iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 11 **Issue:** V **Month of publication:** May 2023

DOI: https://doi.org/10.22214/ijraset.2023.51469

www.ijraset.com

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 11 Issue V May 2023- Available at www.ijraset.com

Neuropathy and Serum Vitamin B 12 Level in Metformin Treated Type2 Diabetic Patients of North India: A Single Centre Observational Study

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Abstract: ***Aim: To determine the prevalence of neuropathy with the help of MNSI questionnaire (Michigan neuropathy screening instrument)***
Method: A single Centre observational study was completed in a tertiary care hospital between jan 2020 to april 2021. .In our study, 95 type 2 diabetes patients who had been taking metformin for a minimum of three months were included in a row. The severity of peripheral neuropathy (as measured by MNSI) and severe characteristics were compared. The length of diabetes, the length of metformin medication, dietary history, and HbA1c levels were some of these. B12 below 200 pg/ml was considered a definitive B12 deficit, while 220pg/ml was considered a potential B12 insufficiency.
Result: In our research, we discovered a weak negative relationship (r=0.19) between the duration of metformin administration and vitamin B12 levels. In our investigation, the average vitamin B12 concentration was 99.22 pg/mL. Peripheral neuropathy and metformin medication duration had a favourable connection (r=1). The typical MNSI result was 11.2. Patients without peripheral neuropathy took metformin for an average of 3.5 years, whereas those with the condition took the drug for an average of 8.04 years.
Conclusion: Peripheral neuropathy and Vitamin B12 insufficiency are serious risks for patients on long-term metformin therapy. Interval Even though Vitamin B12 levels seem to be within the normal range, patients taking metformin should be screened for peripheral neuropathy.
Keywords: Diabetes Mellitus, Peripheral neuropathy, MNSI score, Vitamin B12, Metformin.

I. BACKGROUND

In addition to being a chronic disease characterized by elevated blood glucose levels, diabetes occurs when the body cannot effectively use the insulin produced by the pancreas [1].
Diabetic type 2 (T2DM) has become a worldwide pandemic in developed and developing countries alike[2]. Insulin resistance is a distinguishing feature of type 2 diabetes, which arises when cells are unable to respond fully to insulin, insulin levels decrease, and a beta-cell fails. As a result, glucose is less readily transported into liver, muscle, and fat cells. As a result, fat is broken down more rapidly. Diabetes type 2 can also be caused by factors such as genetics, environment, and behaviour [3].
As a biguanide, metformin is the preferred oral therapy for both American and European guidelines for patients with type 2 diabetes mellitus (DM) [4,5,6]. As an insulin sensitizer, metformin does not increase insulin production but increases insulin sensitivity and reduces cardiovascular risk [7]. The medication has been shown to induce weight loss, improve carbohydrate metabolism, and protect vascular pathways [8 9]. Metformin comes with mild adverse effects, including abdominal discomfort and diarrhea. In contrast, metformin is thought to impair cobalamin (vitamin B12) absorption in the terminal ileum [10]. Constitutive mechanisms by which chronic metformin use causes vitamin B12 deficiency are still obscure. In spite of this, proposed mechanisms include altered small intestine motility with subsequent dysbiosis and reduced vitamin B12 absorption. It has been demonstrated that calcium-dependent absorption of the intrinsic factor at the ileum level is inhibited, B12 complex at the ileum level has been demonstrated, competitive inhibition of vitamin B12 absorption and alterations of the intrinsic factor and cubilin (CUBN) receptor have also been proposed [11]. Numerous studies have demonstrated that metformin consumption over the long term leads to a reduction in vitamin B12 absorption, with a decrease in serum vitamin B12 concentrations of 14% to 30% [10].

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Multiple neurological and neurocognitive symptoms are associated with vitamin B12 deficiency, including peripheral neuropathy and autonomic neuropathy coupled with subacute spinal cord atrophy, delirium, dementia, and axonal demyelination. Peripheral neuropathy can also become more severe in patients with T2DM if they are deficient in vitamin B12. A wide range of prevalence of metformin-induced Vit B12 deficiency has been reported through previous significant studies. This wide range may be explained by differences [12]. The aforementioned differences can be explained by differences in the cut-points to determine the deficiency such as the mean age, study settings, and metformin dose and duration.

During the course of diabetes, neuropathy can occur at any time and is not only a late complication [13]. Neuropathy in diabetes is a heterogeneous condition that manifests differently. It may affect the proximal or distal nerves, may manifest as mononeuritis, or as setups involving large or small fibers, that may affect the somatic or autonomic nervous system [14]. Diabetic patients on metformin may misinterpret these neurological manifestations as diabetic neuropathy. Diabetic peripheral neuropathy (DPN) is the most common complication seen in hyperglycaemic patients, with an annual occurrence of approximately 2 % [15]. Several pathogenic mechanisms of diabetes-related neuropathy involve severity of factors such as oxidative stress, advanced glycation end products, polyol pathway flux, and protein kinase C activation [16, 17]. Furthermore, the reduction in vitamin B12 with metformin could exacerbate the neuropathy in the diabetic. A careful assessment should be conducted as the neurological symptoms and low quality of life are closely linked. The diagnosis of diabetic neuropathy is based on ruling out other causes for peripheral neuropathy and is also increasingly discovered in diabetes mellitus patients with pre-diabetes.

In addition, the manifestation of symptoms varies and may be acute, subacute, or chronic. Nerve damage predominantly affects the toes, feet, or legs, with symmetrical decreasing sensation at the distal pole or impaired ankle reflexes [18]. A combination of positive neuropathic sensory symptoms (such as tingling, prickling, burning, and aching pain) and negative neuropathic sensory symptoms (such as weakness, numbness, and unsteadiness) [19].

The clinical assessment and scoring system for the assessment of neuropathy are significant steps in arriving at the correct diagnosis. These assessments would include the Michigan Neuropathy Screening Instrument (MNSI) is a good screening tool for diabetic neuropathy symptoms, the Neuropathy Disability Score or the Neuropathy Impairment Score (NIS) for neuropathic pain and the Michigan Diabetic Neuropathy Score (MDNS)indicate a higher correlation with nerve conduction studies[13, 20].

II. EPIDEMIOLOGY

Almost half a billion people worldwide have diabetes, making it a leading global health issue[21]. According to a demographic survey performed in 2011, there were 366 million diabetics, and the rate of occurrence is on the rise. According to the World Health Organization, 80 percent of diabetics live in lower- and middle-income nations. In 2011, diabetic-related deaths killed 4.6 million people[22].

Diabetes, as reported by the International Diabetes Federation (IDF) in its 9th edition, is a global health crisis that has become increasingly complex. Diabetes is estimated to affect 463 million people worldwide in 2019, and 578 million by 2030, and 700 million by 2045 (figure 1). Approximately two thirds of diabetics live in cities and three out of four are employed. A significant variation exists between regions around the world in terms of the incidence of type 2 diabetes differentiating according to lifestyle risk and environmental factors[22].

A total of over four million people aged 20 to 79 died from diabetes-related causes in 2019. Every year, more children and adolescents (aged up to 19) are diagnosed with diabetes. In 2019, over one million children and adolescents have type 1 diabetes[23]. Based on previous studies, an estimate of 136 million people over 65 years of age have diabetes, and the prevalence of diabetes varies significantly among IDF regions[24].

The prevalence of type 2 DM in India as a whole was found to be relatively low based on our literature search. Research examining data trends in India suggests both rural and urban areas have experienced dramatic increases and both sexes are affected equally. In India, more than 90% of diabetes cases seem to be type 2, with less than 10% being type 1. A 2019 International Diabetes Federation(IDF) report estimates that 88 million people in South East Asia have diabetes.

III. MATERIALS AND METHOD

From January 2020 to April 2021, a prospective, descriptive, observational study was conducted at a hospital. 95 patients from the NIMS Multispeciality Hospital in Jaipur, India, who were in the endrocrinology department as outpatients and inpatients were studied in total. The study group's patients met the following criteria for inclusion: Age (18 years or older), gender (male or female), outpatient, and a diagnosis of type 2 diabetes older than three months. Metformin therapy for at least three months, patient participation required

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Patients with chronic alcoholism, gastrointestinal disorders, previous blood transfusions, other drugs (methotrexate), and pregnant or nursing women were excluded from the study. The NIMS University's ethical committee gave its blessing to this work.
Patients who have been diagnosed with Diabetes Mellitus Type 2 in the general medical department (ward/OPD) and who meet the inclusion and exclusion criteria will be included in our study. The lab investigation will determine the level of vitamin B12. Diabetic Management Using the MNSI Scale surveys, satisfaction and symptoms of peripheral neuropathy will be evaluated. The prevalence rate will be shown as percentages, graphs, and tables following analysis of the data using excel spreadsheets and other statistical applications.

IV. RESULT

Here we tabulated the various observation of our study below:

Table 1: Sex distribution in the study group

S.No.	Gender	No. of cases	Percentage(%)
1.	Male	63	66%
2.	Female	32	34%

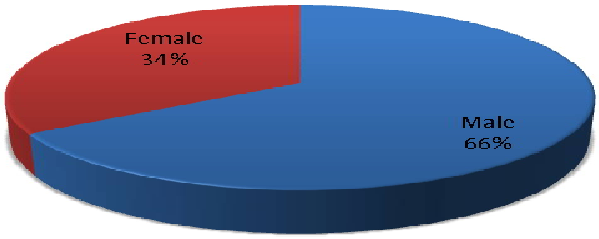

Figure 1: Graph represent sex distribution in the study group

This table and pie graph shows that among 95 cases of diabetic mellitus in the study, 63(55%) were male and 32(34%) were female.

Table 2: Age study distribution in the study group

Age group	No. of cases	MALE	FEMALE
20-30	14	11	3
30-40	25	15	10
40-50	26	19	7
50-60	18	12	6
60-70	7	4	3
70-80	5	2	3
Total	95	63	32

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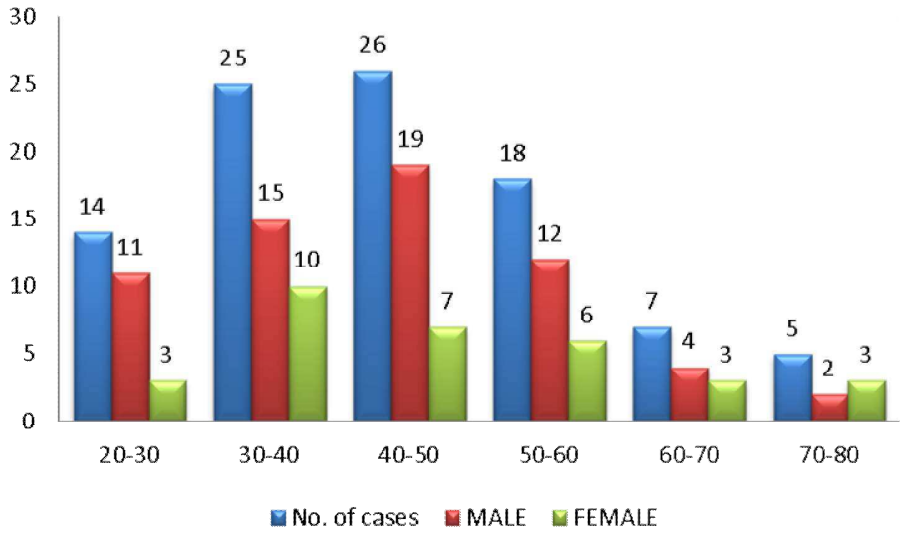

Figure 2: Graph show age study distribution in the study group

The age of patients ranged from 25 to 80 years. The mean age was 44.8 years (SD=14.06. Out of the 95 patients included in the study, 32 were female and 63 were male.

Table 3: Vitamin B 12 level and peripheral neuropathy

Vit B 12 level	No. of cases	Peripheral neuropathy	
		Present	Absent
Normal (200-600pg/Ml)	12	0	12
Bordeline (100-200 Pg/Ml)	10	6	4
Low(Below 100 Pg/Ml)	73	71	2
Total	95	77	18

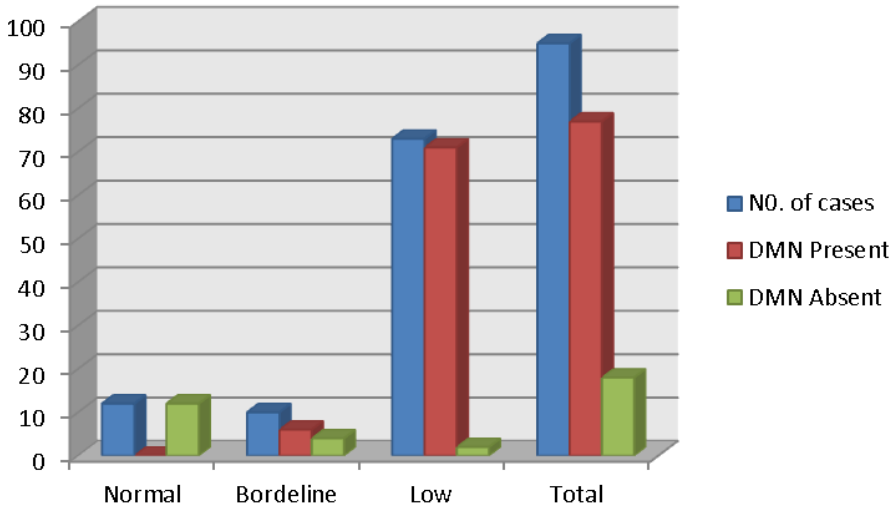

Figure 3. Graph represent Vitamin B 12 level and peripheral neuropathy

There are three categories for vitamin B12 levels: normal, borderline, and low. Out of the 95 patients, 73 had a Vitamin B12 deficiency that was unmistakable, 10 had a possible deficiency, and the remaining 12 had levels that were normal. We observed that patients with confirmed Vitamin B12 insufficiency have a greater incidence of peripheral neuropathy compared to the patient group with probable or normal Vitamin B12 levels when the presence or absence of peripheral neuropathy in each subgroup was analysed.

A. HbA1c Levels, Diabetes Duration, and Peripheral Neuropathy

The individuals in the study had diabetes for an average of 8.6 years. Patients with and without neuropathies had a mean duration of diabetes of 38.5 and 9 years, respectively. In the study population, the average HbA1C level was 8.02. However, patients without neuropathy had average HbA1C levels of 6.8, while those with neuropathy had average HbA1C levels of 10.12. By examining the MNSI scores, we may also compare the degree of neuropathy with the HbA1C levels. The severity of neuropathy tends to rise along with the length of diabetes or the HbA1C levels.

B. Vitamin B12 Levels with the Length of Metformin Treatment

In the population under study, metformin use lasted an average of 5.9 years. When we compare Vitamin B12 insufficiency to the length of metformin use, we observe that as the length of metformin use increases.

C. By using MNSI, Peripheral Neuropathy was Found

In contrast to the MNSI study, which found that 71 individuals had severe neuropathy, 77 patients were found to have some degree of neuropathy. Thus, 6 patients (MNSI Score normal) lacked bordline neuropathy.

V. DISCUSSION

The Netherlands conducted a large-scale multiple sites randomized controlled trial of 390 patients over 4 years in 2010 and found that patients who were prescribed metformin had an 11.2% higher risk of low vitamin B12 levels. A Korean study evaluated the vitamin B12 status of 799 diabetic patients and metformin use in 2014. This study concluded that 9.5% of participants were deficient in Vitamin B12. Researchers evaluated whether vitamin B12 deficiency correlates with metformin dosage and duration. People taking metformin for >4 years at a dose of >1g/day were found to have the highest risk of vitamin B12 deficiency. Earlier this year, the Diabetic Prevention Program, funded by the National Institutes of Health, published results of a randomized control trial of a 13-year study of metformin's effects in pre-diabetic patients. 2155 obese people with impaired glucose tolerance served as study subjects. They were randomized to metformin or placebo groups and monitored for 3.2 years. In an open-label trial, the researchers followed the group of patients prescribed metformin for nine additional years. The study found that there is a 19% risk of low or borderline nutritional status among people who take metformin for more than 5 years and 20% in those taking it for 13 years. For patients treated with metformin, it is recommended that vitamin B12 levels be evaluated periodically. Various ethnic groups may differ in their vitamin B12 levels, according to the research done by de Jager et al. De Jager et al. discovered that prolonged metformin treatment gradually reduces vitamin B12 levels. There has been research that indicates that black people have higher serum vitamin B12 concentrations than white people. There is a high level of vitamin B12-binding proteins in black populations, contributing to this.

Over half a century ago, it was noticed that metformin therapy caused a significant decline in vitamin B12. Vitamin B12 levels have been found to be affected by metformin in observational and placebo-controlled studies. In a recent study it was observed that about 29.7% of patients who were on Metformin therapy in Pakistan had B12 deficiency and another similar study showed that 22.4% of patients with T2DM on Metformin in Brazil experienced a deficiency of vitamin B12, and the deficiency was further reduced in patients who were on proton pump inhibitors (PPI)/ H2-antagonists. Nevertheless, a recent meta-analysis concluded that only 10 out of 17 studies showed B12 deficiency among Metformin users, and in four prospective studies B12 concentrations declined by approximately 57 pmol/L within six weeks to three months after Metformin therapy began.

VI. CONCLUSION

Metformin use anteceding peripheral neuropathy was hypothesized to cause vitamin B12 malabsorption. In the gathered evidence, there were varying results, highlighting the complexity of the relationship between low levels of vitamin B12 in metformin-treated patients and nerve damage in T2DM patients. Analyses of multiple studies revealed that a deficiency of vitamin B12 can result from long-term use of metformin in high doses. Several factors regarding the screening and treatment of T2DM patients were considered when developing the triangular treatment plan using metformin, vitamin B12, and peripheral neuropathy.

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A number of recent studies have concluded that metformin-induced deficiencies of Vitamin B12 can cause or aggravate peripheral neuropathy. However, this does not indicate the cause of Vitamin B12 deficiency caused by metformin use. Understanding these processes on a clinical level will be critically important if we are to reach on confirming the possibility that metformin can cause severe vitamin B12 deficiencies, which will further lead us to therapeutic advancement in the treatment of peripheral neuropathy caused by metformin-induced vitamin B12 deficiency.

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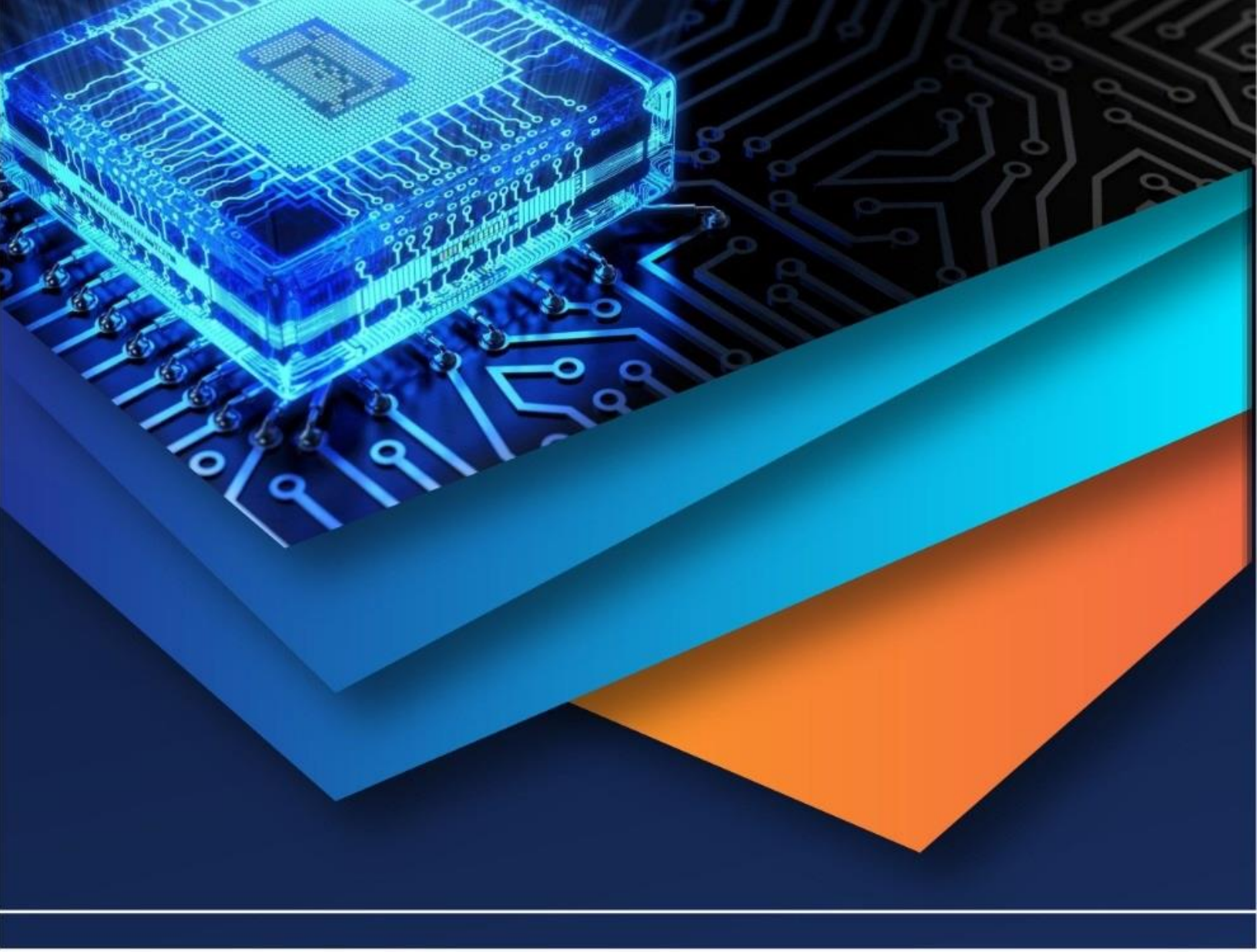

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