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IP International Journal of Comprehensive and Advanced Pharmacology

Journal homepage: https://www.ijcap.in/

Review Article

An updated review on diabetes mellitus: Exploring its etiology, pathophysiology, complications and treatment approach

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ARTICLE INFO

Article history:
Received 15-11-2023
Accepted 20-01-2024
Available online 16-03-2024

Keywords:
Diabetes
Atherosclerosis
Insulin
Metabolic Disorder

ABSTRACT

Diabetes mellitus, a prevalent chronic metabolic disorder, encompasses types like Type 1 (T1DM), Type 2 (T2DM), and gestational diabetes, marked by elevated blood sugar levels. T1DM, an autoimmune disease, entails genetic susceptibility triggering pancreatic beta cell destruction, necessitating insulin replacement. T2DM, linked to metabolic syndrome and insulin resistance, is influenced by genetics, obesity, inactivity, and ethnicity. Gestational Diabetes Mellitus (GDM) in pregnancy elevates offspring obesity and T2DM risk. Diagnosis involves fasting glucose, oral glucose tolerance, HbA1c tests, and specific antibody assessments. Chronic complications include atherosclerosis, retinopathy, neuropathy, nephropathy, and osmotic cell death, emphasizing glycaemic control. Treatment strategies differ, with T1DM requiring insulin therapy and T2DM involving lifestyle changes, medication, and potential insulin use, underscoring the need to understand diabetes for effective management and improved quality of life.

1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by high blood sugar levels. It's one type of metabolic disorder characterized by deficiency of Insulin and resistancy of Insulin. There are different types of diabetes mellitus, including type 1, type 2, and gestational diabetes. It is a prevalent condition worldwide, affecting millions of people. Various risk factors, such as obesity and sedentary lifestyle, contribute to its development. Diagnostic criteria, such as fasting plasma glucose levels, help identify the condition. The management of diabetes mellitus has evolved over time, with current trends focusing on lifestyle modifications, medication, and regular monitoring. Understanding diabetes mellitus is crucial for effective prevention and treatment strategies.

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2. Classification of Diabetes Melitus

2.1. Insulin dependent biabetes melitus (Type 1 diabetes melitus)

Type 1 diabetes mellitus, also known as autoimmune diabetes or previously referred to as juvenile-onset or ketosis-prone diabetes, is a condition where the body's immune system attacks and damages the insulin-producing beta cells in the pancreas. This type of diabetes is commonly diagnosed in children and young adults, with a sudden and potentially life-threatening onset. People with Type 1 diabetes often have other autoimmune disorders, such as Graves' disease, Hashimoto's thyroiditis, and Addison's disease.[1] It's characterized by the presence of specific antibodies like anti-glutamic acid decarboxylase, islet cell, or insulin antibodies, which signify the autoimmune process responsible for the destruction of beta cells (American Diabetes Association, 2014). The rate of beta-

https://doi.org/10.18231/j.ijcaap.2024.005

cell destruction can vary from person to person, happening rapidly in some and slowly in others.[2] As a result of this destruction, there is a severe deficiency or absence of insulin secretion, necessitating the use of insulin injections for treatment. Typically, individuals with Type 1 diabetes have markers of immune destruction, such as islet cell auto-antibodies, auto-antibodies to insulin, and auto-antibodies to glutamic acid decarboxylase (GAD), present when fasting diabetic hyperglycaemia is initially detected, occurring in about 85-90% of cases.[3] Although the exact cause of diabetes mellitus remains uncertain, in most cases, there is evidence of an autoimmune mechanism at play.[1]

2.2. Non-insulin dependent diabetes mellitus (Type 2 Diabetes Melitus)

Type 2 diabetes mellitus, which is also called adult-onset diabetes, is a disease where your body has trouble using insulin, a hormone that helps control your blood sugar (American Diabetes Association, 2014).[4] People with this type of diabetes often have a hard time with insulin's job.[5] Over time, it can lead to problems with blood vessels, kidneys, eyes, and nerves, and these issues can make people sick or even cause them to pass away because of diabetes.[6] There are many reasons why someone might get type 2 diabetes, like being overweight, not getting enough exercise, getting older (especially for middle-aged and older folks), or it could be in their genes (Ross and Wilson 2010). People with this type of diabetes also have a higher chance of having big or small blood vessel problems, which can be really serious.[7,8]

3. Gestational Diabetes Melitus

Gestational diabetes mellitus (GDM) is a type of diabetes that can occur for the first time or be diagnosed during pregnancy.[9] It includes women who develop Type 1 diabetes during pregnancy and those with undiagnosed, symptom-free Type 2 diabetes that's found during pregnancy.[10] GDM is a form of diabetes diagnosed during pregnancy, but it might not continue after the baby is born [.[4] Over time, children born to mothers with GDM have a higher chance of becoming overweight and developing type 2 diabetes when they grow up. This increased risk is linked to exposure to high blood sugar levels while they were in the womb.

4. Etiology of Diabetes Melitus Type 1

Type 1 Diabetes Mellitus (T1DM) is a complex autoimmune disease characterized by the immune system's misdirected assault on the body's own pancreatic beta cells, which are responsible for insulin production.[11] This autoimmune response in T1DM involves a dual-component mechanism: an environmental component and an immune component.[12] The environmental factor is speculated to be an unidentified virus that invades specific cells within the body. Notably, viral proteins from the infected cells are displayed on Major Histocompatibility Complex class 1 (MHC-1) complexes, subsequently recognized by cytotoxic T-cells, inciting a vigorous immune response. However, the immune component, largely dictated by genetic factors, notably the HLA-DR3 and HLA-DR4 susceptibility genes, exacerbates the inappropriate immune response.[12] This genetic predisposition results in T-cells releasing cytokines, activating plasma cells that produce antibodies. Remarkably, these HLA susceptibility genes are not exclusive to T1DM; they are also implicated in other autoimmune conditions, including Rheumatoid arthritis, Systemic lupus erythematosus, Celiac disease, and Vitiligo.[13] In the context of T1DM, the produced antibodies perpetrate the ultimate damage, targeting the pancreatic beta cells, and impairing the body's ability to produce insulin, leading to the hallmark symptoms and the requirement for insulin replacement therapy. Understanding the intricate interplay between genetic susceptibility, viral triggers, and the immune response is vital in unravelling the enigma of T1DM and exploring potential avenues for prevention and treatment.[14,15]

5. Pathophysiology of Diabetes Melitus Type 1

In Type 1 Diabetes Mellitus, the intricate effects on cellular processes play a pivotal role in the pathogenesis of the disease. Glucose, the primary fuel for our bodies, enters pancreatic beta cells via glucose transporters (GLUT) and undergoes aerobic metabolism to produce adenosine triphosphate (ATP). These ATP molecules, in turn, bind to potassium-sensitive channels, leading to their closure. Consequently, potassium (K+) accumulates within the cell, creating a positive charge that activates voltage-gated calcium channels. The influx of calcium stimulates vesicles containing insulin, ultimately facilitating its release, a crucial process for glucose regulation.[16,17]

Moreover, an enzyme known as glutamic acid decarboxylase plays a protective role in beta cells by converting glutamic acid into gamma-aminobutyric acid (GABA), a molecule associated with insulin production stimulation.[18] However, in the context of Type 1 Diabetes, the presence of three sets of antibodies complicates this delicate balance. These include cell antibodies that target specific self-antigens on pancreatic islet cells, anti-glutamic acid antibodies which focus on glutamic acid decarboxylase, and anti-insulin antibodies. The relentless attack of these antibodies on beta cells and associated proteins leads to a decrease in the number of beta cells, reduced insulin production, and a subsequent increase in blood glucose levels.[19]

Insulin itself, as a key regulator of glucose metabolism, binds to insulin receptors on various cells throughout the body, initiating an intracellular cascade. This cascade

increases the expression of glucose transporters on the cell membrane, allowing for enhanced glucose uptake.[20] However, in the face of reduced insulin production, the expression of these glucose transporters decreases, inhibiting glucose entry into the cells and resulting in elevated blood glucose levels. Understanding these complex cellular interactions is critical in the quest for innovative therapeutic approaches that target not only insulin replacement but also the preservation and regeneration of beta cells in the treatment of Type 1 Diabetes Mellitus.

6. Etiology of Diabetes Melitus Type 2

Metabolic syndrome can be a major cause of Type 2 diabetes, a common form of diabetes that affects many people. It's like a group of signals your body sends when something might be wrong. To say someone has metabolic syndrome, they need to have at least three of these signals: high fasting glucose levels (meaning there's a lot of sugar in their blood), high triglycerides (a kind of fat in the blood), low levels of HDL cholesterol (that's the good kind of cholesterol), high blood pressure, or a high BMI, which measures how much someone weighs compared to their height.[21]

Metabolic syndrome is linked to something called insulin resistance, which means your body doesn't use insulin properly. Insulin helps control your blood sugar. If you have metabolic syndrome, it could mean your body is having trouble with this.[22]

Some studies also suggest that genetics play a part. If someone in your close family has diabetes or if you belong to certain ethnic groups, like Pacific Islanders, you might have a higher risk of getting it (office of Minority Health).[23] Understanding these factors is really important in preventing and managing Type 2 diabetes, a condition that affects a lot of people around the world.

7. Pathophysiology of Diabetes Melitus Type 2

Inside our bodies, a remarkable dance takes place involving glucose, the fuel that keeps us going. When glucose enters a beta cell, it travels through a special doorway called a glucose transporter (GLUT). Once inside, it undergoes a sort of magic trick called "aerobic metabolism," transforming into ATP, an energy molecule.

But the real show begins when these ATP molecules play a role in closing potassium-sensitive channels, trapping potassium (K+) inside the cell. This creates a positive charge and activates voltage-gated calcium channels. Calcium rushes in, leading to a grand finale: the stimulation of vesicles carrying insulin. Like a release of confetti, insulin bursts out, helping to manage our blood sugars.[16,17]

Now, imagine there's a guardian named glutamic acid decarboxylase, who converts glutamic acid into GABA, another special molecule associated with insulin production. This guardian's work is like a protective shield for beta cells.[18]

In another part of this story, insulin finds its way to insulin receptors on different cells in our body. This interaction boosts glucose transport, making sure our cells get the energy they need.[20]

However, in the case of Type 2 diabetes, things get a bit tangled. There's a decreased response inside our cells. This means the stimulation for glucose transporters lessens, and less glucose enters the cells, causing blood sugar levels to rise. To compensate, pancreatic beta cells work overtime, trying to produce more insulin (mayoclinic.org).

But there's a twist. To force glucose into the cells, an excess of insulin is produced, leading to a condition called hyperinsulinemia.[24] Over time, the beta cells tire out. They produce less insulin, leading to fewer glucose transporters and less glucose getting in. This, in turn, results in high blood sugar levels, known as hyperglycaemia.

To add to the drama, another character called amylin joins the scene, releasing a protein that accumulates around beta cells. This buildup, called amyloid deposition, causes damage to the beta cells, further decreasing their activity, and insulin production continues to plummet. Glucose transporters are reduced, and the glucose struggle intensifies, leading to persistent high blood sugar levels.

Understanding this intricate play of glucose, insulin, and the role of different cells is essential in managing Type 2 diabetes and preventing complications. It's like a finely choreographed dance that keeps our bodies in harmony.

8. Clinical Manifestation

Experiencing hyperglycaemia, which is when there's too much sugar in your blood, can set off a chain of events in your body. First, it causes an overflow of glucose to be filtered into the kidney tubules through a process called glomerular filtration. However, the kidney tubules can't reabsorb all that extra glucose, so it ends up being lost in your urine, a condition known as glycosuria. Because glucose is like a magnet for water, it pulls a lot of water with it, resulting in a large volume of urine, which is called polyuria.[25] This massive loss of water also makes your blood more concentrated, leading to hyperosmolar blood.[26] With less water and more glucose in your blood, your body tries to make up for the lost water by making you incredibly thirsty, known as polydipsia.[25]

On the other hand, decreased glucose utilization forces your body to look for alternative sources of energy. It starts breaking down fat in your fat cells through lipolysis, turning triglycerides into free fatty acids and glycerol, both of which can be used to produce energy. Additionally, your muscles undergo proteolysis, breaking down proteins into amino acids that can also be used for energy production.[27] This combination of processes can lead to unexplained

weight loss, increased calorie consumption, and heightened hunger, as your body tries to replace the lost calories, a condition referred to as polyphagia. So, hyperglycaemia and decreased glucose utilization set off a series of changes in your body, affecting various aspects of your health.

8.1. Diagnosis

Understanding your blood work results is crucial in monitoring your health. There are various tests that can help diagnose diabetes. The fasting glucose test measures your blood sugar after a period of not eating. If it's equal to or greater than 126mg/dl, it might indicate diabetes, especially if you have other symptoms.[28] (American Diabetes Association). The random glucose test, on the other hand, doesn't require fasting and a result of 200 mg/dl or higher, along with other symptoms, can diagnose diabetes[28] (American Diabetes Association).

The two-hour oral glucose tolerance test involves drinking a sugary solution to see how your body handles glucose. In diabetics, either there's not enough insulin or your cells don't respond well to it, leading to high blood sugar levels. This test requires two confirmatory tests. The Haemoglobin A1c test is another important tool, reflecting your average blood sugar levels over three months by measuring glycated haemoglobin. This is because red blood cells live for about three months, and haemoglobin is found in them. This observation suggests that once an individual's A1C level reaches or exceeds 6.5%, or when their FPG and 2-h PG values cross their respective diagnostic threshold indicating the clinical importance of these diagnostic markers in monitoring and managing diabetes-related Complications[28] (American Diabetes Association).

Additionally, doctors might also consider checking for specific antibodies like anti-islet cell antibodies, anti-glutamic acid antibodies, and anti-insulin antibodies, especially when assessing your age and risk factors.[29] These antibodies can provide valuable insights into your body's immune response and help in determining the likelihood of developing diabetes. Understanding your blood work and considering antibody tests can be instrumental in managing your health.

9. Chronic Complications

Non-enzymatic glycation is like a hidden process that occurs in our bodies when our blood sugar levels are too high. It's like sugar molecules linking up with other important molecules in our body, such as proteins and lipids. The strange thing is, it doesn't need any enzymes to make this happen, which is why it's called "non-enzymatic."[30] This whole situation can lead to some serious trouble. These sugar-linked molecules can become like troublemakers, causing inflammation in our blood vessels. It's like inviting a bunch of LDLS (bad cholesterol) to the party, which can result in a condition called atherosclerosis,[31] where our blood vessels get all clogged up. This can lead to reduced blood flow, trouble breathing for our tissues, and even diseases that show up physically.

Atherosclerosis, the name itself is a mouthful, but it's a condition where these clogs happen in different parts of our body. In the heart's blood vessels, it can lead to coronary artery disease, which can even cause heart attacks.[31] In the vessels of our legs, it's called peripheral artery disease, and it can make our legs hurt when we walk.[32] Sometimes, it can even create ulcers on our skin. In the vessels that supply our brains, atherosclerosis can lead to a stroke, which can be very serious.[33] And in the tiny blood vessels of our eyes, it can cause retinopathy,[34] where we might see things like microaneurysms, cotton wool spots, and flame haemorrhages, and it can mess with our vision.[35]

Hyaline arteriolosclerosis is another tricky word, and it can harm our kidneys.[36] This condition can damage the glomeruli, which are like tiny filters in our kidneys. When that happens, more protein, like albumin, enters our urine, which they call "microalbuminuria.[36]" If this keeps going, it can lead to chronic kidney disease. Those deposits inside the glomeruli even get a fancy name – Kimmelstiel-Wilson nodules.[37]

Osmotic cell death is like a domino effect. When we have too much glucose in our cells, it gets turned into sorbitol and then fructose. Some cells can't handle this, and they become like sponges, soaking up water because of the osmotic effect of sorbitol.[38] It can harm different parts of our body. In our eyes, it can lead to cataracts, which can blur our vision.[39] In our kidneys, it can make kidney problems worse. For the nerves in our body, it can damage the insulation on the wires, which affects things like our stomach's ability to work,[40] our bladder, our blood vessels, and even the nerves controlling the movements of our eyes. It can also make our skin feel strange, like a burning or tingling sensation, and over time, we might not even notice if we get hurt.[41] Plus, it makes wounds harder to heal, which can lead to foot ulcers.[42] So, keeping our blood sugar in check is super important to avoid all these complicated problems.

10. Treatment

Managing diabetes, whether it's Type 1 or Type 2, involves a variety of treatments and precautions to stay healthy. In Type 1 diabetes, the key is insulin. This hormone helps regulate your blood sugar levels, and people with Type 1 diabetes need to take insulin to stay healthy.

Type 2 diabetes often starts with making important lifestyle changes. Things like exercise and changes to your diet can help promote weight loss and better blood sugar control.[43] In Type 2 diabetes, often caused by metabolic syndrome, which is linked to obesity and poor diets, various medications can help. Metformin is usually the first choice,[44] but there are other options like GLP-1

agonists, DPP-4 inhibitors, SGLT2 inhibitors, and more.[45] Sometimes, insulin may be needed if multiple medications don't keep blood sugar levels in check.

When you have diabetes, it's crucial to watch out for chronic complications. Neuropathy, which can cause numbness and pain, can be managed with medications like gabapentin and pregabalin, and regular podiatry visits are essential for foot care.[46] Nephropathy, which affects the kidneys, is treated with medications like ACE inhibitors and ARBs.[47] It's vital to monitor kidney function and check for increased creatinine and blood urea nitrogen in the blood. Regularly checking the amount of albumin in the urine is also important.

For retinopathy, a condition that affects the eyes, medications like VEGF inhibitors can help, and procedures like laser photocoagulation or vitrectomy may be necessary.[48] Regular optometry visits are a must. Atherosclerosis, a condition affecting blood vessels, can be managed with aspirin and monitoring lipid levels. In cases of high atherosclerotic disease risk, a statin may be prescribed to reduce complications.

Keeping blood sugar levels under control is a top priority. The HbA1c level should be below 7%, and if it's uncontrolled (above 7%), it should be checked every three months. If it's well controlled (7% or less), checking every six months is recommended. Managing diabetes involves a combination of treatments, regular check-ups, and a healthy lifestyle to lead a happy and healthy life.

11. Conclusion

In conclusion, diabetes mellitus is a complex and prevalent chronic metabolic disorder with distinct types, each characterized by unique etiological factors and pathophysiological processes. Type 1 diabetes is an autoimmune disease involving the destruction of insulin-producing beta cells, necessitating insulin therapy. Type 2 diabetes is often associated with metabolic syndrome and insulin resistance, where lifestyle changes, medication, and potential insulin use play pivotal roles in management. Gestational diabetes poses risks for both the mother and her offspring. Diagnosis relies on various tests, including fasting glucose, oral glucose tolerance, and HbA1c tests, with specific antibody assessments in some cases. Chronic complications, such as atherosclerosis, retinopathy, neuropathy, and nephropathy, highlight the importance of vigilant glycaemic control and regular medical monitoring. Effective prevention and management strategies for diabetes mellitus must encompass a comprehensive understanding of its multifaceted nature. This knowledge empowers healthcare providers and patients to make informed decisions, emphasizing the significance of a healthy lifestyle, regular check-ups, and optimal blood sugar control to enhance the quality of life for individuals affected by this widespread condition.

12. Source of Funding

None.

13. Conflict of Interest

None.

14. Acknowledgment

I would like to thanks Professor Keval Raval for his expert advice and encouragement throughout this article.

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Cite this article: Savan C, Viroja D, Kyada A. An updated review on diabetes mellitus: Exploring its etiology, pathophysiology, complications and treatment approach. *IP Int J Comprehensive Adv Pharmacol* 2024;9(1):31-36.