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Original Article

AN OBSERVATIONAL STUDY OF PERIPHERAL NEUROPATHY IN DIABETES PATIENTS ON METFORMIN THERAPY AND THE ROLE OF VITAMIN B-12 SUPPLEMENTATION

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ABSTRACT

Objective: This study aims to assess the prevalence of peripheral neuropathy in diabetic patients on metformin therapy using the Douleur Neuropathique 4 (DN-4) scale, explore the relationship between long-term metformin use and serum vitamin B-12 levels, and identify how metformin contributes to neuropathy. Additionally, it seeks to raise awareness about the importance of vitamin B-12 monitoring and supplementation for improving patient quality of life.

Methods: An observational study was conducted involving diabetes patients on metformin therapy. Data were collected on patient demographics, clinical characteristics, and vitamin B-12 levels. Peripheral neuropathy was assessed using the DN-4 questionnaire. Correlations between metformin duration, dosage, vitamin B-12 levels, and neuropathy prevalence were analyzed.

Results: The results indicated that the majority of the study population were male (61.2%) and aged 51-60 years (41.8%), with a majority proportion residing in urban areas (74%). A significant finding was that Peripheral neuropathy was prevalent in 44.8% of patients, with 51.5% exhibiting vitamin B-12 deficiency. Furthermore, the study identified a high prevalence of peripheral neuropathy with a significant correlation between longer metformin use and increased neuropathy (r =0.9372), additionally, a strong negative correlation between metformin dosage and Vitamin B-12 levels (r=-0.9189) highlighted the risk of deficiency with higher doses.

Conclusion: The study underscores the critical role of monitoring and supplementing vitamin B-12 in diabetes patients on metformin therapy to mitigate peripheral neuropathy. Regular screening and proactive supplementation could potentially reduce neuropathic complications associated with long-term metformin use.

Keywords: Peripheral neuropathy, Diabetes, Metformin therapy, Vitamin B-12 supplementation, Vitamin B-12 deficiency, Dosage correlation, Metformin duration

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INTRODUCTION

Millions of people worldwide suffer from diabetes mellitus. Unfortunately, it is widespread in India, and the country's diabetes rate is worryingly rising. By 2030, there will be 79.4 million more people with diabetes in India alone than there were in 2006 [1].

Type 2 diabetes mellitus (T2DM) is a long-term metabolic disorder characterized by dysregulated insulin secretion or action, along with elevated blood sugar levels with a state of hyperglycemia [2]. It is linked to the irregular metabolism of proteins, fats, and carbohydrates, resulting in chronic difficulties such as micro and macrovascular disorders [3].

Metformin is a crucial component of diabetic care and is frequently given due to its efficiency in lowering blood sugar levels. Peripheral neuropathy is one of the many adverse effects of long-term metformin use despite its advantages. The symptoms of peripheral neuropathy, a disorder involving damage to the peripheral nerves, include tingling, burning, and pain in the extremities [4, 5]. A Patient's quality of life is greatly affected by these symptoms [6].

In Diabetes patients, peripheral neuropathy is a developing issue since it can make managing their condition more complex and frequently results in incapacitating symptoms. Although metformin is generally well-tolerated, it has been linked to a deficit in vitamin B-12, a water-soluble vitamin that is essential for the health of nerves, proper hematopoiesis, brain function, and DNA assembly, which may also play a role in the development of peripheral neuropathy [7]. A lack of vitamin B-12 can cause neurological symptoms and exacerbate the neuropathic consequences that diabetes patients experience. This correlation draws attention to a crucial area of concern for individuals on long-term metformin therapy [8].

The expanding number of patients on metformin and the increasing awareness of vitamin B-12 deficiency as a potential risk factor for neuropathy need further investigation into the link between metformin therapy, vitamin B-12 levels, and peripheral neuropathy. Although metformin has been shown to help with diabetic management, its effects on vitamin B-12 levels and the ensuing neuropathic consequences are still poorly understood. Preventative treatment has a significant vacuum since current guidelines do not often call for patients taking metformin to evaluate their vitamin B-12 levels or take supplements routinely [9, 10].

By performing an observational analysis of peripheral neuropathy in diabetes patients receiving metformin therapy and concentrating on the function of vitamin B-12 supplementation, this study seeks to close this gap. By analyzing the frequency of neuropathy, the relationship between the duration and dosage of metformin and vitamin B-12 levels, and the efficacy of vitamin B-12 supplementation in reducing neuropathic symptoms, this study aims to offer essential insights into enhancing diabetes care and improving patient outcomes [11, 12].

This study is significant because it can potentially improve patient care and clinical practice. When metformin-using individuals have a high incidence of peripheral neuropathy and vitamin B-12 deficiency, specific therapies, such as routine vitamin B-12 level monitoring and specialized supplementation regimens, can be developed. By lowering the likelihood of neuropathy, these

interventions could enhance the general quality of life for people with diabetes and lessen the burden of side effects from long-term metformin treatment [13, 14].

This study aims to assess the prevalence of peripheral neuropathy in diabetic patients on metformin therapy using the Douleur Neuropathique 4 (DN-4) scale, explore the relationship between long-term metformin use and serum vitamin B-12 levels, and identify how metformin contributes to neuropathy. Additionally, it seeks to raise awareness about the importance of vitamin B-12 monitoring and supplementation for improving patient quality of life [15, 16].

MATERIALS AND METHODS

Study method

This was a Prospective, observational study conducted on patients with diabetes at the Department of General Medicine, Durgabai Deshmukh Hospital, a 300-bed multispeciality hospital. A total of 165 patients were enrolled in this study. Demographic and clinical data were collected, including metformin dosage, duration of therapy, and vitamin B-12 levels. Peripheral neuropathy was evaluated using the DN-4 questionnaire. Correlation analyses were conducted to examine relationships between metformin use, vitamin B-12 deficiency, and neuropathy prevalence. Additionally, the effectiveness of vitamin B-12 supplementation in alleviating neuropathic symptoms was assessed, providing insights into potential preventative measures.

Study criteria

Inclusion criteria

Type 2 diabetes mellitus (T2DM) patients who have been on metformin therapy for at least one year or more

Exclusion criteria

Individuals with diabetes mellitus who were under the age of eighteen, type 1 diabetes, chronic kidney disease, heart failure, liver cirrhosis, or known malignancies prior to receiving vitamin B-12 injections and colectomy patients were excluded. Further, patients who have discontinued metformin treatment were also excluded.

Statistical analysis

The data will be statistically evaluated using the appropriate Pearson Correlation Coefficient. All data was entered into an Excel Spreadsheet. Analysis was performed using simple statistical methods to generate Frequencies and percentages.

Ethical approval

The study was conducted after obtaining permission from the Institutional Ethical Committee of Durgabai Deshmukh Hospital and Research Centre, Vidyanagar, Hyderabad (Registration No: ECR/477/Inst/AP/2013/RR-20). Objectives of the study were explained to the participants and informed consent form was taken from participants willing to take part in the study.

RESULTS

The study aimed to evaluate the prevalence of peripheral neuropathy in diabetic patients undergoing metformin therapy and to assess the role of vitamin B-12 supplementation in mitigating this condition. The results, summarized in seven tables, provide a comprehensive view of the demographic characteristics, diabetic parameters, vitamin B-12 levels, DN-4 scores, and correlations between these variables.

Table 1 represents demographic and clinical data for a study population, and the study population consisted of 165 diabetic patients on metformin therapy, with a majority being male (61.2%) and aged between 51-60 y (41.8%). The patients predominantly resided in urban areas (74%) and were primarily literate (70%). The most common comorbidities observed were hypertension (81.2%) and dyslipidemia (78.8%), while 42% of the participants reported smoking as a social habit.

Table 1: Demographic and clinical characteristics

Subject characteristics		No. of patients	Percentage (%)
Gender	Female	64	38.8
	Male	101	61.2
Age	41-50	26	15.8
	51-60	69	41.8
	61-70	47	28.5
	>=71	23	13.9
Area of residence	Rural	43	26
	Urban	122	74
Educational status	Illiterate	49	30
	Literate	116	70
Occupational status	Employed	38	23
	Housewife	63	38.2
	Retired	17	10.3
	Self-employed	37	22.4
	Unemployed	10	6.1
Social habits	Smoking	70	42
	Alcohol	40	24.2
Chief complaints	Abdominal pain	4	2.4
	Altered sensorium	8	4.8
	Body pains	19	11.5
	Burning feet	12	7.3
	Chest pain	16	9.7
	Dyspnea	20	12.1
	Giddiness	19	11.5
	Nausea and vomiting	19	11.5
	Palpitation	20	12.1
	Sweating	16	9.7
	Tingling sensation	12	7.3
Comorbidities/Risk factors	Hypothyroid	46	27.9
	Hypertension	134	81.2
	Dyslipidemia	130	78.8
	Physical inactivity	106	64.2
	Both veg and non veg diet	142	86.1

Table 2 shows that the duration of diabetes and metformin usage varied among the participants, with 40% having diabetes for less than five years and 40% using metformin for a similar duration. Notably, 29.1% had diabetes and were on metformin therapy for more than 15 y. Most patients (54.5%) took a metformin dose between 1000 and 1500 mg daily, while 25.5% were on doses exceeding 1500 mg.

Table 2: Distribution according to duration of diabetes, duration of metformin usage, and metformin dose

Diabetic characteristics		No. of patients	Percentage (%)
Duration of Diabetes	<5 Y	66	40
	5 to 10 y	51	30.9
	>15 y	48	29.1
Duration of Metformin usage	<5 Y	66	40
	5 to 10 y	51	30.9
	>15 y	48	29.1
Metformin Dose	<1000	33	20
	1000-1500	90	54.5
	>1500	42	25.5

Tables 3 and 4 summarise the patients' distribution according to their vitamin B-12 levels and DN-4 scores. The distribution of vitamin B-12 levels revealed that 51.5% of the patients had a deficiency (<200 pg/ml), while only 17% had levels above 300 pg/ml. The Douleur Neuropathique (DN-4) score, used to assess peripheral neuropathy, showed that 32.1% of patients had a score of 4, indicating moderate neuropathic pain. A significant proportion (44.8%) had Douleur Neuropathique (DN-4) scores of 4 or higher, signifying the prevalence of neuropathy among the study group.

Table 3: Distribution according to vitamin B-12 levels and DN-4 score

Vitamin B-12 levels and DN-4 score		No. of patients	Percentage (%)
Vitamin B-12 levels (Pg/ml)	<200	85	51.5
	200 – 300	52	31.5
	>300	28	17
DN-4 score	0	10	6.1
	1	33	20
	2	40	24.2
	3	8	4.8
	4	53	32.1
	5	21	12.7

Table 4: Prevalence of vitamin B-12 deficiency and peripheral neuropathy

Prevalence of vitamin B-12 deficiency and peripheral neuropathy	No. of patients	Prevalence (%)
DN-4 score – 4 or more	74	44.8
Vitamin B-12 levels<200	85	51.5

Tables 5 and 6 indicate a strong positive correlation (r=0.9372) was observed between the duration of metformin therapy and the prevalence of peripheral neuropathy, indicating that longer therapy durations are associated with higher neuropathy risks. Additionally, a moderate positive correlation (r=0.6051) was found between metformin dosage and neuropathy prevalence, suggesting increased risk with higher doses. Conversely, a strong negative correlation (r=-0.9189) was identified between metformin dosage and vitamin B-12 levels, highlighting the risk of deficiency with higher metformin doses.

Table 5: Correlation of peripheral neuropathy, vitamin-B12 deficiency with duration of metformin use

Correlation of peripheral neuropathy, vitamin--B 12 deficiency with duration of metformin use	<5 Y	5 to 10 y	>15 y	Correlation coefficient (r-value)
mean duration (Years)	3.8	7.7	19	
Peripheral neuropathy (No of patients)	21	25	28	0.9372
mean vitamin B 12 levels	195	282	230	0.1368

Table 6: Correlation of peripheral neuropathy, vitamin B-12 Deficiency with metformin dose

Correlation of peripheral neuropathy, vitamin B-12 deficiency with metformin dose	<1000 mg	1000 to 1500 mg	>1500 mg	Correlation coefficient (r-value)
mean metformin dose	740	1375	1920	
Peripheral neuropathy	21	28	25	0.6051
mean vitamin B-12 levels	250	240	192	-0.9189

Table 7 reveals that patients with lower vitamin B-12 levels had a higher incidence of peripheral neuropathy. Specifically, 43 patients with vitamin B-12 levels below 200 pg/ml exhibited neuropathic symptoms, underscoring the potential role of B-12 deficiency in the development of neuropathy among diabetic patients on metformin therapy.

Table 7: Distribution according to mean vitamin B-12 levels and peripheral neuropathy

Vitamin B-12 levels	mean vitamin B-12 levels	No of patients with peripheral neuropathy
<200	132	43
200 to 300	295	21
>300	400	10

DISCUSSION

This study examined peripheral neuropathy among diabetes patients receiving metformin medication, focusing on the function of vitamin B-12 supplementation. Patient demographic and clinical data were gathered. Most patients (61.2%) were male, and 41.8% were between the ages of 51 and 60. This suggests that middle-aged males are more likely to have neuropathy. The majority of patients (74%), who were mostly employed (23%), were literate (70%) and lived in urban areas. Notably, a significant number of patients reported using alcohol (24.2%) and smoking (42%), both of which may raise the risk of neuropathy. The complaints in this study were burning feet, tingling sensations, and body pains, which highlighted the prevalent neuropathic symptoms.

In particular, 40% of patients have been diagnosed with diabetes and have been taking metformin for fewer than five years. This suggests that neuropathy can develop even during relatively short treatment periods. Furthermore, 29.1% of the patients have used metformin for over 15 y, and nearly a 30.9% have used it for five to 10 y. This distribution draws attention to the fact that metformin use for diabetes treatment is a chronic condition and raises questions about potential long-term side effects, such as vitamin B-12 insufficiency and its potential to aggravate neuropathy.

Additionally, a considerable percentage of patients are taking metformin at moderate to high levels, according to the dosage statistics, with 25.5% taking more than 1500 mg daily and 54.5% taking between 1000 and 1500 mg. The increased dosage may raise the likelihood of vitamin B-12 insufficiency, highlighting the necessity of closely monitoring and potentially supplementing these individuals with vitamin B-12 to prevent or lessen peripheral neuropathy. These findings are nearly similar to the study conducted by Farooq MD [17].

The data indicates that 51.5% of patients have a substantial deficit of vitamin B-12, and 44.8% of patients score 4 or above on the DN-4, indicating a notable prevalence of peripheral neuropathy. This emphasizes how vital it is for diabetic people to use metformin to monitor their vitamin B-12 levels and receive supplements. These findings are nearly similar to the study conducted by Al Quran T [18].

The study found a strong positive correlation (r=0.9372) between the duration of metformin therapy and the prevalence of peripheral neuropathy, indicating increased risk with prolonged use of metformin. Conversely, the weak correlation (r=0.1368) between vitamin B-12 levels and metformin duration suggests that B-12 levels might slightly increase over time, though not significantly. These findings are nearly similar to the previous research published by Al Zoubi [19].

The study identified a moderate positive correlation (r=0.6051) between metformin dosage and the prevalence of peripheral neuropathy, suggesting increased risk with higher doses. Additionally, a strong negative correlation (r=-0.9189) was found between metformin dosage and vitamin B-12 levels, indicating a significant decrease in B-12 levels with higher metformin doses. These findings are similar to those of the study conducted by Yang R [20].

Given that the majority of patients with peripheral neuropathy also had low vitamin B-12 levels, the study indicates a clear correlation between low vitamin B-12 levels and the development of peripheral neuropathy in diabetic patients on metformin therapy. This research emphasizes how crucial it is to monitor and take vitamin B-12 supplements to lower the risk of neuropathy. These findings are similar to the study of Alvarez M [21].

LIMITATIONS

One limitation of this study is that it did not account for dietary differences between vegetarian and non-vegetarian participants, which could significantly impact vitamin B-12 levels. Additionally, the study did not consider whether participants had undergone prior vitamin B-12 supplementation or treatment, which may have influenced their baseline levels. Addressing these factors in future research would provide a more comprehensive and accurate understanding of vitamin B-12 levels in the population studied.

CONCLUSION

This study comprehensively investigates the correlation between metformin therapy, vitamin B-12 deficiency, and peripheral neuropathy in Type 2 Diabetes Mellitus patients. The study also found a significant correlation between higher metformin doses and longer treatment durations and an increased risk of peripheral neuropathy, affecting 44.8% of the population. Therefore, the study emphasizes the need for screening and regular monitoring of vitamin B-12 levels in patients on long-term metformin therapy and its supplementation as a prophylactic measure for Type 2 Diabetes Mellitus (T2DM) patients on metformin, especially those on high doses or long-term treatment plans.

Future research should further elucidate the mechanisms underlying metformin-induced vitamin B-12 deficiency and peripheral neuropathy and explore the effectiveness of different supplementation strategies. Additionally, long-term, randomized controlled trials are warranted to validate these findings and refine the guidelines for managing Type 2 Diabetes Mellitus (T2DM) patients on metformin therapy.

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Nil

ABBREVIATION

Douleur Neuropathique DN-4, Type 2 Diabetes Mellitus T2DM

AUTHORS CONTRIBUTIONS

All authors have been part of this work's planning, conducting, and reporting. Sameena Tahseen and Mohammed Shahzaib Anwer were responsible for the preparation of the protocol, data input, and documentation. Syeda Amara Fatima and Samreen Fathima focused on data collection and compilation. The study was planned and supervised by Mrs. Haritha, Dr. Swathi, and Mrs. Sandhya. Finally, Sameena Tahseen and Mrs. Haritha worked on the manuscript submission and its subsequent revision.

CONFLICTS OF INTERESTS

Declared none

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