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Significance of Inflammation, Angiogenesis and Cardiovascular Risk Factors in the Development of Neuroischemic Form of Diabetic Foot Syndrome

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Annotation: People with type 2 diabetes mellitus (T2DM) are at increased risk of many complications, which are mainly related to complex and interrelated mechanisms such as hyperglycemia, insulin resistance, mild inflammation, and accelerated atherogenesis. [1].

I. INTRODUCTION

Cardiovascular disease is often associated with type 2 diabetes and can become life-threatening, especially coronary disease, stroke, and heart failure. Their clinical picture is sometimes atypical and asymptomatic for a long time. Type 2 diabetes should be considered as an independent cardiovascular risk factor. Nephropathy is common in type 2 diabetes, but has a mixed origin. It is now the highest cause of end-stage renal disease. Improving metabolic and blood pressure control, as well as improving the treatment of microalbuminuria, can slow down the course of the disease. However, retinopathy, which, paradoxically, is not progressive, should be evaluated and treated in these rather old patients, who are globally at high ophthalmic risk. Diabetic foot is a severe complication secondary to microangiopathy, microangiopathy, and neuropathy. It can be considered as a supercomplication of several complications. It should be screened on a regular basis. Some cancers can be seen as an emerging complication of type 2 diabetes, as well as cognitive decline, sleep apnea, mood disorders, and disorders of bone metabolism. Most complications of type 2 diabetes can be prevented with a strategy that combines systematic screening and multi-interventional therapy. Diabetic foot is a severe complication secondary to microangiopathy, microangiopathy, and neuropathy. It can be considered as a supercomplication of several complications [1].

A 2017 Brazilian paper reviewed the most recent work (2016) discussing or providing clinical evidence for possible common pathways leading to diabetic foot syndrome (DFS) and increased mortality: foot mortality rate is more than twice that of non-ulcerated diabetic patients. In addition, the 5-year mortality after amputation is estimated at 39-68%, life expectancy is comparable to aggressive forms of cancer or severe congestive heart failure. Most patients with diabetic foot ulcers also have insulin resistance, central obesity, dyslipidemia, and hypertension, which characterize the metabolic syndrome, which in turn is associated with an increased risk of serious cardiovascular events. Elevated triglycerides have been shown to be an independent risk factor for lower limb amputation in diabetic patients. In addition, toxic obesity, oxidative stress, mitochondrial dysfunction, polyol pathway activation, glycosylation end products (AGE) accumulation, and increased inflammatory markers are also associated with diabetic vascular disease and neuropathy. The hypothesis that the association between DFS and increased mortality reflects the progression of micro- and macrovascular complications is supported by the additional association of diabetic foot ulcer (DNS) with renal failure and retinopathy [2].

According to a German-Austrian multicentric study in 2017, new concepts are needed to prevent amputations caused by DFS and to reduce cardiovascular risk factors before the onset of DFS. [3]. The cross-sectional study included 45,722 patients with T1DM (n DFS = 2966) and 313,264 patients with T2DM (n DFS = 30,904). In DFS, small/large amputations were analyzed. Regression models were performed to compare HbA 1C , neuropathy, nephropathy, risk factors for cardiovascular disease and macrovascular complications in patients with or without DFS. Risk factors: age, sex, duration of diabetes. In patients with DFS, minor amputation was recorded in 27.2% (DM1) and 25.9% (DM2), major amputation in 10.2% (DM1) and 11, 3% (DM2).

Regression models showed that neuropathy was more common in patients with DFS than in patients without DFS (D1D: 70.7 vs. 29.8%; DD2: 59.4% vs. 36.9%; both P < 0.0001). Hypertension, nephropathy, peripheral vascular disease, stroke, or myocardial infarction were more common than in patients without DFS (all P<0.0001). [3].

The aim of the Italian authors, who performed a review in 2014, is to focus on the immunoinflammatory features of DFS and its possible role as a marker of cardiovascular risk in patients with diabetes. This expression of the "adipovascular axis" at lower plasma levels of adiponectin and higher plasma levels of IL-6 may be associated with the pathogenesis of foot ulcers through microvascular and inflammatory mechanisms [4].

II. THE PREVALENCE OF DIABETIC FOOT SYNDROME

Approximately 82,000 lower limb amputations directly related to diabetes are performed annually in the United States [4]. Of these amputations, most (80%) were preceded by foot ulceration [5]. Foot ulcers are the most common precursor of lower limb amputation in diabetics [6]. The presence of foot ulcers is considered an important risk factor for morbidity, mortality, and disability, as evidenced by the fact that about 80% of non-traumatic amputations are caused by the presence of diabetes, and 85% of these amputations are preceded by foot ulcers [7].]. It is estimated that 15% of diabetic patients will develop a lower extremity ulcer during their illness [8].

Several population-based studies indicate a cumulative incidence of diabetic foot ulcers of 0.5% to 3% per year [9]. The prevalence of foot ulcers in different populations ranges from 2% to 10% [10]. In a retrospective US cohort study of 8905 patients with type 1 and type 2 diabetes, the incidence of SDS was 5.8% over a 3-year follow-up period [9].

III. THE PATHOGENESIS OF DIABETIC FOOT ULCERS

Is complex and multifactorial, and it is well known that these lesions rarely result from a single pathology. Several causes work together to produce foot ulcers in patients with type 2 diabetes. The most common components of this detrimental pathway that lead to foot ulceration include peripheral neuropathy, foot deformity, abnormal foot pressure, joint limitation, external trauma, peripheral vascular disease, and peripheral edema. A frequent complication associated with diabetes is neuropathy, which is the most important comorbid cause on the path to ulcers. Diabetic peripheral neuropathy (DPN) is a disruption in the normal functioning of nerves throughout the body and can alter autonomic, motor, and sensory functions [11]. In sensory neuropathy, the lack of protective sensitivity makes the foot vulnerable to unattended minor injuries caused by excessive pressure, mechanical or thermal injuries. According to an important prospective multicenter study, sensory neuropathy was the most common component of a causal relationship with ulceration in patients with diabetes [12, 13]. Other forms of neuropathy may also play a role in the formation of foot ulcers. Motor neuropathy alters the biomechanics and, progressively, the anatomy of the foot, causing foot deformities, limited joint mobility, and changes in foot loading. These disorders can also change the distribution of forces during walking and cause reactive thickening of the skin (corns) in places of abnormal load. In addition, ischemic tissue necrosis under the callus leads to the destruction of the skin and subcutaneous tissue, which leads to a neuropathic ulcer. Autonomic neuropathy often results in changes in skin texture and turgor, such as dryness and cracking, which creates a portal of entry for bacteria.

IV. CARDIOVASCULAR DISEASE AND MORTALITY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS WITH DFS

Patients with diabetes have a higher mortality compared to patients without diabetes. Several studies have reported that rates of mortality and morbidity from cardiovascular disease are 2 to 4 times higher among patients with type 2 diabetes than among non-diabetics. Various studies also show that foot ulcers in diabetic patients are associated with higher mortality. In fact, diabetic foot is the main cause of morbidity in patients with type 2 diabetes, and the mortality rate is about twice as high as in patients without foot ulceration [14–16].

In a study [17] by Pinto et al., these authors hypothesized that type 2 diabetic patients with DFS may have a worse prognosis in terms of faster progression of cardiovascular damage and higher cardiovascular morbidity. To this end, the authors assessed differences between people with type 2 diabetes with and without diabetic foot in terms of (1) cardiovascular risk profile, (2) retrospective prevalence of cardiovascular disease, (3) prevalence of markers of subclinical cardiovascular pathology. damage during recruitment; and (4) the rate of new vascular events in a prospective analysis. They showed a higher prevalence of the main cardiovascular risk factor, subclinical CVD markers, and previous and new cardiovascular and cerebrovascular events in diabetic patients with foot complications. These results may explain previous reports of high morbidity and mortality in diabetic patients with amputations.18–20].

The main cause of death in diabetic patients was coronary heart disease (CHD) [18–20]. In this study, the authors also reported a higher prevalence of major cardiovascular risk factors such as hypercholesterolemia, plasma LDL levels > 130 mg/dl, hypertriglyceridemia, and microalbuminuria/proteinuria in patients with diabetic foot compared with patients with uncomplicated diabetes. with the foot, and this finding is consistent with the hypothesis that DFS in patients with type 2 diabetes may represent a possible marker of cardiovascular risk. They also reported that diabetic foot patients were more likely to have cerebrovascular events (TIA and ischemic stroke) both retrospectively (previous TIA and ischemic stroke) and prospectively (new TIA and stroke in a 5-year study). The most common stroke subtypes were the lacunar subtype and the LAAS subtype, with a slightly higher prevalence of the lacunar subtype, and this finding may indicate a role for both microvascular disease and atherosclerotic macroangiopathy, a determinant of vascular morbidity in diabetic foot patients. The higher cardiovascular risk associated with diabetic foot may be due to the cumulative effect of a single risk factor associated with neuropathy and PAD, which are two well-known diseases recently associated with increased cardiovascular morbidity. [18, 19], but another explanation for the role of microangiopathy as a determinant of overall vascular risk can be recognized. However, because the groups assessed in this study did not start out with balanced CVD and CVD risk factors, the authors cannot accurately adjust for so many other important variables, especially those with few and relatively few events; Thus, our findings can only alert clinicians that diabetic foot should prompt a vital search for treatable cardiovascular risk factors and diseases.

Diabetic foot syndrome is the most common cause of hospitalization in patients with type 2 diabetes and one of the economically most severe complications of type 2 diabetes. Mortality has been shown to be higher in people with diabetes than in people without diabetes, but the cerebrovascular risk profile in these patients is not fully understood. Another study [21] was conducted to evaluate the possible role of diabetic foot as a marker of cerebrovascular risk in patients with type 2 diabetes. The authors enrolled 102 type 2 diabetic patients with diabetic foot and 123 diabetic patients without diabetic foot. Statistically significant differences were found in the distribution of major cardiovascular risk factors, with the exception of arterial hypertension. They observed a higher prevalence of previous cerebrovascular events (transient ischemic attack, ischemic stroke) and a higher incidence of new cerebrovascular events at 5-year follow-up. With respect to the clinical subtype of ischemic stroke classified according to the ORG 10172 study in the Classification of Treatment of Acute Stroke (TOAST) on a retrospective and prospective basis, the authors observed a higher prevalence of both the lacunar subtype and the large artery atherosclerosis subtype, with a slightly higher prevalence of the lacunar subtype in patients with diabetic foot. These results showed a worse cerebrovascular risk profile in T2DM patients with diabetic foot than in T2DM patients without foot ulceration, with a higher prevalence of cardiovascular risk factors and history of cerebrovascular events and rates of new cerebrovascular events at 5-year follow-up.

V. CARDIOVASCULAR RISK FACTORS IN DIABETIC PATIENTS

A. Microalbuminuria

Microalbuminuria is defined as urinary albumin excretion levels of 30 to 300 mg in a 24-hour urine collection. This is still the only kidney anomaly in early type 2 diabetes that has prognostic value. In fact, the appearance of microalbuminuria in patients with type 2 diabetes is a very important indicator of the progression of the most serious kidney disease. It is an indicator of cardiovascular risk in diabetics, as well as in hypertensive patients and the general population. The authors showed a significant positive correlation between several clinical and laboratory variables, including microalbuminuria and levels of interleukin 6 (IL-6) and resistin, which are adipocytokines that can contribute to insulin resistance and the development of inflammatory responses. [22]

B. Hypertension

Hypertension is defined according to the 1993 World Health Organization criteria as a systolic blood pressure of 140 mmHg. Art. and/or diastolic blood pressure of 90 mm Hg. Art. in subjects not taking antihypertensive drugs. Type 2 diabetes and hypertension are common diseases and are two powerful independent risk factors for cardiovascular, renal and atherosclerotic diseases. The pathogenesis of hypertension in type 1 and type 2 diabetes is different. Diabetic nephropathy is considered the main factor contributing to the development of arterial hypertension in patients with type 1 diabetes mellitus. In type 2 diabetes, arterial hypertension is more often of an essential nature and is part of the plurimetabolic syndrome against the background of insulin resistance. In all cases, arterial hypertension worsens the prognosis of patients, increases the risk of both macrovascular and microvascular complications. Indeed, within the framework of diabetes and hypertension, the development of diabetic retinopathy, nephropathy and peripheral vascular disease is accelerated. In patients with type 2 diabetes with arterial hypertension, lowering blood pressure helps to significantly reduce the treatment of cardiovascular and renal complications. Therefore, it is necessary and reasonable to treat hypertension in patients with diabetes mellitus, which should include non-drug interventions, drug therapy,

regular monitoring of blood pressure and educational activities. A study by Pinto et al. [23] In patients with type 2 diabetes with arterial hypertension, lowering blood pressure helps to significantly reduce the treatment of cardiovascular and renal complications. Therefore, it is necessary and reasonable to treat hypertension in patients with type 2 diabetes, which should include non-drug interventions, drug therapy, regular monitoring of blood pressure, and educational activities.

C. Dyslipidemia

There are many cardiovascular diseases that occur in patients with both type 1 and type 2 diabetes. Dyslipidemia is one of the main risk factors for cardiovascular disease in diabetes mellitus. Defects in the synthesis and clearance of plasma lipoproteins are among the most common metabolic disorders that accompany diabetes. Diabetic dyslipidemia, a characteristic pattern characterized by low high-density lipoprotein (HDL) cholesterol, hypertriglyceridemia, and postprandial lipemia, which is more common in type 2 diabetes, is one of several factors that contribute to the acceleration of macrovascular disease in patients with diabetes mellitus. Among the various factors involved in the development of diabetic dyslipidemia, the effect of insulin on the production of hepatic apoproteins, the regulation of lipoprotein lipase (LpL), the action of cholesterol ester transfer protein (CETP) and the peripheral action of insulin on adipose and muscle tissues should be considered. Thus, the detection and treatment of dyslipidemia are two important elements of an interdisciplinary approach aimed at the prevention of coronary heart disease. According to current recommendations for the prevention of coronary heart disease in patients with type 2 diabetes, elevated LDL cholesterol is the main goal of lipid-lowering therapy, and statins are recommended as first-line therapy for diabetic dyslipidemia. However, given the complexity of dyslipidemia profiles in patients with type 2 diabetes, multiple drugs are often required to achieve therapeutic goals. In addition, other risk factors commonly associated with T2DM, such as hypertension, hyperglycemia, and obesity, should be effectively controlled to enhance the effect of lipid-lowering therapy. In our recent study, we [17, 24] showed a higher prevalence of dyslipidemia in patients with diabetic foot ulcers than in patients without diabetic foot. In addition, we also showed a significant positive correlation between several clinical and laboratory variables, including dyslipidemia and levels of IL-6 and resistin, which are adipocytokines that can contribute to insulin resistance and inflammatory responses.

VI. MARKERS OF INFLAMMATION AND THEIR ROLE IN CARDIOVASCULAR MORBIDITY IN DFS

Since some cytokines are also produced by adipose tissue [25], it has been suggested that the “adipovascular” axis [26] may contribute to an increased risk of cardiovascular events in patients with type 2 DM. In patients with diabetic foot, this "adipovascular axis" expression at lower plasma levels of adiponectin and higher plasma levels of IL-6 may be associated with the pathogenesis of foot ulcers through microvascular and inflammatory mechanisms. In addition, obesity correlates with the metabolic complications of obesity.

These results further support the existence of a adipose-inflammatory vascular axis strongly implicated in diabetic complications such as DFS due to the fact that obesity and related conditions such as diabetes are both pro-inflammatory and inflammatory conditions. hs-CRP levels and negative correlation between adipocyte size and adiponectin levels. These results further support the existence of a adipose-inflammatory vascular axis strongly implicated in diabetic complications such as DFS due to the fact that obesity and related conditions such as diabetes are both pro-inflammatory and inflammatory conditions.

There are few data on the role of systemic inflammation in patients with diabetic foot syndrome, although mild immune activation is an important risk factor not only for type 2 diabetes but also for some vascular complications of diabetes, such as macrovascular. myocardial infarction and stroke) and microvascular (neuropathy and nephropathy). The state of the immune system may be important at several stages in the development of chronic wounds. Immune activation may precede the onset of a diabetic foot ulcer in the same way that it precedes the onset of type 2 diabetes and CAD. Since pro-inflammatory and anti-inflammatory processes play a critical role in the various phases of wound healing,

VII. CONCLUSION

Thus, at present, in diabetology, there is a problem of long-term non-healing and recurrence of ulcerative defects in patients with DFS, which needs to be resolved.

Diabetic foot ulcers are widely described as a vascular complication of type 2 diabetes associated with high morbidity and mortality. Some authors have shown a higher prevalence of serious, previous and new, cardiovascular and cerebrovascular events in patients with type 2 diabetes with foot ulcers than in patients without these complications. This is consistent with the fact that in T2DM there is a complex interplay of several variables with inflammatory metabolic abnormalities and their effects on the cardiovascular system, which may explain previous reports of high morbidity and mortality in T2DM patients with amputations. The involvement

of inflammatory markers such as plasma levels of IL-6 and resistin in patients with type 2 diabetes has confirmed the pathogenetic problem of the "adipovascular" axis, which may contribute to cardiovascular risk in patients with type 2 diabetes. In patients with diabetic foot, this "adipovascular axis" expression at lower plasma levels of adiponectin and higher plasma levels of IL-6 may be associated with the pathogenesis of foot ulcers through microvascular and inflammatory mechanisms. [4].

In addition, the authors observed a significant negative correlation between plasma adiponectin levels and certain CV risk factors such as hypertension, dyslipidaemia, and clinical variables indicative of prior CV morbidity such as prior TIA/stroke and emerging vascular morbidity, such as neuropathy, microalbuminuria, and PAD, and these results also suggest a possible role for hypoadiponectinemia as a putative marker of cardiovascular morbidity, both common and incidental [27,28–39].

According to several studies, the "adipovascular" axis may contribute to an increased risk of cardiovascular events in patients with type 2 diabetes. In patients with diabetic foot, this "adipovascular axis" expression at lower plasma levels of adiponectin and higher plasma levels of IL-6 may be associated with the pathogenesis of foot ulcers through microvascular and inflammatory mechanisms. These results further highlight the importance of the inflammatory and metabolic environment, such as cytokines and adipose hormones, in foot complications in T2DM patients, as has been reported for other vascular complications of diabetes. [27, 28-39].

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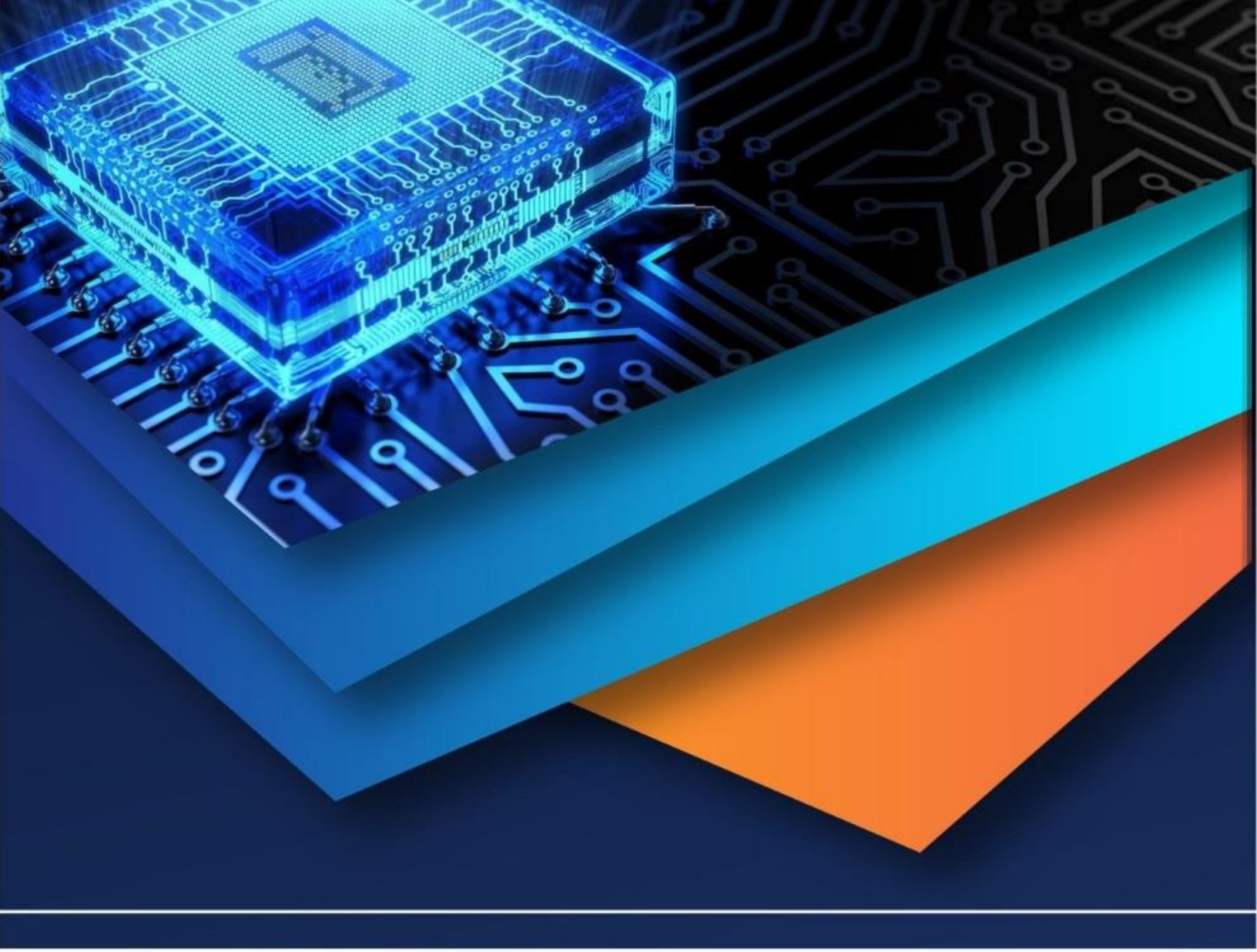

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