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A Review on Diabetes Mellitus

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Abstract: ***Diabetes mellitus has become a major global health issue due to its rising prevalence. This review discusses the definition and classification of diabetes, including type 1 diabetes (both idiopathic and fulminant), type 2 diabetes, and gestational diabetes. It also highlights important terms and abbreviations related to diabetes, its causes, complications, and the biological processes involved. Diabetes mellitus is one of the most widespread non-communicable diseases globally. In India, managing diabetes presents several challenges, such as increasing cases in both cities and villages, low public awareness, limited healthcare access, high treatment costs, poor blood sugar control, and growing complications. Insulin is usually given through subcutaneous injections several times a day, which can be uncomfortable and affects how well patients stick to their treatment. Although type 1 diabetes is becoming more common, type 2 diabetes is the main driver of the diabetes epidemic, making up over 90% of all cases. Type 2 diabetes is a serious long-term condition caused by a mix of genetic and environmental factors, along with risks like obesity and lack of physical activity. Many medical terms and short forms are connected to diabetes and related health problems. Some of these include methylamine-N-oxide, which affects metabolism, and NAFLD, a type of liver disease common in diabetes. Other related issues include NASH, hepatitis C virus (HCV), and kidney damage caused by contrast agents (CIN). Kidney function is checked using GFR. Proteins like TGF-β1 and the JAK-STAT pathway help explain how these diseases develop. Other proteins like SMPDL3b, JAML, and CaMKII help cells function properly, while SERCA2a controls calcium inside cells. Gene activity can also be affected by HDACs. Immune cells (PBMCs) and signals like HIF1α and VEGF-1 are linked to inflammation and blood vessel growth. Blood vessel health is supported by proteins like VE-cadherin and Ang1. Good fats like EPA and DHA are important for heart and brain health. Molecules such as 12-HETE, DPP4 inhibitors (used to treat diabetes), and proteins like ApoE, HCN2, NT-3, NGF, and NTR are involved in nerve, heart, and metabolic functions.***

I. INTRODUCTION

Diabetes is a complex condition marked by high blood sugar levels and is grouped into type 1 diabetes (T1D), type 2 diabetes (T2D), specific other types, and gestational diabetes. T2D is the most common form, making up about 96% of all diabetes cases. It usually involves a gradual decrease in the ability of the pancreas to produce insulin, often alongside insulin resistance. This is commonly seen with what is known as metabolic syndrome. However, since "metabolism" alone doesn't clearly describe whether the condition is normal or not, the term "metabolic dysfunction syndrome (MDS)" is more accurate. T2D is a major long-term health issue worldwide, and its exact causes are still not fully understood.

A. Definition of Diabetes Mellitus (DM)

Diabetes mellitus is a long-term condition that causes high blood sugar levels. It happens due to a lack of insulin, poor insulin function, or both. Insulin is a hormone that helps the body store and use energy from food. It plays a key role in how the body processes carbohydrates, fats, and proteins. In diabetes, insulin does not work properly, which affects tissues like fat, muscles, and the liver. This leads to insulin resistance. Symptoms of diabetes can be different depending on how long the person has had it and the type of diabetes. People with very high blood sugar, especially those with no insulin, like children with type 1 diabetes, may feel very hungry, thirsty, and tired. They may also urinate more, lose weight, or have blurred vision. Some people, especially those with type 2 diabetes, may not notice any symptoms in the early stages. If not treated, diabetes can lead to serious health problems. These may include confusion, coma, and in rare cases, death due to conditions like diabetic ketoacidosis or hyperosmolar syndrome.

B. Type 1 Diabetes and Treatment Challenges

People with type 1 diabetes need to take insulin for their entire lives because their bodies cannot make it. They often use technology to help deliver insulin and check their blood sugar levels. Even with these tools, they can still face problems like unstable blood sugar, weight gain, blood vessel damage, diabetic ketoacidosis, low blood sugar episodes, and mental stress.

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Heart disease and kidney disease are the main causes of illness and death in people with type 1 diabetes. Common risk factors like smoking, high blood pressure, high cholesterol, obesity, and high blood sugar do not fully explain these health issues. New research shows that insulin resistance, inflammation, and blood vessel problems—made worse by current insulin injections—also play a big role, even in people who are not overweight.

Because of this, experts are now exploring new ways to treat type 1 diabetes. These include improved insulin types, non-insulin drugs, and better technology. Some promising ideas are insulin pumps that work with other hormones, real-time monitoring of sugar and ketone levels, and systems that adjust insulin doses automatically.

Researchers are also looking into therapies that use hormones released after eating, as well as drugs like insulin-sensitizers and SGLT2 inhibitors. These may help create treatment plans that combine different types of therapies specifically for type 1 diabetes. However, large studies with placebo control are needed to see if these treatments can truly lower health risks and make life easier for people with type 1 diabetes.

Diabetes is a complex condition that causes high blood sugar levels. It includes type 1 diabetes (T1D), type 2 diabetes (T2D), specific types of diabetes, and gestational diabetes.

Type 2 diabetes is not caused by the immune system. It happens due to a gradual loss of insulin production from the pancreatic β cells. This often occurs along with insulin resistance and a group of related health issues.

Instead of using the term "metabolic syndrome," some experts prefer "metabolic dysfunction syndrome (MDS)" because it more clearly reflects the abnormal changes in body function.

Type 2 diabetes makes up about 96% of all diabetes cases. It is a major long-term disease that harms global health. However, the exact cause of type 2 diabetes is still not fully understood.

II. CLASSIFICATION OF DIABETES MELLITUS

A. Type 1 Diabetes

Type 1 diabetes (T1D) can be detected before insulin levels become abnormal. The decline in insulin production starts at least two years before the disease is diagnosed. At the same time, the β-cells in the pancreas become less responsive to glucose. As the initial insulin response goes down, the later phase of insulin release increases, which might be the body's way of trying to compensate.

After diagnosis, insulin production continues to decrease rapidly. During the first few years, this drop happens in two phases, with a sharper decline in the first year. Over time, insulin production may almost completely stop. Blood sugar levels can appear high even when they are still within the normal range. Large variations in glucose levels are also seen when T1D starts.

It is possible to predict the risk of T1D more accurately in people at risk by using metabolic markers like dysglycemia. Changes in blood sugar and C-peptide levels can also help improve risk predictions.

1) Idiopathic Type 1 Diabetes

Idiopathic T1D is a rare form of diabetes. It is not caused by the immune system and is usually less severe than autoimmune T1D. People with this condition may have occasional episodes of ketoacidosis and low insulin levels. It is more commonly found in individuals of Asian or African descent.

2) Fulminant Type 1 Diabetes

Fulminant T1D is a rare and aggressive form of diabetes first recognized in 2000. Like idiopathic T1D, it is not caused by immune system attacks. In this condition, ketoacidosis occurs soon after high blood sugar begins. At that time, C-peptide levels (which show natural insulin production) are undetectable, even though blood sugar is very high (around 288 mg/dL).

This type of T1D is mostly seen in East Asian countries and affects about 20% of Japanese patients with sudden-onset T1D. It causes the near-total destruction of β-cells in a very short time, leading to no remaining insulin production. The condition may be linked to both genetic and environmental factors. A strong antiviral immune reaction may destroy β-cells, even without the usual autoantibodies. This type of diabetes has also been reported during pregnancy

B. Type 2 Diabetes

In type 2 diabetes (T2D), one of the main problems is poor insulin production. The amount of insulin released depends on how sensitive the body is to insulin. To measure this balance, scientists use something called the "disposition index," which shows the relationship between insulin sensitivity and insulin secretion. Patients with T2D have a low disposition index. This means they cannot make enough insulin to overcome insulin resistance. In obese T2D patients, even if they have higher insulin levels than lean healthy people, it is still not enough due to their severe insulin resistance.

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In T2D, the first phase of insulin response to glucose is either very low or absent. These patients also tend to have a high ratio of proinsulin to insulin or C-peptide. Their total insulin-producing ability and the extra insulin response to other triggers are also reduced. As the disease progresses, blood sugar control becomes more difficult. A continuous loss of β-cell function is another key feature of T2D.

III. DIABETES MELLITUS IS A COMPLICATED DISEASE WITH MANY CAUSES.

A. *Type 1 Diabetes*

1) The immune system attacks and destroys the insulin-producing beta cells in the pancreas, causing a lack of insulin.
2) Genetics play a role in the risk of developing type 1 diabetes.
3) Certain environmental factors, like viral infections, may trigger the immune system to attack the pancreas.

B. *Type 2 Diabetes*

1) The body's cells become less responsive to insulin, making it difficult for glucose to enter the cells.
2) The pancreas does not produce enough insulin to keep blood sugar levels normal.
3) Genetic factors increase the chance of developing type 2 diabetes.
4) Lifestyle habits such as being overweight, lack of exercise, and poor diet contribute to the disease.

IV. CAUSES OF DIABETES MELLITUS

1) Problems with the glucose receptors on beta cells cause them to respond only to high glucose levels or there may be a lack of beta cells. In both cases, insulin production is reduced and may eventually stop
2) Problems with the glucose receptors on beta cells cause them to respond only to high glucose levels or there may be a lack of beta cells. In both cases, insulin production is reduced and may eventually stop.
3) Microvascular disease can cause low oxygen to nerves, and high blood sugar directly harms nerve metabolism
4) Peripheral tissues become less sensitive to insulin due to fewer insulin receptors or receptor downregulation. Some people have high insulin levels but normal blood sugar, along with issues like abnormal blood fats, high uric acid, and belly fat. This leads to insulin resistance, especially in the liver, muscles, and fat. High insulin levels may cause blood vessel damage
5) Too much glucagon (a hormone that raises blood sugar) and obesity cause relative insulin deficiency because beta cells cannot keep up. Changes in nitric oxide metabolism may reduce blood flow around nerves and cause nerve damage
6) Rare forms of diabetes include genetic defects like MODY (maturity onset diabetes of the young), other hormone disorders, removal of the pancreas, and gestational diabetes

V. PATHOPHYSIOLOGY AND SIGNALING PATHWAYS INVOLVED

Type 2 diabetes (T2D) is a complex metabolic disease often linked with other features of metabolic dysfunction syndrome (MDS). The main causes of T2D are insulin resistance and problems with β-cell function.

Inflammation, fat buildup in unusual places, stress in the cell's protein-making machinery (called endoplasmic reticulum stress), and oxidative stress all play a role in causing and worsening T2D and related organ damage. These factors harm insulin sensitivity and β-cell function, creating a cycle with other metabolic problems.

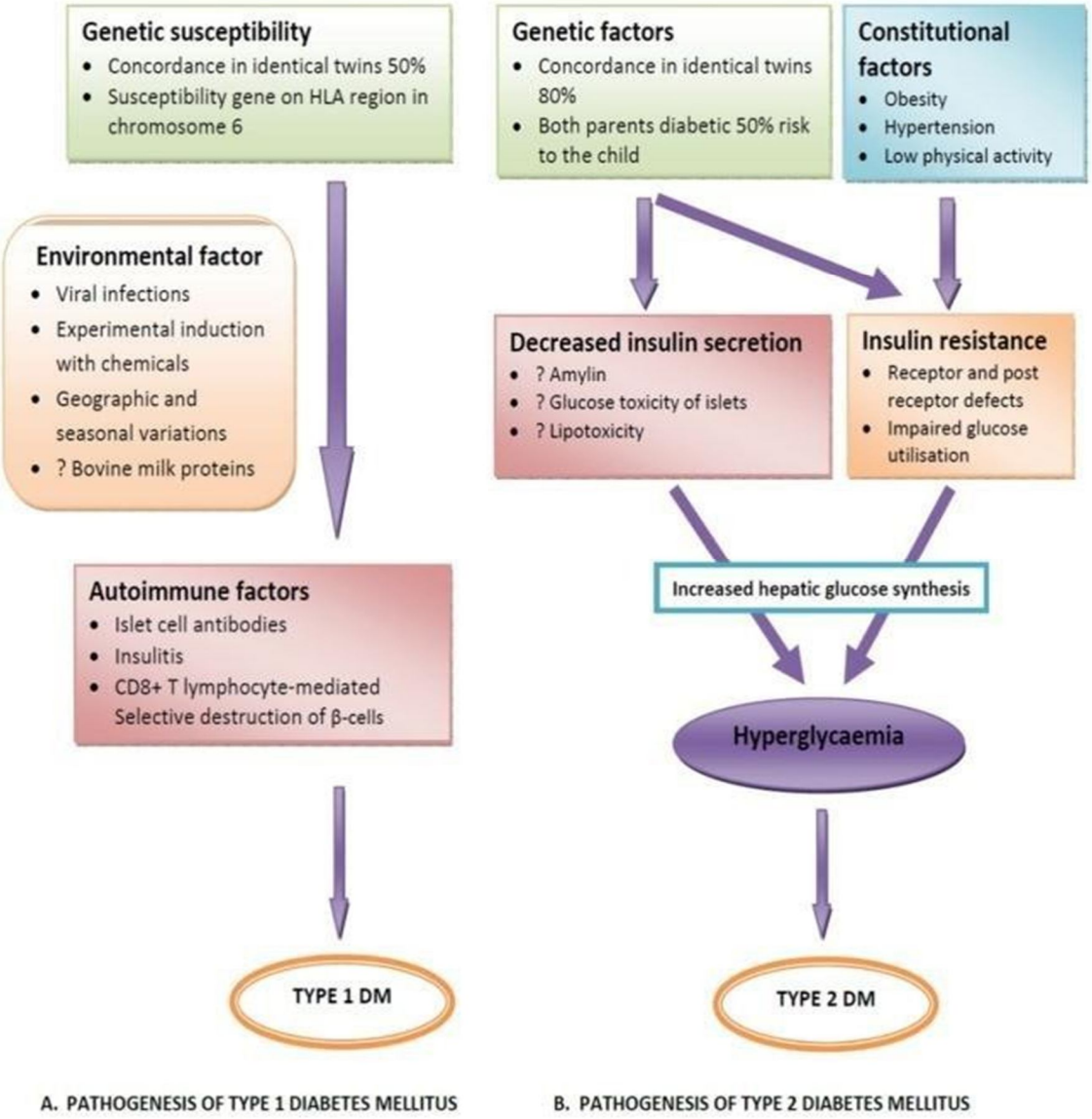
Studies using the hyperinsulinemic-euglycemic clamp show that people with type 1 diabetes have insulin resistance in their muscles, fat tissue, and liver. Insulin resistance in the liver increases glucose production, while insulin resistance in fat tissue increases the breakdown of fat and the release of free fatty acids.

Whole-body insulin resistance is linked to problems with mitochondria, blood vessel lining, and oxidative stress. It is also connected to stiff arteries and calcium build-up in the heart's arteries, which may lead to atherosclerosis.

The DCCT/EDIC study found that keeping blood sugar near normal helps reduce small and large blood vessel problems in type 1 diabetes. However, intensive insulin treatment often causes weight gain, which worsens insulin resistance. This creates a cycle of needing more insulin and gaining more weight.

Because of this challenge, there is a need for treatments that control blood sugar while also reducing insulin resistance.

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A. PATHOGENESIS OF TYPE 1 DIABETES MELLITUS B. PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

In the early stage of insulin resistance (IR), β cells produce extra insulin to keep blood sugar stable. The ability to do this depends largely on genetics. As the condition worsens, β cells cannot make enough insulin to control high blood sugar. This leads to prediabetes or type 2 diabetes. Obesity caused by overeating leads to inflammation in fat tissue. This happens because immune cells called macrophages gather and low oxygen levels cause chronic, low-level inflammation. This inflammation releases substances like interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α), which harm insulin signaling in several ways.

First, these substances reduce the production of molecules needed for insulin signaling. Second, they activate inflammatory pathways like NF-κB, JAK/STAT, and JNK, which disrupt insulin action. Third, they increase the production of ceramides, which worsens abnormal fat buildup in tissues.

A. Hyperglucagonemia

In type 1 diabetes, glucagon regulation is complicated. High glucagon levels after meals happen because the communication between alpha cells and beta cells is lost. Also, a hormone called amylin, which normally helps control glucagon, is missing.

Too much glucagon makes blood sugar control worse and increases insulin resistance. It may also increase the risk of heart disease. However, in type 1 diabetes, the usual rise in glucagon that protects against low blood sugar is weakened. This means glucagon causes problems and is also affected by the disease.

VI. TREATMENT OF DIABETES MELLITUS

The treatment aims to fix the cause and give high doses of regular insulin. Insulin needs return to normal once the condition is controlled. The main goals are:

1) To restore the body's metabolism to as close to normal as possible, while keeping the patient safe and comfortable.
2) To prevent or slow down both short-term and long-term complications of diabetes.
3) To teach and motivate patients to take good care of themselves.

A. *Types of Therapy*

1) Stem Cell Therapy: Researchers found that certain immune cells, like monocytes and macrophages, play a role in inflammation and insulin resistance in type 2 diabetes. Stem cell educator therapy is a new method to fix immune problems. It works by collecting a patient's blood, cleaning lymphocytes, growing them with special stem cells, and then returning the treated lymphocytes to the patient.
2) Antioxidant Therapy: Antioxidants like vitamins C and E, beta-carotene, and other supplements help reduce oxidative stress in type 2 diabetes. These antioxidants lower the risk of diabetes and its complications.
3) Anti-inflammatory Treatment: Inflammation is important in the development of type 2 diabetes and its complications. Inflammation affects fat tissue, the pancreas, liver, blood vessels, and immune cells. Drugs that modify the immune response are used for treatment

B. *Dietary Management*

Both diabetic and non-diabetic people should follow proper diets:

1) Balance proteins, carbohydrates, and faPts, while limiting carbohydrates.
2) Diet should be as close to normal as possible.
3) Eat regular meals spaced evenly throughout the day.
4) Cut down total calories by reducing fats and carbohydrates.
5) Maintain consistent eating habits every day

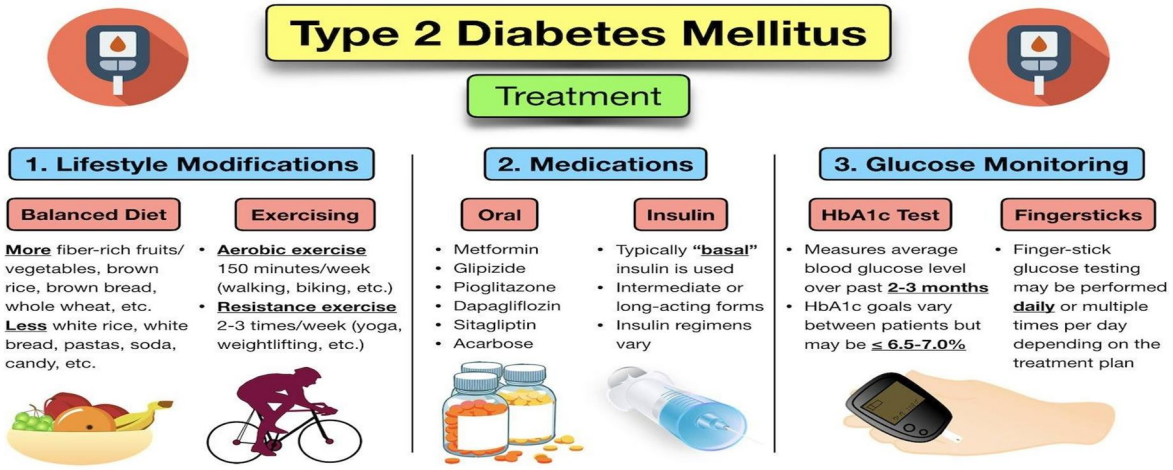
C. *New Insulin Delivery Devices*

Many devices have been developed to make insulin use easier and more accurate. These include insulin syringes, pens, inhalers, pumps, and implantable devices

D. *Oral Hypoglycemic Agents*

Oral diabetes medicines started with drugs like biguanides and sulfonylureas in the 1950s. Newer drugs include thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, and DPP-4 inhibitors.

Diabetes causes serious health problems and lowers quality of life. It can also happen due to conditions like Cushing syndrome, which is caused by long-term exposure to glucocorticoids. Symptoms include obesity, muscle weakness, excess hair growth, nerve problems, and complications like heart disease, nerve damage, digestion issues, and dental problems.



People with type 2 diabetes (T2D) often have other health problems like high cholesterol, obesity, kidney disease, and heart disease. These issues can lead to damage in different organs. So, treating T2D usually means managing all these related conditions together. This includes controlling blood sugar, cholesterol, blood pressure, and weight through lifestyle changes and medicines. This approach helps protect the heart and kidneys, improves quality of life, and may help people live longer.

Unfortunately, many people with diabetes face stigma because some wrongly think diabetes is just caused by eating poorly, ignoring other factors like genetics, environment, and social issues. This stigma can harm patients emotionally and socially. It's important for society to reduce this stigma and for patients to better understand their condition to avoid feeling ashamed.

There are many medicines to lower blood sugar, from older ones like metformin and insulin to newer drugs like DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT inhibitors (such as dapagliflozin and empagliflozin). Choosing the right medicine depends on the patient's blood sugar levels, health conditions, treatment goals, cost, and personal preferences. Doctors should personalize treatment to protect organs and meet individual needs.

VII. CONCLUSION

This review and our ideas aim to help newly diagnosed patients with type 2 diabetes (T2D) who are undergoing blood sugar-lowering treatment. The causes of T2D are not fully clear, and there is no cure yet. However, T2D and related organ damage caused by metabolic dysfunction syndrome (MDS) can be prevented. Important steps include preventing and treating early overweight, obesity, and metabolic-associated fatty liver disease (MASLD), which can greatly reduce the chance of developing T2D.

If prevention fails, it is important to detect diabetes early. Once diagnosed, treatment should focus on protecting organs by managing MDS because most people with T2D also have MDS. This article does not cover emergency conditions like diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS), nor does it discuss treatment for elderly patients, pregnant women with gestational diabetes, or patients with both T2D and cardiovascular disease.

T2D itself is a simple condition, but patients often have more complex health issues because many develop MDS. T2D usually comes after preobesity, obesity, and MASLD. Therefore, terms like “complications” should be used carefully, especially for kidney disease (DKD) or large blood vessel problems. If not, treatment might wrongly focus only on controlling blood sugar.

To improve patients' quality and length of life, managing MDS as a whole is necessary, not just focusing on blood sugar control.

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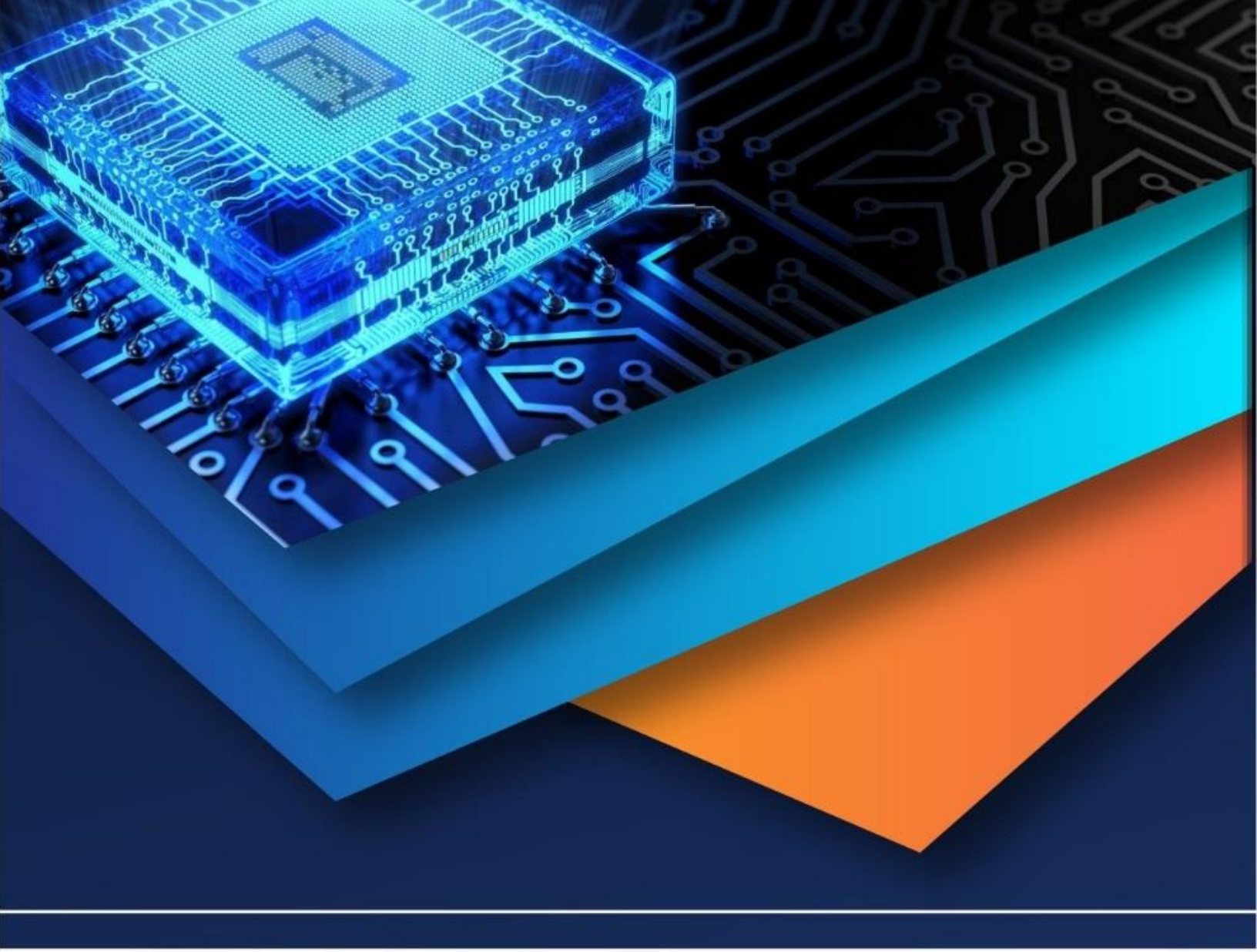
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