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Research Article

Randomized Controlled Trial of the Antinociceptive Effect of Menaquinone-7 (MK-7) in Patients with Peripheral Neuropathy

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Abstract

A randomized, placebo-controlled double-blind study was conducted to evaluate the efficacy and safety of menaquinone-7 (MK-7) in comparison to placebo in patients with peripheral neuropathy due to Type 2 diabetes mellitus (DN) or vitamin B12 deficiency (BN). A 100 µg capsule of MK-7 or identical placebo capsule was given twice daily for 8 weeks to 60 ambulatory patients of both genders to evaluate symptoms of peripheral neuropathy in DN and BN patients. The patients were followed for an additional 4 weeks (total of 12 weeks) and the intensity of the symptoms was self-assessed using a pain Visual Analog Scale (VAS).

There was a statistically significant decrease in the pain VAS score in DN and BN patients receiving MK-7 supplementation vs the corresponding placebo groups. The VAS pain score at baseline was on average approximately 8 to 9 out of 10. It was reduced to an average score of about 2 by week 12 in the DN and BN groups supplemented with MK-7 vs scores greater than 8 by week 12 in the placebo groups. The MK-7 was well-tolerated without subjective and objective adverse effects reported during the 8-week therapy and during the additional 4 weeks of follow-up.

Keywords: *MK-7; Menaquinone-7; Type 2 Diabetes Mellitus; Vitamin B12 Deficiency; Peripheral Neuropathy; VAS Score*

Introduction

Diabetes mellitus peripheral neuropathy (DN) is diagnosed in approximately one-third of patients with diabetes, predominantly Type 2 diabetes mellitus, affecting function and structure of the peripheral nerves in those patients [1-5]. In non-diabetic patients, vitamin B12 deficiency peripheral neuropathy (BN) is caused by vitamin B12-deficient diets (vegetarian and vegan diets), and as a result of autoimmune gastritis, infection with *Helicobacter pylori*, and gastrointestinal disease resulting in dysbacteriosis [6-9]. Vitamin B12 deficiency is highly prevalent in diabetic patients, and an inverse correlation has been shown to exist between diabetic neuropathy and plasma levels of vitamin B12 [10].

Currently, management of DN and BN is limited to: symptomatic pain relief; body mass index control; glycemic, lipid, and blood pressure control; and vitamin B12 supplementation with monitoring of B12 blood levels [2,11-14]. These treatment modalities are largely

ineffective, and peripheral neuropathy continues to be a therapeutic challenge and one of the causes of musculoskeletal pain, morbidity, and disability [14-16].

A recent clinical observation has indicated that MK-7, also known as vitamin K2-7, at a dose of 100 µg twice a day for several weeks may be safe and effective in the management of peripheral neuropathy [17,18]. Vitamin K, occurs in nature as phylloquinone (vitamin K1) and menaquinone (vitamin K2), with its primary function as a calcium chaperone, controlling a family of at least 18 calcium and vitamin K-dependent proteins, sometimes referred to as a multitasking vitamin [19].

The present study was a 12-week randomized, placebo-controlled, double-blind trial employing vitamin K2 as the long-chain menaquinone-7 (MK-7), in managing peripheral neuropathy in patients with clinically diagnosed Type 2 diabetes mellitus (DN) or patients presenting with vitamin B12 deficiency (BN).

Materials and Methods

Study design

The randomized, double-blind, placebo-controlled, 12-week parallel study was conducted to compare tolerability and efficacy of long chain menaquinone-7 (MK-7) in patients with Type 2 diabetes mellitus (DN) or vitamin B12 deficiency (BN) presenting with peripheral neuropathy.

The 4-month study was approved by the Inter System BioMedica Ethics Committee Mumbai, India, dated 25/4/2017. The trial was conducted at Kokan Hospital, Mumbai, India. The study was registered with Clinical Trials Registry-India (CTRI), registered on 28/06/2017 as CTRI/2017/06/008925. CTRI is searchable from the World Health Organization's' (WHO's) International Clinical Trials Registry Platform (ICTRP) (https://www.who.int/clinical-trials-registry-platform) as well as from CTRI (www.ctri.nic.in). The study was conducted in accordance with the International Conference on Harmonization of Good Clinical Practice (ICH-GCP E6) (R2) Consensus Guidelines, ethical principles based on the Declaration of Helsinki, and the applicable regulatory requirements.

Subjects

Seventy patients with clinically confirmed Type 2 diabetes mellitus (DN) or vitamin B12 deficiency (BN) and peripheral neuropathy were considered for the study. A detailed flow chart of the various steps taken in the study from initial patient assessment through data analysis is provided in figure 1.

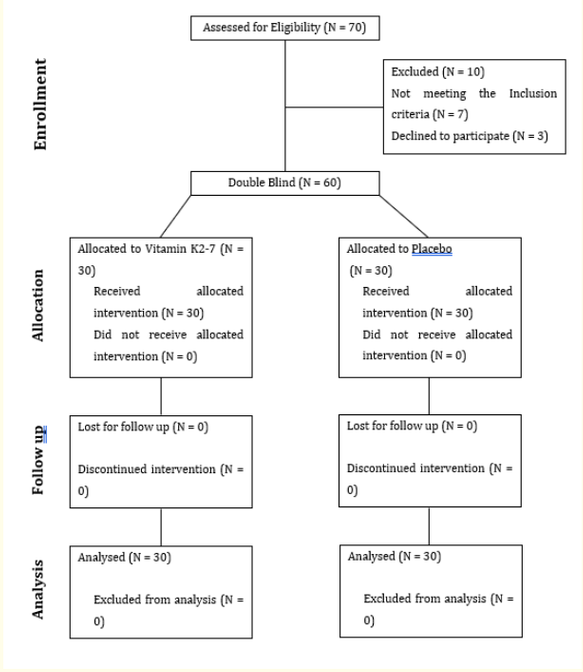


Figure 1: *Flow chart of MK-7 in peripheral neuropathy (population 60 subjects).*

Neuropathy was diagnosed by the principal investigator (PI), a physician, in patients with a history of diabetes or history of stand-alone persistent low serum levels of vitamin B12. Neuropathy was diagnosed based on the presence of symptoms of peripheral neuropathy including decreased sensation, positive neuropathic sensory symptoms e.g., "asleep numbness," prickling or stabbing sensation, burning or aching pain predominantly in the toes, feet, or legs, accompanied by symmetric decrease of distal sensation or decreased/absent ankle reflexes. On physical examination, a symmetrical stocking like distribution of sensory abnormalities more commonly in both lower limbs and in more severe cases in upper limbs were noted.

Inclusion criteria:

1. Male and female subjects 18 to 65 years old suffering from DN or BN.
2. Symptomatic neuropathy score > 4 on the Visual Analogue Scale (VAS).
3. Willing to sign the informed consent.

Exclusion criteria:

1. Suffering from systemic illness other than Type 2 diabetes mellitus or vitamin B12 deficiency.
2. Patients who are on corticosteroids.
3. Patients who are on coumarin analogues.
4. Patients who are on quinine hydrochloride.
5. Patients on oral contraceptives.
6. Pregnant or nursing mothers.
7. Participation in clinical trials evaluating investigational pharmaceuticals or biologics within 3 months, or devices within 30 days of admission to the study.
8. History of alcohol and/or substance abuse within one year prior to admission to the study.

Seventy patients with an initial diagnosis of Type 2 diabetes mellitus (DN) and/or vitamin B12 deficiency (BN) suffering from peripheral neuropathy, were seen by the principal investigator (PI) in the Department of Medicine outpatient clinic, Kokan Hospital, Mumbai, India. Upon anamnesis and physical examination, the diagnosis was confirmed and the eligibility criteria based on the Protocol approved by the Ethics Committee was reviewed with each patient (Figure 1). Of the 70 subjects, 7 patients did not meet the admission criteria and 3 subject declined participation in the study. The informed consent approved by the Ethics Committee was reviewed with the individual patients, explaining the printed image of Visual Analog Scale (VAS). Each subject was asked to point out the number from 0 to 10 (0 - no pain, 10 - unbearable pain), based on the severity of his/her symptoms of peripheral neuropathy. Based on a severity score above 4, 60 patients (34 men and 26 women), were eligible for the study and the informed consent was signed by each individual patient and the PI (Figure 1). The disease data of the admitted patients and conventional treatments received before and after entering the study are detailed in the below table.

No. of Subjects	Average Duration	Average PN# duration	Treatment
Diabetes mellitus (Vitamin K2-7 group)			
9	2 - 3 years	7 - 8 months	Metformin 500 mg
5	3 - 4 years	10 - 11 months	Teneligliptin (20 mg) + Metformin (500 mg)
2	2 - 3	9 - 11 months	Metformin (500 mg) + Vildagliptin (50 mg)
Diabetes mellitus (Placebo group)			
7	3 - 4 years	7 - 8 months	Metformin 500 mg
4	2 - 3 years	4 - 6 months	Teneligliptin (20 mg) + Metformin (500 mg)
5	3 - 5 years	10 - 11 months	Metformin (500 mg) + Vildagliptin (50 mg)
Vitamin B12 deficiency (Vitamin K2-7 group)			
2	6 - 7 months	2 - 3 months	Becosules-Z
4	7 - 8 months	2 - 4 months	Cobadex-Z
6	6 - 8 months	3 - 4 months	Neurobion forte
2	7 - 8 months	1 - 3 months	Neurobion Plus
Vitamin B12 deficiency (Placebo group)			
5	7 - 8 months	2-3 months	Becosules-Z
2	8 - 9 months	3-4 months	Cobadex-Z
3	7 - 8 months	2-3 months	Neurobion forte
4	12 - 13 months	3-5 months	Neurobion Plus

Table: *Diabetes and B12 deficiency neuropathy patients receiving conventional therapy.*

#: Peripheral Neuropathy.

Becosules-Z contains Calcium pantothenate 50 mg, Vitamin B12 15 mcg, Folic acid 1.5 mg, Thiamine mononitrate 10 mg, Riboflavin 10 mg, Pyridoxine hydrochloride 3 mg, Niacinamide 100 mg, Ascorbic acid 150 mg, Biotin 100 mcg and Elemental zinc 41.4 mg.

Cobadex-Z contains Zinc Sulphate Monohydrate 61.8 mg, Vitamin B1 10 mg, Vitamin B2 10 mg, Nicotinamide 100 mg, Vitamin B6 3 mg, Calcium pantothenate 50 mg, Folic Acid 1.5 mg, Vitamin B12 15 mcg and Vitamin C1 50 mg.

Neurobion Forte contains Vitamin B1 (Thiamine) 10 mg, Vitamin B2 (Riboflavin), 10 mg; Vitamin B3 (Nicotinamide) 45 mg, Vitamin B5 (Calcium pantothenate) 50 mg; Vitamin B6 (Pyridoxine) 3 mg and Vitamin B12 (Cobalamin) 15 mcg.

Neurobion Plus contains Vitamin B12 - 750 mcg, Vitamin B3 - 45 mg and, Vitamin B6 - 1.5 mg.

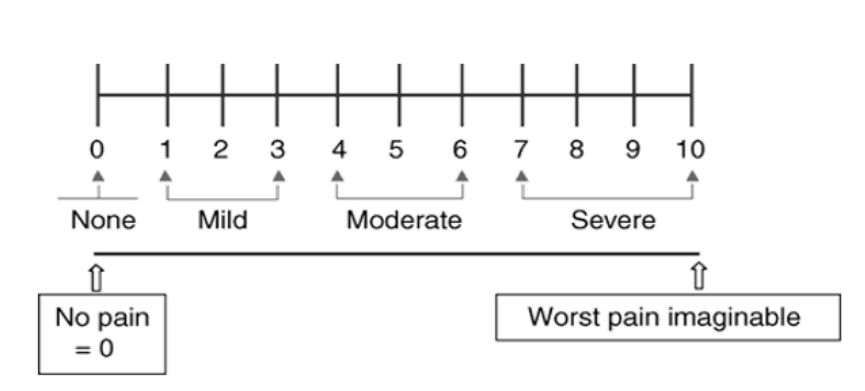
The study procedure

The test substance (MK-7 100 ug per HPMC (Hydroxypropyl Methylcellulose) hard-gel capsule) as well as the identical placebo capsules were manufactured and provided by Synergia Life Sciences Pvt. Ltd., Mumbai, India. Each product was packed 30 capsules per bottle and prepared by the pharmacist in Synergia Life Sciences pharmacy. The pharmacist coded each bottle containing MK-7 or placebo and was therefore the only person in the research team who knew the contents of the bottles.

The patients were randomized by the PI at the outpatient clinic, Kokan Hospital, with a simple numerical randomization method and assigned a Subject Identification within the DN and BN groups. The randomized groups of patients received the coded bottles with study substance and were instructed to take daily one capsule with a breakfast and one capsule with a dinner for 8 weeks.

The patients were examined by the PI at baseline, week 2, week 4, week 8, and week 12. The subjective severity of the symptoms of peripheral neuropathy was assessed with a validated pain VAS scale, as described in the literature and summarized in graphic form below ---- from 0 to 10 score (0 - no pain, 10 - unbearable pain) at baseline and thereafter every second week until week 12 [20].

Visual analog scale (VAS) with gradation of the peripheral neuropathy



Figure

The gradation of peripheral neuropathy pain based on the following criteria:

0 - 10 points Visual Analog Scale (VAS): 0 = Absent, 1 - 3 = Mild, 4 - 6 = Moderate, 7 - 10 = Severe.

Subjective and objective side effects and adverse events were assessed at all study time points. Therapeutic activity was measured by assessing the reduction in the severity of the symptoms of peripheral neuropathy, including: pain, tingling, pricking sensation, burning sensation, and cramps along with a physical weakness and fatigue. These signs and symptoms were compared to baseline and the placebo-receiving study group at the end of the study.

Once the 12-week study was completed, the codes of MK-7 and placebo receiving subjects were decoded by the pharmacist and handed over to the investigators for evaluation and statistical analysis of the results.

Determination of vitamin B12

Venous blood samples were collected on an empty stomach. The samples were centrifuged within one hour of collection and the sera were stored at -40°C until analyzed. Serum vitamin B12 was measured by the chemiluminescence, competitive immunoassay method using a commercial automatic electrochemical immuno-analyzer (Roche E170) and electrochemiluminescence immunoassay (ECLIA) kit (Immulite 2000-BIODPC).

Organ function monitoring

Blood chemical analyses included blood morphology, erythrocyte sedimentation rate (ESR), vitamin B-12, homocysteine, glycosylated hemoglobin, fasting and post-prandial plasma glucose, prothrombin time-international normalized ratio (PT-INR), liver function tests, and renal function tests at baseline, week 4, week 8 and week 12. All routine blood parameters were performed at the National Accreditation Board for Testing and Calibration Laboratories (NABL) Accredited Laboratory of the study site, Kokan Hospital in Mumbai, India.

Complete blood counts were determined using a PC 210 ERMA Blood Cell Counter. ESR was determined by the Wintrobe method. Liver function test and renal function test were assessed by standard biochemical blood chemistry methods. Prothrombin time was done by the coagulation method. Fasting and post-prandial plasma glucose was estimated by the glucose oxidase-peroxidase (GOD–POD) enzymatic method. Glycosylated hemoglobin was measured by the boronate affinity test with a Nycocard device. For Homocysteine was determined by RIA/ELISA/CLIA methods.

Intervention drug, dosage and compliance

The MK-7 (100 µg) and the identical placebo were manufactured by Synergia Life Sciences Pvt. Ltd., in the form of hard-gel capsules packaged 30 capsules per bottle. The capsules were supplied to patients at the time of the enrollment and every 15 days thereafter during the course of the study. Patients ingested 100 µg MK-7 capsule or the placebo twice a day, every morning and evening after eating, for 8 weeks. The supplement compliance was assessed by counting the capsules in the bottle brought back at the follow-up visits.

Statistical analysis

Statistical analysis and significance involving groups with small sample size were performed as described by de Winter [21]. Analyzed data of 60 patients used the unpaired t-test method. This method determines the significance of two sets of data. Analyses were made between various time points within a treatment group and between placebo and treated at each time point.

For Diabetes group: A sample size of 16 in each group (treatment and placebo group) had a 99% power to detect a difference between means of 0.94 with a significance level (alpha) of 0.05 (two-tailed).

For Vitamin B12 deficiency group: A sample size of 14 in each group (treatment and placebo group) had a 99% power to detect a difference between means of 1.18 with a significance level (alpha) of 0.05 (two-tailed).

Results

Of the 32 patients with Type 2 diabetes mellitus (DN) and 28 patients with vitamin B12 deficiency (BN) and peripheral neuropathy allocated to the study, all subjects completed the allocated intervention, none discontinued intervention, none was lost to follow-up, and none was excluded from the analysis of the results (Figure 1 and table 1).

	Type 2 diabetes mellitus group				Vitamin B12 deficiency group			
	MK-7		Placebo		MK-7		Placebo	
	Male	Female	Male	Female	Male	Female	Male	Female
N	12	4	9	7	7	7	6	8
Age (yrs.)	40.08 ± 5.04	42.5 ± 3.70	41.33 ± 7.19	41.29 ± 7.45	45.29 ± 6.07	45.43 ± 9.69	41.50 ± 3.67	44.25 ± 7.36

Table 1: *Demographics of the patients in each of the experimental groups.*
Values expressed as Mean ± SD; SD: Standard Deviation.

The average baseline VAS score for DN and BN patients ranged from 8 to 9, indicating a severe, self-assessed pain including tingling, prickling, and burning sensation, combined with muscular weakness and numbness accompanied by general fatigue. The BN group also experienced frequent muscle cramps (Table 2 and 3).

By the end of week 4 of the study, the VAS score in DN and BN patients receiving MK-7 supplement had improved to an approximate range from 6 to 7 with a reduction in the intensity of the pain symptoms as compared to the placebo groups. Patients receiving MK-7 for four weeks reported better quality of daily life with a reduced feeling of weakness and fatigue and less burning pain in DN, and less intensity of muscle cramps in BN patients (Table 2 and 3).

	Tingling		Pricking sensation		Burning	
	MK-7	Placebo	MK-7	Placebo	MK-7	Placebo
No. of subjects	16	16	16	16	16	16
Baseline	8.63 ± 0.62	8.75 ± 0.68	8.63 ± 0.62	8.75 ± 0.68	8.63 ± 0.62	8.75 ± 0.68
End of week 2	8.31 ± 0.6[a]	8.75 ± 0.68[a]	8.31 ± 0.6[a]	8.75 ± 0.68[a]	8.31 ± 0.6[a]	8.75 ± 0.68[a]
End of week 4	6.44 ± 0.89[b]	8.56 ± 0.51[a]	6.44 ± 0.89[b]	8.56 ± 0.51[a]	6.44 ± 0.89[b]	8.56 ± 0.51[a]
End of week 8	3.88 ± 0.96[c]	8.38 ± 0.5[a]	3.88 ± 0.96[c]	8.38 ± 0.5[a]	3.88 ± 0.96[c]	8.38 ± 0.5[a]
End of week 12	1.5 ± 0.63[d]	8.25 ± 0.58[a]	1.5 ± 0.63[d]	8.25 ± 0.58[a]	1.5 ± 0.63[d]	8.25 ± 0.58[a]

Table 2: *VAS scores in type 2 diabetes mellitus patients receiving vitamin K (MK-7) or placebo. Values are expressed as mean ± SD (Standard Deviation). Values within columns as well as with respect to the corresponding placebo group with non-identical superscript letters are statistically significant (p < 0.05).*

By the end of week 8, the VAS scores of patients with DN and BN supplementing with MK-7 had improved to an approximate range from 3 to 4. The tingling, prickling sensation and numbness had reduced along with a decrease in the muscular weakness and feeling of fatigue. Cramps and burning pain were occasional and decreased in intensity (Table 2 and 3).

By the end of week 12, 4 weeks after discontinuing MK-7 and placebo supplements, the VAS score of patients with DN and BN previously on the vitamin supplement held at an average range from 1 to 2. The VAS score from baseline to 12 weeks in the DN and BN patients receiving placebo consistently ranged from 8 to 9 at all testing points. Patients receiving placebo were not feeling better with persistent weakness and fatigue, and unrelenting intensity of cramps in vitamin B12 deficient patients and burning pain sensation in DN patients (Table 2 and 3).

	Tingling		Pricking sensation		Cramps	
	MK-7	Placebo	MK-7	Placebo	MK-7	Placebo
No. of subjects	14	14	14	14	14	14
Baseline	8.71 ± 0.73	8.57 ± 0.51	8.71 ± 0.73	8.57 ± 0.51	8.71 ± 0.73	8.57 ± 0.51
End of week 2	8.64 ± 0.74[a]	8.50 ± 0.52[a]	8.64 ± 0.74[a]	8.50 ± 0.52[a]	8.64 ± 0.74[a]	8.50 ± 0.52[a]
End of week 4	6.21 ± 0.89[b]	8.29 ± 0.73[a]	6.21 ± 0.89[b]	8.29 ± 0.73[a]	6.21 ± 0.89[b]	8.29 ± 0.73[a]
End of week 8	3.86 ± 1.03[c]	8.29 ± 0.73[a]	3.86 ± 1.03[c]	8.29 ± 0.73[a]	3.86 ± 1.03[c]	8.29 ± 0.73[a]
End of week 12	1.64 ± 0.93[d]	8.50 ± 0.52[a]	1.64 ± 0.93[d]	8.50 ± 0.52[a]	1.64 ± 0.93[d]	8.50 ± 0.52[a]

Table 3: *VAS scores in vitamin B12 deficiency patients receiving vitamin K (MK-7) or placebo. Values are expressed as mean ± SD (Standard Deviation). Values within columns as well as with respect to the corresponding placebo group with non-identical superscript letters are statistically significant (p < 0.05).*

Blood chemistries and hematology and organ function tests were performed at baseline, week 4, week 8, and week 12. Glycosylated hemoglobin levels (normal 4 - 6%) in patients with DN receiving placebo and MK-7 were elevated throughout the study with no effects of

MK-7 supplementation. In patients with BN, glycosylated hemoglobin levels remained within the normal range from baseline to week 12. Fasting (normal 60 - 100 pg/dl) and postprandial (> 160 pg/dL) glucose in DN patients was elevated throughout the study with no effects of MK-7 supplementation. Blood glucose levels in the BN group remained within the normal range throughout the study (data not shown).

The vitamin B12 levels (normal 245 - 900 pg/mL) were within the normal range at baseline and throughout the 12-week study in DN placebo and MK-7 supplemented patients and below the normal values in BN patients receiving placebo or MK-7 (data not shown).

The mean corpuscular volume (MCV) values in patients with B12 deficiency and peripheral neuropathy were within normal upper limits throughout the 12-week study and not affected by vitamin MK-7 supplementation. The MCV values in DN patients also remained within normal limits throughout the study (data not shown). Based on MCV values and normal hematological parameters, the BN and DN patients did not present with megaloblastic anemia at the time of accruement to the study and during its duration.

The additional blood studies, including blood morphology, ESR, homocysteine, PT-INR, liver function tests, and renal function tests, were conducted at baseline, week 4, week 8, and week 12, and were within normal limits throughout the study in all study patients (data not shown).

Tolerability and safety

The MK-7 as well as matching placebo capsules were well tolerated by all patients during the 8 weeks of administration. No side effects or subjective and objective adverse events were reported during the period of therapy and follow-up in all 60 patients.

Compliance

Monitoring the capsule intake during the eight weeks of the trial indicated that the intake was regular by the patients. Capsule consumption was monitored by counting the number of capsules remaining in the bottle at the end of 15 days from the date of dispensing the bottle in each phase of the study.

Discussion and Conclusion

This randomized, placebo-controlled double-blind study provides evidence linking the administration of MK-7 with the improvement in the debilitating pain, cramps, and symptoms of peripheral neuropathy in diabetes Type 2 and vitamin B12 deficiency---two distinct clinical conditions linked by symptomatology and possibly underlying pathology [10].

The intervention with the long-chain MK-7 in the peripheral neuropathy patients may involve vitamin K in its calcium chaperone multitasking role, carboxylating and activating a family of proteins with the glutamic acid residues which maintains the cardiovascular, immune, metabolic, neuro-muscular, and bone-building functions [19].

One of the emerging possibilities is the peripheral neuropathy as an inflammatory autoimmune condition that damages the myelin sheet of peripheral nerves with vitamin K operating through the carboxylation of growth arrest–specific gene 6 (GAS6) protein to stimulate oligodendrocytes and myelin sheet repair [22-25].

Another vitamin K-dependent protein, matrix Gla protein (MGP), may alleviate neuropathy by improving cardiovascular and endothelial functions and oxygenation of peripheral nerves [19,26,27]. The high-circulating concentrations of uncarboxylated and inactive MGP (ucMGP) have been shown to correlate positively with cardiovascular and endothelial dysfunction, and supplemental MK-7 has been shown to reduce ucMGP levels in a cohort of mixed gender adults [27].

The MK-7 may also improve peripheral neuropathy, preventing Type 2 diabetes and alleviating its clinical course by carboxylation and activation of osteocalcin, a hormone which increases insulin sensitivity in humans [28,29].

In summary, the results indicate a significant potential benefit of MK-7 for the management of neuropathic pain and provides a framework for conducting a larger randomized control trial.

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Disclosures

DSM and SSJ are in the management of Synergia Life Sciences. MD is the Principal Investigator. RV is consultant in endocrinology. VB serves on an advisory board of Synergia Life Sciences Pvt. Ltd. SJS has no potential conflicts to disclose.

Data Sharing

Data described in the article, code book, and analytic code will be made available upon request.

Bibliography

1. Martyn CN and Hughes RA. "Epidemiology of peripheral neuropathy". *Journal of Neurology, Neurosurgery, and Psychiatry* 62.4 (1997): 310-318.

2. Hilton TN., *et al*. "Excessive adipose tissue infiltration in skeletal muscles in individuals with obesity, diabetes mellitus, and peripheral neuropathy: Association with performance and function". *Physical Therapy* 88.11 (2008): 1336-1344.

3. Trivedi S., *et al*. "Epidemiology of peripheral neuropathy: An Indian perspective". *Annals of Indian Academy of Neurology* 20.3 (2017): 173-184.

4. Gill HK., *et al*. "A prospective study of prevalence and association of peripheral neuropathy in Indian patients with newly diagnosed type 2 diabetes mellitus". *The Journal of Postgraduate Medicine* 60.3 (2017): 270-275.

5. Bansal D., *et al*. "Prevalence and risk factors of development of peripheral diabetic neuropathy in Type 2 diabetes mellitus in a tertiary care setting". *Journal of Diabetes Investigation* 5.6 (2014): 714-721.

6. Kumar N. "Neurologic aspects of cobalamin (B12) deficiency". *Handbook of Clinical Neurology* 120 (2014): 915-926.

7. Oosterhuis WP., *et al*. "Diagnostic value of the mean corpuscular volume in the detection of vitamin B12 deficiency". *The Scandinavian Journal of Clinical and Laboratory Investigation* 60 (2000): 9-18.

8. Tanaka H. "Old or new medicine? Vitamin B12 and peripheral nerve neuropathy". *Brain and Nervous* 65.9 (2013): 1077-1082.

9. Franques J and Gazzola S. "Metabolic and nutritional neuropathies: update in diabetes, vitamin B12 and copper deficiency". *Revue Neurologique* 169.12 (2013): 991-996.

10. Alvarez M., *et al*. "Vitamin B12 deficiency and diabetic neuropathy in patients taking metformin: a cross-sectional study". *Endocrine Connections* 8.10 (2019): 1324-1329.

11. Rosenberg CJ and Watson JC. "Treatment of painful diabetic peripheral neuropathy". *Prosthetics and Orthotics International* 39.1 (2015): 17-28.

12. Ong CK., *et al*. "An evidence-based update on nonsteroidal anti-inflammatory drugs". *Clinical Medicine and Research* 5.1 (2007): 19-34.

13. Lakhan SE., *et al*. "Botulinum Toxin-A for Painful Diabetic Neuropathy: A Meta-Analysis". *Pain Medicine* 16.9 (2015): 1773-1780.

14. Boyle J., *et al*. "Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life". *Diabetes Care* 35.12 (2012): 2451-2458.

15. Alleman CJ., *et al*. "Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: A review of the literature". *Diabetes Research and Clinical Practice* 109.2 (2015): 2015-2025.

16. Schreiber AK., *et al*. "Diabetic neuropathic pain: Physiopathology and treatment". *World Journal of Diabetes* 6.3 (2015): 432-444.

17. Kulkarni VK., *et al*. "The effect of vitamin K2-7 in peripheral neuropathy due to vitamin B12 deficiency and/or diabetes mellitus: A preliminary study". *The Indian Practitioner* 66.10 (2013): 625-629.

18. Mehta DS., *et al*. "A novel potential role of vitamin K2-7 in relieving peripheral neuropathy". *Journal of Pharmacology and Pharmacotherapeutics* 9.4 (2018): 180-185.

19. Karamzad N., *et al*. "A systematic review on the mechanisms of vitamin K effects on the complications of diabetes and pre-diabetes". *Biofactors* 46.1 (2020): 21-37.

20. Wewers ME and Lowe NK. "A critical review of visual analogue scales in the measurement of clinical phenomena". *Research in Nursing and Health* 13.4 (1990): 227-236.

21. De Winter JCF. "Using Student's t-test with extremely small sample sizes". *Practical Assessment, Research and Evaluation* 18.10 (2013).

22. Dunnigan SK., *et al*. "Comparison of diabetes patients with "demyelinating" diabetic sensorimotor polyneuropathy to those diagnosed with CIDP". *Brain and Behavior* 3.6 (2013): 656-663.

23. Sharma KR., *et al*. "Diabetic demyelinating polyneuropathy responsive to intravenous immunoglobulin therapy". *Archives of Neurology* 59.5 (2002): 751-757.

24. Sharma KR., *et al*. "Demyelinating neuropathy in diabetes mellitus". *Archives of Neurology* 59.5 (2002): 758-765.

25. Guylaine F. "Vitamin K and the Nervous System: An Overview of its Actions". *Advances in Nutrition* 3 (2012): 204-212.

26. Abbott CA., *et al*. "Explanations for the lower rates of diabetic neuropathy in Indian Asians versus Europeans". *Diabetes Care* 33.6 (2010): 1325-1330.

27. Theuwissen E., *et al*. "Low-dose menaquinone-7 supplementation improved extra-hepatic vitamin K status but had no effect on thrombin generation in healthy subjects". *British Journal of Nutrition* 108 (2012): 1652-1657.

28. Choi HJ., *et al*. "Vitamin K2 Supplementation Improves Insulin Sensitivity via Osteocalcin Metabolism: A Placebo-Controlled Trial". *Diabetes Care* 34.9 (2011): e147.

29. Beulens J., *et al*. "Dietary Phylloquinone and Menaquinones Intakes and Risk of Type 2 Diabetes". *Diabetes Care* 33.8 (2010): 1699-1705.

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