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Brief Review on Diabetes Mellitus

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Abstract: Approximately 422 million people (8.5% of the world's population) have been diagnosed with diabetes, making it one of the top causes of death worldwide. Despite significant efforts being made to find effective treatment options, the prevalence is expected to keep rising. An overview of diabetes mellitus, its management, and the role of various healthcare experts is provided in this article. The incidence is predicted to continue expanding despite great efforts on the means of treatments are exerted. This article provides an overview on diabetes mellitus, its treatment and the role of different healthcare professionals in its management. Diabetes has a direct impact on the development of particular retinopathy, nephropathy, neuropathy, heart vascular, and cerebrovascular illnesses. For many disorders, combination therapy is preferable to monotherapy. For chronic disorders, oral hypoglycemic medication combination therapy is best. Important components of combination therapy include sulfonyl urea, alpha glucosidase inhibitors, biguanides, meglitinides, and thiazolidinediones.
Keywords: Anti-diabetes drugs, Causes, Diabetes Mellitus, Management, Prevention, Risk factor for diabetes

I. INTRODUCTION

Defination

Diabetes is a multifactorial, progressive and chronic disorder characterized by chronic hyperglycemia because of defects within the metabolism of carbohydrate, fat and protein. Persistent hyperglycemia is related to semipermanent damage, dysfunction, and failure of multiple organs, particularly the eyes, kidneys, nerves, heart, and blood vessels [1]

The World Health Organization (WHO) Global report on diabetes indicates that Approximately 422 million humans globally have diabetes, and is predicted to growth to 693 million by the means of 2045, maximum of them in low- and middle-earnings countries, and every year 1.5 million peoples are dying due to diabetes. Both the wide variety of instances and the prevalence of diabetes have risen gradually in recent decade.

Diabetes mellitus is a chronic disorder of carbohydrates, fats and protein metabolism. A defective or deficient insulin secretary response, that interprets into impaired carbohydrates (glucose) use, is a characteristic feature of polygenic disease i.e (DM), as is the resulting hyperglycemias. (DM) is usually noted as a “sugar” and it's the most common endocrine disorder and typically happens once there's deficiency or absence of insulin or rarely impairment of insulin activity (insulin resistance).

Insulin and glucagon hormones each are secreted by the pancreas. Insulin is secreted by the beta (ß) cells and glucagon is secreted by the alpha (α) cells both are situated within the islets of Langerhan’s. Insulin decreases the glucose level by the glycogenesis and transport glucose into the muscles, liver and fatty tissue. Neural tissue and erythrocytes does not needed insulin for glucose utilization where alpha (α) cells plays a vital role in controlling blood glucose by producing the glucagon and it will increase the blood glucose level by quicken the glycogenolysis.[2] It is caused by deficiency or infective production of insulin by pancreas which results in increase or decrease in concentration of glucose and the blood. It is found to damage several body systems significantly blood vessels, eyes, kidney, heart and nerves. Various kinds of hypoglycemic agents which include biguanides and sulfonylureas are also available for treatment of diabetes.

However none of those medicines is good because of their toxic side effects and diminution of responses is found sometimes in their extended use . The main disadvantage of currently available drugs is that they have to be given throughout the life and produce side effects. Medicinal plant life and their bioactive elements may be used for remedy of DM throughout the world particularly in countries in which access to the conventional anti-DM agents is deficient. Various experimental models are also available to screen antidiabetic activity of plant. The present review therefore is an attempt to know more precisely about diabetes mellitus, its clinical presentation, epidemiological data, complications and current available treatment of diabetics.[3]Pharmacological therapy and/or insulin may be required in order to maintain the blood glucose level as near as possible to normal and to delay or possibly to prevent the development of diabetes-related health problems

II. CLASSIFICATION

1) *Diabetes Mellitus (DM)* [4]

a) *Insulin Dependent Diabetes Mellitus:* Type 1 diabetes generally influences kids and people below thirty years of age, however also can have an effect on older adults. Although the pathogenesis isn't always completely understood, type 1 diabetes is characterized by lack of insulin secretion due to idiopathic attack or auto-immune destruction of insulin-secreting beta cells of the islets of Langerhans in the pancreas. Therefore; it is mainly treated by insulin replacement therapy

b) *Non-Insulin Dependent Diabetes Mellitus:* Type 2 diabetes is the most common globally. It predominantly impacts adults above thirty years of age despite the fact that many cases have recently been diagnosed among obese children. Type 2 diabetes has also been referred to as non-insulin-based diabetes mellitus (NIDDM) or late onset diabetes; however, that term is no longer used because of confusion it can cause if patients have been categorized on the basis of treatment rather than pathogenesis.[1]

2) *Impaired Glucose Tolerance (IGT):* describes an intermediate state "at risk'' group- between diabetes mellitus and a normality. It can only be described by the oral glucose tolerance test. many people with IGT are euglycemic in their daily lives and might have normal or near normal glycated hemoglobin levels. Individuals with IGT often occur hyperglycemia only when challenged with the oral glucose load used within the standardized OGTT.[5]

3) *Gestational Diabetes Mellitus (GDM):* occurs when glucose intolerance is first found during pregnancy. The criteria for abnormal glucose tolerance in pregnancy, which are widely used in the U.S., were proposed by O'Sullivan and Mahan in the year 1964 and have been based on facts acquired from OGTTs performed on 752 pregnant women. Abnormal glucose tolerance is defined as two or more blood glucose values out of four that have been greater than or equal to two standard deviations above the mean. These values have been set primarily based totally on the prediction of diabetes developing later in life. The pathogenesis of GDM still remains largely unknown; nonetheless research have shown involvement of dysregulation and defects in the insulin signaling pathway, resulting in reduced glucose uptake and delivers in skeletal muscles and adipocytes.[1]

III. DIAGNOSIS

The diagnosis of a diabetes in an asymptomatic challenge should never be made on the basis of a single abnormal blood glucose value.[2] All types of diabetes including type 2 are diagnosed when fasting plasma glucose is more than 7mmol/L on at least two occasions [1]

1) *Fasting Plasma Glucose Test:* Data from the National Health and Nutrition Examination Survey shows that fasting plasma glucose values may identify up to one third more undiagnosed cases of diabetes compared to A1C levels. Fasting plasma glucose measurement should be done by venous blood draw; Elevated glucometer or continuous glucose monitor readings are not considered diagnostic.[6]This test is best done in the morning after an 8-hour fast (no food or drink except sips of water).

2) *Random Plasma Glucose Test:* Diabetes may also be diagnosed with a random blood glucose level of 200 mg per dl (11.1 mmol per L) or larger if classic symptoms of diabetes (e.g. weight loss, polyuria, polydipsia, fatigue, blurred vision) are present. Lower random blood glucose values (i.e 140 to 180 mg per dl [7.8 to 10.0 mmol per L]) have a reasonably high specificity of 92 to 98%. Therefore, patients with these values should undergo a lot of definitive testing. A low sensitivity of 39 to 55% limits the use of random glucose testing.[8] This test can be performed at any time without fasting. Along with an assessment of symptoms, it is used to diagnose diabetes but not prediabetes.[9] People with fasting glucose levels of 100 to 125 mg/dl are considered to have impaired fasting glucose, also known as prediabetes. Fasting plasma glucose is preferred mainly because of its low cost and very easy handling.[10]

3) *A1c Test:* This test, also called as the HbA1C or Glycated Hemoglobin test, provides your average blood glucose level over the past two to three months[7] and has been suggested as a useful alternative test for T2D because it overcomes many of the obstacles associated with OGTT. Glycated Hemoglobin is better than Fasting glucose to determine the risk of cardiovascular disease and death from any cause. HbA1c should be considered in the clinical setting as it is easier and less expensive to measure. HbA1c has been proposed to be superior to FPG for predicting vascular disease and all-cause of death in non-diabetics subjects.[10] Despite efforts to standardize laboratory tests, there are a few limitations to A1C testing, and an incomplete correlation between A1C level and average glucose level in some individuals.[6] This test also measures the amount of glucose attached to hemoglobin and the protein in red blood cells that carries the oxygen. You do not have to fasting before this test.[7]A1C testing must be performed in a laboratory using a method certified by the National Glycohemoglobin Standardization Program and in accordance with the Diabetes Control and Complications Trial reference assay.[10]

4) *Oral Glucose Tolerance Test:* The oral glucose tolerance test is considered a first-line diagnostic test.[8] during this test, blood sugar level is first measured once an overnight fast. Then you drink a sweetened drink.

Your blood glucose level is then checked at hours one, two and three.[7] The criterion for diabetes is serum blood glucose level of greater than 199mg per dL (11.0 mmolperL)[8]

IV. CAUSES OF DIABETES MELLITUS

Disturbances or abnormality in gluco receptor of ß cell so that they respond to higher glucose concentration or relative ß cell deficiency. In both way, insulin secretion is impaired; may progress to ß cell failure.[2]There are different causes are associated with each type of diabetes [11]

1) *Type-1 Diabetes:* Type 1 diabetes is an auto-immune disease wherein the immune system destroys tiny part of the pancreatic tissue (The organ which produces the insulin hormone). It is diagnosed when approx 90% of the beta-cells that produce insulin are destroyed. It is a genetic disease, but not an hereditary. Those are likely to develop Type Diabetes have a gene mutation that causes the antibodies. Pancreas needed enzyme Glutamic Acid Decarboxylase (GAD) to function normally. Antibodies that target this enzyme are known as GAD antibodies. The genetic code for diabetes is present on one of the genes (chromosome 6). It was reported that Human Leukocyte Antigen (HLA-DR) genes are liable for causing Type 1 diabetes.[12] The pathogenesis of type 1 diabetes isn't always completely understood however is thought to stem from a couple of factors involving genetic abnormalities and/or environmental factors, leading to both a loss of insulin secretion or a decrease in insulin action[1]
2) *Type-2 Diabetes:* Type 2 diabetes stems from a combination of genetics and life-style factors. Being obese or overweight will increase your risk too[11]Although aging, obesity, inadequate energy consumption, alcohol drinking, smoking, Carrying more weight and many others are independent risk factors of the pathogenesis of type 2 diabetes mellitus[13]makes your cells more resistant to the results of insulin on your blood sugar level.[11]
3) *Gestation Diabetes Causes:* When you eat, your pancreas releases insulin, a hormone that helps to move a sugar known as glucose from your blood to your cells, which use it for energy. During pregnancy, your placenta makes hormones that causes glucose to accumulate in your blood. Usually, your pancreas can send out sufficient insulin to deal with it. But if your body can’t make enough insulin or stops the usage of insulin as it should, your blood sugar level rises, and also you get gestational diabetes[14]

V. DIETARY MANAGEMENT

Adequate caloric value Dietary management should be taken properly by the both diabetic and non-diabetic patient such as: (pharma innovation)

1) Balanced in regard to protein, carbohydrate and fats, in all cases it is necessary to restrict carbohydrate intake.
2) Should conform as closely as possible to normal.
3) Reduce total calorie intake by decreasing both fat and carbohydrate.
4) Food intake should be divided into regularly spaced meals of similar size.
5) Patient must be advised to be constant in his dietary habits from day to day.[2]

VI. GENETIC SYNDROME

Diabetes has been detected in patients with various genetic syndromes such as a Down Syndrome, Klinefelter Syndrome, Turner Syndrome and Wolfram Syndrome[15]

VII. SYMPTOMS OF DIABETES

1) Weight loss-Insufficient insulin prevents the body from getting glucose from the blood into cells to use as an energy. The body starts burning fats and muscle for energy, causing a reduction in weight.
2) Fatigue.
3) Frequent headaches because of high sugars.
4) Excessive hunger.
5) Chest burns & Indigestion When stomach can’t get empty quick enough (gastroparesis), unpleasant Stomach issues like nausea, vomiting, bloating, heartburn or feeling of fullness right after eating or long time afterwards
6) Excessive thirst & common urination-Blood sugar rises, the kidneys can't maintain extra sugar that is dumped into the urine, increasing urination & causes dehydration. Significant loss of potassium & different salts in excessive urination.
7) Breathlessness while exercising, which include walking.

8) Diabetic Ketoacidosis (DKA)- In DKA body makes use of fats for fuel. Fat is transformed to fatty acids and glycerol and fatty acids in addition transformed to ketone bodies. Therefore, ketones become the alternative fuels for the body when cells are low on glucose for a extended period of time. Excess of ketones makes the blood acidic (ketoacidosis). A person becomes dehydrated. The body produces stress response, hormones (glucagon, growth hormone & adrenaline) break down muscle, fats, liver cells into glucose & fatty acids to be used as fuel. If not treated may lead to coma and death of person[12]

VIII. RISK FACTORS FOR DIABETES

Several risk factors had been associated with the development of type 2 diabetes. Genetic factors in a few ethnic groups, family history of diabetes, and growing population age are examples of unmodifiable risk factors. However, lifestyle factors related to unhealthy diet, physical state of being inactive and smoking usually leading to overweight, high blood pressure, dyslipidemia and impaired glucose tolerance. (IGT) are some of the most common risk factors for escalating diabetes epidemiology. Environmental factors such as exposure to arsenic and mercury, physical living conditions, stress levels, job strains and low socioeconomic status also are believed to make contributions to diabetes improvement. The fact that people with type 2 diabetes can stay undiagnosed for many years or to be unaware of the long-time period damage being caused by the disease warrants health system screening measures.[1] Many research have proven that awareness about the diabetes and its complications is terrible amongst the general population especially within the rural areas. There is an urgent need to create awareness to many of the population regarding diabetes and about the serious consequences of this chronic disorder. Epidemiological statistics from India have proven the presence of a number of risk factors which may be easily recognized by simple non-invasive risk scores.[15]

IX. GOALS OF MANAGEMENT

Primary prevention is the main intention at preventing diabetes from occurring in susceptible individuals or in standard population. Regular physical activity is an vital component of the prevention and control of type 2 diabetes mellitus. Prospective cohort research have shown that extended physical activity, independently of other risk factors, has a protecting effect towards the development of type 2 diabetes. Dietary and lifestyle modifications are the primary goals of treatment and management for type 2 diabetes. The majority of humans with type 2 diabetes is overweight and generally has other metabolic disorders of the insulin resistance syndrome, so the major objectives of dietary and lifestyle changes are to reduce weight, improve glycemic control and reduce the risk factor of coronary heart disease (CHD), which accounts for 70% to 80% of deaths amongst the people with diabetes. Insulin replacement therapy is the anchor for patients with type 1 DM while diet and lifestyle modifications are taken into consideration the cornerstone for the treatment and management of type 2 DM.

Insulin is also important in type 2 DM when blood glucose levels can't be managed through diet, weight loss, exercising and oral medications. Oral hypoglycemic agents are also beneficial in the treatment of type 2 DM. Oral hypoglycemic agents consist of sulphonyl urea, biguanides, alpha glucosidase inhibitors and thiazolidinediones. Their main purpose is to restore normal metabolic disorder which include insulin resistance and inadequate insulin secretion from pancreas. Diet and lifestyle techniques are to reduce weight, improve glycemic control and reduce the risk of cardiovascular complications, which account for 70% to 80% of deaths amongst people with diabetes[16]

Complex cases are treated in specialized secondary care diabetes centers where multidisciplinary diabetes professionals are available following national guidelines or local protocols adapted to national guidelines or a known evidence-based algorithm. The diabetes team is usually led by a medical diabetologist and in most cases includes diabetes specialist nurses, nutritionists, podiatrists and other staff such as ophthalmologists, nephrologists and pharmacists, in addition to the support services provided by family medics. This has improved clinical efficiency, communication and patient-centric care. In the past decade, new evidence on lifestyle monitoring, self-management education and monitoring, and several new treatments for various aspects of control have been introduced.[1]

X. THERAPY FOR DIABETES MELLITUS

The aims of treating diabetes mellitus are to achieve stable and near-normal metabolic control without inducing an unacceptable level of hypoglycemia and to prevent or delay the progression of diabetic complications.[17] Antidiabetic drugs treat diabetes mellitus by lowering blood sugar levels. With the exception of insulin, exenatide and pramlintide, all are administered orally and are therefore also known as oral hypoglycemic agents or oral anti-hypoglycemic agents.

There are several classes of antidiabetic drugs, and their selection depends on the type of diabetes, the person's age and condition, and other factors. Type 1 diabetes mellitus is a disease caused by insulin deficiency. Insulin must be used for Type I, which must be injected or inhaled. Type 2 diabetes mellitus is a disease of insulin resistance in cells.

Treatments consist of agents that increase the quantity of insulin secreted by the pancreas, agents that increase the sensitivity of targeted organs to insulin, and agents that lower the rate at which glucose is absorbed from the gastrointestinal tract. (American Diabetes Association. Clinical Practice Recommendations, Year - 2003)[18].Self-management training, diet, regular exercise, medication, and ways to identify and treat complications are key elements of overall diabetes management.[17]

XI. NEED FOR COMBINATION THERAPY

Fixed-dose combination therapy (FDC) is a combination of two or more actives in a fixed dose ratio. The International Diabetic Federation (IDA) and the American Diabetic Federation (FDA) tend to suggest that if monotherapy along with lifestyle modification fails, the patient should use combination therapy [19].

Combination therapy is based on the logic of a multi-targeted approach and helps to achieve and maintain desired therapeutic goals. The advantages of the fixed-dose combination are ease of administration, convenience, synergistic effect, complementary mechanism of action, fewer side effects at low doses, economical, reduces pill burden and thus improves therapy adherence, improves strict glycemic control, reduces the incidence/severity of adverse drug reactions, and delays the Need for insulin therapy.

Marketed available Combination medicines for Diabetes mellitus

Drugs	Brands
Voglibose + Metformin	Voliix
Metformin + Glipizide	Metaglip
Saxagliptin + MetforminER	Kombiglyze XR
Vidagliptin + Metformin	Janumet R
Metformin + Rosiglitazone	Avandamet R
Glimepiride + Metformin	Diapred-m2
Metformin + Glimepiride	Glycifit G1, Glycifit G2
Metformin (SR) + Glimepiride and Pioglitazone	Glycifit G1
Metformin + Glimepiride + and Pioglitazone	Glycifit Trio G2
Metformin + Voglibose	Glycifit V 0.2, Glycifit V 0.3
Sitagliptin,+ Metformin	Istamet
Gliclazide + Metformin	Diamicron XR
Pioglitazone + Metformin	Pioglu
Glimepiride + Metformin	Gluconorm

XII. INSULIN AND ORAL HYPOGLYCEMIC AGENTS

Various types of insulin preparations are marketed. Insulin is usually given subcutaneously, either by injection or by an insulin pump. Other routes of administration are currently being explored. In acute care, insulin can also be given intravenously. There are different types of insulin that are characterized by the rate at which the body metabolizes them. Insulin is essential for the treatment of type 1 diabetes.

1) Rapid-acting insulin: Starts to work in 15 minutes and lasts 2 to 4 hours.
2) Short-acting insulin: Starts to work in 30 minutes and lasts 3 to 6 hours.
3) Intermediate-acting insulin: Starts to work in 2 to 4 hours and lasts 12 to 18 hours.
4) Long-acting insulin: Starts to work 2 hours after injection and lasts up to 24 hours.
5) Ultra-long-acting insulin: Starts to work 6 hours after injection and lasts 36 Hours or more.
6) Pre-mixed insulin: works in 5 to 60 minutes and lasts 10 to 16 hours.[20]

a) *Biguanides:* Metformin is most commonly used in overweight and obese patients, suppresses hepatic glucose production, increases insulin sensitivity, improves glucose uptake through phosphorylation of GLUT-elevating factor, increases fatty acid oxidation, and decreases glucose absorption from the gastrointestinal tract .

- *Mechanism of Action:* Metformin as activation of AMP-activated protein kinase, an enzyme that plays a role in hepatic gluconeogenic gene expression. Due to concerns about the development of lactic acidosis, metformin should be used with caution in elderly diabetic patients with renal impairment. Compared to sulfonylureas, it has a low incidence of hypoglycemia.[21].Motorman has become the most commonly used agent for type 2 diabetes in children and teenagers. Eg: Metformin, Phenformin, Buformin[18]

b) *Sulfonylureas:* Sulfonylureas were the first widely used oral hypoglycemic medications. [22]Sulfonylureas are a classic first or second-line therapy for patients with T2DM) (This are insulin secretagogues, triggering insulin release by direct action on the KATP channel of the pancreatic beta cells) Examples include; Glimepiride, Glibenclamide, Chlorpropamide, Glipizide, Glyburide etc[18]

c) *Meglitinides:* Meglitinides help the pancreas produce insulin and are often referred to as "short-acting secretagogues". Its mode of action is original and affects the channels. By closing the potassium channels of the beta cells of the pancreas, they open the calcium channels & thus increase insulin secretion. Ex.repaglinide, nateglinide, nateglinide (However, they require more frequent dosing)[18]

- *Mechanism of Action:* Both sulfonylureas and glinide base their mechanism of action on increasing insulin secretion, which is regulated by ATP-sensitive potassium channels (channel potassium KATP), which affect the Pancreatic beta cell membrane. Although the receptor binding site for sulfonylureas and glinide is different, both induce channel closure and cell depolarization, leading to an increase in cytoplasmic calcium levels and consequent insulin secretion[22]

d) *Thiazolidinediones:* Thiazolidinediones are insulin sensitizers, selective ligands transcription factor peroxisomes proliferator-activated gamma. They are the first drugs to address the underlying problem of insulin resistance in patients with type 2 DM, a class that now primarily includes pioglitazone after the Food and Drug Administration (FDA) recently restricted the use of rosiglitazone due to increased cardiovascular events that have been reported with rosiglitazone. Pioglitazone use is not associated with hypoglycemia and can be used in renal impairment and is therefore well tolerated in older adults. On the other hand, due to concerns about peripheral edema, the fluid Retention and fracture risk in women, its use may be limited in older adults with DM. Pioglitazone should be avoided in elderly patients with congestive heart failure and is contraindicated in patients with class III-IV heart failure[21]

- *Mechanism of Action:* Involves activation of the peroxisome proliferator-activated receptor (PPAR gamma), a nuclear receptor. This action alters the transcription of several genes that play a role in glucose and lipid metabolism and energy balance (Hauner, 2002). The main derivatives of TZDs are pioglitazone, rosiglitazone and lobeglitazone.[18] Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of oral diabetes drugs that help with weight loss and lower blood sugar and work through an enzyme that destroys a group of gastrointestinal hormones called incretins. DPP-4 inhibitors are prescribed for patients with type 2 diabetes mellitus who do not respond well to metformin and sulfonylureas. Amylin Analogues or Agonists These are injectable used to treat bothtype 1 & type 2 Diabetes and are administered before meals. They inhibit the release of glucagon when eating, slow down the emptying of food from the stomach. Pramlintide acetate (SYMLIN) is the class of drugs available in the United States that are administered by subcutaneous injection. In the UK, it is not approved by the National Institute for Health and Care Excellence (NICE) because it can significantly increase the risk of severe hypoglycemia[18]

XIII. CONCLUSION

In conclusion, effective lifestyle modifications including counselling on weight loss, adoption of a healthy dietary pattern like the Mediterranean diet, together with physical activity are the cornerstone in the prevention of type-2 diabetes. Therefore, emphasis must be given to promoting a healthier lifestyle and finding solutions in order to increase adherence and compliance to the lifestyle modifications, especially for high-risk individuals. Results from epidemiological studies and clinical trials evaluating the role of the Mediterranean dietary pattern regarding the development and treatment of type-2 diabetes indicate the protective role of this pattern. As a result, promoting adherence to the Mediterranean diet is of considerable public health importance as this dietary pattern, apart from its various health benefits, is tasty and easy to follow in the long-term. Diet is an important aspect in the management of a diabetic patient. The diabetic healthcare provider and the patient should understand the basic dietary needs of the patient. In this form, there may be plenty of insulin in the bloodstream, but the cells are resistant to it. Glucose cannot easily get into the cells, and it backs up in the bloodstream. Over the short run, people with uncontrolled diabetes may experience fatigue, thirst, frequent urination, and blurred vision. In the long run, they are at risk for heart disease, kidney problems, disorders of vision, nerve damage, and other difficulties. Type 2 DM is a metabolic disease that can be prevented through lifestyle modification, diet control and control of weight and obesity. Novel drugs are being developed, yet no cure is available.

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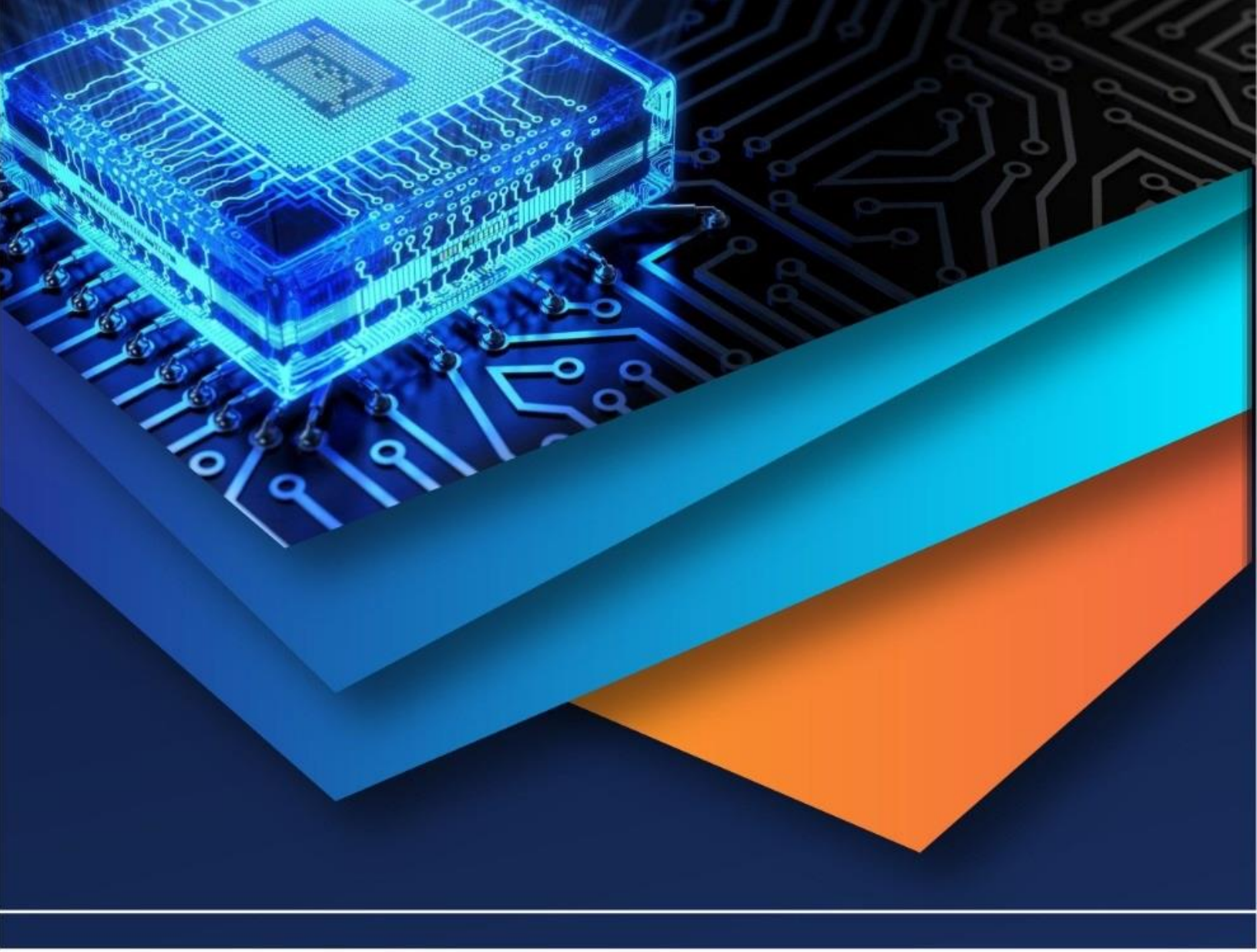

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