Synergistic Effects of Vitamin D and Mindfulness Training in Pain Severity, Pain-Related Disability and Neuropathy-Specific Quality of Life Dimensions in Painful Diabetic Neuropathy: A Randomized Clinical Trial with Placebo-controlled

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Abstract

Background: This study aimed to examining Synergistic effect of Vitamin D (VD) Supplement and mindfulness on neuropathic pain severity, Pain-Related Disability and Neuropathy-Specific Quality of Life dimensions in painful diabetic neuropathy.

Methods: In this randomized controlled trial, totally 225 patients with painful diabetic neuropathy were randomly allocated to five groups: (1) mindfulness and placebo, (2) placebo, (3) mindfulness, (4) VD, and (5) mindfulness and VD. Mindfulness training includes twelves sessions and VD patients received a daily four thousand IU oral dosage (four capsules) with 28,000 IU vitamin D weekly for 12 weeks. Laboratory analyses, Sun exposure time, Vitamin D intake, BMI and Physical activity measured in pre-test and posttest. Pain-Related Disability measured with The Pain Disability Index (PDI). For other outcome variables Neuropathy Specific Quality of Life questionnaire and Neuropathic pain severity scale was utilized.

Results: In baseline, measures were not different among the groups. At the end-of-treatment, for outcome variables results showed improvement in all groups except the “placebo” group. About other groups, there was not any difference between VD and mindfulness groups (in and not combined with placebo). However, “VD + mindfulness” has a greater improvement rather than VD and mindfulness groups ($P<0.05$). Moreover, both protocols have no significant effects on, FBS, BMI and energy intakes ($P>0.05$).

Conclusion: Combining VD and mindfulness can reduce pain severity and pain-related disability, so with these changes patients improve their quality of life.

Background

Today's, more than 500 million type-2 diabetic patients living in all around the world and this prevalence steadily increasing(1). Painful diabetic neuropathy (PDN) with 60% prevalence is the main complication of diabetic patients, specified by feet cramps, burning, numbness and tingling. The major problems in diabetic neuropathy patients are pains severity, and pain related disability. consequently these problems reduce their quality of life (QOL) (2).

For pain relief and improving QOL, there are various advocated treatments. But, the therapeutic efficacy is at best approximately 50% and is restricted due to side effects (3). So, we need novel treatment packages with higher efficacy. Also, as bio-psycho-social nature of pain and related problem, these new treatments must include multi-dimensional effects (2, 3).

Recently, growing evidences shown that adjunctive treatments can play a key role in better outcome in improving diseases and disorders without adding any side effect(4, 5).

one of these adjunctive treatments can be Vitamin D supplement. Vitamin D deficiency is more prevalent in middle east with 40–80% prevalence. vitamin D (VD) insufficiency happened in more than 80% of neuropathic diabetic cases (6). VD or neurotrophic hormone has a neuroprotective effect and enhances sensory neural response and axonogenesis. Results shown that VD can improve QOL and relief pain in neuropathy. But, the effect size of VD on pain are somewhat low and results reported mixed results(7, 8). in fact, pain has bio-

psycho-social aspects and consist of constellation of affective, cognitive and sensory factors, we needs to adding psychological training for better improving these problems(9, 10).

On the other hand, mindfulness shown promising effects on pain reduction and enhance QOL. mindfulness with enhancing on OFC, right anterior insula, sgACC and PFC function can reduce severity experiencing pain. Therefore, short mental practice in mindfulness engages cortico– thalamic–cortical interactions to decrease pain by mechanisms such as reappraisal or inhibitory control to basically “close the gate” on rising nociceptive information (11).results showed mindfulness can reduce pain severity and enhancing QOL in various physical conditions such as migraine (12), Chronic Pelvic Pain (13) and IBS(14). For neuropathic pain, results are mixed. In fact, some studies showed efficacy of mindfulness on neuropathic pain (15) and others showed inefficacy (16). In fact, mindfulness can have implemented as a part of the comprehensive pain treatment program, just like VD.

As both VD and mindfulness are effective on pain reduction and QOL, but there is not any RCT study about synergistic effects of combined of VD and mindfulness. So, this study aims to examination of Synergistic effects of Vitamin D and mindfulness training for neuropathic pain symptoms, pain-related disability and QOL in PDN. Also we try to eliminate the limitations of previous studies such as lack of placebo groups and small sample size (2).

Methods

Study design and participants

This randomized placebo-controlled trial was conducted between September 2019 and January 2020, in the Beheshti hospital (section of Endocrinology) in Kermanshah, Iran. participants include all neuropathic diabetic patients (type 2 diabetes Mellitus) with VD deficiency referred to Beheshti hospital, Kermanshah, Iran, between 1 September 2019 and 18 October 2019. Type 2 diabetes mellitus and neuropathy were diagnosed by a group include endocrinologist and neurologist physicians.

Inclusion and Exclusion criteria

Inclusion criteria include (1) lack of major co-morbid disease such as coronary heart disease or psychotic disorder (2) age of 20 to 70 years, (3) willingness to participate to study and (4) VD insufficiency or deficiency [between 10 (ng/mL) to 30 (ng/mL) serum vitamin D]. Exclusion criteria include (1) existence of psychiatric or neurological diseases, (2) took VD or any multi-vitamins during the last three months, (3) using any substance and drinking alcohol, (4) pregnancy, and (5) more than one session absent in mindfulness groups.

Randomization and blinding

Participants were randomly allocated into groups using a random table. All patients were blinded to receive VD or placebo groups. Also as these treatments are adjunctive treatments, so, they received usual treatment based on neurologist prescribes.

Sample size

Concerning 0.2 as type 2 error (with 80%power) and 0.05 as type 1 error; and regarding pervious research, 35 participants are required for each group. toward covering potential dropouts, the sample size increased 25% and reaches to 45 subjects for each group (17).

Grouping

The patients are randomly allocated into the following groups:

- group 1: mindfulness training
- group 2: mindfulness training + VD supplement
- group 3: mindfulness training + Placebo
- group 4: VD supplement
- group 5: placebo

interventions

supplement:

Between 1, November 2019 to 24, January 2020 (12 weeks), VD groups received a daily four thousand IU oral dosage (four capsules) with 28,000 IU vitamin D weekly. This supplement includes twenty-eight oily drops weekly (JALINOUS CO, Iran). Placebo (JALINOUS) groups receive totally similar drops in shape (without any VD) and duration.

Mindfulness:

patients allocated to the mindfulness groups received 12 weeks (90 minutes per session) of modified mindfulness manual which based on pain relief protocols(18, 19). the intervention has been implemented by a three trained psychotherapist in mindfulness with three assistances. they were blinded about study aims and the existence of other groups (VDs and other mindfulness groups). *For comparing adherence, audios of sessions were recorded with the permission of all the members. Then a mindfulness psychotherapist checked contents secession. Sessions were divided into 15 minutes' modules that were taken for adherence checks randomly. The treatment position and the occurrence processes were evaluated. Based on the intervention manual, the modules assessed the adherence level as either enough or not sufficient. The majority of content (88%) was judged as implemented adequately.*

Session content are including:

- familiarity with participants. Discuss about neuropathy and its nature. giving a pamphlet about neuropathy for home reading. free discussion about the psychological aspect of neuropathy and pain.

- Introduce the content of the intervention. Teaching about the relationship between mind and body.
- learn about meditation and body scan, then practicing them.
- teaching relaxation skills (belly breathing, guided imagery and progressive muscle relaxation).
- Teaching regarding chronic pain, relationships between physical, emotional and thoughts reactions. Also explain pain coping strategies with brain storming.
- Learn to experience negative emotions and pay attention to them.
- Meditation in sitting posture while concentrating on breathing and external sounds.
- Meditation in sitting posture while concentrating on internal emotions and thoughts.

Measures

Laboratory analyses:

Ten ML of fasting blood units from each participant was taken after ten hours of fasting at the first stage and at the end of the study. The blood samples stored at −80°C (with 10minutes centrifuging at 3000 Revolutions per minute) until future analysis with centrifuged to isolate serums. Fasting blood glucose (FBS) was measured by spectrophotometry utilizing the Pars Azmun kit in auto-analyzer equipment (BT3000, China).

Pain-Related Disability:

The Pain Disability Index (PDI) is a seven-items scale to examine the extent of self-reported pain-related inability, independent from the region of pain or diagnosis. The items of the scale are evaluated on a 0–10 numeric evaluation scale in which 0 indicates no inability and 10 is the maximum disability. Higher scores indicating higher interference of the pain with regular activities. The PDI showed high test-retest reliability in many studies (20).

Neuropathic pain severity:

The Neuropathic pain scale(NPS) is measured for severity of neuropathic pain. This scale calculated as the sum of ten pain descriptor items (each item rated on 0 to 10 with ten representing the most severe pain). Thus, this scale total score varies from 0 to 100. in many studies, psychometric properties were examined and results showed adequate properties(21).

Neuropathy Specific Quality of Life:

The Neuropathy Specific Quality of Life questionnaire (NeuroQol) with 28 items is a particular validated scale for neuropathic QOL. NeuroQol evaluates diabetic neuropathy-related emotional and physical difficulties affecting diurnal life and well-being. this scale consists of painful symptoms, paresthesia, unsteadiness while walking or standing, emotional distress, interpersonal problems, emotional and physical dependence on others, restriction in daily activities and e.t in five subscales. Higher scores mean more impairments of QOL. Reliability

of the subscales ranged from 0.86 to 0.95(22).As four items repeated in more than one subscale, the total score is between 31 to 155.

Sun exposure time:

before implementing intervention and in the post-test by a validated questionnaire the sun exposure rate was assessed. The span of sun exposure was measured by total minutes exposing to the sun in the last two week and divided into two.(23).

Vitamin D intake:

for assessing Vitamin D intake, the fourth version Modified Nutritionist software program was used by a trained nutritionist (three-days food recording include one weekend day and two weekdays.

Anthropometric assessments:

BMI (Body mass index) by dividing weight (kg) to square height (m2) was calculated. at the baseline and post-test(24).

Physical activity:

The short version of the International Physical Activity Questionnaire (SF-IPAQ) was applied for determining the level of physical activity (MET-minutes/week) participants(25).

Statistical analysis

For assessing data SPSS version 26 was employed and we used paired sample t-test, the one-way ANOVA and, post-hoc test (Scheffe). P-values <0.05 were considered statistically significant.

Results

225 TDM2 with neuropathy diagnosis were involved in our investigation. Ultimately, 204 patients completed the study [Figure 1]. In the administration of Vitamin D and placebo for neuropathic diabetic patients, no side effects were reported.

Demographic Measures

Demographic variables were measured in the pre-test and end of invention. In the pre-test phase, participants were not statistically different among groups. ($P > 0.05$). In the post-test, there is statically differentiation for Physical activity among groups ($P < 0.05$) [Table 1].

Table 1
scores of the participants by groups

Characteristic	placebo	Placebo + mindfulness	mindfulness	Vitamin	Vitamin + Mindfulness	P value
Age (years)a	56.25 ± 9.89	53.3 ± 8.94	54.8 ± 9.44	54.5 ± 9	56.6 ± 9.8	0.49
sex (female)[b] (N)	16 (40%)	17(42.5%)	16(39.2%)	22(55%)	21(48.8%)	0.56
base line Vitamin D level (ng/mL)	24.6 ± 5.5	25.4 ± 5.4	25.3 ± 5.2	27.4 ± 5.07	26.2 ± 5.7	0.1
Duration of diabetes (years)	14.7 ± 5.3	15.8 ± 4.8	14.8 ± 6.6	14.6 ± 4.6	15.3 ± 5.06	0.82
FBS (pre-test)	178.9 ± 29.2	172.5 ± 33.8	172.2 ± 28.9	170.37 ± 27.28	175.13 ± 28.19	.73
FBS (post-test)	178.1 ± 27.2	169 ± 27.14	165.31 ± 28.09	163.7 ± 27.92	167.51 ± 30.92	0.18
P value	P > 0.05	P > 0.05	P > 0.05	P > 0.05	P > 0.05	
sun (pre-test)	38.7 ± 14.1	41.7 ± 14.4	40.1 ± 15.8	39.5 ± 13.9	42.7 ± 14.02	0.7
sun (post-test)	42.5 ± 15.14	41 ± 14.8	39.2 ± 15.3	45.5 ± 13.7	43.4 ± 15.01	0.38
P VALUE	P > 0.05	P > 0.05	P > 0.05	P > 0.05	P > 0.05	
VD(pre)	3.7 ± 2.08	4.6 ± 1.9	3.7 ± 1.9	4.2 ± 2.01	4.09 ± 2.03	0.194
VD(post)	3.9 ± 2.1	4.1 ± 1.8	3.9 ± 2.05	3.5 ± 1.7	4.1 ± 2.1	0.71
P VALUE	P > 0.05	P > 0.05	P > 0.05	P > 0.05	P > 0.05	
Energy (pre)	2390.1 ± 279.2	2338.45 ± 269.8	2395.51 ± 276.35	2462.12 ± 293.2	2404.48 ± 313.87	0.44
Energy (post)	2377.15 ± 306.01	2452.17 ± 275.54	2374.46 ± 302.01	2446.05 ± 328.78	2357.46 ± 278.26	0.46
P VALUE	P > 0.05	P > 0.05	P > 0.05	P > 0.05	P > 0.05	
PHY (pre)	251.8 ± 81.8	260.75 ± 93.4	256.87 ± 91.46	255.22 ± 89.04	273.48 ± 95.25	0.247
PHY (post)	253.32 ± 79.4	378.8 ± 84.7	397.19 ± 96.82	403.67 ± 91.45	496.03 ± 76.92	0.00
P VALUE	P > 0.05	P < 0.05*	P < 0.05*	P < 0.05*	P < 0.05*	

a = one way anova, B = chi-square test, c = paired sample t-test, FBS = Fasting blood sugar(mg/dL), Sun: Sunlight exposure (minutes/week), Energy: Energy intake (k Cal/day), PHY: Physical activity (MET/minute*week), VD = Vitamin D intake (mcg/day)

For physical activity, all groups except “placebo” showed statically improvement in post-intervention rather than pre-test($p < 0.5$). Beside, both Vitamin D and mindfulness training can improve physical activity. A comparison among groups done with post-hoc (Scheffe) analysis. Table 2 demonstrated that “Vitamin + Mindfulness” significantly greater that others can improve the physical activity. Also there is not any significantly difference between “mindfulness” and “Vitamin D” in physical activity (with/without combination with placebo) ($P < 0.05$).

Table 2
post hoc for physical activity in post-test

Group I	Group J	Mean difference	P value	Group I	Group J	Mean difference	P value
placebo	Placebo + mindfulness	-134.5	0.00*	Placebo + mindfulness	mindfulness	-9.3	0.98
	mindfulness	-143.8	0.00*		Vitamin	-15.85	0.95
	Vitamin	-150.35	0.00*		Vitamin + Mindfulness	-108.2	0.00*
	Vitamin + Mindfulness	-242.7	0.00*				
mindfulness	Vitamin	-6.47	0.9				
	Vitamin + Mindfulness	-98.8	0.00*	Vitamin	Vitamin + Mindfulness	-92.35	0.00*

Outcome measures

Quality of life

For QOL (as total measure) results showed that there is not significant difference among groups in base-line ($P > 0.05$). But, at posttest, result showed significant improvement in all groups except “placebo”. Moreover, there is not any difference between mindfulness and Vitamin D groups to enhance QOL. Yet, the “vitamin D + mindfulness” showed the most improvement regarding other groups. these results repeated in all QOL subscale except “reduced feeling” and “diffuse sensory motor” [Tables 3 and 4].

Table 3
outcome measures from baseline to end of treatment

variable	Characteristic	placebo	Placebo + mind	mind	Vitamin	Vitamin + Mind	P value
QOL	**pre pain** [A]	21.07 ± 7.03	19.6 ± 5.9	20.4 ± 5.8	18.9 ± 7.1	19.9 ± 5.6	0.6
	post pain [A]	20.3 ± 5.4	15.2 ± 5.4	16.3 ± 6.7	14.8 ± 5.8	10.3 ± 4.7	0.00*
	p value [B]	P > 0.05	P < 0.05*	P < 0.05*	P < 0.05*	P < 0.05*	
	pre feeling [A]	4.4 ± 1.7	5.2 ± 1.5	4.8 ± 1.3	4.6 ± 1.4	4.4 ± 1.5	0.1
	POST feeling [A]	4.2 ± 1.4	5.1 ± 1.49	5.17 ± 1.44	4.4 ± 1.3	5.1 ± 2.1	0.1
	P VALUE[B]	P > 0.05	P > 0.05	P > 0.05	P > 0.05	P > 0.05	
	pre sensory [A]	5.6 ± 1.9	6.02 ± 1.8	6.1 ± 2.2	6.02 ± 1.09	6.1 ± 2.08	0.86
	POST sensory [A]	5.8 ± 1.9	5.9 ± 2.3	6.6 ± 1.7	5.8 ± 2.06	6.8 ± 1.9	0.08
	P VALUE[B]	P > 0.05	P > 0.05	P > 0.05	P > 0.05	P > 0.05	
	PRE inter	32.49 ± 9.3	32.7 ± 10.8	33.5 ± 10.4	34.8 ± 11.1	31.9 ± 11.3	0.7
	POST inter	32.5 ± 10.2	26.1 ± 9.4	25.6 ± 7.9	25.6 ± 8.3	17.8 ± 6.5	0.00*
	P VALUE[B]	P > 0.05	P < 0.05*	P < 0.05*	P < 0.05*	P < 0.05*	
	PRE ACTIVITY[A]	24.7 ± 5.5	23.3 ± 6.7	23.8 ± 4.7	23.7 ± 6.1	22.8 ± 5.6	0.6
	POST ACTIVITY[A]	24.2 ± 7.02	17.9 ± 5.5	19.4 ± 5.6	18.4 ± 4.5	13.02 ± 4.6	0.00*
	P VALUE[B]	P > 0.05	P < 0.05*	P < 0.05*	P < 0.05*	P < 0.05*	
	PRE TOTLA[A]	88.3 ± 12.5	87.05 ± 15.05	88.8 ± 12.4	88.5 ± 17.5	86.2 ± 15.2	0.9
	POST TOTAL[A]	87.09 ± 14.9	69.6 ± 12.7	73.2 ± 11.2	69.3 ± 13.02	53.16 ± 11.5	0.00*

a = one way anova, b = paired sample t-test, feeling: reduced feeling, sensory: diffuse sensory motor, inter: interpersonal and emotional burden, ACTIVITY: activity limitations, Inter: interpersonal emotional burden, **ACTIVITY**: activity limitations, MIND: **mindfulness**

variable	Characteristic	placebo	Placebo + mind	mind	Vitamin	Vitamin + Mind	P value
	P VALUE[B]	P > 0.05	P < 0.05*	P < 0.05*	P < 0.05*	P < 0.05*	
pAIN SEVERITY	**PRE TEST**	47.02 ± 13.7	45.6 ± 13.5	50.8 ± 13.5	49.4 ± 14.7	46.02 ± 14.5	0.3
	POST TEST	45.6 ± 13.4	30.6 ± 14.6	33.7 ± 12.8	31.03 ± 14..8	21.02 ± 9.09	0.00*
	P VALUE	P > 0.05	P < 0.05*	P < 0.05*	P < 0.05*	P < 0.05*	
DISABILITY	**PRE TEST**	42.6 ± 14.2	42.5 ± 14.1	41.5 ± 13.5	38.08 ± 13.05	42.2 ± 13.2	0.7
	POST TEST	41.8 ± 12.5	31.6 ± 11.7	31.2 ± 12.3	29.7 ± 11.7	21.5 ± 9.4	0.00*
	P VALUE	P > 0.05	P < 0.05*	P < 0.05*	P < 0.05*	P < 0.05*	

a = one way anova, b = paired sample t-test, feeling: reduced feeling, sensory: diffuse sensory motor, inter: interpersonal and emotional burden, ACTIVITY: activity limitations, Inter: interpersonal emotional burden, **ACTIVITY**: activity limitations, MIND: **mindfulness**

Table 4
post. hoc analysis for QOL subscales measures

				PAIN (QOL subscale)			
Group I	Group J	Mean difference	P value	Group I	Group J	Mean difference	P value
placebo	Placebo + mindfulness	5.1	0.003*	Placebo + mindfulness	mindfulness	-1.04	0.95
	mindfulness	4.07	0.03*		Vitamin	0.45	0.99
	Vitamin	5.5	0.001*		Vitamin + Mindfulness	4.8	0.005*
	Vitamin + Mindfulness	9.9	0.00				
mindfulness	Vitamin	1.4	0.84				
	Vitamin + Mindfulness	5.9	0.001*	Vitamin	Vitamin + Mindfulness		
				Inter			
Group I	Group J	Mean difference	P value	Group I	Group J	Mean difference	P value
placebo	Placebo + mindfulness	6.3	0.02*	Placebo + mindfulness	mindfulness	0.49	0.9
	mindfulness	6.8	0.01*		Vitamin	0.45	0.9
	Vitamin	6.84	0.01*		Vitamin + Mindfulness	8.3	0.001*
	Vitamin + Mindfulness	14.7	0.001*				
mindfulness	Vitamin	-0.03	0.9				
	Vitamin + Mindfulness	7.8	0.002*	Vitamin	Vitamin + Mindfulness	7.87	0.001*
				Activity			
Group I	Group J	Mean difference	P value	Group I	Group J	Mean difference	P value
placebo	Placebo + mindfulness	6.3	0.00*	Placebo + mindfulness	mindfulness	-1.5	0.81
	mindfulness	4.8	0.005*		Vitamin	-0.5	0.9

Inter: interpersonal emotional burden, Activity: activity limitations.

				PAIN (QOL subscale)			
	Vitamin	5.8	0.00*		Vitamin + Mindfulness	4.9	0.005*
	Vitamin + Mindfulness	11.2	0.00*				
mindfulness	Vitamin	0.97	0.9				
	Vitamin + Mindfulness	6.4	0.00*	Vitamin	Vitamin + Mindfulness	5.4	0.001
				Total			
Group I	Group J	Mean difference	P value	Group I	Group J	Mean difference	P value
placebo	Placebo + mindfulness	17.4	0.001*	Placebo + mindfulness	mindfulness	-3.5	0.8
	mindfulness	13.8	0.001*		Vitamin	0.34	0.9
	Vitamin	17.7	0.001*		Vitamin + Mindfulness	16.5	0.001*
	Vitamin + Mindfulness	33.9	0.001*				
mindfulness	Vitamin	3.9	0.75				
	Vitamin + Mindfulness	20.08	0.001*	Vitamin	Vitamin + Mindfulness	16.17	0.001*
Inter: interpersonal emotional burden, Activity: activity limitations.							

For pain-related disability, and pain severity results showed that there were not significant difference among groups in base-line ($P > 0.05$). But, at posttest, result showed significant reduction in all groups except “placebo”. Moreover, there is not any difference between mindfulness and Vitamin D groups to reduce pain disability and pain severity. Yet, the “vitamin D + mindfulness” group showed the most improvement rather than other groups [Tables 3 and 5].

Table 5
post. hoc analysis for pain severity and pain-related disability measures

				Pain Severity			
Group I	Group J	Mean difference	P value	Group I	Group J	Mean difference	P value
placebo	Placebo + mindfulness	15	*0.00	Placebo + mindfulness	mindfulness	-3.3	0.9
	mindfulness	11.9	*0.006		Vitamin	-0.6	0.9
	Vitamin	14.3	*0.00		Vitamin + Mindfulness	9.6	0.02*
	Vitamin + Mindfulness	24.6	*0.00				
mindfulness	Vitamin	2.3	0.9				
	Vitamin + Mindfulness	12.6	0.001*	Vitamin	Vitamin + Mindfulness	10.3	0.026*
				Pain Disability			
Group I	Group J	Mean difference	P value	Group I	Group J	Mean difference	P value
placebo	Placebo + mindfulness	10.2	0.003*	Placebo + mindfulness	mindfulness	0.3	0.9
	mindfulness	10.5	0.001*		Vitamin	1.8	9.7
	Vitamin	12.05	0.001*		Vitamin + Mindfulness	10.08	0.004*
	Vitamin + Mindfulness	20.2	0.001*				
mindfulness	Vitamin	1.4	0.9				
	Vitamin + Mindfulness	8.4	0.02*	Vitamin	Vitamin + Mindfulness	8.2	0.037*

Discussion

The present study demonstrated that VD supplement and mindfulness training separately reduce pain severity and pain-related disability and then improved QOL in PDN. Moreover, our research provides substantial evidence confirming that VD combined with mindfulness has a synergistic effect on pain severity, pain related disability and QOL in PDN. Yet, in two of the QOL subscales, there were not any significantly difference between baseline and post-test for reduced feeling and diffuse sensory motor. As these subscale was low in baseline (without destructive role in QOL), they do not need to improvement, so they remained steady.

This is the first study which combining VD and mindfulness on diabetic neuropathy. But, pervious results showed that VD and mindfulness as a separate intervention have promising effects. For example, Basit et.al (2015) demonstrated that intramuscular injection of vitamin D reduced pain scores in PDN (2).Also, recently, one research conducted by Izgu (2020) showed that mindfulness meditation had a significant impact on pain severity in Patients With Type 2 Diabetes(26). This result repeated about efficacy on mindfulness on quality of life in diabetic patients(27). Also, pervious researches showed that mindfulness training increased physical function and decreased pain related disability and pain intensity in patients with chronic pain(28, 29). Also, Nathan et.al (2017) showed that MBSR training reduced pain severity, perceived stress, pain catastrophizing and with these reductions, improved QOL(16).

About efficacy of mindfulness on pain severity, the organization and modulation of pain are mediated by cognitive, affective and sensory factors. mindfulness training with significant activation of thalamus and insula as the sensory processing–related brain areas and decreased activation in brain regions that process the appraisement of pain (orbitofrontal cortex and medial PFC). also, there was a significant association among lower pain reports with meditative experience and higher deactivation of the orbitofrontal cortex and medial PFC. By reducing the severity of the pain, patients are empowered to do things they were previously unable to do. For example, their social activity increases, and sexual behavior problems decrease. Also, with mindful abilities patients learn to reduction of catastrophizing of pain and accepting some grades of pain as a part of their life.so were be able to find recreation and interpersonal activities despite presence of pain. So, with these improvements, their pain-related disability reduced and so on improved their QOL(13, 27, 30). On the other hand, in animal models Overall, several genes such as Oxt, Penk, Pomc Payne, Pth, and Tgfb1-encoding for peptides are top candidates to describe the remedial advantage of vitamin D supplementation on neuropathic pain(31). Potential mechanisms for VD effects in pain reduction are the anti-inflammatory consequences mediated by effects on T-cell responses, reduced cytokines and prostaglandins (PG) release(32). So with reduction in pain severity and pain disability, their QOL were improved.as stated in former sentences, pain is a bio-psycho-social problem and with targeting behavior (with mindfulness) and physical aspects (VD supplement), the pain severity can reduce in great amount and patients can managing pain with mulita-dimensional benefits. So combining VD and mindfulness enhancing patients QOL without increasing side effects.

Moreover, both protocols have no significant effects on, FBS, BMI and energy intakes. About energy intake and BMI, as these variables are highly associated with the life-style, patients need extensive changes in habits, attitudes and behaviors. Also, VD supplementation was not efficient into fat mass. but with a reduction in pain severity and pain-related disability, patients abler to self-care behaviors and find recreation in life -situations, so their physical activity improved(33, 34). But, there is not any comparable investigation for mindfulness on FBS, so we need more studies for mindfulness in FBS.

Although various strengths of this study, we have some limitations. As a limitation of our research, we were unable to examine the seasonal changes that could influence the result. Also, we need examining follow-up but as there is the first pilot these limitations must be eliminated to future researches

Conclusion

Combining Vitamin D and mindfulness training could have reduced pain severity, Pain-Related Disability and then improved Neuropathy-Specific Quality of Life dimensions in PDN.

Abbreviations

ACT: Acceptance and Commitment Therapy, QOL: Quality of Life, VD: Vitamin D, PDN: Painful diabetic neuropathy

Declarations

Ethics approval and consent to participate:

Written informed consent (about participation in the study) was received from all patients before the beginning of the study. The scales used in this research were all filled anonymously and a numeric code was used. This project was assessed and certified by the ethics committee of Kermanshah University of medical science (Ir.kums.rce.1399.0403). Moreover, this study is registered in the Thailand Registry of Clinical Trials (TCTR20200629004).

Consent for publication:

During sampling individual session was held. We received consent for publication results from each participant.

Availability of data and material:

Data of participants who consented to the public sharing of data are accessible from the corresponding author upon reasonable demands.

Competing interests:

The authors certify that they have no competing interests.

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Authors' contributions:

The RT and AAT conceived of the presented idea. The SMA with RT developed the protocols and performed the sampling. RT and AAT operating the analytical methods. The AAT encouraged the MD to investigate this matter

and supervised the results of the findings. All authors discussed, read and approved the manuscript.

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Figures

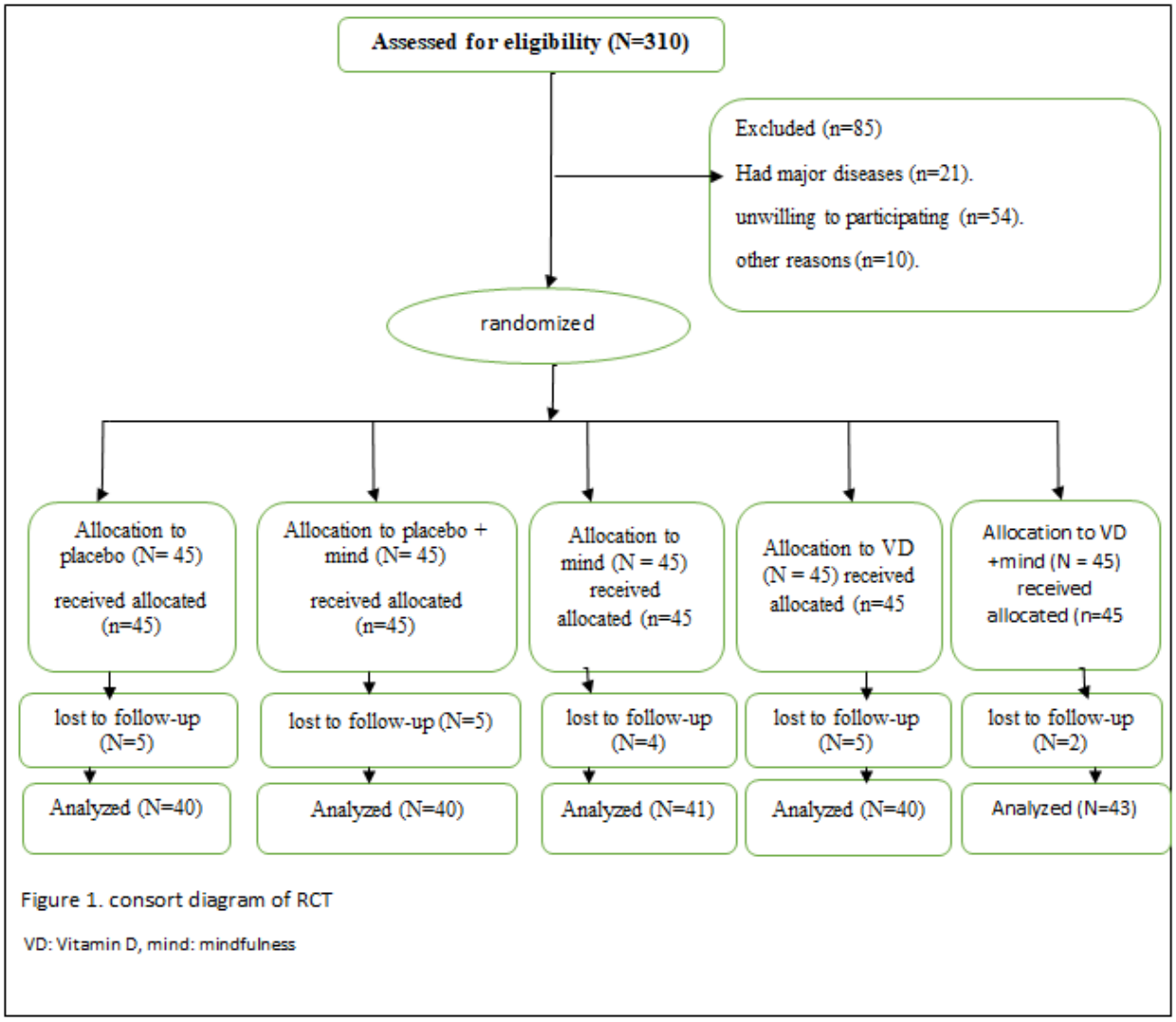

Figure 1. consort diagram of RCT

VD: Vitamin D, mind: mindfulness

Figure 1

consort diagram of RCT VD: Vitamin D, mind: mindfulness