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REVIEW ARTICLE

Effects of exercises and manual therapy on nerve conduction studies of lower limb in patients with diabetes and diabetic peripheral neuropathy: A systematic review

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Abstract

Background Diabetes and related peripheral neuropathy result in various sensory and motor complications. Such changes are documented early and more precisely in nerve conduction studies than in clinical evaluation and quantitative sensory testing. Different exercises and mobilization also affect the same differently.

Objective This review aimed to compile the current evidence on the effectiveness of exercises and manual therapy on nerve conduction studies of lower limbs in patients with diabetes and diabetic peripheral neuropathy and to evaluate the underlying mechanisms.

Methods Studies that examined the effects of different exercises and manual therapy on nerve conduction studies of lower limbs in patients with diabetes mellitus and diabetic peripheral neuropathy were searched on available databases. The PRISMA statement was followed. Quality check was done using the Pedro scale.

Results Thirteen studies matched the inclusion criteria. Interventions included moderate-intensity aerobic exercises, resistance exercises, tai chi exercises, sensorimotor and gait training, neurodynamic mobilization, and a combination of aerobics and resistance training.

Conclusion The present systematic review suggests that 8 to 12 weeks of physical exercise improves nerve conduction velocity of the motor tibial, peroneal nerve, and sensory sural nerve in diabetes with or without peripheral neuropathy.

Keywords Diabetes · Diabetic neuropathy · Manual therapy · Exercises · Nerve conduction studies

Abbreviations

CMAP	Compound muscle action potential
DM	Diabetes mellitus
DPN	Diabetic peripheral neuropathy
IENFD	Intra epidermal nerve fiber density
NAPA	Nerve action potential amplitude
NCS	Nerve conduction studies
NCV	Nerve conduction velocity
SNAP	Sensory nerve action potential
PEDRO	Physiotherapy evidence database
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
PICOS	Population, intervention, comparison, outcomes, study design
TENS	Transcutaneous electrical nerve stimulation
ADA	American diabetes association
HbA1c	Hemoglobin A1c
BMI	Body mass index
QST	Quantitative sensory testing

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Introduction

Diabetic peripheral neuropathy (DPN) is the most common debilitating complication of diabetes. The prevalence of DPN is 21.3 to 34.5% [1], and it increases with age and duration of diabetes [2]. During the course of the disease, 40–59% of patients develop neuropathic symptoms due to the involvement of sensory and motor peripheral nerves [3–5]. Symptoms present as electric, burning, stabbing, shooting, sharp aching pain, and dysesthesias that occur mostly at night and disturb sleep [6–8]. Loss of innervation of motor axons results in reduced muscle strength and atrophy in lower limb musculature [9–11]. These nerve function changes result from hypoxia induced by microvascular changes and impaired nerve perfusion [12–14]. If not diagnosed in the early phase of the disease can impose the risk of falls [15–17], lower limb amputations [18], impaired quality of life [19], anxiety, and depression [20, 21]. Thus, glycemic control, lifestyle modification, exercises, and early diagnosis are the keys to preventing disease progression [22, 23]. NCS are one such diagnostic tool that is considered the gold standard for the diagnosis of DPN [24, 25]. Various parameters of nerve conduction like distal and proximal latency [26], NCV [27], sensory nerve action potentials [28], and amplitude of motor/sensory response [29] all shows variations in DPN patients in comparison to healthy population. Since nerve functions are sensitive to changes in diabetic patients with or without clinical neuropathy [30], electrophysiological abnormalities are also noticed among asymptomatic diabetic patients [31].

Different systematic reviews and meta-analysis showed lifestyle modification along with exercises have been found to be effective on various clinical outcome measures in the diabetes and DPN. Similar studies are available describing the positive impact of changes in lifestyle and various types of exercise on lower limb nerve conduction measures in such individuals. But no systematic review or meta-analysis has examined the efficacy of such exercise trials on nerve conduction parameters of lower limb in population of concern. Therefore, purpose of this study was to review the current evidence on effectiveness of exercises and manual therapy on NCS of lower limb nerves in diabetes and DPN.

Methods

Search and information sources, Google Scholar, PubMed, and Cochrane library, were searched. Studies published between January 2005 and December 2022 were included. Studies with different exercise interventions and have seen its effects on nerve conduction of lower limb nerves in DM and DPN were considered. Strategy used to search related articles was done by using population, intervention, comparison, outcome measures, and study design (PICOS) method; population of diabetes with or without peripheral neuropathy; interventions such as physical exercises, balance, whole body vibration, tai chi, manual therapy, and its comparison with control; and placebo, no treatment, other type of exercises, electrotherapy, or pharmacotherapy. Outcome measures searched were NCS, nerve functions, and NCV. Search was not limited to any specific study type. Reference list of all the selected articles and related systematic review was also searched. Search strategy is listed in Table 1.

Inclusion criteria

1) Diagnosis of DM with and without peripheral neuropathy.
2) Exercises, balance, manual therapy as main intervention compared with controls, no intervention, electrotherapy or usual care.
3) NCS of sural, peroneal, and tibial nerve (one or all) as outcome measures (NCV, distal latency, proximal latency, nerve action potential amplitude).
4) Studies enrolling participants of any age or gender.
5) Studies published in English language.
6) Human studies.
7) Studies with quantitative results.

Exclusion criteria

Studies were excluded with diagnosis of neuropathy other than diabetic neuropathy. Studies published before 2005.

Selection process

Abstract and title of retrieved articles was screened by two independent authors. All the full text articles that fulfilled eligibility criteria were included for analysis. After selection

Table 1 Search strategy

Database	Search strategy (Mesh work)
PubMed	“Diabetes Mellitus” [Mesh] AND (“Diabetes Complications” [Mesh] OR “Peripheral Nervous System Diseases” [Mesh] OR “Diabetic Neuropathies” [Mesh]) AND (“Musculoskeletal Manipulations” [Mesh] OR “Therapy, Soft Tissue” [Mesh] OR “Manual therapy” OR “Physical Therapy” OR “Resistance Training” [Mesh] OR “Exercise Therapy” [Mesh])
Cochrane Library	“Diabetes Mellitus” OR “Diabetes complications” OR “Type 2 Diabetes” OR “Diabetic neuropathy” AND “Neural conduction” OR “Nerve conduction studies” OR “Nerve functions” OR “Nerve conduction velocity” AND “Musculoskeletal manipulations” OR “Manual therapy” OR “physical therapy” OR “Resistance training” OR “Aerobic exercises” OR “Physical exercises” OR “Balance exercises” OR “Tai chi”
Google Scholar	diabetes mellitus OR type 2 diabetes OR diabetic neuropathy AND nerve conduction studies OR nerve functions OR nerve conduction velocity AND physical exercises OR manual therapy OR balance exercises OR aerobic exercises OR tai chi

of studies, data was extracted about author and year of publication, study design, participant characteristics, inclusion criteria, exclusion criteria, interventions, outcomes, and results. Two independent authors used the PEDRO scale to rate the methodological quality of included articles (Table 2). Third author was consulted in case of confusion between first two authors. Internal validity score was also calculated for selected studies which was calculated using sum of 7 items (2, 3, and 5 through 9). Methodological quality of studies was further classified on the basis of Internal validity Score as limited (0–3 IV score), moderate (4–5 IV score), and high quality (6–7 IV score).

Results

Selection of studies: A total of 1616 studies were found on effects of different exercises/physiotherapy on nerve functions in DM or DPN after a detailed search of mentioned databases. After removal of duplicates, titles of 1578 studies were screened. After removal of irrelevant studies and studies other than DM or DPN, 115 studies were further considered. Eighty-eight studies plus two studies (using snowballing references), total 90 studies were screened for abstract reading after removal of systematic/ narrative reviews. Seventy-five studies were removed through PICOS method and eligibility criteria; 15 studies were considered for full text review. Of these, 13 studies were selected for analysis (PRISMA flow chart, Fig. 1). After rating the PEDRO score through two independent authors, inter-rater agreement between the two reviewers was found 10/13, which suggests a percentage of 76.923%.

Study characteristics

Out of 13 selected studies, seven studies [32–38] were randomized controlled. One study [29] was parallel group comparative study. One study [39] was prospective cohort study, and four studies [40–43] were single group prepost study design. Total sample of 641 was offered by all studies. Average age of participants ranges from 40 to 70 years in most of studies covered for review. Research population selected was of type 2 DM in nine publications [29, 33–35, 37–41]. Two studies [32, 36] included participants of both types 1 and 2 DM, and two studies did not specified the type of DM [42, 43]. Two studies [32, 39] included patients of diabetes without any signs and symptoms of neuropathy. Eleven studies [29, 33–38, 40–43] included population of diabetes with peripheral neuropathy. Different authors used different methods for initial screening of DPN. Most of studies [29, 32, 34, 35, 37, 43] used NCS to confirm presence of diabetic neuropathy. Others [32, 35, 36, 38] used Michigan neuropathy screening instrument, physical examination by specialist [41], Michigan diabetic neuropathic score [33, 35, 38], neuropathy scale score and Utah early neuropathic scale [39], and pin prick sensation on sole of foot [42]. Study characteristics are mentioned in Table 3.

Interventions

All the studies included in the review have seen effects of different kind of exercises on diabetes and diabetic neuropathy. Most of interventions used were supervised moderate intensity aerobic exercises on treadmill or stationary bicycle [32–35, 37, 41, 43], manual therapy (tibial nerve mobilization) [42], resistance training [37, 38], combined aerobics

Table 2 Scores for PEDro criteria

Author. year	1	2	3	4	5	6	7	8	9	10	11	QS/10	IVS	Variability
Dixit et al. 2014	Yes	1	1	0	0	0	1	0	0	1	1	5	Limited	3
Singleton et al. 2014	Yes	1	0	1	0	1	1	1	1	1	1	8	Moderate	5
Hung et al. 2009	Yes	0	0	1	0	0	1	1	0	1	1	5	Limited	2
Serry et al. 2016	Yes	1	0	1	0	0	0	1	1	1	1	6	Limited	3
Balducci et al. 2006	Yes	1	0	1	0	0	0	1	1	1	1	6	Limited	3
Gholami et al. 2018	Yes	1	1	1	0	0	1	1	0	1	1	7	Moderate	4
Gholami et al. 2021	Yes	1	1	1	0	0	1	1	0	1	1	7	Moderate	4
Ahmad et al. 2020	Yes	1	1	1	0	0	1	1	0	1	1	7	Moderate	4
Stubbs et al. 2019	Yes	1	1	1	0	0	1	0	0	1	1	6	Limited	3
Alsubiheen et al. 2017	Yes	0	0	0	0	0	0	0	0	0	1	1	-	0
Azizi et al. 2019	Yes	0	0	0	0	0	1	1	0	0	1	3	Limited	2
Kluding et al. 2012	Yes	0	0	0	0	0	0	0	0	0	1	1	-	0
Doshi and Singarvalen. 2019	Yes	0	0	0	0	0	0	1	1	0	1	3	Limited	2

QS Overall quality score; *IVS* internal validity score

*Criteria 1 score is not included in the overall PEDro rating

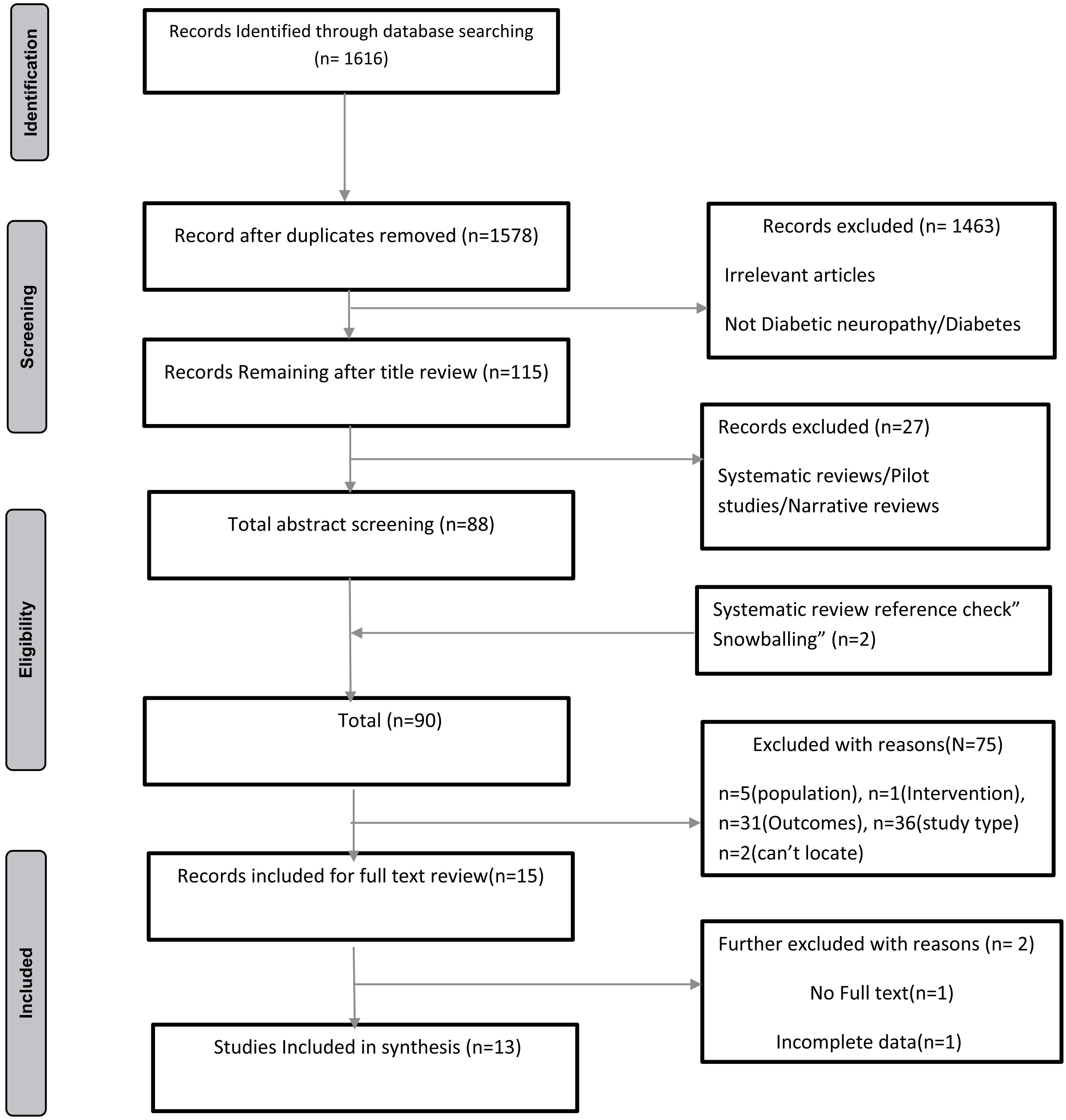

Fig. 1 PRISMA flowchart

and resistance exercises [37, 39, 43], sensorimotor exercises and gait training [36], stretching and breathing exercises along with tai chi exercises, mental imaginary exercises [40], and with Cheng's tai chi exercises [29]. Study duration of aforesaid studies varied from 3 weeks [42], 8 weeks [33, 34, 36, 40, 41] to 12 weeks [29, 35, 37, 38]. Few studies were of even longer duration of 1 year [39] and 4 years [32]. Frequency of exercises varied from 30 to 90 min per week [39], 2 times a week [40, 43], 3 sessions per week [29, 32, 34–38, 41], 5 sessions a week [42], and 3 to 6 sessions a week [33].

Comparators

Other than four studies [40–43] which were single group prepost study design, intervention group was compared with

Table 3 Study characteristics

Author	Subjects (without dropouts) Age ± S.D Study design	Inclusion criteria	Exclusion criteria	Intervention	Outcome measures
Balducci et al. 2006 [32]	$N = 78$	Type 2/type 1 diabetes	CNS (central nervous system) dysfunction	G1: sedentary patients	Peroneal motor NCV, NAPA, DL
	Male = 39	No signs/symptoms of DPN	MS (musculoskeletal deformity) that prevents participation,	G2: Treadmill brisk walk on 50% to 85% of the heart rate reserve	Sensory sural NCV, NAPA, DL
	Females = 39	Able to walk 1.6 km distance without/with assistance	L/L (lower limb) arthritis/pain that limits exercise	4-sessions per week for 4 years	VPT at malleolus/Hallux
	G1: control, $n = 47$ diabetics, with sedentary lifestyle		H/o severe CV diseases that contraindicate the exercise	Study duration: 4 years	
	Age: 52.9 ± 13.4		vestibular dysfunction, H/o of angina, postural hypotension, Plantar skin pressure ulcers		
	G2: Supervised exercise group, $n = 31$		MNSI (Michigan Neuropathy Screening Instrument scores) ≥ 2.5		
	Age: 49 ± 15.5 years		Sural nerve amplitude < 6 μs, distal latency < 3 ms		
	4-year prospective randomized intervention study.		Peroneal nerve amplitude of < 2mv, distal latency of < 6.2mv		
Hung et al. 2009 [29]	$N = 65$	Type 2 DM,	Contraindications to moderate exercise	Both groups practice	Fasting blood sugar
	G1: control, $n = 28$, healthy participants	On oral hypoglycemic agents receiving metformin, sulfonylurea, or both	H/O of cardiovascular, pulmonary/neurologic disorders other than DM	Cheng's TCC, for 3 sessions a week, 60 min a session	Mean insulin resistance
	Age: (56.6 ± 13.3) years		Previously practiced TCC	10-min warm-up (including stretching and balancing exercises), 40 min TCC exercise (includes 37 movements), 10-min cool-down	NCV, distal latency, proximal amplitude of tibial, peroneal, sural, median, ulnar nerves bilaterally
	G2: intervention, $n = 32$, with DM			Study duration: 12 weeks	
	Age: (58.1 ± 13.4) years				
	Parallel group comparative study with a pre- and post-design				
Dixit et al. 2014 [33]	$N = 87$, both gender	Type 2 DM	Vitamin B12 deficiency	G1: Standard medical care, foot care, diet	Latency, amplitude, duration, and NCV of motor peroneal and sensory sural nerve

Table 3 (continued)

Author	Subjects (without dropouts) Age ± S.D Study design	Inclusion criteria	Exclusion criteria	Intervention	Outcome measures
	G1: control group: $n = 40$	MDNS >7 (Michigan Diabetic Neuropathy Score)	Postural hypotension	G2: Exercise training in the range of 40–60% of heart rate reserve	MDNS (Michigan Diabetic Neuropathy Score)
	Age: 59.45 ± 1.16		Foot ulcers	Sessions: 3–6 days of the week	
	G2: experimental group: $n = 47$		Walking with assistive devices	moderate intensity treadmill exercises, minimum of 150 min/week to a maximum of 360 min/week of work out	
	Age: 54.40 ± 1.24		Foot amputation	Study duration: 8 weeks	
	Parallel group randomized controlled trial		Peripheral arterial disease		
			Vision impairments		
			Neurological/ musculoskeletal impairments (acute sciatica or vestibular dysfunction)		
			Cognitive impairments		
			Score of ≥ 30 on MDNS		
			H/O active retinal hemorrhage, recent laser therapy, cardiac risks, revascularization of CABG		
			Seeking any other therapy for DPN		
			Age > 70 years		
Singleton et al. 2014 [39]	$N = 100$	Age 30–70 years	Utah early neuropathy scale score > 4	G1: Quarterly counseling on diet and moderate home exercise	IENFD (ankle/proximal thigh)
	G1: counseling, $n = 40$, age: 58.4 ± 6.7	Type 2 diabetes	symptoms of distal L/L, Sensory loss, numbness/neuropathic pain consistent with peripheral neuropathy,	G2: supervised exercise for 30–90 min weekly. Aerobic and resistance training (leg press, biceps curls)	Six-minute walk distance
	G2: Intervention group $n = 60$, Age: 56.4 ± 6.9, supervised exercises		On coumadin,	Baseline fitness for 1 year	Metabolic parameters

Table 3 (continued)

Author	Subjects (without dropouts) Age ± S.D Study design	Inclusion criteria	Exclusion criteria	Intervention	Outcome measures
	Prospective, single-blinded cohort study		Pregnant women	Progression in aerobic exercises according to RPE and resistance according to maximum weight lifted for one repetition	Sural, radial sensory response
			Significant CV (cardiovascular) disease	Study duration:12 months	Tibial, peroneal motor response
					F responses, proximal conduction velocity
Serry et al. 2016 [34]	$N=60$	Type 2 DM ≥ 10 years	BMI ≥ 30 kg/m 2	G1: TENS at 15 Hz, pulse width 250 µs both L/L 3 times a week for 8 weeks, with regular pharmacological therapy	Medial plantar NCV
	Age 40–60 years	DPN ≥ 5 years	H/o renal failure myocardial infarction, heart failure	G2: Aerobic exercise on a stationary bicycle,3 times a week for 8 weeks, regular pharmacological therapy	VAS
	Males: 28	BMI:18.5 to 29.9 kg/m	Sensory manifestations due to any other diseases (lumbar disc prolapsed)	G3: Nerve growth stimulant; vitamin B complex and oral hypoglycemics	
	Females: 32	HbA1c < 6.5%	Circulatory problems such as intermittent claudication		
	G1: TENS group, $n=20$	Ambulant/independent patient	Skin diseases/ foot ulcers;	Study duration:8 week	
	Age: 51.6 ± 4.75	MMT (manual muscle testing) L/L ≥ grade 4			
	G2: exercise group, $n=20$				
	Age: 51.7 ± 4.44				
	G3: pharmacological group, $n=20$				
	Age: 51.95 ± 4.38				
	Randomized controlled trial				
Gholami et al. 2018 [35]	$N=31$	Type 2 diabetes and peripheral neuropathy	Patient on insulin therapy	G1: maintain habitual physical activity level	NCV/NAPA of sural, peroneal, tibial nerves

Table 3 (continued)

Author	Subjects (without dropouts) Age ± S.D Study design	Inclusion criteria	Exclusion criteria	Intervention	Outcome measures
	All male patients	Diabetes > 5 years,	DM < 5 years,	G2: 3-familiarization sessions: 10 min warm up, 15 min treadmill walk,10 min cool down followed by aerobic exercise program for 3 months (walking, jogging. or running on treadmill, 50–70% of heart rate reserve)	EST (exercise stress test)
	G1: control group, $n = 15$	HbA1c: Between 6.6% and 12%, -Diagnosed DPN	No neuropathy, medical history, exercise restriction	Three sessions per week	Glycemic control/body composition
	Mean age: 42 ± 4.6 years, mean weight: 89.3 ± 11.9 kg	MNSI score ≥ 3	Patient on regular exercises	Study duration:12 weeks	
	G2: Experimental group, $n = 16$ Mean age: 43 ± 6.4 years, mean weight: 86.5 ± 15.3 kg	Moderate neuropathy according to MDNS			
	Randomized controlled study	Absent amplitude in nerve conduction studies			
		No contraindication to exercise,			
		Inactive patients as per rapid assessment of physical activity (RAPA) questionnaire			
Gholami et al. 2021 [38]	$N = 34$	H/o diabetes > 5 years,	Not permitted to participate in exercise	G1: Control group	NCV and NAPA of sural and peroneal nerve
	Age > 60 years	HbA1c > 6.6%, inactive lifestyle	Orthopedic issues, foot deformity, ulcers, absent nerve action potential amplitude	G2: The resistance exercise program: Thrice a week /12 week ~ 90 min per session	CAVI (cardio-ankle vascular index)
	All males	mild to moderate stage of DSPN		11 exercises for large muscle groups with free weights / machines	MDNS
	G1: control ($n = 14$)			1–3 circuits with 10–15 reps for each exercise at between 50 and 60% of 1RM	MNSI
	Age: 64 ± 3 years				ABI (ankle brachial index)

Table 3 (continued)

Author	Subjects (without dropouts) Age ± S.D Study design	Inclusion criteria	Exclusion criteria	Intervention	Outcome measures
	G2: experimental ($n = 15$)				
	Age: 63 ± 3 years				
	Randomized controlled trial			Study duration-12 weeks	
Ahmad et al. 2020 [36]	$N = 44$, Both gender	Age between 45 and 75 years	Neurological impairment	G1: Diabetes foot care education	Proprioception
	G1: control group, $n = 22$	Type 1 DM or 2 ≥ 7 years	Major vascular complication	G2: sensorimotor and gait training thrice a week for 8 weeks (total 24 sessions)	conduction velocity, duration, amplitude of peroneal and tibial nerve
	Age:57.24 ± 8.85	BMI between 18.5 and 29.9 kg/m^2	Severe retinopathy	50–60 min of exercise	Surface EMG of tibialis anterior, medial gastrocnemius, vastus lateralis and multifidus
	G2: intervention group, $n = 22$	Score > 2/13 in the MNSI questionnaire	Severe nephropathy	Both groups received education regarding foot care and diabetes control once every two weeks for 30 min	
	Age: 60.33 ± 8.48	Scored > 1/10-point scale of MNSI physical examination	Severe musculoskeletal impairment to lower limb	Study duration:8 weeks	
	Two-arm, parallel group randomized controlled trial with single blinding	Impaired vibration perception	Cardiovascular complication		
		Ability to walk independently	Receiving any supervised Physical intervention		
			Plantar ulceration		
			Partial or total amputation		
Stubbs et al. 2019 [37]	$N = 45$	Fasting plasma glucose ≥ 126 mg/dL or 2-h plasma glucose concentration ≥ 200 mg/dL after a 75 g oral glucose tolerance test	Foot ulceration	G1: sedentary control	Latency, NCV, SNAP of sensory sural, median, ulnar nerves
	Males' = 43	Stable levels of (HbA1c) defined as having ≤ 1.5% change in HbA1c levels during the previous 6 months	Unstable heart disease/co-morbid conditions limiting exercise	Attends 12-week health education promotion	Latency NCV, CMAP of tibial/peroneal motor nerves
	Females' = 2	Positive or negative distal sensory symptoms and nerve conduction abnormalities in at least two distal nerves	Disorders of the central nervous system causing weakness or sensory loss	G2: aerobic exercises	QST

Table 3 (continued)

Author	Subjects (without dropouts) Age ± S.D Study design	Inclusion criteria	Exclusion criteria	Intervention	Outcome measures
	Age: 45–80 years	Positive/negative sensory symptoms	medical conditions associated with neuropathies such as alcoholism, liver disease, kidney disease, toxic exposure, vitamin deficiency	10 min Warm up/30–40 min treadmill walking, 10 min cool down	SF-36 V health survey questionnaire
	G1: sedentary controls ($n=12$)		Autoimmune disorders immunoglobulin abnormalities, cancer or hypothyroidism	G3: isokinetic strengthening:	ENFD (epidermal nerve fiber density)
	Age: 61.0 ± 7.0 years			3 to 6 sets of 10 repetitions each of isokinetic leg extensions	Treadmill endurance
	G2: aerobic ($n=11$)			G4: aerobics + isokinetic exercises	Metabolic parameters
	Age: 61.9 ± 8.3 years			36-sessions treadmill walking + 36 sessions isokinetic strengthening	
	G3: isokinetic strength ($n=11$)			10 min active cool down	
	Age: 64.2 ± 9.5 years			Study duration: 12 weeks	
	G4: combination aerobic–isokinetic strength training ($n=11$)			Follow up at 12 weeks and 24 weeks	
	Age: 63.0 ± 6.6 years				
	Randomized controlled trial				
Azizi et al. 2019 [41]	$N=38$	Type 2 DM	Foot ulcers, vascular, musculoskeletal, neurological disorders	Light stretching, warm-up exercises, treadmill walking with moderate intensity, and cooldown exercises	Distal sensory latency and amplitude for the sural nerve
	Age: 56.9 ± 6.2 years	Distal peripheral neuropathy	Impaired balance or walking,	Exercise 40 to 45 min with the intensity of 70–85% of their maximum HR(heart rate)	Distal motor amplitude, velocity, and F-wave for tibial and deep peroneal nerves
	Males: 14	systolic/diastolic blood pressure < 160/100 mm Hg,	Disabilities such as peripheral arterial disease, postural hypotension, visual defect, vestibular disorders, herniated disc	Study duration:8 weeks	
	Females: 21	HbA 1c < 7%,	DM > 10 years		

Table 3 (continued)

Author	Subjects (without dropouts) Age ± S.D Study design	Inclusion criteria	Exclusion criteria	Intervention	Outcome measures
	Single-blind, 1-group, before-and-after clinical trial	Fasting blood glucose < 200 mg/dL	neuropathy > 5 years		
			H/o seeking treatment for peripheral neuropathy		
			Unwilling to follow the exercise program		
Kluding et al. 2012 [43]	$N = 19$	Signs and symptoms of DPN	Serious cardiac pathology—Musculoskeletal problems that would limit exercise ability	Moderate level of aerobic exercises using recumbent stepper, upright cycle and treadmill after light stretches, (50–70% of VO2 reserve) and strengthening exercises of moderate resistance in range (7–8 out of 10). Abdomial curls, bicep curl, chest press, lateral pulldown, leg extensions, seated leg curls, seated rows, shoulder press, squats, triceps press	100 mm VAS scale
	One group	Age group of 40–70 years	Open feet wounds	Study duration:10 weeks	HbA1C
	Age: 58.4 ± 5.98 years		Inability to ambulate independently		MNSI symptom score
	Male—8		Stroke/other CNS pathology		IENF
	Females—9		Stage 2 hypertension		Quantitative sensory testing
	Age—58.4 ± 5.98		H/o lidocaine allergy		MNSI physical exam score
	pre-test post-test design				NCV, amplitude, latency of sural, peroneal and tibial nerve
Doshi and Singarvalen. 2019 [42]	$N = 20$	Diabetic neuropathy with bilateral pinprick sensation over the sole of foot	Diabetic ulcer	Tibial nerve mobilization	Sensory sural nerve conduction velocity
	Males: $n = 9$	Both male and female participants	Comorbid disorders	Five sessions/week for 3 weeks	
	Age: 46.33 ± 4.79 years	Age group of 50–60 years		Study duration: 5 months	
	Females = 11	Ability to understand and co-operate for instructions of the test			

Table 3 (continued)

Author	Subjects (without dropouts) Age ± S.D Study design	Inclusion criteria	Exclusion criteria	Intervention	Outcome measures
	Age: 50.36 ± 7.24 years				
	Experimental prepost study design				
Alsubiheen et al. 2017 [40]	*N* = 20	Type 2 DM (2–20 years)	On medications which can affect balance,	TC (tai chi) exercise combined with mental imaginary 1-h sessions, 2 times a week for 8 weeks	HbA1c
	Age: 63.8 ± 8.1 years	Duration of onset of diabetes was 10.8 ± 5.4 years	H/o of frequent falling, vision problems, orthopedic/ neuromuscular/cardiovascular impairments that restrict exercise	15 min of warm-up exercises, including stretching, loosening the muscles, breathing exercises,	ABC scale (the activities-specific balance confidence)
	Prepost study design	Mean HbA1C 6.8 ± 0.8		10 min of basic walking drills with and without hand techniques,	FRT distance (functional reach test)
		Hb a1c > 6.5,		15 min of TC Yang style technique teaching	OLS time (one leg standing test)
		Fasting blood glucose > 129 mg % before intervention		Study duration: 8 weeks	Soleus H-reflex latency and H/M ratio
		Full blown diabetes			NCV, latency and amplitude of sural and superficial peroneal nerve
		not practiced TC			
		Do not exercise more than once per week			
		BMI between 10 and 35 kg/m^2			
		Normal/ controlled blood pressure			
		normal ROM			
		Atleast 5/5 muscle power bilaterally			

standard care [33, 34, 36, 38], moderate home exercises [39], and habitual physical activity [35]. Balducci et al. [32] compared the supervised exercise group with diabetic patients of sedentary lifestyle. Hung et al. [29] made comparison between healthy participants and diabetic population using tai chi exercises. Stubbs et al. [37] compared standard care against aerobic exercises, isokinetic exercises, and with combination of aerobics and isokinetic exercises. One study [34] even compared the aerobic exercise group with two other groups, one group was given TENS (transcutaneous electrical nerve stimulation) and another one was on oral hypoglycemic drugs and nerve growth stimulants.

Outcome measures

Sensory nerve functions

Total of eight studies [32, 33, 35, 37, 38, 40–43] included NCS of sural sensory nerve as outcome measure. One study [40] included superficial peroneal nerve along with sural nerve and another study [34] included NCS of medial plantar nerve.

Sural nerve

Balducci et al. [32] showed non-significant increase in experimental group and a significant decrease in the control group in NCV of sensory sural nerve. Difference in distal latency and NAPA of sural nerve was also non-significant in both groups after 4 years of aerobic exercise training on treadmill. After 8 weeks of moderate intensity aerobic exercises on treadmill, Dixit et al. [33] found a significant difference for conduction velocity and a non-significant difference for latency, duration, and amplitude in the two groups. Gholami et al. [35] showed NCV of sural nerve increased significantly in the exercise group and non-significant changes in NAPA after 12 weeks of aerobic exercises on treadmill. Kluding et al. [43] showed non-significant changes in NCS of sensory sural nerve after 10 weeks of moderate intensity aerobic exercises on treadmill, stepper, upright cycle along with strengthening exercises. Alsubiheen et al. [40] observed significant improvement in velocity, amplitude and latency of sural nerve after completing 8 weeks of tai chi exercises. Azizi et al. [41] demonstrated statistically significant increase in sural sensory nerve action potential amplitude and non-significant changes in latency after 8 weeks of aerobic exercise program on treadmill with moderate intensity. Doshi and Singarvelan. [42] showed statistically significant difference in NCV of sural nerve after 3 weeks of tibial nerve mobilization. No changes were seen in electrophysiological parameters of sural nerve by Stubbs et al. [37] irrespective of kind of exercise for 12 weeks. Though, Gholami et al. [38] achieved significant improvements in NCV of sural nerves, without any improvement in NAPA.

Medial plantar nerve

Serry et al. [34] showed that there was no statistically significant differences in sensory conduction velocity of medial plantar nerve in any of three groups after 8 weeks of aerobic exercises on stationary bicycle or TENS treatment when compared to standard medical care.

Superficial peroneal nerve

Significant improvements were noticed by Alsubiheen et al. [40] in velocity, amplitude and latency of superficial peroneal nerve after 8 weeks of tai chi exercises.

Motor nerve functions

Ten studies [29, 32, 33, 35–39, 41, 43] observed effects of different exercise interventions on motor functions of peroneal nerve and eight studies [29, 35–39, 41, 43] assessed such effects on both peroneal and tibial nerves.

Peroneal and tibial nerves Balducci et al. [32] showed that after four years of aerobic exercise training, there was significant increase in NCV of peroneal motor nerve in intervention group whereas control group showed insignificant decrease in conduction velocity. There was no significant difference in DL and NAPA of peroneal nerve between the two groups. Hung et al. [29] showed significant improvements in NCV of motor tibial nerve in DM group after 12 weeks of tai chi exercises. No significant changes were observed in distal latency and proximal/distal amplitudes in DM group post intervention.

Following 8 weeks of moderate intensity aerobic exercises, Dixit et al. [33] found that there was a significant difference in the conduction velocity of the distal segment of the peroneal nerve. However, there was no significant difference for latency and duration. Also, there was significant increase in the peroneal nerve's mean velocity. Singleton et al. [39] observed no significant improvements in tibial F-response latency and Peroneal NCV after 1 year of aerobics and resistance exercises.

According to Gholami et al. [35], the peroneal motor nerve's NCV increased from 39 m/s at week 0 to 40.4 m/s at week 12 ($p = 0.021$). In the motor NCV of the peroneal and tibial nerves, however, the time group interaction was not statistically significant. There were no statistically significant changes in NAPA of tibial or peroneal nerve in any of the groups after 12 weeks of aerobic exercise. Ahmad et al. [36] observed 6.43% increase in the intervention group in conduction velocity of the peroneal nerve in comparison to 0.6% increase in control group. It was also notable that there was a difference in the peroneal nerve's conduction velocity for both the time effect and the time group interaction. Tibial nerve's conduction velocity likewise shown a significant temporal effect. Intervention group showed 12.46% increase in conduction velocity and control group showed and 8.83 increase in conduction velocity of tibial nerve. There were significant improvements in time × group interaction for tibial nerve latency. Although the distal latency of the tibial nerve decreased in the sensorimotor exercise and gait training group, the latency increased in the control group. With regard to time or group, the peroneal nerve's amplitude and duration did not significantly change.

Kluding et al. [43] did not observed any significant changes in latency, amplitude or conduction velocity of peroneal and tibial nerve after combination of 10 weeks of moderate intensity aerobic exercises and strengthening exercises. Azizi et al. [41] observed significant increase in CMAP amplitude of tibial nerve and significant decrease in NCV and F-wave of tibial nerve. For deep peroneal nerve, there was statistically significant increase in NCV and non-significant changes in CMAP, amplitude and F-wave after 8 weeks of moderate intensity aerobic exercises. Stubbs et al. [37] did not achieved any significant improvements in motor nerve conduction of either nerve in any intervention of 12 weeks. On the contrary, Gholami et al. [38] achieved significant improvements in MNCV of peroneal nerve after 12 weeks of resistance exercises (changes in NCS with different exercises are mentioned in Table 4).

Discussion

This systematic review evaluated the changes in NCS of lower limb sensory as well as motor nerves after different exercises and manual therapy in patients with DM with and without peripheral neuropathy. All the studies that included tai chi exercises, sensorimotor training, neurodynamic mobilization and most of studies with moderate intensity aerobic exercises on treadmill or bicycle have showed improvement in NCVs of motor peroneal, tibial nerves and sensory sural nerve with non-significant effects on that sensory NAPA and latency in DM with or without peripheral neuropathy.

NCS are known to document the severity and changes in neuropathy and the outcomes are reproducible and standardized [44]. Nerve conduction detects neuropathy even before signs develop, thus diagnostic value of NCS is better than clinical examination, Vibration perception threshold or other neuropathy symptom scores as sensory neuropathies are better picked by SNAP than VPT and motor neuropathies are appreciated more in CMAP than clinical examinations [45].

Sensory symptoms presented in diabetic neuropathy patients begins with injury to sensory nerve fibers that results from demyelination which precedes axonal loss as evident in neurophysiological studies [46, 47], Later involving the motor fibers [48]. Conduction velocity and amplitude of sural and peroneal nerves are known to be reduced in diabetics in comparison to healthy individuals [49]. Thus, predicting the changes in nerve conduction can better predict the effects of different exercises on neuropathy than other outcome measures.

Moderate intensity exercises

Amongst the six studies [32–35, 37, 41] that examined effects of moderate intensity aerobic exercises, two studies [33, 35] observed improvements in sensory NCV of sural nerve without any significant changes in NAPA, latency and duration after 8 weeks and 12 weeks of moderate intensity aerobic exercises respectively. Gholami et al. [35] also observed significant reduction in fasting glucose levels, HbA1c, and BMI levels indicating that the exercises has resulted in improved glucose control that facilitated blood flow to peripheral nerves. As has been suggested sensory nerves are more sensitive to hyperglycemia and exercise related adaptations, so gets affected in early course of disease and shows improvements even faster [50, 51].Though Dixit et al. [33] did not find any improvements in metabolic parameters but observed reduction in insulin dosage in experimental group whereas the control group had increased insulin dosage.

Authors suggested reversal of impaired oxygenation brought about by improved nitrous oxide production could have prevented micro- and macrovascular complications that might have reversed the neuropathy [52]. On the contrary Azizi et al. [41] found significant improvements in sural sensory NAPA without any changes in latency. As suggested by Orlando et al. [53], electrical activities of nerves improve by improving neural collateral sprouting brought about by exercises by means of increased blood flow to meet metabolic requirements. Azizi et al. [41] stated that improved action potential amplitude is the result of reduced lower limb edema and distance between the nerve and point of recording electrical activity. Over the course of 12 weeks of intervention, Stubbs et al. [37] found no differences in HbA1c in the group that received moderate intensity aerobic exercises. Even the other two groups with resistance exercises and combined aerobic and resistance training did not showed any changes in nerve conduction or glucose parameters. Although there were minor improvements in sensory nerve functioning ($p = 0.01$) and noticeable improvement in nerve fiber density in the intervention groups, the authors credit this to the enhanced localized production of several neurotrophic (BDNF, NGF, NT-3) and associated factors by the sensory ganglia. Serry et al. [34] who compared aerobic exercises with pharmacological group and group receiving TENS also did not observed any changes in medial plantar nerve SCV. Though the reason they gave for the same is that medial plantar sensory NCS provided a more sensitive diagnosis of DPN, even in patients with normal range measurements in the sural nerve [54, 55]. On the contrary, Frigeni et al. [56] recommended examination of dorsal sural nerve rather than medial plantar nerve for comfortable and accurate diagnosis. Similarly, Kural et al. [57] concluded that distal nerve NCS, particularly the dorsal sural nerve, has excellent diagnostic power comparable to sural NNT recording in DPN.

Another study that examined effects of moderate intensity aerobic exercises was Balducci et al. [32] who observed non-significant increase in NCV of sural nerve and significant reduction of same in control group without any significant changes in DL and NAPA of sural nerve. Since Balducci et al. [32] enrolled patients of diabetes without neuropathy unlike Dixit et al. [33] and Gholami et al. [35] who included patients with neuropathy symptoms observed that the patients who performed moderate intensity aerobic exercises developed less sensory and motor neuropathy as compared to sedentary patients over 4 years of duration. Though he did not achieve any changes in glucose parameters and BMI and considered the local microvascular changes in peripheral nerves resulted from exercises responsible for the outcomes of study. Improvement in metabolic requirements, endothelial vasodilation [58, 59], and higher vascular growth factor expression resulted from exercises are considered as the factors responsible for the effects [60]. Amongst the studies that investigated effects of moderate intensity aerobic exercises on motor nerve conduction three studies [32, 33, 41] observed significant improvements in NCV of peroneal nerve; however, two studies [35, 37] did not observed any significant improvements in motor peroneal/tibial nerve conduction. Possible explanation for same is differential nerve fiber involvement among DSPN patients as small unmyelinated sensory nerve fibers can regenerate faster than large myelinated motor fibers [48, 61, 62].

Resistance training

Resistance training is known to induce neuroplasticity [63] and enhance nerve regeneration by activating the effects of neurotrophin and increasing expression of brain derived neurotrophic factors [64]. Four studies [37–39, 43] observed effects of resistance training either alone or in combination with other exercises on nerve conduction parameters of lower limb nerves. Amongst these, three studies [37, 39, 43] included moderate intensity aerobic exercises in combination with moderate resistance strengthening exercises but did not observe any significant improvements in sural, tibial, or peroneal nerve conduction parameters; however, there were appreciable changes in IENFD in all three studies. As Singleton et al. [39] observed significant improvements in proximal thigh and distal ankle IENFD, Kluding et al. [43] found increased axonal branching at the proximal biopsy site and Stubbs et al. [37] noticed marked improvement in about 50% patients in ENFD, suggesting regeneration of distal nerves. In a different study that looked at how resistance training alone affected DPN, Gholami et al. [38] found that there were significant improvements in sural sensory NCV both among and between groups, but no significant changes in SNAP. Motor peroneal NCV and NAPA also improved significantly in experimental group and between groups after 12 weeks of training.

Tai Chi

Two studies [29, 40] observed effects of tai chi exercises on type 2 DM patients. Alsubiheen et al. [40] observed significant improvements in NCV, amplitude as well as latency of sural sensory and superficial peroneal nerves after 8 weeks of tai chi exercises 1 h daily with mental imaginary session and TC yang exercises twice daily. They suggested that improved peripheral micro circulation brought about by increased cardiac output was responsible for improved nerve conduction. Hung et al. [29] who examined effects of tai chi exercises of 12 weeks duration observed significant improvements in Motor NCV of tibial nerve without any changes in CMAP. Tai chi is a body-mind exercise that includes combination of weight shifting, postural alignment, coordinated with synchronized deep breathing [65, 66], and concentration on complete movement as complex series of movements which is essential for re learning of damaged nervous system makes it different from other exercises [7, 67]. Tai chi exercises may be related to improve blood sugar control and insulin resistance, along with improved NO release that is responsible for bringing improvement in NCV.

Manual therapy

Doshi and Singarvalem. [42] achieved significant improvements in SNCV of sural nerve after 3 weeks of neurodynamic mobilization of tibial nerve in DPN patients. Neurodynamic mobilization is known to reduce neural edema and concentration of proinflammatory mediators, thereby promoting nerve regeneration and neural plasticity [68, 69]. Neurodynamic mobilization also improves vibration perception thresholds [70], neuropathic pain, and quality of life in DPN patients [71]. Various cadaver [72, 73] and animal studies [74] also shows the effectiveness of manual therapy in DPN.

Table 4 Results

Author. year	Outcome measurement	Results					Conclusion
		Pre control	Post control	Pre intervention	Post intervention	*p*-value	
Balducci et al. 2006 [32]	Peroneal motor						Significant differences in delta in NCV for both peroneal and sural nerve between the intervention and control group. Peroneal motor NCV significantly increased in the intervention group and insignificantly decreased in the control group. No significant increase in sensory sural nerve in the intervention group and significant decrease in the control group. No significant difference in both peroneal and sural DL and NAPA between the two groups.
	NCV (m/s)	46.6 ± 3.2	46 ± 5.36	47 ± 3.27	48.8 ± 2.24*	$p < 0.05$, Delta NCV, $p < 0.001$	
	NAPA (mV)	2.93 ± 1.68	2.70 ± 1.07	3.19 ± 1.9	2.81 ± 0.98		
	DL (m/s)	4.41 ± 0.64	4.40 ± 0.61	4.38 ± 0.83	4.34 ± 0.49		
	Sural sensory						
	NCV (m/s)	47.0 ± 3.5	44.3 ± 7.84*	47.1 ± 4.01	47.5 ± 3.18	$p < 0.05$, Delta NCV, $p < 0.001$	
	NAPA (µV)	20.3 ± 5.02	19.4 ± 4.66	21.5 ± 5.24	21.7 ± 5.44		
	DL (m/s)	3.43 ± 0.54	3.27 ± 0.52	3.40 ± 0.92	3.25 ± 0.50		
Hung et al. 2009 [29]	Right Peroneal motor						Patients with DM improved significantly, both in right NCVs and left NCVs. No significant improvements in the control group. Proximal amplitudes increased in the DM group, did not reach a significant increase (right: $p = 0.077$; left: $p = 0.085$). No significant improvements in the control group. Proximal amplitudes increased in the DM group, did not reach a significant increase (right: $p = 0.077$; left: $p = 0.085$). Distal amplitude of any nerve in the DM group did not significantly change. Non-significant changes in both groups in distal latency after intervention.
	NCV(m/Sec)	48.4 ± 3.9	48.8 ± 4.1	45.8 ± 4.4	45.6 ± 3.3	($p = 0.046$)	
	DL (msec)	3.38 ± 0.56	3.43 ± 0.46	3.62 ± 0.74	3.62 ± 0.70		
	Proximal amplitude(mV)	7.74 ± 3.30	8.29 ± 3.95	6.04 ± 2.25	6.18 ± 2.34		
	Left Peroneal motor.						
	NCV (m/sec)	48.4 ± 3.3	48.4 ± 4.1	45.9 ± 4.9	45.6 ± 3.2	($p = 0.041$)	
	DL (msec)	3.48 ± 0.51	3.44 ± 0.47	3.45 ± 0.50	3.45 ± 0.53		
	Proximal amplitude (mV)	7.54 ± 3.32	8.01 ± 3.89	5.96 ± 2.54	6.30 ± 2.53		
	Right tibial motor						
	NCV (m/sec)	47.8 ± 4.4	47.9 ± 4.0	43.4 ± 5.2	45.5 ± 4.4	$p = 0.027$	
	DL (msec)	3.63 ± 0.53	3.59 ± 0.60	3.89 ± 0.77	3.89 ± 1.0		
	Proximal amplitude (mV)	16.3 ± 5.16	16.8 ± 4.79	11.5 ± 6.41	11.7 ± 7.13		
	Left tibial motor						
	NCV (m/sec)	47.5 ± 4.4	47.4 ± 4.5	44.1 ± 4.9	45.3 ± 4.3	$p = 0.036$	
	DL (msec)	3.73 ± 0.58	3.68 ± 0.52	4.08 ± 0.86	3.86 ± 0.83		
	Proximal amplitude (mV)	17.0 ± 5.78	17.3 ± 5.29	10.3 ± 6.37	10.7 ± 6.52		
Dixit et al. 2014 [33]	Peroneal motor						Distal peroneal NCV: significant difference in two groups at 8 weeks. (*p* value less than 0.05 was considered significant) Sural sensory nerve at 8 weeks: significant difference in two groups for conduction velocity. No significant differences in latency, amplitude and duration in either nerve.
	NCV (m/s)	38.40 ± 1.36	38.21 ± 1.31	42.48 ± 1.25	45.56 ± 1.24	$p = 0.03$	
	Latency (msec)	3.33 ± 1.78	3.16 ± 1.83	4.04 ± 1.57	4.34 ± 1.25	$p = 0.11$	
	Amplitude (mV)	4.55 ± 2.28	4.75 ± 2.13	6.81 ± 2.07	6.31 ± 2	$p = 0.65$	
	Duration (msec)	10.69 ± 1.27	10.89 ± 1.23	9.99 ± 1.27	10.76 ± 1.23	$p = 0.08$	

Table 4 (continued)

Author. year	Outcome measurement	Results					Conclusion
		Pre control	Post control	Pre intervention	Post intervention	*p*-value	
	Sural Sensory						
	NCV (m/s)	28.23 ± 1.49	28.53 ± 1.49	23.67 ± 1.81	31.39 ± 1.58	P < 0.001	
	Latency (msec)	3.39 ± 1.35	3.39 ± 1.45	3.51 ± 1.50	3.45 ± 1.38	$p = 0.33$	
	Amplitude (mV)	3.23 ± 2.19	3.94 ± 2.23	2.48 ± 2.55	2.14 ± 2.38	$p = 0.85$	
	Duration (msec)	1.49 ± 1.50	1.46 ± 1.90	1.45 ± 1.89	1.86 ± 1.75	$p = 0.27$	
Singleton et al. 2014 [39]	Peroneal Motor						Non-significant changes in neuropathy measures between groups at 12 months. Significant improvements in IENFD in exercise group.
	NCV (m/sec)	44.9 ± 4.0	2.4 ± 8.3	44.7 ± 4.4	0.8 ± 7.7	$p = 0.36$	
	Tibial F-wave						
	F-response Latency (msec)	52.7 ± 6.9	0.7 ± 4.0	53.1 ± 5.7	-0.2 ± 2.9	$p = 0.28$	
Gholami et al. 2021 [38]	Peroneal motor						There was significant difference between groups in sural sensory and peroneal motor NCV. Increase of motor Peroneal APA in the experimental group.
	NCV (m/s)	36.02 ± 9.41	35.90 ± 8.97	33.01 ± 8.88	35.38 ± 8.72	$p = 0.001$	
	NAPA (mV)	2.95 ± 1.33	2.98 ± 1.29	2.92 ± 1.16	3.12 ± 1.15	$p = 0.034$	
	Sural sensory						
	NCV (m/s)	28.56 ± 8.92	28.93 ± 8.69	27.62 ± 8.75	30.06 ± 8.56	$p = 0.001$	
	NAPA (μV)	4.67 ± 2.01	4.64 ± 1.99	4.54 ± 2.06	4.63 ± 2.05	$p = 0.139$	
Kluding et al. 2012 [43]	Peroneal motor	NA	NA				No significant changes in any of the nerve conduction study or quantitative sensory testing. Significant improvements were found in ratings of the worst pain over the past months. IENF branching at the proximal biopsy site (0.16 to 0.27 branch nodes/fiber, $p = .008$).
	NCV (m/s)			39.6 ± 11.5	38.9 ± 10.9	$p = 0.46$	
	Latency (ms)			4.1 ± 1.25	4.1 ± 1.17	$p = 1.0$	
	Amplitude (mV)			4.48 ± 2.5	4.53 ± 2.6	$p = 0.85$	
	Tibial motor	NA	NA				
	NCV (m/s)			35.1 ± 10.8	38.4 ± 10.8	$p = 0.71$	
	Latency (ms)			3.63 ± 1.04	3.69 ± 1.13	$p = 0.58$	
	Amplitude (mV)			6.66 ± 5.3	6.6 ± 5.2	$p = 0.85$	
	Sural sensory	NA	NA				
	Latency (ms)			2.99 ± 1.8	2.69 ± 1.8	$p = 0.23$	
	Amplitude (μV)			6.41 ± 5.9	5.59 ± 5.14	$p = 0.35$	

Table 4 (continued)

Author. year	Outcome measurement	Results						Conclusion
		Pre control	Post control	Pre intervention	Post intervention	*p*-value		
Alsubiheen et al. 2017 [40]	Superficial peroneal	NA	NA					Significant improvements in velocity, amplitude and latency of sural nerve. In the superficial peroneal nerve, significant improvements were observed in velocity and latency, No significant changes in amplitude. Soleus H-reflex amplitude significantly increased ($p = 0.02$), no significant changes for latency and H/M ratio.
	NCV (m/s)			28.3 ± 4.8	32.4 ± 5	$p = 0.02$		
	Amplitude (μV)			8.4 ± 2.1	8.3 ± 1.9	$p = 0.96$		
	Latency (ms)			3.2 ± 0.5	2.8 ± 0.5	$p = 0.01$		
	Sural sensory	NA	NA					
	NCV (m/s)			30.9 ± 3.6	33.8 ± 3.9	$p = 0.01$		
	Amplitude (μV)			18.2 ± 4.1	7.6 ± 1.2	$p = 0.01$		
	Latency (ms)			3.7 ± 0.4	3.4 ± 0.4	$p = 0.01$		
Azizi et al. 2019 [41]	Deep peroneal motor	NA	NA					Significant increase in sural sensory nerve action potential amplitude, tibial amplitude of compound muscle action potential, and deep peroneal nerve conduction velocity. Decrease in tibial F-wave and nerve conduction velocity.
	NCV (m/s)			46.5 ± 0.5	48.3 ± 0.6	$p = 0.001$		
	NAPA (mV)			2.5 ± 0.7	2.5 ± 0.8	$p = 0.552$		
	F-wave (ms)			58.5 ± 2.1	58.2 ± 2.4	$p = 0.086$		
	Tibial motor	NA	NA					
	NCV (m/s)			45.0 ± 2.4	43.3 ± 3.1	$p = 0.001$		
	NAPA (mv)			2.8 ± 0.9	3.1 ± 1.1	$p = 0.001$		
	F-wave (ms)			59.4 ± 1.9	58.9 ± 2.3	$p = 0.024$		
	Sensory sural	NA	NA					
	NAPA (μV)			5.9 ± 1.7	7.9 ± 2.5	$p < 0.001$		
	Latency (ms)			3.8 ± 0.6	3.9 ± 0.3	$p = 0.702$		
Doshi & Singarvalem. 2019 [42]	Sensory NCV	N/A	N/A	21.42 ± 3.08	25.37 ± 4.90	$p < 0.05$		Statistically significant difference in the nerve conduction velocity of sural nerve after giving the intervention for three weeks.
		Pre control	Post control	Pre-intervention	Post-intervention	*p*-value (Pre-Post or Group effect)	*p*-value (Time × group)	
Gholami et al. 2018 [35]	Peroneal motor							Sural NCV in the exercise group increased significantly. Changes in peroneal and tibial motor NCV and (NAPA) in all nerves studied were not different between groups ($p > 0.05$).
	NCV(m/s)	41.8 ± 4.4	42.0 ± 5.2	39.0 ± 3.6	40.4 ± 4.4	$p = 0.021$	$p = 0.113$	
	NAPA (μV)	3.0 ± 0.6	3. ± 0.6	3.2 ± 1.7	3.3 ± 1.3	$p = 0.418$	$p = 0.976$	

Table 4 (continued)

Author. year	Outcome measurement	Results						Conclusion
		Pre control	Post control	Pre intervention	Post intervention	*p*-value		
	Tibial motor							
	NCV(m/s)	40.0 ± 3.9	40.5 ± 4.8	38.3 ± 6.6	40.2 ± 6.1	NA	$p = 0.278$	
	NAPA (µV)	4.7 ± 2.0	4.8 ± 1.8	5.0 ± 1.3	5.4 ± 1.5	$p = 0.684$	$p = 0.366$	
	Sural sensory							
	NCV(m/s)	33.7 ± 2.5	33.0 ± 2.8	35.2 ± 4.3	37.3 ± 6.2	$p = < 0.05$	$p = 0.07$	
	NAPA (µV)	6.7 ± 2.1	6.8 ± 2.1	7.1 ± 2.6	7.4 ± 2.5	$P = 0.364$	$P = 0.654$	
Ahmad et al. 2020 [36]	Peroneal motor							Conduction velocity of the peroneal nerve showed 6.43% increase in the intervention group. No significant changes in latency, amplitude and duration of the peroneal nerve within and between-group comparisons. There was an increase in conduction velocity of tibial nerve in both groups. Decrease in distal latency of tibial nerve in intervention group.
	NCV (m/Sec)	36.37 ± 7.9	36.60 ± 8.47	38.37 ± 6.62	40.84 ± 5.88	$p = 0.183$	$p = 0.022$	
	Latency (msec)	4.12 ± 1.32	4.15 ± 1.2	4.19 ± 1.2	3.70 ± 0.75	$p = 0.579$	$p = 0.061$	
	Amplitude (mV)	4.45 ± 1.85	4.34 ± 1.67	4.44 ± 2.21	4.44 ± 2.05	$p = 0.507$	$p = 0.061$	
	Duration (msec)	10.61 ± 2.8	10.86 ± 2.4	10.32 ± 2.02	10.06 ± 2.03	$p = 0.453$	$p = 0.222$	
	Tibial motor							
	NCV (m/sec)	38.39 ± 11.69	41.78 ± 10.8	37.94 ± 7.35	42.67 ± 8.57	$p = 0.941$	$p = 0.503$	
	Latency (msec)	4.59 ± 0.79	4.91 ± 0.94	4.80 ± 1.13	4.39 ± 0.92	$p = 0.574$	$p = 0.03$	
	Amplitude (mV)	6.12 ± 3.89	6.56 ± 4.3	6.74 ± 3.83	6.72 ± 3.56	$p = 0.758$	$p = 0.279$	
	Duration (msec)	7.92 ± 2.02	8.33 ± 2.03	8.04 ± 1.34	8.03 ± 1.71	$p = 0.872$	$p = 0.346$	
		Group A (TENS) Pre	Group A (TENS) Post	Group B (Exercise) Pre	Group B (Exercise) Post	Group C (Pharma) Pre	Group C (Pharma) Post	
Serry et al. 2016 [34]	Medial Plantar Sensory							No significant effect on medial plantar NCV in any group. No significant difference between three groups in NCV.
	NCV(m/sec)	27.69 ± 3.14	27.74 ± 3.15	28.01 ± 2.67	28.07 ± 2.62	27.89 ± 3.13	27.91 ± 3.07	
		At Baseline (Sedentary group)	At 12 weeks (Sedentary group)	At Baseline (Exercise groups) Three different Exercise groups: Aerobic, Strength, Combine	At 12 weeks (Exercise groups)	No. of individual patients exhibiting improvement of individual responses		

Table 4 (continued)

Author. year	Outcome measurement	Results					Conclusion
		Pre control	Post control	Pre intervention	Post intervention	*p*-value	
Stubbs et al. 2019 [37]	Peroneal & Tibial Motor						No significant difference was observed in tibial and peroneal motor nerve within and across experimental groups (among any of the group exercise), regardless of type of exercise.
	NCV	Values NR	Values NR	Values NR	Values NR	> 10% increase	
	Latency	Values NR	Values NR	Values NR	Values NR	> 10% decrease	
	Amplitude	Values NR	Values NR	Values NR	Values NR	> 10% increase	
	Sural Sensory						Qualitative improvement in NAPA of sensory sural nerve that had been absent in prior baseline evaluation.
	NCV	Values NR	Values NR	Values NR	Values NR	> 10% increase	
	Latency	Values NR	Values NR	Values NR	Values NR	> 10% decrease	
	Amplitude	Values NR	Values NR	Values NR	Values NR	> 10% increase	

DL Distal Latency; *NAPA* Nerve action potential amplitude; *NCV* Nerve conduction velocity; *NA* Not Available; *NR* Not reported; $p < 0.05$ was considered as significant difference

Sensorimotor training

Sensorimotor training is known to improve sensory inputs and muscle activation that aids in preserving joint stability [75]. These techniques regulate the movement through central nervous system and are known to improve balance, proprioception [3, 76], and gait parameters [77] in DPN. Ahmad et al. [36] showed significant improvements in NCV of peroneal and tibial nerve after 8 weeks of sensorimotor and gait training without any significant improvements in latency, duration, and amplitude. This restoration in nerve function mechanism might be due to reversal of chronic hypoxia of nerves brought about by increase in endoneural blood flow, decrease in nitrous oxide that prevented polyol pathway in diabetes and had deleterious effects on Schwann cells and endothelium [52, 60, 78].

Most of the studies included in this review that showed improvements in NCS of lower limb nerves have followed the exercise recommendation of at least every alternate day and minimum 150 min/week of physical activity including aerobic exercises and resistance training for optimal glycemic and health outcomes as suggested by "The American Diabetes Association"(ADA) [79]. Other than two studies [39, 43] that did not show significant improvements in nerve conduction parameters of lower limb nerves have given weekly exercises of less frequency and duration than recommended by ADA. This points towards the importance of duration and frequency of exercises.

Though chronic hyperglycemia and dyslipidemia caused by insulin resistance causes oxidative stress and thus cellular damage resulting in neuropathic symptoms in DPN [80, 81], studies [35, 36, 38, 43] had shown improvements in metabolic parameters along with NCS while others [32, 33, 37, 41] do not. Neuropathy develops even in prediabetic patients and diabetic patients with glycemic control [22] indicating that there can be some other mechanisms other than glucose control through which physical exercises can enhance nerve regeneration [32, 39, 82–84]. Exercise was thought to promote the expression of neurotrophins, including glial-derived neurotrophic factor (GDNF) and brain-derived neurotropic factors (BDNF) [83] and insulin-like growth factor-1 (IGF-1) that modulates axonal plasticity [85]. According to a study done by Asensio-Pinilla et al. [82], mice trained on a treadmill had higher numbers and larger sizes of regenerated axons, more mature myelination, and more pronounced muscular hypertrophy than mice who received no exercise interventions. Wilhelm et al. [84] also observed that exercise training increases BDNF in neurons by which regenerating axons overcome a lack of BDNF expression in cells in the pathway through which they regenerate. In a study, exercise group has shown improvements in the amplitude of the CMAP and shorter distal latency in the exercise group compared to no-exercise indicating better myelination of the regenerating fibers [85].

Limitations of the review

This review has included both RCT's as well as prepost study designs that has compromised the quality of study. Inaccessibility of some databases that was proposed prospectively in PROSPERO registration has further limited the scope of findings. There was heterogeneity in inclusion criteria, diagnostic measures, duration, and frequency of exercises given, so proposed meta-analysis could not be done, and outcomes cannot be generalized. Small sample size and shorter duration of studies can affect the outcomes in NCS.

Strength of study

This is the first study to analyze effects of different exercises on NCS of lower limb in diabetes and diabetic peripheral neuropathy. The study examined the scientific literature on both diabetes and diabetic neuropathy to ensure that the findings can be applicable to a wider population and demonstrate the risk of neuropathy that may arise in diabetic patients even before clinical presentation. This study contributes significant clinical data for a health problem that needs urgent attention both domestically and internationally to the body of existing research and can be used as a reference to incorporate physical exercises and early detection of nerve conduction parameters to halt the disease's progression.

Implications for future studies

Neuropathic symptoms associated with diabetes are result of changes in axons that take a specific time period to be presented in nerve conduction depending on rate of degeneration or regeneration. Thus, to evaluate such changes and effects of different physical exercises on same needs more homogenous studies of longer duration.

Conclusion

Majority of studies included in this review used moderate intensity aerobic exercises, though they varied in methodological quality, dosage, and duration of intervention. This systematic review indicates that moderate intensity aerobic exercises, tai chi exercises, sensorimotor training, and manual therapy modifies neuropathic symptoms caused by hyperglycemia and improves NCV of sensory sural and motor peroneal/tibial nerves. Manual therapy seems to be a promising management in treatment of symptoms associated with DPN, though due to limited number of studies results cannot be generalized.

Declarations

Competing interests The authors declare no competing interests.

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