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Original Research Article

Vitamin B Supplementation for Diabetic Peripheral Neuropathy

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ABSTRACT

Background
Vitamin B12 deficiency has been associated with significant neurological pathology, especially peripheral neuropathy. Combination medicines and pure methylcobalamin seems to improve symptoms rather than electrophysiologic outcomes in individuals with diabetic peripheral neuropathy. The aim of present study was to assess the effect of Vitamin B supplementation for diabetic peripheral neuropathy.

Methods
The present cross-sectional study was conducted at department of general medicine among 100 patients with diabetic peripheral neuropathy who visited during the study period of one year. Patients were divided into two groups (group B and group P). The entire neuropathy and laboratory test were done. With IBM SPSS v25.0, statistical analyses were carried out.

Results
There were no significant differences between the group B and group P regarding demographics, anthropometric and laboratory measurements. Vitamin B12 levels significantly increased in the group B from 237.8±70.3 pmol/L at baseline to 775.8±234.2 pmol/L at follow-up. In the group B, there was a significant improvement in the vibration perception threshold (VPT), MNSIQ, pain score, quality of life (QoL), sural nerve conduction velocity (SNCV), sural nerve action potential (amplitude) (SNAP), and electrochemical skin conductance in feet (ESCF) during the follow-up ($p = 0.001$, $p = 0.003$, $p = 0.0001$, $p = 0.0001$, and $p = 0.013$, respectively).

Conclusion
Patients with DN who received an oral methylcobalamin treatment for a whole year had improvements in their QoL, pain score, sudomotor function, plasma B12 levels, and all neurorophysiological markers; however, CARTS and MNSIE did not show any improvement.

Keywords – autonomic neuropathy, diabetes mellitus, metformin, neuropathy, peripheral neuropathy, vitamin B12.

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INTRODUCTION

One of the most prevalent microvascular consequences of diabetes is diabetic neuropathy (DN). Peripheral (DPN), autonomic (DAN; cardiovascular autonomic neuropathy (CAN) is the most frequently diagnosed kind), and painful (PDN) are its most common manifestations. Nerve damage affects 10–18% of patients when they are diagnosed with diabetes, however neuropathy can also happen in those with prediabetes [1]. Up to 50% of patients may develop peripheral/distal symmetric polyneuropathy [2], which can result in sensory complaints [3], foot infections, ulcers, Charcot arthropathy, fractures, and amputations . When type 2 diabetes (DM2) is first diagnosed, the prevalence of CAN is approximately 7%. It then rises by 4.6% to 6% year as diabetes duration grows [4,5], and it can affect up to 65% of persons with diabetes for longer [6]. CAN is frequently underdiagnosed, despite the fact that it is thought to be an independent predictor of cardiovascular mortality [7]. Neuropathic pain and symptoms, including burning, "pins and needles," excruciating cold or hot sensations, "electric shock"-like pain, numbness and dead feeling in the legs and feet, and contact pain (allodynia), affect one-third of patients with PDN [8]. These symptoms have a significant negative influence on quality of life.

Deficits in vitamin B12, also called cobalamin, lead to methylcobalamin deficiency, which has been linked to severe neurological disorders, including peripheral neuropathy.[9,10] Additionally, it is linked to the development of diabetic neuropathy. Metformin and other antidiabetic medications may be the cause of vitamin B12 insufficiency in people with DPN.[11,12]

Vitamin B12 and its coenzymes have been used to relieve pain for a long time. Vitamin B12 is classified as an analgesic in several nations. There have been suggestions that vitamin B12 may improve noradrenaline and 5-hydroxytryptamine's availability and efficacy in the descending inhibitory nociceptive system.[13] Morphological and histological data in animal models have also demonstrated that methylcobalamin given over an extended period of time stimulates myelin production and regeneration.[14]

Various studies conducted in the past showed that treatment with both combination medicines and pure methylcobalamin seems to improve symptoms rather than electrophysiologic outcomes in individuals with diabetic neuropathy. The most significant outcome measure of these studies were the reduction of symptoms, which was followed by objective measurements such nerve conduction and vibration perception threshold (VPT).[15]

Hence the aim of present study was to assess the effect of Vitamin B supplementation for diabetic peripheral neuropathy.

MATERIAL AND METHODS

The present cross-sectional study was conducted at department of general medicine among patients with diabetic peripheral neuropathy who visited during the study period of one year. Ethical permission was taken from the institutional ethical committee before commencement of study. Patients were asked to sign an informed consent form after explaining them the complete procedure.

After consecutive sampling total of 100 patients with diabetic peripheral neuropathy were selected on the basis of following inclusion and exclusion criteria.

Inclusion criteria

1. Patients with age above 18 years and diagnosed with diabetes mellitus.
2. Patients having a good glycemic control.

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3. Patients taking medicine (metformin) as a part of their treatment for at least 4 years.
4. Patients having low vitamin B12 levels.

Exclusion criteria

1. Patients with pernicious anemia, alcoholism, gastrectomy, gastric bypass surgery, pancreatic insufficiency, malabsorption syndromes, chronic giardiasis, acute infection or cardiovascular event in the last 6 months.
2. Patients who had surgery involving the small intestine, or HIV infection.
3. Patients with an estimated glomerular filtration rate (e-GFR) <50 mL/min/1.73 m^2 .
4. Patients taking multivitamins or B12 supplements in the last 12 months.

Patients were divided into two groups i.e. group B (who received vitamin B12 supplementation- 1000 µg of methylcobalamin) and group P (who received placebo). The allocation and randomization of participants in the two groups were performed by a computerized random sequence of numbers.

The following test will be done at baseline and at the end of study for detecting cardiovascular autonomic reflex and neuropathy- Michigan Neuropathy Screening Instrument Questionnaire (MNSIQ); Michigan Neuropathy Screening Instrument Examination (MNSIE); Diabetes Quality of Life Questionnaire (DQoL); sural nerve action potential (amplitude) (SNAP); sural sensory nerve conduction velocity (SNCV); vibration perception threshold (VPT); mean circular resultant (MCR); postural index (PI); postural hypotension; Pain; electrochemical skin conductance in feet (ESCF) and electrochemical skin conductance in hands (ESCH).

Vitamin B12 level was measured at baseline and at the end of the study. All other biochemical parameters (blood count, lipids, lipoproteins, etc.) were measured.

With IBM SPSS v25.0, statistical analyses were carried out. The continuous variables were all represented as mean ± standard deviation and had a normal distribution. The independent samples two-tailed t-test was used to compare the baseline differences in parameters between the two groups. An analysis of differences in variables between each group's baseline and follow-up was conducted using paired samples t-tests. Adjusted for HbA1c and antiglycemic medication, multiple general linear regression (ANCOVA) was performed to assess the mean difference of the change between two groups. A value of $p < 0.05$ was deemed statistically significant.

RESULTS

In the present study the number of male patients were lower as compared to female patients in both the groups (20/30;22/28) , mean age of patients in both the groups was above 60 years. The mean duration of diabetes was 14.0±4.7 years in group B and 12.1±5.8 years in group P. There were no significant differences between the group B and group P regarding demographics and anthropometric measurements as shown in table 1.

Table 1: Demographic and clinical characteristics of patients

Variable	Group B (mean ± SD/ frequency)	Group P (mean ± SD/ frequency)	P value
Gender (m/f)	20/30	22/28	0.456
Age (yr)	65.0±8.3	62.3±7.9	0.321

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Body weight (kg)	88.7±17.8	91.6±20.9	0.569
Diabetes duration (yr)	14.0±4.7	12.1±5.8	0.453
Metformin and other OAD	25	27	0.168
Smoking	8	13	0.669
Cardiovascular disease	13	14	0.654
Dyslipidemia	30	32	0.213
Hypertension	35	33	0.498
Metformin therapy	13.8±9.6	11.3±5.9	0.850

All the basic laboratory test were done and it was found that there were no significant differences between the two groups regarding laboratory measurements as shown in table 2.

Table 2: Laboratory measurements at baseline in both groups

Variable	Group B (mean ± SD)	Group P (mean ± SD)	P value
HbA1c (%)	7.23±0.8	6.93±0.9	0.832
HbA1c (mmol/L)	52.6±8.2	51.8±8.3	0.845
Vitamin B12 (pmol/L)	237.8±70.3	238.6±83.8	0.794
WBC (10^3/ul)	7.65±1.4	8.19±0.9	0.245
Haemoglobin (g/dL)	14.52±1.2	14.67±2.1	0.229
Mean Coposcular volume (fL)	89.3±5.9	87.3±4.9	0.394
Platelets (103/µL)	259.2±36.1	284.23±56.1	0.398
Folic acid (ng/mL)	17.3±8.0	26.9±14.5	0.174
Creatinine (mg/dL)	0.98±0.4	0.89±0.1	0.103
Cholesterol (mg/dL)	175.2±44.2	176.4±47.6	0.945
Triglycerides (mg/dL)	162.4±52.1	149.9±10.3	0.324
High Density Lipoprotein (mg/dL)	47.8±2.4	48.9±10.2	0.673
Low Density Lipoprotein (mg/dL)	103.4±46.5	105.2±42.1	0.560

Vitamin B12 levels significantly increased in the group B from 237.8±70.3 pmol/L at baseline to 775.8±234.2 pmol/L at follow-up, but they did not significantly change in the group P. In the group B, there was a significant improvement in the vibration perception threshold (VPT), MNSIQ, pain score, quality of life (QoL), sural nerve conduction velocity (SNCV), sural nerve action potential (amplitude) (SNAP), and electrochemical skin conductance in feet (ESCF) during the follow-up ($p = 0.001$, $p = 0.003$, $p = 0.0001$, $p = 0.0001$, and $p = 0.013$, respectively). However, the indices of CARTS and MNSIE did not significantly improve . Notably, the MCR, MNSIQ, SNCV, SNAP, and pain score all markedly declined in the group P, and none of the examined measures improved as shown in table 3.

Table 3 Changes in indices from baseline to end of the study in both groups.

Variable	Group B			Group P		
	Baseline	1 year	P value	Baseline	1 year	P value
HbA1c	7.23±0.8	7.21±0.8	0.234	6.93±0.9	6.89±0.9	0.313
HbA1c	52.6±8.2	51.23±7.8	0.232	51.8±8.3	50.8±6.7	0.315

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B12	237.8±70.3	775.8±234.2	0.001	238.6±83.8	243.7±101.4	0.337
MNSIQ	5.9±2.3	5.4±2.0	0.003	5.98±2.0	6.15±1.9	0.018
MNSIE	3.76±10.2	3.79±2.1	0.665	3.9±2.1	3.7±1.5	0.619
DQOL	40.2±10.1	39.4±10.3	0.001	41.2±12.1	41.2±12.1	0.934
SNAP	5.5±4.1	7.8±4.5	0.002	5.3±2.1	4.9±3	0.001
SNCV	27.3±22.5	30.34±22.1	0.003	35.3±23.1	33.7±22.1	0.043
VPT	32.3±13.1	22.4±12.2	0.001	27.8±12.1	24.3±12.4	0.254
MCR	10.8±9.6	13.4±20.4	0.408	17.3±23	8.7±11.7	0.024
Valsalva	1.56±0.20	1.67±0.25	0.987	1.51±0.2	1.60±0.25	0.876
PI	4.3±3.5	4.5±5.3	0.894	3.0±2.1	3.4±9.7	0.845
PO	8.9±12.1	5.5±9.8	0.113	7.5±8.6	7.9±9	0.678
Pain score	19.8±8.7	18.9±8	0.002	20.4±8.6	21.3±7.8	0.001
ESCF	73.4±11.1	75.9±9.9	0.013	73.98±11.3	72.24±10.4	0.146
ESCH	70.89±13.1	73.21±13.4	0.265	68.7±10	68.8±8.2	0.675

DISCUSSION

At the moment, anticonvulsants, tricyclic antidepressants, and opioid or opioid-like analgesics are used to treat DPN by reducing pain symptoms. Regretfully, there isn't any proof that these medications alter the fundamental pathogenesis of peripheral neuropathy.[16] Research has demonstrated that in streptozotocin-diabetic rats, high dosages of methylcobalamin enhanced neuronal conduction.[17] In experimental acrylamide neuropathy, large methylcobalamin dosages were linked to a marked increase in the rate of motor nerve fiber regeneration, providing further evidence of this.[18] This could be the method by which methylcobalamin alters and addresses the pathophysiology that underlies peripheral neuropathy.

The present study was conducted at department of medicine among 100 patient of diabetic neuropathy. Patients were divided into two groups on the basis of dose of vitamin B given or not during the study. The tests were conducted at the end of one year to compare with baseline values.

From the results of the study it was found that the sole administration of methylcobalamin in a daily dose of 1000 µg in diabetes mellitus patients for a year exerted a beneficial effect on all indices, except for CARTs and MNSIE, of peripheral neuropathy, including neurophysiological parameters, sudomotor function, level of pain, and quality of life. Given that over 95% of the subjects in our study had this "relative" B12 deficit and that B12 delivery had an overall positive effect on DN, it makes sense to advise B12 supplementation for all patients with DN and B12 levels below 400 pmol/L.

According to earlier research, individuals with diabetes who have B12 levels between 150 and 400 pmol/L should be regarded as having a "relative" B12 insufficiency [19]. B12 levels at baseline were either not assessed or stated in a number of published research [20,21], most likely because B12 was administered primarily for its alleged analgesic effect. Baseline B12 levels were normal in previous investigations [22]. Although the results varied, these investigations usually revealed that B12 had no influence on DN [23].

Our results showed that the increase in SNCV was consistent with those of previous research [24]. The results were consistent with the documented effects of methylcobalamin on nerve conduction, neurotransmitter levels, and myelin production and regeneration [25].More significantly, we discovered that somatosensory symptoms including pain and paresthesia improved with B12 treatment. Similar results were observed in other investigations [26] as well

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as in our earlier work [27]. These results indicate the analgesic effect of B12 [28], which may be mediated by increasing noradrenaline and 5-hydroxytryptamine availability and efficacy [29] in the endogenous opioid pathway, a descending inhibitory pain modulation mechanism.

There were certain limitations in our research. Every participant was Caucasian and followed up in a single diabetes facility. Although the sample population's homogeneity was guaranteed, this prevented results from being extrapolated to other populations. We did not assess autoantibodies against glutamic acid decarboxylase, intrinsic factor, or parietal cells because individuals with pernicious anemia had been removed from our population and DM2 had been confirmed in our community. Furthermore, we did not assess the functionality of the nerves in the hands or arms—only the sural nerve. It is often acknowledged that the evaluation of sural nerve function also reflects the function of other nerves. Additionally, we did not assess homocysteine or methylmalonic acid since these tests are expensive, frequently unavailable in diabetic clinics, and not always necessary for diagnosing vitamin B12 deficiency.

CONCLUSION

This study concluded that raising B12 levels in DN patients using an oral dispersible tablet containing 1000 µg methylcobalamin for a year improved the patients' neurophysiological parameters, sudomotor function, pain score, and quality of life. However, there are still unanswered questions that need to be addressed in future research, such as whether vitamin B12 supplementation has any effect on established DN in the absence of B12 deficiency, whether B12 administration has positive effects on DN prevention or the prevention of subclinical DN deterioration, and which types of DN are most improved by B12 supplementation.

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