Neuropathy and Neuropathic Pain in Patients with Type 2 Diabetes Mellitus Receiving Metformin - A Cross-Sectional Study from Navi Mumbai, Maharashtra

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ABSTRACT

BACKGROUND

Metformin is reported to induce vitamin B12 deficiency and distinguishing peripheral neuropathy due to vitamin B12 deficiency from diabetic peripheral neuropathy can be challenging. The present study was conducted to assess and compare the clinical presentation of diabetic patients taking metformin with those not taking metformin using Toronto clinical scoring system (TCSS).

METHODS

This cross-sectional study included 60 patients with diabetes mellitus, 30 patients on metformin therapy (at least 6 months) and 30 patients not on metformin use. Clinical presentation of the patients was assessed using the TCSS. Patients were diagnosed according to the American diabetic association criteria.

RESULTS

The mean age of the patients in metformin and non-metformin group was 57.27 ± 9.38 and 58.63 ± 10.27 years respectively. Gender distribution was observed to be similar in both the study groups. Mean duration of diabetes mellitus was found to be similar in both the study groups (5.4 ± 1.01 vs 5.2 ± 1.27 years) and duration of peripheral neuropathy was also found to be similar in the two study groups (3.2 ± 1.6 vs 3.3 ± 1.5 years). Numbness was observed in maximum number of cases in both study groups. It was seen in 100 % (n = 30) patients on metformin drug while in 90 % (n = 27) patients without metformin. Pain accounts to be approximately 77 % (n = 23) and 24 % (n = 7) in patients on metformin and without metformin. Neuropathic symptoms and neuropathic reflex scoring appear to be higher common in patients on metformin as compared to those without metformin. Mean pain score was found to be significantly higher among patients on metformin as compared to those not on metformin (8.43 ± 2.13 vs 4.03 ± 3.13; P value < 0.001).

CONCLUSIONS

Our results show that patients on metformin for diabetes mellitus experience higher neuropathic symptoms as compared to those not taking metformin.

KEYWORDS

Diabetes Mellitus, Metformin, Peripheral Neuropathy, Vitamin B12

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BACKGROUND

Type 2 diabetes mellitus (DM) is becoming a problem of public health concern not only in India but across the globe. Due to the changing lifestyle, which includes eating habits and physical inactivity, the prevalence of DM is expected to increase in future. DM affects various organ systems of the body, including the peripheral nervous system. Diabetic peripheral neuropathy is one of the most common complications of type 2 DM. Metformin, a biguanide, is the cornerstone of pharmacological treatment of DM. Metformin has beneficial effects on carbohydrate metabolism, weight loss, and vascular protection.[1] In addition to its antihyperglycemic effect, metformin has a major effect in overall cardiovascular morbidity and mortality. Majority of the adverse effects associated with metformin are mild, such as abdominal distress and diarrhea.[2]

However, scientific evidence suggests vitamin B12 deficiency with long term use of metformin.[3] It is reported to reduce vitamin B12 uptake in the terminal ileum and thus long-term use of metformin is associated with low vitamin B12 levels.[4] Various mechanisms include altering intrinsic factor levels, competitive inhibition of vitamin B12 absorption, an impaired calcium dependent membrane activity, including uptake of vitamin B12 intrinsic factor complex.[2] Moreover, metformin use can result in decreased folate concentration, though the underlying mechanism is not clearly understood.[5] In fact, the American diabetes association (ADA) guidelines recommend periodic testing of vitamin B12 in metformin-treated patients, especially in those with peripheral neuropathy.[6] The clinical presentation of vitamin B12 deficiency generally includes haematological and neurological manifestations. In some cases, neuropathy can be the only manifestation of the deficiency, without a haematologic presentation.[7] Over the last few decades, the clinical manifestations of vitamin B12 deficiency have shown notable trends towards neurological signs and symptoms.[8] Distinguishing peripheral neuropathy due to vitamin B12 deficiency from diabetic peripheral neuropathy can be challenging for the clinician.

Objectives

The present study was conducted to assess and compare the clinical presentation of diabetic patients taking metformin with those not taking metformin using Toronto clinical scoring system.

METHODS

This comparative cross-sectional study was conducted in the Department of Medicine, Padmashree Dr. D.Y. Patil Medical College and Hospital, Navi Mumbai, in which patients with diabetes mellitus were studied from January 2017 to December 2017. All patients were diagnosed with diabetes mellitus based on American diabetic association criteria.[2] We included patients who had symptomatic peripheral neuropathy. The metformin group had patients taking metformin for at least 6 months during the 12 months of study duration. The non-metformin group included diabetic patients who did not take metformin during the duration of study. We excluded patients who were previously treated with metformin but discontinued it within 6 months, received vitamin B12 and calcium supplementation, malabsorption syndrome, type 1 diabetes mellitus, diagnosed with other forms of neuropathy, suffered from malabsorption syndrome or alcoholism. For sample size calculation, Singh et al. used the TCSS to compare the severity of peripheral neuropathy in patients with type 2 diabetes mellitus treated with or without metformin and found mean neuropathy score to be significantly higher in metformin exposed group (5.72 ± 2.04 versus 4.62 ± 2.12).[9] Using this data, effect size was calculated as 0.56 in G*Power software. Considering α error of 10 % and power of the study at 80 %, we calculated the total sample size to be 60, 30 in each group. Patients were explained the purpose of the study and an informed written consent was obtained from them before enrolment. The study was approved by the Institutional Ethics Committee (Ref number 21171, dated 21.12.2016).

Data Collection

Eligible patients were enrolled and detailed history about their diabetes mellitus and other relevant past medical history was obtained. Clinical presentation of the patients was assessed using the TCSS.[10] The TCSS comprises of three parts: symptom scores, reflex scores and sensory test scores. Though it is a subjective score, it includes elements of history as well as clinical examination. The data was collected using a pre-designed semi-structured study proforma. The investigators filled and complied the data obtained.

Statistical Analysis

The data were analysed using statistical package for social sciences (SPSS) software (version 23, IBM). The data was presented as mean and standard deviation or frequency distribution. Means of various variables of the two study groups (metformin users versus metformin no-users) were compared using student's t test, while proportions were compared using chi-square or Fisher's exact test. A P value of less than 0.05 was considered statistically significant.

RESULTS

During the study period, 32 patients in the metformin group and 31 patients in the non-metformin group fulfilled the study criteria. However, two patients in the metformin group could not complete the study proforma and were lost to follow up and one patient in the non-metformin group refused consent to participate in the study. As a result, in the final analysis, a total of 60 patients were included, 30 each in metformin and non-metformin group. The mean age of the patients in metformin and non-metformin group was 57.27 ± 9.38 and 58.63 ± 10.27 years respectively. Majority of the patients were in the age group of 30 to 50 years (Table 1). Gender distribution was observed to be similar in

both the study groups. Mean duration of diabetes mellitus was found to be similar in both the study groups (5.4 ± 1.01 vs 5.2 ± 1.27 years) and duration of peripheral neuropathy was also found to be similar in the two study groups (3.2 ± 1.6 vs 3.3 ± 1.5 years). Of the 30 patients on metformin, 17 (57 %) patients were taking a glyburide, 10 (33 %) gliclazide and 5 (17 %) were on insulin as well. Of the 30 patients not receiving metformin, 9 (30 %) patients were taking glyburide and gliclazide each and 15 (50 %) were on insulin. Clinical symptoms were assessed using TCSS system. Numbness was observed in maximum number of cases in both study groups (Table 2). It was seen in 100 % (n = 30) patients on metformin drug while in 90 % (n = 27) patients without metformin. Tingling was present in 96.67 % (n=29) and 80 % (n = 24) on patient with and without metformin therapy respectively. Weakness was the third most symptoms which was seen in 66.67 % (n = 20) in cases with metformin therapy and in 53.33 % (n = 16) on patients without metformin therapy.

Pain accounts to be approximately 77 % (n = 23) and 24 % (n = 7) in patients on metformin and without metformin. There was no case who presented with ataxia and upper limb symptoms in non-metformin cases while there were 13 % (n = 4) and 6 % (n = 2) in patients on metformin. From these results, neuropathic symptoms appear to be more common in patients on metformin as compared to those without metformin. Similarly, neuropathic reflex scoring was observed to be considerably higher among patients receiving metformin as compared to those without metformin. Mean pain score was found to be significantly higher among patients on metformin as compared to those not on metformin (8.43 ± 2.13 vs 4.03 ± 3.13; P value < 0.001) (Figure 1).

	Patient Variables	Metformin Group (n = 30)	Non-Metformin Group (n = 30)
Age distribution (in years)	Less than 30	4 (13 %)	2 (7 %)
	30 to 50	17 (57 %)	19 (63 %)
	More than 50	9 (40 %)	9 (30 %)
	Mean ± SD	57.27 ± 9.38	58.63 ± 10.27
Gender distribution	Female	13 (43%)	15 (50%)
	Male	17 (57%)	15 (50%)
	Duration of diabetes (in years)	5.4 ± 1.01	5.2 ± 1.27
	Duration of peripheral neuropathy (in years)	3.2 ± 1.6	3.3 ± 1.5
Medications taken	Glyburide	17 (57 %)	9 (30 %)
	Gliclazide	10 (33 %)	9 (30 %)
	Insulin	5 (17 %)	15 (50 %)

Table 1. Baseline Characteristics of the Patients Included in the Study

	Clinical Symptoms	Metformin Group (n = 30)	Non-Metformin Group (n = 30)
Current symptoms	Pain	23 (77 %)	7 (23 %)
	Numbness	30 (100 %)	27 (90 %)
	Tingling	29 (97 %)	24 (80 %)
	Weakness	20 (67 %)	16 (53 %)
	Ataxia	4 (13 %)	0 (0 %)
	Upper limb symptoms	2 (7 %)	0 (0 %)
Abnormal reflexes	Knee	13 (43 %)	3 (10 %)
	Ankle	16 (67 %)	5 (17 %)
	Pin prick	30 (100 %)	16 (53 %)
	Light	11 (37 %)	1 (3 %)
	Temperature	30 (100 %)	11 (36 %)
	Vibration	26 (87 %)	5 (17 %)
	Position sensing	19 (63 %)	6 (20 %)

Table 2. Assessment According to Toronto Clinical Scoring System

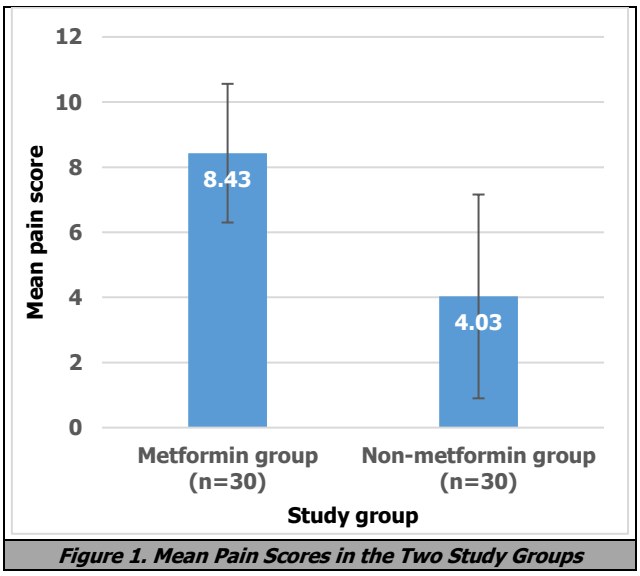

Figure 1. Mean Pain Scores in the Two Study Groups

DISCUSSION

The present study found that neuropathic symptoms were more common in patients on metformin as compared to those without metformin. Pain, weakness and ataxia were found to be more common among our patients taking metformin. Animal studies have demonstrated that metformin can exert neuro-protective and anti-neuropathic activities that are independent of its euglycemic effect. Numbness and neuropathic pain induced by chemotherapy in mice was reduced by the use of metformin.[11] Clinically it is important, as the sensory symptoms of pain, dysaesthesia, and paraesthesia characterize both diabetic peripheral neuropathy and chemotherapy-induced peripheral neuropathy. Animal studies have also reported that metformin reduce pain which is caused by activation of sensory neurons,[12] ethanol-induced neuronal apoptosis, and enhanced neurogenesis.[13] However, Greibe et al. reported that a six-month treatment with metformin resulted in lower serum vitamin B12.[14] The authors investigated changes in the markers for vitamin B12 in women who were treated with metformin for polycystic ovarian syndrome. Although the serum cobalamin levels were lower, physiological markers like transcobalamin and methylmalonic acid were not changed. As a result, vitamin B12 deficiency-mediated effects of metformin may blunt its anti-neuropathic and neuroprotective effects. However, the authors also cautioned against using serum vitamin B12 levels to judge vitamin B12 status, as the reduction in cobalamin levels was linked to the fluctuations in the vitamin B12 binding proteins.

Wile and Toth[15] investigated the relationship between metformin exposure, levels of vitamin B12 and severity of peripheral neuropathy in diabetic patients. The authors found that the median TCSS total score was higher in the metformin-treated group (10 vs. 5; P <0.001), with a strong positive correlation to increasing cumulative metformin dose. In addition, the authors also used neuropathy impairment score (NIS), which was also found to be significantly higher in the metformin-treated group (10 vs. 4; P < 0.001) and also had a strong positive correlation with

increasing cumulative metformin dose (Spearman correlation = 0.8, P value < 0.001). The authors concluded that diabetic patients on metformin had significantly more severe peripheral neuropathy, compared to those not taking metformin. Despite this knowledge, it is still unknown that could this clinical worsening be prevented by nutritional supplementation. Currently oral and intramuscular therapy is widely used. Calcium supplementation has been shown to improve bioavailability of vitamin B12 in metformin treated patients.

Singh et al.[9] used the TCSS and compared the severity of peripheral neuropathy in patients with type 2 diabetes mellitus treated with or without metformin. They found that the mean neuropathy score was significantly higher in metformin exposed group. (5.72 ± 2.04 versus 4.62 ± 2.12, P = 0.0064). The authors found that the proportion of the patients with no neuropathy was significantly higher in non-metformin exposed group [39/52 (75 %) versus 39/84 (46.4 %), mean difference = 28.6 %, 95 % CI 12.72 - 44.48 %, P value = 0.0019) while proportion of patients with mild neuropathy was higher in metformin exposed group 41/84 (48.4 %) versus 11/52 (21.2 %), mean difference = 27.6 %, 95 % CI 12.2 - 43.02 %, P = 0.0024). Additionally, similar to the results of Wile and Toth, there was a positive correlation between cumulative metformin dose and neuropathy score (r = 0.529, 95 % CI 035 - 0.65, P < 0.001). In contrast, Dunstan et al. found no difference in neuropathy scores between metformin users and non-users. The authors used neuropathy total symptom score (NTSS) in their study.[16] It is possible that this difference could be because NTSS is based on history of sensory symptoms alone, while TCSS includes elements of both history and examination. In addition, TCSS is validated, highly reproducible and easy to calculate. Despite a significant association found in the study by Singh et al. it is noted that many confounders were not adjusted, like duration on diabetes, HbA1c levels and nutritional status.

Elhadd et al. compared vitamin B12 levels in type 2 diabetes mellitus patients with or without metformin use. The authors used the vibration perception threshold (VPT) to assess diabetic peripheral neuropathy and the Douleur neuropathique 4 (DN4) to identify neuropathic pain in patients with type 2 diabetes mellitus.[17] The authors found that the prevalence of neuropathy (30 vs 39 %) and neuropathic pain (31 vs 33 %) were comparable between metformin and non-metformin users. Among those with vitamin B12 deficiency, the percentage taking metformin was significantly lower than in those without B12 deficiency (60 vs 80 %, P value = 0.03). In addition, patients with B12 deficiency were significantly younger (49.16 ± 9.72 vs 54.56 ± 12.71 years, P value = 0.01) and had a shorter duration of diabetes (7.03 ± 5.39 vs 11.68 ± 7.89 years, P value < 0.001), but the two groups were comparable with respect to systolic blood pressure, diastolic blood pressure, body mass index, HbA1c, serum cholesterol, triglyceride, high and low density lipoproteins. In their study, vitamin B12 levels were found to be significantly associated with duration of diabetes, HbA1c, vitamin D, proton pump inhibitor use and multivitamin use. From these evidences, it is clear that using different assessment scales brings in some observer's bias, and thus standardisation is needed to aid the clinicians make the correct assessment. In a recent prospective study of 150 patients with type 2 diabetes mellitus, Hashem et al. evaluated the association between the severity of diabetic neuropathy and metformin use.[18] The clinical assessment in their study was done using TCSS. With similar baseline characteristics of metformin users and non-users, the authors found that metformin users had significantly more severe diabetic neuropathy as compared to metformin non-users. This was demonstrated by significantly higher TCSS scores (10 ± 7.5 vs 5 ± 9.5, P value < 0.001). Furthermore, the authors supported these findings with the help of laboratory investigations. They found significantly lower median serum cobalamin levels in metformin treated patients as compared to metformin non-users (222 vs 471 pmol/l, P value < 0.001). The serum homocysteine and methylmalonic acid levels were also significantly higher among metformin users. In addition, serum cobalamin levels had a significantly inverse correlation with metformin dose (r = -0.52, P value < 0.01) and a significant positive correlation with TCSS (r = 0.89, P value < 0.01). Not only the dose, the authors also found duration of metformin use to be significantly associated with severity of diabetic neuropathy. Based on these findings, the authors recommended monitoring serum cobalamin levels in diabetic patients taking metformin.

In contrast, de Groot-Kamphuis et al. assessed diabetic patients on metformin for vitamin B12 levels and development of diabetic neuropathy.[19] In their cohort of 298 patients, vitamin B12 deficiency was found in 9.7 %, 14.1 % among metformin users and 4.4 % among metformin non-users. However, the prevalence of neuropathy was significantly less in metformin users (17.4 %) as compared to metformin non-users (28.1 %). Despite these observations, the authors cautioned to interpret the results carefully, as no objective measure of clinical assessment was used. In fact, only duration diabetes could significantly predict the development of neuropathy in their patients. Similar observations were made by Russo et al. who found that vitamin B12 levels were significantly lower in diabetic patients taking metformin, while folate and homocysteine levels were comparable.[20]

However, diabetic neuropathy was similar in the two patient groups. It was present in 33 % of the patients taking metformin and in 27 % of those not taking metformin, with no statistical difference between them. On the other hand, age of the patient, duration of diabetes, and HbA1c levels were significantly associated with diabetic neuropathy, thus confirming the role of glycaemic control in its pathophysiology. Interestingly, the authors found deranged high-density lipoprotein levels, presence of coronary heart disease and serum creatinine levels to be significantly associated with the development of diabetic neuropathy. The underlying mechanisms of deranged lipids and heart disease in causing neuropathy is not clearly understood, but these point towards the concomitance of various macro and micro-angiopathic complications of diabetes mellitus. In another study by Roy and colleagues, mean vitamin B12 levels were significantly higher in diabetic patients not taking metformin.[21] In this study, neuropathy was assessed

objectively using nerve conduction studies. The authors found that metformin users had higher prevalence of neuropathy (54 %) as compared to metformin non-users, however the difference was not statistically significant. Ahmed et al. correlated vitamin B12 levels with peripheral neuropathy.[22] It was found that 32.3 % of those with vitamin B12 deficiency had peripheral neuropathy as compared to 36.8 % with normal vitamin B12 levels. Thus, the association was found to be non-significant. It should be noted that the authors used neuropathy total symptom score-6 for clinical assessment of peripheral neuropathy, which could affect the results.

Thus, it appears from the above points that interpreting metformin induced vitamin B12 deficiency, consequently leading to peripheral neuropathy requires caution. Reports of neuroprotective effect of metformin makes matters more complicated. It is also possible that the neuroprotective impact of metformin may be masked or overwhelmed by vitamin B12 deficiency. Basic biomedical research involving laboratory investigations are needed to understand the dynamic relationship of metformin, vitamin B12 and development of neuropathy. This should also take into consideration duration of diabetes, glycaemic control as measured by HbA1c and dose and duration of metformin. Racial and ethnic variations have also been studies recently.[23]

Limitations of Our Study

There are a few limitations of this study. Compliance with metformin treatment was not assessed during the study, and was assumed based on the history provided. Secondly, electro-diagnostic tests for neuropathy were not conducted for our participants. Third, patients were not asked about the medications not related to diabetes, higher intake of proton pump inhibitors could lead to vitamin B12 deficiency. Last, the glycaemic control of the patients was not assessed, which can affect the severity of peripheral neuropathy and affect the severity of symptoms.

CONCLUSIONS

Our results show that patients on metformin for diabetes mellitus experience higher neuropathic symptoms as compared to those not taking metformin. However, as discussed above, the literature is divided about the role of metformin in worsening diabetic neuropathy. Although, vitamin B12 deficiency is widely reported, this resulting in development or worsening of diabetic neuropathy is still debated. Thus, we recommend future studies with a larger sample size of diabetic patients to investigate this issue in greater detail. Also, there are many conditions in which metformin is medically indicated, like polycystic ovarian disease. Future studies are needed to assess the impact of metformin in those patients as well.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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