bloodstream, it requires insulin to reach its final destination, causing hyperglycemia. Consistently high blood glucose levels can lead to health issues like heart disease, nerve damage, and eye issues. Diabetes mellitus is the medical term for diabetes, while diabetes insipidus is a separate condition that causes increased thirst and frequent urination. Both conditions are rarer than diabetes mellitus.

Types of 2 Diabetes is the most common form of diabetes, accounting for approximately 90-95% of all cases. It typically develops in adulthood, but it is increasingly being diagnosed in children and adolescents due torising obesity rates [2]. In T2DM, the body becomes resistant to the effects of insulin, and the pancreas may not produce enough insulin to meet the body's demands. Lifestyle factors such as sedentary behaviour, unhealthy eating habits, obesity, and genetics contribute to the development of type 2 diabetes [2]. Lifestyle modifications and oral medications are initially prescribed, but some individuals may require insulin therapy as the disease progresses.

Type 1 diabetes is an autoimmune disease involving the immune system attacking and destroying insulin-producing cells in the pancreas. It affects up to 10% of individuals, typically diagnosed in children and young adults, and can develop at any age.

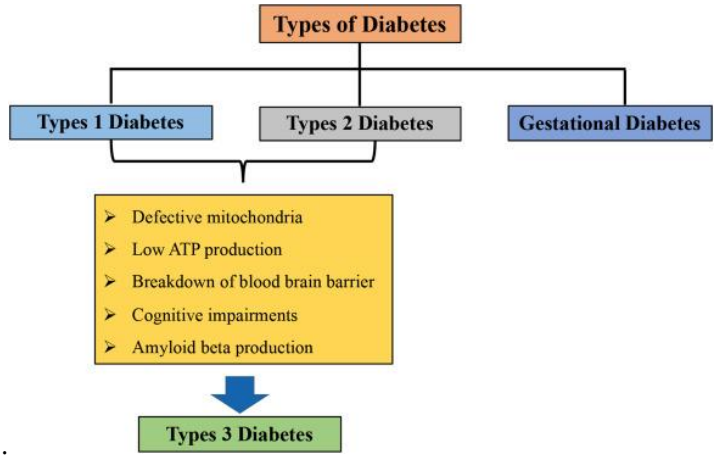
Gestational Diabetes Mellitus (GDM) [5] Gestational diabetes occurs during pregnancy and usually resolves after childbirth. It is characterized by high blood glucose levels that develop as a result of hormonal changes and increased insulin resistance during pregnancy [5]. GDM increases the risk of complications for boththe mother and the baby. Women with a history of GDM are also at a higher risk of developing type 2 diabetes later in life.

Type 3c diabetes occurs when the pancreas experiences damage, such as pancreatitis, pancreatic cancer, cystic fibrosis, or hemochromatosis, affecting insulin production. Pancreatectomy can also result in Type 3c.

LADA is a slow-developing type of autoimmune diabetes, affecting adults over 30 years old, resulting from an autoimmune reaction.

MODY, or monogenic diabetes, is caused by an inherited genetic mutation affecting insulin production and usage. With over 10 types, it affects up to 5% of diabetes patients and is often passed down through families.

Neonatal diabetes is a rare form of monogenic diabetes that occurs within the first six months of life. About 50% of babies have permanent neonatal diabetes mellitus, while the other half experience transient diabetes mellitus, which disappears within a few months but can return later in life.



A Type 1 disorder called **brittle diabetes** is characterized by recurrent high and low blood sugar episodes, which frequently necessitate hospitalization. Rarely, a pancreas transplant may be required for long-term care.

Diabetes symptoms include:

Dry tongue and increased thirst (polydipsia).
A lot of urine.
Fatigue.
The vision is hazy.
Loss of weight without cause.
Tingling or numbness in your feet or hands.
Slow-healing cuts or sores.
Frequent yeast infections of the skin or vagina.

Type 1 diabetes symptoms can develop quickly, with symptoms like vomiting, stomach pains, fruity-smelling breath, and labored breathing. Severe complications like diabetes-related ketoacidosis (DKA) may also occur, requiring immediate medical treatment. DKA is life-threatening and requires immediate attention. Type 2 diabetes and prediabetes may develop slowly, with high blood sugar levels and darkened skin on certain body parts being possible signs. Routine bloodwork may show high blood sugar levels before symptoms are recognized. Gestational diabetes typically doesn't show symptoms, but healthcare providers will test for it between 24 and 28 weeks of pregnancy.

Etiology of Diabetes Mellitus

•Diabetes mellitus, often referred to as diabetes, is a chronic metabolic disorder characterized by elevated blood glucose levels (hyperglycemia) resulting from defects in insulin secretion, insulin action, or both. Insulin, a hormone produced by the pancreas, plays a crucial role in regulating blood glucose levels and facilitating its uptake by cells forenergy production.

There are several types of diabetes mellitus, each with distinct characteristics:

- Type 1 Diabetes Mellitus (T1DM) [2]: Also known as insulin-dependent diabetes orjuvenile-onset diabetes, T1DM is an autoimmune condition in which the immune system mistakenly attacks and destroys the insulin-producing beta cells in the pancreas. As a result, individuals with type 1 diabetes require lifelong insulin replacement therapy [2].
- Type 2 Diabetes Mellitus (T2DM) [1]: Type 2 diabetes is the most common form of diabetes, accounting for

approximately 90-95% of all cases. It typically develops in adulthood, but it is increasingly being diagnosed in children and adolescents due torising obesity rates [2]. In T2DM, the body becomes resistant to the effects of insulin, and the pancreas may not produce enough insulin to meet the body's demands. Lifestyle factors such as sedentary behavior, unhealthy eating habits, obesity, and genetics contribute to the development of type 2 diabetes [2]. Initially,lifestyle modifications and oral medications are prescribed, but some individuals may require insulin therapy as the disease progresses.

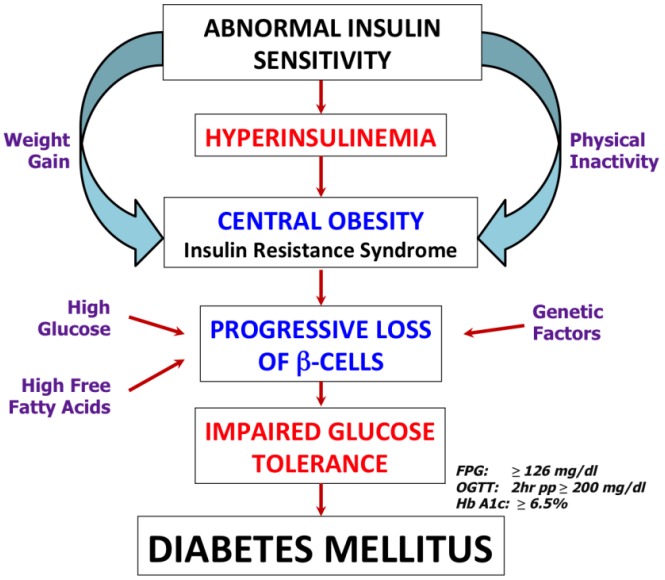
- Gestational Diabetes Mellitus (GDM) [5]: Gestational diabetes occurs during pregnancy and usually resolves after childbirth. It is characterized by high blood glucose levels that develop as a result of hormonal changes and increased insulin resistance during pregnancy [5]. GDM increases the risk of complications for boththe mother and the baby. Women with a history of GDM are also at a higher risk of developing type 2 diabetes later in life.
- Other Forms of Diabetes: This category includes various fewer common forms of diabetes, such as monogenic diabetes (caused by specific genetic mutations), drug-induced diabetes, and diabetes associated with certain medical conditions [5].

Pathophysiology of DM

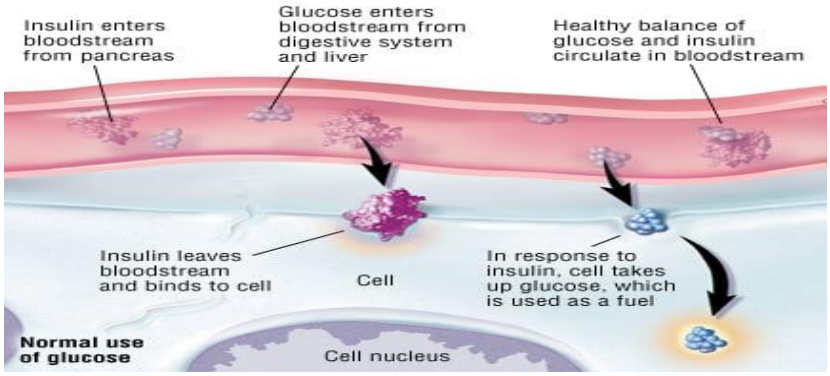
Diabetes mellitus is a syndrome causing disordered metabolism and inappropriate hyperglycemia due to insulin deficiency or insulin resistance. Type 1 diabetes is caused by autoimmune processes, causing ketoacidosis, while type 2 diabetes is more prevalent due to insulin resistance and compensatory insulin secretion defects. Diabetes can lead to serious complications, affecting multiple systems and potentially causing premature death. Further research is needed to understand the pathophysiology of diabetes mellitus.

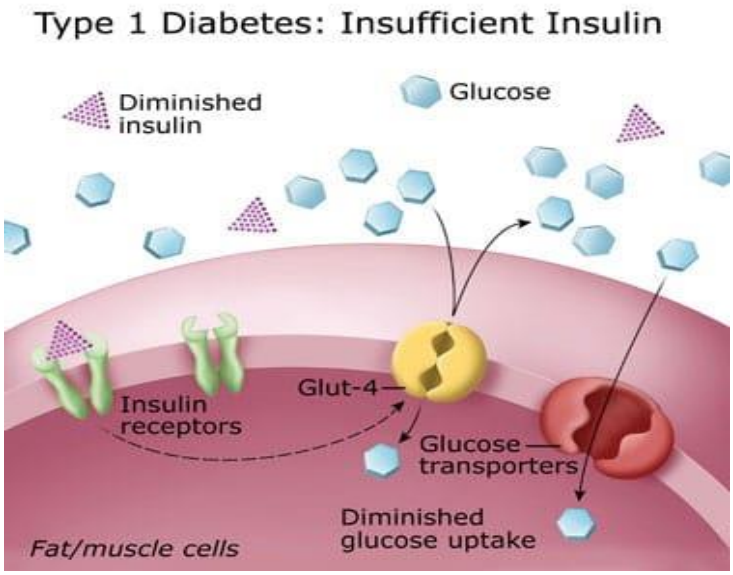
Normal human body pathology: The pancreas, located behind the liver and stomach, secretes digestive enzymes and hormones like insulin and glucagon to regulate glucose levels in the body. Insulin lowers blood glucose levels by allowing glucose to enter body cells for metabolism. If blood glucose levels are too low, the pancreas secretes glucagon to stimulate the release of glucose from the liver. After a meal, glucose and amino acids are absorbed, leading to a sharp rise in blood glucose levels. Beta cells in the pancreas secrete insulin, which enters the bloodstream within 20 minutes. Insulin allows glucose to enter cells, particularly muscle and liver cells, where it is burned for energy or stored for future use. When insulin levels are high, the liver stops producing glucose and stores it in other forms until the body needs it again. As blood glucose levels reach their peak, the pancreas reduces insulin production, resulting in low levels of both blood glucose and insulin about 2-4 hours after a meal.

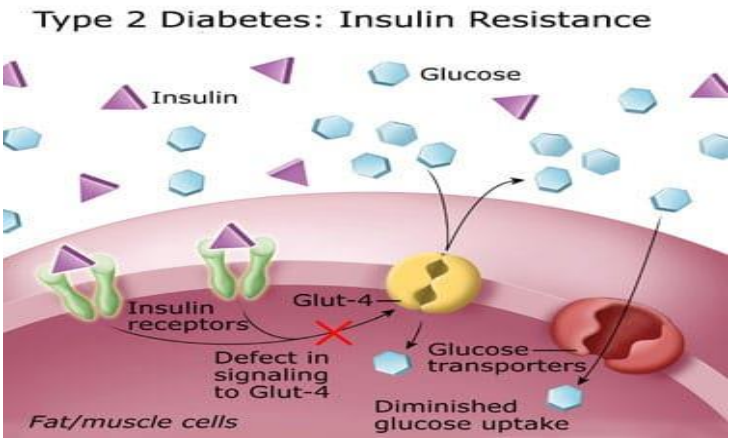
Type 1: Type 1 diabetes is a rare condition affecting children and young adults, resulting from the immune system's destruction of pancreatic beta cells. Only 5% of individuals have this form, and to survive, insulin must be delivered via injection or pump.



Type 2: Type 2 diabetes is the most common form of diabetes, resulting from a combination of genetic and environmental factors affecting beta-cell function and insulin sensitivity in various tissues. Insulin resistance, a disorder where cells fail to use insulin properly, is the main cause of type 2 diabetes. As insulin needs increase, the pancreas loses its ability to produce it. This leads to health issues like heart disease, nerve damage, and kidney damage. Diabetes is the leading cause of kidney failure, non-traumatic lower-limb amputations, and new cases of blindness in the United States. To prevent or delay type 2 diabetes, individuals can adopt a healthy lifestyle, including a balanced diet, increased physical activity, and weight management. By adopting these positive steps, individuals can stay healthier and reduce their diabetes risk.







Treatment and Management of *Diabetes mellitus*

The treatment and management of diabetes mellitus involves a comprehensive approach aimed at achieving and maintaining optimal blood glucose control, preventing complications, and improving overall well-being [1]. The management strategies may vary depending on the type of diabetes and individual circumstances. Here are the keycomponents of treatment and management for diabetes mellitus:

- Lifestyle Modifications: Lifestyle changes are essential for all individuals withdiabetes, regardless of the type. These include:
- Healthy Eating: Following a well-balanced diet that includes a variety of nutrient-rich foods, focusing on whole grains, lean proteins, fruits, vegetables, and healthy fats. Limiting the intake of processed foods, sugary beverages, and high-fat foods isimportant [5,6].
- Regular Physical Activity: Engaging in regular physical activity, such as walking, jogging, cycling, or swimming, helps improve insulin sensitivity, lower blood glucoselevels, and maintain a healthy weight. Aim for at least 150 minutes of moderate-intensity aerobic exercise per week, along with strength training exercises [5,6].
- Weight Management: Achieving and maintaining a healthy weight is crucial, especially for individuals with type 2 diabetes. Weight loss, if overweight or obese,can improve insulin sensitivity and glycemic control [6].
- Smoking Cessation: Smoking increases the risk of cardiovascular complications indiabetes. Quitting smoking is highly recommended [6].
- Medications:
- Insulin Therapy: Individuals with type 1 diabetes and some with type 2 diabetes mayrequire insulin therapy. Insulin can be administered through multiple daily injectionsor an insulin pump. The type, dosage, and timing of insulin depend on individual needs and blood glucose levels [6].
- Oral Medications: Various oral medications, such as metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists, are available for the management of type 2 diabetes. These medicationswork in different ways to lower blood glucose levels and improve insulin sensitivity[5].
- Blood Glucose Monitoring: Regular monitoring of blood glucose levels is crucial to assess glycemic control, make necessary adjustments to medications or lifestyle, and prevent complications. Self-monitoring of blood glucose (SMBG) involves usinga glucometer to measure blood glucose levels at home. Continuous glucose monitoring (CGM) systems provide real-time glucose readings throughout the day [4].
- Education and Support: Diabetes education is vital for individuals to understand their condition, learn self-management skills, and make informed decisions about their health. Diabetes self-management education and support (DSMES) programsprovide guidance on nutrition, exercise, medication management, monitoring, and coping with diabetes-related challenges [6].
- Regular Medical Check-ups: Regular visits to healthcare professionals, including primary care physicians, endocrinologists, and diabetes educators, are important for ongoing monitoring of diabetes control, assessment of complications, andadjustment of treatment plans as needed [6].
- Prevention and Management of Complications: Diabetes increases the risk of various complications, including cardiovascular disease, kidney disease, eye disease, and nerve damage. Good glycemic control, blood pressure management,cholesterol control, and regular screening for complications are essential components of diabetes management [6].
- Psychosocial Support: Managing diabetes can be challenging emotionally and mentally. Psychosocial support, such as counseling, support groups, and access tomental health services, can help individuals cope with the psychological and emotional aspects of living with diabetes [6].

Diagnosis of Diabetes mellitus

The diagnosis of diabetes mellitus involves several tests and criteria to assess blood glucose levels and determine whether an individual has the condition. The diagnostic process considers different factors, including symptoms, risk factors, and laboratory tests.Here are the key aspects of diagnosing diabetes mellitus [5]:

Symptom-Based Diagnosis:

- Classic Symptoms: The presence of classic symptoms such as frequent urination(polyuria), excessive thirst (polydipsia), unexplained weight loss, and increased hunger may indicate the possibility of diabetes [5,6]. However, relying solely onsymptoms is not sufficient for a definitive diagnosis.
- Fasting Plasma Glucose (FPG) Test:
- FPG Test: This test measures blood glucose levels after an overnight fast of at least8 hours. A fasting plasma glucose level of 126 mg/dL (7.0 mmol/L) or higher on twoseparate occasions indicates diabetes [5].
- Oral Glucose Tolerance Test (OGTT):
- OGTT: This test is performed to evaluate how the body processes glucose. After anovernight fast, the individual consumes a glucose-rich drink, and blood glucose levels are measured periodically over a 2-hour period. A blood glucose level of 200mg/dL (11.1 mmol/L) or higher at 2 hours indicates diabetes [5.2].
- Random Plasma Glucose Test:
- Random Plasma Glucose Test: This test measures blood glucose levels at any time of the day, regardless of the last meal. A random plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher, combined with classic symptoms of diabetes, indicates thepresence of the condition [5,6].
- Glycated Hemoglobin (HbA1c) Test:
- HbA1c Test: This test reflects average blood glucose levels over the past 2 to 3 months. An HbA1c level of 6.5% or higher on two separate occasions indicates diabetes. It is important to note that the HbA1c test is not recommended for diagnosing diabetes in certain populations, such as children, pregnant women, andindividuals with certain medical conditions [2].
- Confirmatory Testing:
- If the initial test results indicate diabetes, it is recommended to repeat the test on adifferent day to confirm the diagnosis. This helps to rule out temporary fluctuations or laboratory errors [2].

Additional Considerations:

- For individuals with classic symptoms of hyperglycemia or hyperglycemic crisis, adiagnosis of diabetes can be made without the need for further testing [5].
- In some cases, when blood glucose levels are not clearly indicative of diabetes, further tests, such as a fructosamine test or continuous glucose monitoring (CGM),may be used to assess glycemic control and aid in diagnosis [5].

It is important to consult a healthcare professional for proper evaluation, interpretation oftest results, and accurate diagnosis. Early diagnosis of diabetes mellitus allows for timely management and reduces the risk of complications associated with the condition [2].

Pathophysiology of Diabetes Mellitus

Insulin and glucagon are the two hormones responsible for maintaining glucose homeostasis in the body. Insulin is secreted by β cells when glucose concentration rises, causing blood glucose levels to decrease or increase**.**

a) inhibiting liver glucose production through glycogenolysis and gluconeogenesis.

b) increasing glucose uptake by liver, muscle, and fat tissue.

Glucagon secreted by pancreatic α cells to regulate glucose concentration. Glucagon acts by:

a) Enhancing liver glycogenolysis and gluconeogenesis to counteract insulin's effects.

b) Glucagon, cortisol, and catecholamines increase plasma glucose levels.

Amylin, glucagon-1 (GLP-1), and glucose dependent insulinotropic polypeptide (GIP) are hormones involved in maintaining normal glucose levels. Amylin decreases gastric emptying and enhances glucose absorption after meals. GLP and GIP are incretins derived from the gut that facilitate insulin synthesis and secretion from pancreatic β cells. Glucose is not absorbed from the intestine or by cells requiring energy freely, so glucose is distributed to cells through glucose transporters, a family of membrane-bound glycoproteins.

i) Sodium glucose co-transporter (SGLT)

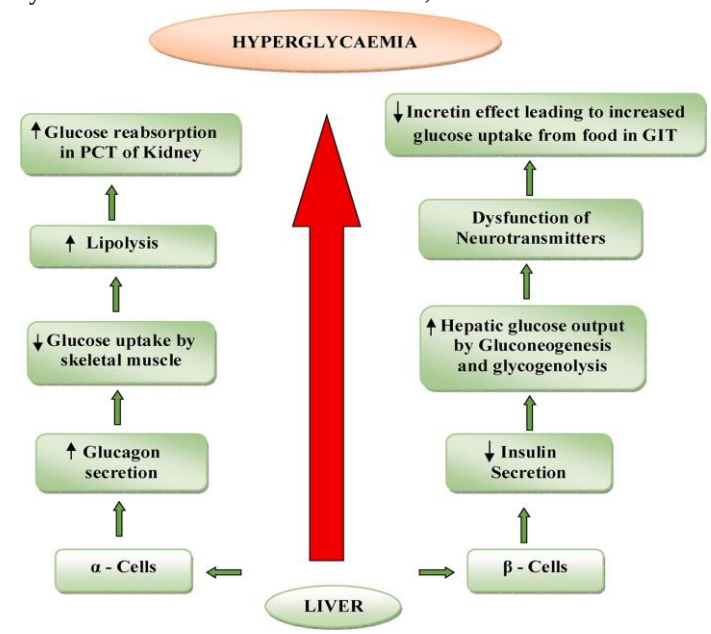
ii) Facilitative glucose transporter (GLUT)

Diabetes mellitus has two major subtypes, with varying causes.

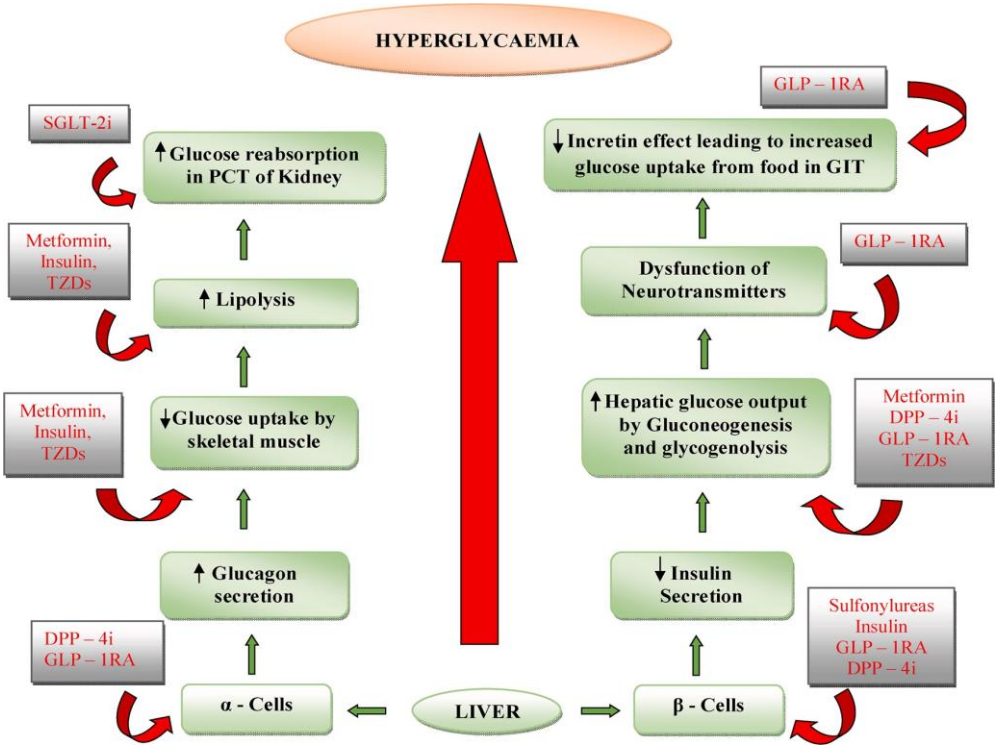
Type I diabetes (T1DM) involves the immune system attacking pancreatic β cells, with genes playing a crucial role.

Type II diabetes (T2DM) involves genetics and lifestyle factors, with obesity or overweight increasing associated risks.

T2DM pathophysiology may involve "ominous octet" mechanisms, as below



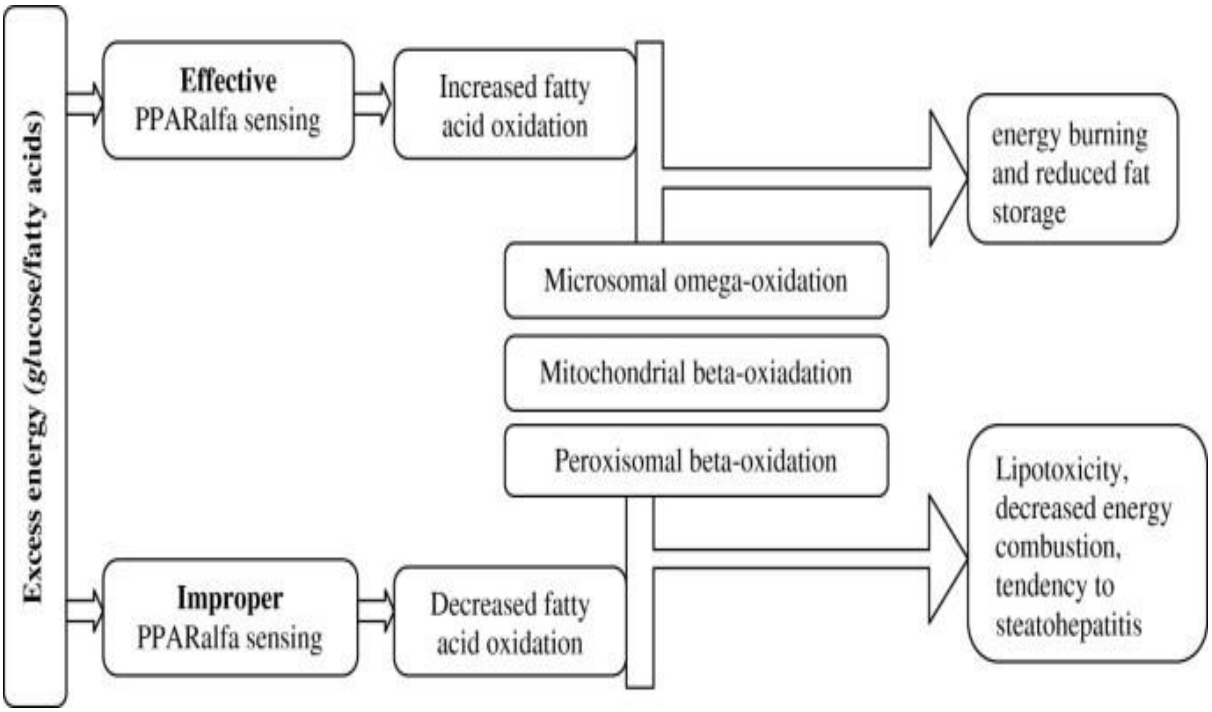
Pathophysiology of T2DM – Ominous octet.



Targets of treatment for T2DM [TZDs – Thiazolidinediones**, DPP – 4i –** Dipetidyl peptide – 4 inhibitor**, GLP-1RA –** Glucagon like peptide – 1 receptoragonist**, SGLT-2i -** Sodium–Glucose co-transporter 2 inhibitor**].**

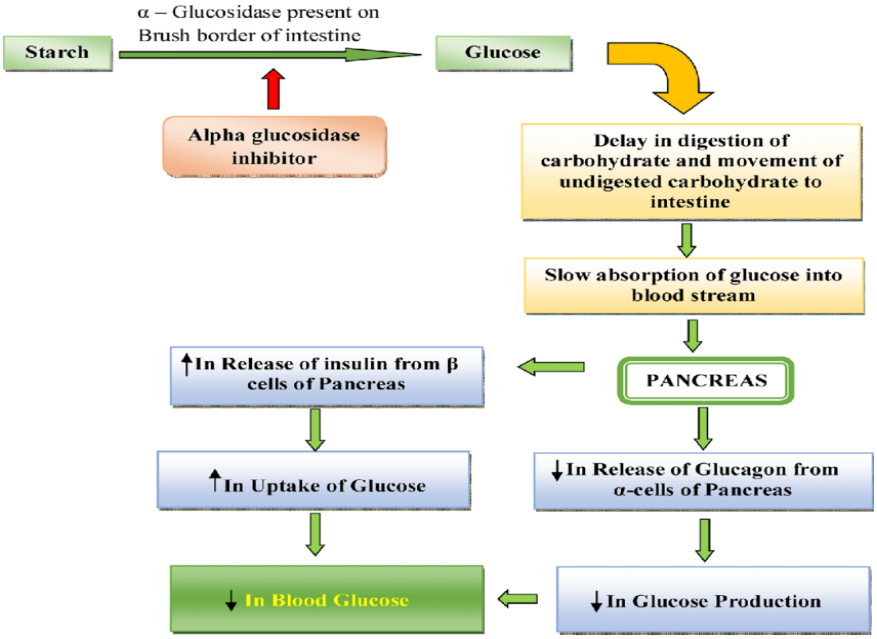
a) Insulin secretion from β cells of islets of Langerhans is reduced.
b) Glucagon secretion is increased, glucose production is increased.
c) Neurotransmitter dysfunction and resistance in the brain is disrupted, lipolysis increases, kidney reabsorption increases, incretin's effect reduced, and peripheral tissues like skeletal muscle, liver, and adipose tissue impaired or decreased glucose uptake.
d) Neurotransmitter dysfunction, insulin resistance, lipolysis, kidney reabsorption, incretin reduction, and peripheral tissue impairment can lead to glucose uptake issues. These issues can affect skeletal muscle, liver, and adipose tissue.

When a woman is pregnant, her hormone levels alter, and the placenta releases hormones that reduce the sensitivity of her cells to the effects of insulin. Diabetes mellitus can result from genetic abnormalities that cause diseases such monogenic diabetes, cystic fibrosis, and hemochromatosis. Diabetes can be brought on by hormonal conditions such Cushing's syndrome, acromegaly, and hyperthyroidism. Diabetes can be caused by pancreatic damage or removal from conditions including pancreatitis, cancer, or trauma that injure beta cells or decrease their ability to produce insulin. The activity of beta cells can be impacted by a number of pharmaceuticals, including niacin, certain diuretics, anti-seizure medications, psychiatric medications, HIV therapies, pentamide, glucocorticoids, anti-rejection drugs, and statins. Addressing these problems is essential for preventing the onset of diabetes and maintaining general health.



There are various factors that increases the risk for diabetes [32]. The dominant factors are detailed below:
If a parent or sibling has diabetes, the chance of developing T1DM as a kid or adolescent rises [33]. Risk factors for T2DM include being overweight, having poor eating habits, being older than 45 years old, having a family history of diabetes, being physically inactive, having pre-diabetes or gestational diabetes, and having high cholesterol or triglyceride levels [34–37]. The risk of gestational diabetes rises with age over 25, being overweight, having had gestational diabetes in the past, giving birth to a child that weighed more than 9 pounds, having a family history of T2DM, and having PCOS [38].
As elevated blood sugar destroys organs and tissues all over the body, diabetes has several problems. The likelihood of developing new complications increases the longer the body struggles with elevated blood sugar levels. Diabetes complications include nephropathy, retinopathy, vision loss, neuropathy, infections and sores that don't heal from bacterial and fungal infections, depression, and dementia [39]. Cardiovascular complications include heart disease, heart attack, stroke, and neuropathy. Anyone at risk for developing diabetes mellitus or exhibiting notable signs should undergo routine

testing. Several blood tests, including the following, can be performed to diagnose diabetes and prediabetes.
Fasting plasma glucose (FPG): aids in determining blood sugar levels following an eight-hour fast.
HbA1C test: Measures blood sugar levels over the last three months using the HbA1C test. Within the 24th and 28th weeks of pregnancy, blood tests are performed for the three-hour glucose tolerance test and the glucose challenge test in order to diagnose gestational diabetes [20,40].



Biomarkers for diabetes

Hemoglobin A1c is a better chronic glycemia estimation method than glucose levels at a single time point. It has advantages over fasting, pre-analytical stability, and minimal day-to-day fluctuation during stress and illness. However, there is conflicting evidence regarding the usefulness of HbA1c, as it provides moderate sensitivity in diabetes diagnosis compared to OGTT and FPG. HbA1c levels <5.7% correlate with only 60% of subjects having normal glucose tolerance (NGT). Additionally, HbA1c threshold for prediabetes does not take into account ethnicity, body mass index (BMI), and age, which may significantly alter HbA1c levels.[46,47,48,49,50,51]

Fructosamine (FA) is used as an alternate glycemic marker for diabetes screening and prediabetes, reflecting mean blood glucose levels of previous 1 4 weeks. It is cost-effective and convenient to perform, but has high variability within the subject and in a state of rapid albumin turnover, such as nephrotic syndrome and chronic liver disease. FA is also a good indicator of the risk for microvascular complications.[52,53,54]

Glycated albumin (GA) is a better indicator of glycemic control than HbA1c in individuals with renal failure, hemolytic anemia, and blood transfusions cases. Combining GA with HbA1c has better sensitivity to predict prediabetes than HbA1c alone. However, sometimes GA may be artificially low in individuals with increased BMI, body fat mass, and high visceral fat. [55,56]

Anhydroglucitol (1,5 AG) is a prediabetes marker, reflecting glucose levels within 2 weeks. It is stable, reproducible, and cost-effective than other glycemic diagnostic tests and is better used in identifying postprandial glycemic excursions.[57,58]

Fetuin-A (FetA) is a glycoprotein secreted from the liver and correlates with increased risk of Type 2 Diabetes Mellitus (T2DM) incidence and complications. It acts as an endogenous ligand for TLR4 for induction of lipid-induced insulin resistance (IR) by lipids, potentially serving as a novel therapeutic target for IR.[59,60]

Branched chain amino acids (BCAAs) have been significantly associated with diabetes development, with glutamine, methionine, cysteine, and 2-aminoadipic acid being increased in initial insulin-resistant states. However, glycine levels are lower in prediabetic individuals, suggesting that these changes in circulating amino acid levels may be a significant predictive biomarker for IR and T2DM.[61,62,63]

α-Hydroxybutyrate (α-HB) is a catabolic byproduct of threonine, methionine, and glutathione anabolism in hepatic tissue, leading to chronic shifts in glutathione synthesis and elevated α-HB levels in individuals of IR. Higher insulin may play a role in reducing Lp(a) concentration in IR.

Lipoprotein(a) is synthesized by the liver and is an independent risk factor for the development of CVD. Serum Lp(a) and the prevalence of prediabetes and T2DM have an inverse relationship. Higher insulin may play a role in reducing Lp(a) concentration.

Triglycerides and high-density lipoprotein (HDL) levels in prediabetics are significantly increased compared to HDL-C levels. HDL-C induces insulin secretion, while low HDL-C promotes progression to diabetes. Ceramide, a lipid molecules mediating IR, inhibits insulin action and accumulates in insulin-resistant tissues, causing inflammation and coronary artery disease.

Ferritin and transferrin are intracellular proteins that regulate storage and iron release. High serum ferritin and transferrin saturation are associated with increased risk of prediabetes and diabetes. Dietary iron restriction may prevent the development of diabetes and loss of β-cell function. High levels of MASP1 are found in prediabetes, diabetes, and CVD, with the onset of prediabetes and IR occurring earlier in those with higher MASP1 plasma levels.[59,60]

- **Potential Application of Nanoparticles**

The potential use of nanoparticles in diabetes mellitus is an area of ongoing research andholds promise for improving the diagnosis, treatment, and management of the disease.

Nanoparticles, which are particles with dimensions ranging from 1 to 100 nanometers [11], offer unique properties that can be harnessed to address specific challenges associated with diabetes. Here are some potential applications of nanoparticles in diabetesmellitus [8]:

- Drug Delivery Systems: Nanoparticles can serve as carriers for delivering therapeutic agents, such as insulin, to targeted sites in the body [9]. By encapsulating insulin within nanoparticles, its stability can be enhanced, and controlled release mechanisms can be employed, allowing for more precise dosing and prolonged action [9]. This approach can improve the efficiency and convenience of insulin therapy, reducing the frequency of injections and enhancingpatient compliance.
- Glucose Monitoring: Nanoparticles can be utilized in the development of novel glucose monitoring systems. Functionalized nanoparticles can be designed to bind specifically to glucose molecules, enabling their detection and quantification. TheseNano sensors can provide real-time, non-invasive monitoring of blood glucose levels, eliminating the need for frequent finger-prick testing and enhancing the management of diabetes [10,9}.
- Biosensors: Nanoparticles can be incorporated into biosensor devices for the detection of various biomarkers associated with diabetes, such as insulin, hemoglobin A1c, or inflammatory markers. These nanoscale sensors offer highsensitivity, specificity, and rapid response times, enabling accurate and timely monitoring of disease progression and treatment effectiveness [11,12].
- Tissue Engineering: Nanoparticles can play a role in tissue engineering approaches for pancreatic regeneration. By incorporating nanoparticles into scaffolds or matrices, it is possible to provide a supportive microenvironment for the growth anddifferentiation of pancreatic beta cells, which produce insulin. This approach holdspotential for restoring beta cell function and insulin production in individuals with diabetes [11].
- Wound Healing: Diabetes is often associated with impaired wound healing, leading to chronic ulcers and complications. Nanoparticles can be utilized in advanced wound dressings to promote wound healing by delivering growth factors, antimicrobial agents, and modulating the wound microenvironment. Nanoparticle-based dressings can enhance the regeneration of damaged tissues, reduce infection rates, and improve overall wound healing outcomes [12].
- Imaging and Diagnostics: Nanoparticles can be engineered to serve as contrast agents for various imaging modalities, such as magnetic resonance imaging (MRI), computed tomography (CT), or fluorescence imaging. These nanoparticles can help in the early detection and characterization of diabetic complications, such as retinopathy, nephropathy, or cardiovascular disease, allowing for timely interventionand improved patient outcomes [12,9].

Conclusion

In conclusion, diabetes mellitus is a complex metabolic disorder characterized by chronichyperglycemia resulting from defects

in insulin secretion, insulin action, or both. It is a global health concern with increasing prevalence worldwide [1]. Understanding the etiology, pathophysiology, and management of diabetes is crucial for effective diagnosis, treatment, and prevention of complications [2]. Additionally, the potential use of nanoparticles in diabetes mellitus offers exciting opportunities for improving disease management and patient outcomes. The etiology of diabetes involves a combination of genetic and environmental factors. Both type 1 and type 2 diabetes have distinct underlying mechanisms [1], with type 1 being an autoimmune disease characterized by the destruction of pancreatic beta cells and type 2 primarily associated with insulin resistance and impaired insulin secretion [12]. Gestationaldiabetes occurs during pregnancy due to hormonal changes.

The pathophysiology of diabetes revolves around the disruption of glucose regulation, leading to elevated blood glucose levels. In type 1 diabetes, autoimmune destruction of beta cells leads to insulin deficiency. Type 2 diabetes involves a complex interplay of insulin resistance, impaired insulin secretion, and abnormal glucose production in the liver[4]. These mechanisms contribute to chronic hyperglycemia and the development of diabetes-related complications [4].

The treatment and management of diabetes focuses on achieving and maintaining optimalblood glucose control, preventing complications, and improving overall well-being 5]. Thisinvolves lifestyle modifications, including healthy eating, regular physical activity, weight management, and smoking cessation [6]. Medications, such as insulin therapy and oral medications, are used to lower blood glucose levels and improve insulin sensitivity [5,6].].Regular monitoring of blood glucose, education and support, and prevention and management of complications are also vital components of diabetes management [4].

Diagnosing diabetes mellitus relies on various criteria, including symptom-based assessment, fasting plasma glucose tests, oral glucose tolerance tests, random plasmaglucose tests, and glycated hemoglobin tests [5]. A proper diagnosis allows for timely intervention and effective management of the disease [7].

Furthermore, the potential use of nanoparticles in diabetes mellitus holds great promise.Nanoparticles offer unique properties that can be harnessed for targeted drug delivery, glucose monitoring, biosensing, tissue engineering, wound healing, and imaging/diagnostics [8,11,12]. These applications have the potential to revolutionize diabetes care by enhancing treatment efficacy, improving disease monitoring, and enabling more personalized approaches to management [7].

In conclusion, diabetes mellitus is a multifaceted condition that requires a comprehensive approach encompassing etiology, pathophysiology, treatment and management, diagnosis, and the potential use of nanoparticles [1,2]. With ongoing research and advancements in medical technologies, we are moving towards more effective strategies for managing diabetes and improving the quality of life for individuals living with this chronic condition [4]. By understanding the complexities of diabetes and embracing innovative solutions, we can strive towards better outcomes and ultimately reduce the burden of diabetes on a global scale [1,2].

References

1) American Diabetes Association. (2021). Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes. Diabetes Care, 44(Supplement 1), S15-S33.

2) Atkinson, M. A., & Eisenbarth, G. S. (2001). Type 1 diabetes: new perspectives on disease pathogenesis and treatment. The Lancet, 358(9277), 221-229.

3) Chatterjee, S., Khunti, K., & Davies, M. J. (2017). Type 2 diabetes. The Lancet,389(10085), 2239-2251.

4) DeFronzo, R. A., & Ferrannini, E. (2015). Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care, 14(3), 173-194.

5) Diabetes Association. (2020). Standards of Medical Care in Diabetes—2020 Abridged for Primary Care Providers. Clinical Diabetes, 38(1), 10-38.

6) Rother, K. I. (2007). Diabetes treatment—Bridging the divide. New EnglandJournal of Medicine, 356(15), 1499-1501.

7) Anderson, J. M., & Van Itallie, C. M. (2009). Tight junctions and the molecular basis for regulation of paracellular permeability. American Journal of Physiology-Gastrointestinal and Liver Physiology, 298(6), G849-G861.

8) Lee, J., Lee, S., Zhang, Y., et al. (2020). Nanoparticle-based approaches for thetreatment of diabetes. Theranostics, 10(15), 6563-6581.

9) Rahmani, M., Cruz, L., Nguyen, D. X., et al. (2019). Nanoparticle-mediated delivery of therapeutic agents in the treatment of diabetes mellitus. ACS Nano, 13(5), 4679-4694.

10) Zhang, N., Cheng, Y., Ahmed, S., et al. (2021). Nanoparticle-mediated drug delivery for the treatment of diabetes complications. Frontiers in Pharmacology, 11, 625877.

11) Khanna, V., & Arora, S. (2020). Role of nanoparticles in treatment of diabetes mellitus: A comprehensive review. International Journal of Nanomedicine, 15, 9049-9074.

12) Lutz, A. M., Seale, K. S., Khuntey, P., et al. (2018). Advances in nanoparticle- based delivery systems for antidiabetic drugs. Current Diabetes Reports, 18(12), 134.

13) S.E. Kahn, M.E. Cooper, S.D. Prato, Pathophysiology and Treatment of Type 2 Diabetes: Perspectives on the Past, Present and Future, Lancet 383 (2014) 1068–1083, https://doi.org/10.1016/S0140-6736(13)62154-62156.

14) L. Hieronymus, S. Griffin, Role of Amylin in Type 1 and Type 2 Diabetes, Diabetes. Educ. 41 (2015) 47S–56S, https://doi.org/10.1177/ 0145721715607642.

15) D. Stringer, P. Zahradka, C. Taylor, Glucose transporters: cellular links to hyperglycaemia in insulin resistance and diabetes, Nutr. Rev. 73 (2015) 140–154, https://doi.org/10.1093/nutrit/nuu012.

16) H. Rang, M. Dale, J. Ritter, P. Moore, Pharmacology, ninth ed., 2003, pp. 408–419. Churchill Livingstone, Edinburg.

17) R. DeFronzo, From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus, Diabetes 58 (2009) 773–795, https:// doi.org/10.2337/db09-9028.

18) K. Akhalya, S. Sreelatha, Rajeshwari, K. Shruthi, A review article- gestational diabetes mellitus, Endocrinol. Metab. Int. J. 7 (2019) 26–39, https://doi.org/ 10.15406/emij.2019.07.00238.

19) H.D. McIntyre, P. Catalano, C. Zhang, G. Desoye, E.R. Mathiesen, P. Damm, Gestational diabetes mellitus, Nat. Rev. Dis. Primers. 5 (2019), https://doi.org/ 10.1038/s41572-019-0098-8.

20) X. Sun, W. Yu, C. Hu, Genetics of Type 2 Diabetes: Insights into the Pathogenesis and Its Clinical Application, BioMed Res. Int. 2014 (2014), 926713, https://doi. org/10.1155/2014/926713, 15.

21) K. Kayani, R. Mohammed, H. Mohiaddin, Cystic Fibrosis-Related Diabetes, Front. Endocrinol. 9 (2018), https://doi.org/10.3389/fendo.2018.00020.

22) J.C. Barton, R.T. Acton, Diabetes in *HFE* Hemochromatosis, J. Diabetes. Res. (2017), 9826930, https://doi.org/10.1155/2017/9826930, 16 pages.

23) M. Barbot, F. Ceccato, C. Scaroni, Diabetes Mellitus Secondary to Cushing's disease, Front. Endocrinol. 9 (2018) 284, https://doi.org/10.3389/ fendo.2018.00284.

24)F. Ferraù, A. Albani, A. Ciresi, C. Giordano, S. Cannavò, Diabetes Secondary to Acromegaly: Physiopathology, Clinical Features and Effects of Treatment, Front. Endocrinol. 9 (2018) 358, https://doi.org/10.3389/fendo.2018.00358.

25) C. Wang, The Relationship between Type 2 Diabetes Mellitus and Related Thyroid Diseases, J. Diabetes. Res. 2013 (2013), 390534, https://doi.org/10.1155/2013/ 390534, 9 pages.

26) N. Ewald, P. Hardt, Diagnosis and treatment of diabetes mellitus in chronic pancreatitis, World. J. Gastroenterol. 19 (2013) 7276, https://doi.org/10.3748/ wjg.v19.i42.7276.

27) A. De Souza, K. Irfan, F. Masud, M.W. Saif, Diabetes Type 2 and Pancreatic Cancer: A History Unfolding, JOP 17 (2016) 144–148. PMCID: PMC5860818.

28) Corticosteroids are used to reduce harmful inflammation but can lead to diabetes-often referred to as steroid diabetes, Diabetes (2020) (accessed 10 August 2020), https://www.diabetes.co.uk/drug-induced-diabetes.html.

29) S. Kalra, B. Kalra, N. Agrawal, A. Unnikrishnan, Understanding diabetes in patients with HIV/AIDS, Diabetol. Metab. Syndr. 3 (2011), https://doi.org/ 10.1186/1758-5996-3-2.

30) Y. Wu, Y. Ding, Y. Tanaka, W. Zhang, Risk Factors Contributing to Type 2 Diabetes and Recent Advances in the Treatment and Prevention, Int. J. Med. Sci. 11 (2014) 1185–1200, https://doi.org/10.7150/ijms.10001.

31) R. Streisand, M. Monaghan, Young Children with Type 1 Diabetes: Challenges, Research, and Future Directions, Curr. Diabetes. Rep. 14 (2014), https://doi.org/ 10.1007/s11892-014-0520-2.

32) A. Olokoba, O. Obateru, L. Olokoba, Type 2 Diabetes Mellitus: A Review of Current Trends, Oman Med. J. 27 (2012) 269–273, https://doi.org/10.5001/ omj.2012.68.

33) Y. Khazrai, G. Defeudis, P. Pozzilli, Effect of diet on type 2 diabetes mellitus: a review, Diabetes. Metab. Res. Rev. 30 (2014) 24–33, https://doi.org/10.1002/ dmrr.2515.

34) R. Eckel, S. Kahn, E. Ferrannini, A. Goldfine, D. Nathan, M. Schwartz, et al., Obesity and Type 2 Diabetes: What Can Be Unified and What Needs to Be Individualized? Diabetes Care. 34 (2011) 1424–1430, https://doi.org/10.2337/ dc11-0447.

35) A. Boles, R. Kandimalla, P. Reddy, Dynamics of diabetes and obesity: Epidemiological perspective, Biochim. Biophys. Acta. Mol. Basis Dis. 1863 (2017) 1026–1036, https://doi.org/10.1016/j.bbadis.2017.01.016.

36) A. Gambineri, L. Patton, P. Altieri, U. Pagotto, C. Pizzi, L. Manzoli, et al., Polycystic Ovary Syndrome Is a Risk Factor for Type 2 Diabetes: Results from a Long-Term Prospective Study, Diabetes 61 (2012) 2369–2374, https://doi.org/ 10.2337/db11-1360.

37) K. Papatheodorou, M. Banach, E. Bekiari, M. Rizzo, M. Edmonds, Complications of Diabetes 2017, J. Diabetes. Res. 2018 (2018) 1–4, https://doi.org/10.1155/ 2018/3086167.

38) A. Mirghani Dirar, J. Doupis, Gestational diabetes from A to Z, World. J. Diabetes. 8 (2017) 489–511, https://doi.org/10.4239/wjd.v8.i12.489.

39) S. Seino, K. Sugawara, N. Yokoi, H. Takahashi, β-Cell signalling and insulin secretagogues: A path for improved diabetes therapy, Diabetes. Obes. Metab. 19 (2017) 22–29, https://doi.org/10.1111/dom.12995.

40) S. Kalra, S. Bahendeka, R. Sahay, S. Ghosh, F. Md, A. Orabi, et al., Consensus recommendations on sulfonylurea and sulfonylurea combinations in the management of Type 2 diabetes mellitus – International Task Force, Indian J. Endocr. Metab. 22 (2018) 132, https://doi.org/10.4103/ijem.ijem_556_17.

41) D. Sola, L. Rossi, G. Schianca, P. Maffioli, M. Bigliocca, R. Mella, et al., State of the art paper Sulfonylureas and their use in clinical practice, Arch. Med. Sci. 4 (2015) 840–848, https://doi.org/10.5114/aoms.2015.53304.

42) B. Hemmingsen, D.P. Sonne, M.I. Metzendorf, B. Richter, Insulin secretagogues for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus, Cochrane Database. Syst. Rev. 10 (2016) 1–130, https://doi.org/ 10.1002/14651858.CD012151.pub2.

43) D.M. Quillen, G. Samraj, L. Kuritzky, Improving Management of Type 2 Diabetes Mellitus: 2. Biguanides, Hosp. Pract. 34 (1999) 41–44, https://doi.org/10.1080/ 21548331.1999.11443925.

44) E. Rubiño, E. Carrillo, G. Alcalá, A. Domínguez-Martín, J. Marchal, H. Boulaiz, Phenformin as an Anticancer Agent: Challenges and Prospects, Int. J. Mol. Sci. 20 (2019) 3316, https://doi.org/10.3390/ijms20133316.

45) O. Bourron, M. Daval, I. Hainault, E. Hajduch, J. Servant, J. Gautier, et al., Biguanides and thiazolidinediones inhibit stimulated lipolysis in human adipocytes through activation of AMP-activated protein kinase, Diabetologia 53 (2009) 768–778, https://doi.org/10.1007/s00125-009-1639-6.

46) American Diabetes Association Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;**37**(Suppl 1):S14–S80. [PubMed] [Google Scholar].

47) Bookchin RM, Gallop PM. Structure of hemoglobin AIc: nature of the N-terminal beta chain blocking group. *Biochem Biophys Res Commun*. 1968;**32**(1):86–93.

48) Pfister R, Sharp SJ, Luben R, Khaw KT, Wareham NJ. No evidence of an increased mortality risk associated with low levels of glycated haemoglobin in a non-diabetic UK population. *Diabetologia*. 2011;**54**(8):2025–2032.

49) White NH, Sun W, Cleary PA, et al.DCCT-EDIC Research Group Effect of prior intensive therapy in type 1 diabetes on 10-year progression of retinopathy in the DCCT/EDIC: comparison of adults and adolescents. *Diabetes*. 2010;**59**(5):1244–1253.

50) Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;**321**(7258):405–412.

51) Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 1997;**20**(7):1183–1197.

52) Malmström H, Walldius G, Grill V, Jungner I, Gudbjörnsdottir S, Hammar N. Fructosamine is a useful indicator of hyperglycaemia and glucose control in clinical and epidemiological studies–cross-sectional and longitudinal experience from the AMORIS cohort. *PLoS One*. 2014;**9**(10):e111463.

53) Ribeiro RT, Macedo MP, Raposo JF. HbA1c, fructosamine, and glycated albumin in the detection of dysglycaemic conditions. *Curr Diabetes Rev*. 2016;**12**(1):14–19. [PubMed] [Google Scholar]

54) Austin GE, Wheaton R, Nanes MS, Rubin J, Mullins RE. Usefulness of fructosamine for monitoring

outpatients with diabetes. *Am J Med Sci.* 1999;**318**(5):316–323.

55) Danese E, Montagnana M, Nouvenne A, Lippi G. Advantages and pitfalls of fructosamine and glycated albumin in the diagnosis and treatment of diabetes. *J Diabetes Sci Technol.* 2015;**9**(2):169–176.

56) Wu WC, Ma WY, Wei JN, et al. Serum glycated albumin to guide the diagnosis of diabetes mellitus. *PLoS One.* 2016;**11**(1):e0146780.

57) Yamanouchi T, Akanuma Y. Serum 1,5-anhydroglucitol (1,5 AG): new clinical marker for glycemic control. *Diabetes Res Clin Pract.* 1994;**24**(Suppl):S261–S268.

58) Yamanouchi T, Minoda S, Yabuuchi M, et al. Plasma 1,5-anhydro-D-glucitol as new clinical marker of glycemic control in NIDDM patients. *Diabetes.* 1989;**38**(6):723–729.

59) Stefan N, Sun Q, Fritsche A, et al. Impact of the adipokine adiponectin and the hepatokine fetuin-A on the development of type 2 diabetes: prospective cohort- and cross-sectional phenotyping studies. *PLoS One.* 2014;**9**(3):e92238.

60) Pal D, Dasgupta S, Kundu R, et al. Fetuin-A acts as an endogenous ligand of TLR4 to promote lipid-induced insulin resistance. *Nat Med.* 2012;**18**(8):1279–1285.

61) Shima K, Abe F, Chikakiyo H, Ito N. The relative value of glycated albumin, hemoglobin A1c and fructosamine when screening for diabetes mellitus. *Diabetes Res Clin Pract.* 1989;**7**(4):243–250.

62) Bulló M, García-Lorda P, Megias I, Salas-Salvadó J. Systemic inflammation, adipose tissue tumor necrosis factor, and leptin expression. *Obesity Res.* 2003;**11**(4):525–531.

63) Ma XJ, Pan JM, Bao YQ, et al. Combined assessment of glycated albumin and fasting plasma glucose improves the detection of diabetes in Chinese subjects. *Clin Exp Pharmacol Physiol.* 2010;**37**(10):974–979.

*****