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Physical Exercise as Treatment for Type 2 Diabetes Distal Symmetric Polyneuropathy: A Systematic Review of Randomized and Controlled Studies

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Abstract

Pharmaceuticals targeting the pathogenesis of diabetic distal symmetric polyneuropathy have all failed in clinical trials, limiting recourse to palliative treatments. The American Diabetes Association regards the effectiveness of glycemic control and lifestyle modification therapies on diabetic neuropathies as inconclusive. The objective of this research was to determine if and how physical exercise influences distal symmetric polyneuropathic severity in type 2 diabetes patients. Embase, MEDLINE, and Google Scholar were searched to collect randomized and controlled studies published between January 1, 2012 and April 20, 2020. Titles had to mention diabetes, physical exercise of any type or lifestyle interventions in general, and neuropathy. Abstracts had to indicate satisfaction of PICOS criteria, whereas full-text reviews had to be fully confirmatory. Extracted data was thematically synthesized based primarily on relationships between exercise interventions and effects on distal symmetric polyneuropathic severity outcomes in type 2 diabetes patients. Qualitative analysis scoring criteria objectively mirrored PICO except for the bias and limitation score component, which assessed common markers of validity for randomized trials (as specified in the PRISMA statement). Database searches yielded 379 unique records, 15 of which passed eligibility screening. Thematic synthesis supported exercise as an ameliorative treatment of type 2 diabetes distal symmetric polyneuropathy through improved Michigan Diabetic Neuropathy Scores and increased sural sensory nerve conduction velocity, though efficacy may be limited by neuropathic severity. This is the first systematic review to acquire these results, and to do so within the context

of neuropathic severity. This review protocol is registered on PROSPERO (CRD42020181211) at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020181211.

Keywords

Type 2 Diabetes, Peripheral Neuropathy, Distal Symmetric Polyneuropathy, Physical Exercise, Lifestyle Interventions

1. Introduction

Type 2 diabetes (T2D) is characterized by progressively decreasing pancreatic β-cell insulin secretion alongside increasing insulin resistance of adipocytes, myocytes, hepatocytes, and vascular endothelial cells, which together results in increased lipolysis, impaired peripheral vasodilation, and reduced glucose delivery and uptake [1] [2]. In 2017, the International Diabetes Federation estimated the worldwide prevalence of diabetes at 425 million (90% - 95% of which is T2D), projecting an increase to 628 million by 2045 [3]. As of 2018 in the USA alone, the CDC estimated the prevalence of prediabetes—which annually converts to T2D at a rate of 3% - 11%—at 88 million and T2D at 30 million, which respectively comprised 35% and 10% of the adult population [3] [4]. Most T2D patients are overweight or obese, constitutions which—independently of T2D—can cause decreased insulin sensitivity, increased blood glucose levels, and neuropathies. Body mass index (BMI) values of ≥25.0 kg/m^2 have the strongest association with and remain the most critical risk factor for developing T2D [2] [5]. Glycated hemoglobin (HbA1c) level of ≥6.5% is both an indicator of prolonged hyperglycemia and diagnostic of diabetes. Weight loss and glycemic control (*i.e.*, reduced HbA1c levels) have been associated with improved insulin sensitivity, though the precise mechanisms for this are unclear [1]. Routine exercise may mitigate these risk factors, especially obesity, while enhancing blood flow and glucose delivery to peripheral tissues [6] [7].

Distal symmetric polyneuropathy (DSPN) is a type of diffuse diabetic neuropathy and a predominately sensory peripheral nervous system disorder involving axonal degeneration and impaired regeneration that debilitates up to 50% of diabetes patients, constitutes the majority of neuropathies worldwide, and consumes roughly 25% of diabetes treatment healthcare expenditures in the USA [4] [5]. DSPN accounts for 75% of all diabetic neuropathies and is present in 10% - 15% of newly diagnosed T2D patients regardless of age, increasing to 50% after 10 years [8]. DSPN patients experience increased mortality and severely decreased quality of life due to disability, psychosocial deterioration, insomnia, chronic pain, insensate lower limbs resulting in injuries due to falls, and late complications (such as Charcot neuroarthropathy and foot ulceration) that may ultimately require amputation [4] [8] [9]. The American Diabetes Association

defines DSPN as a diagnosis of exclusion, consequent its multifactorial pathogenesis and the possible co-occurrence of other diabetic and non-diabetic neuropathies. Current research supports a model whereby metabolic and vascular dysfunction restricts oxygen and nutrient delivery while simultaneously inciting inflammatory processes that collectively damage nerve cells, but the underlying causative mechanisms and practical pharmacotherapeutic targets remain uncertain [8].

DSPN occurs as three distinct neuropathic phenotypes, differentiated by the type of nerve fibers involved and their associated general somatic sensory modalities: primarily small fiber, primarily large fiber, and—most common—mixed small and large fiber sensory neuropathies. Small-diameter nerve fibers (SNF; mostly unmyelinated C fibers) primarily supply pain and thermal modalities (nociceptive sensations), whereas large-diameter nerve fibers (LNF; myelinated A and B fibers) primarily supply tactile and peripheral proprioceptive modalities. SNF sensory neuropathy symptoms are painful and include burning, shooting, and stabbing sensations, whereas LNF sensory neuropathy presents as numbness, tingling, and foot weakness and imbalance. Mixed fiber sensory neuropathy involves both sets of symptoms [4] [8]. DSPN diagnosis requires the presentation of certain signs or symptoms of either or both sensory and motor loss in a symmetrical and distal-to-proximal pattern—often referred to as a stocking-and-glove distribution—usually affecting the lower limbs first. These phenomena reflect the differential involvement of the aforementioned nerve types and can be analyzed using quantitative sensory testing (QST). SNF testing involves temperature threshold and pinprick or pain sensations, whereas LNF testing involves ankle reflexes, vibration perception, and 10g monofilament light touch sensation [8] [10]. Proprioception abnormalities are also diagnostic and primarily reflect LNF involvement; they can be evaluated by analyzing gait patterns or balance parameters using posturography assessments, including the one-leg stance or unipedal stance test (OLS/UST) [8] [11] [12]. Although not diagnostic, nerve conduction studies—such as nerve conduction velocity (NCV)—are sensitive and specific measures of LNF functionality, but display significant interobserver variability due to a lack of standardization [4] [13]. Several clinical instruments incorporating these assessments are available to screen for and estimate the severity of DSPN, such as the Michigan Neuropathy Screening Instrument (MNSI) and Michigan Diabetic Neuropathy Score (MDNS) [8] [14].

All pharmaceuticals aimed at potential DSPN pathogenesis targets have failed in clinical trials [8] [9]. The only recourse has been symptomatic relief with medications such as anti-depressants, opiates, and neuropathic pain control agents such as duloxetine and pregabalin [4]. However, non-pharmacologic or combined treatment methods may have therapeutic potential. Three other systematic reviews have explored the effects of exercise on diabetic neuropathies [15] [16] [17]. The objective of this systematic review was to synthesize the findings of randomized and controlled studies published between 2012-2020 to answer the specific question: does physical exercise improve T2D DSPN signs or symptoms

in humans? It was hypothesized that routine exercise could reduce T2D DSPN severity, thereby improving quality of life and serving as a cost-free lifestyle modification and treatment option.

2. Methods

This systematic review protocol is registered on PROSPERO [18] with ID# CRD42020181211 (**File S1** and **File S2**). Submission preceded search strategy initiation. See **Table S1** and **Table S2** for the PRISMA 2020 checklists.

2.1. Search Strategy and Citation Reports

Planning, execution, and interpretation of this systematic review followed the PRISMA statement for evaluating healthcare interventions [19] and recommendations provided by several published guides [20] [21] [22] [23]. According to Bramer *et al.* [24], systematic review searches can optimize result inclusivity by utilizing a combination of Embase, MEDLINE, Google Scholar, and Web of Science databases. Since Web of Science was inaccessible, searches were conducted (without snowballing references) using Embase, MEDLINE, and Google Scholar to collect articles published in English within the last eight years from January 1, 2012 to April 20, 2020. Key search terms included "type 2 diabetes," "polyneuropathy," "exercise," and respective synonyms and acronyms. Query search formulas and original citation reports are presented in **Table S3** and **Supplementary S1**, respectively. Publish or Perish software [25] was used to create the Google Scholar citation report.

2.2. Eligibility Criteria and Qualitative Analysis

Refer to Table 1 for a summary of PICOS elements and corresponding eligibility criteria. Studies were selected for inclusion by sequentially reviewing titles, abstracts, and full-texts. Titles had to mention diabetes, physical exercise of any type or lifestyle interventions in general, and neuropathy, but were excluded if explicitly discordant with any PICOS criteria. Abstracts had to indicate satisfaction of PICOS criteria (especially the primary outcome), whereas full-text reviews had to be fully confirmatory. Since this systematic review was to be conducted by a sole investigator without a meta-analysis, risk-of-bias assessments were intentionally excluded from the eligibility criteria to allow the inclusion of all relevant articles for thematic synthesis and, thereby, prevent study selection bias based on subjective interpretations.

To preserve objectivity, qualitative analysis scores were relative and focused primarily on PICO. Included studies (all randomized and controlled) varied in how strongly they fulfilled the eligibility criteria—distinguished by whether or not they satisfied criteria deemed more accurate or reliable (see Table 1). Risk-of-bias and limitation analyses examined common markers of validity for randomized trials [19], centering on study design and execution. For scoring, one point was added or subtracted for each presence or absence, respectively, of

Table 1. PICOS elements and eligibility criteria.

PICOS Elements	Eligibility Criteria (Concepts of Interest)

Population/ Problem/ Phenomenon	REQUIRED:
	• Humans with clinically-diagnosed T2D and DSPN
	  ○ DSPN is analogous to diabetic peripheral neuropathy and diabetic polyneuropathy
	  ○ Articles fulfilling all criteria—but not specifying the type of clinically-diagnosed diabetes—will be included, since the odds are that most of those patients had T2D
	NOT REQUIRED (but provides greater accuracy or reliability):
	• DSPN diagnosed using recognized criteria, such as those provided by the ADA [8] or IDF [26]

Intervention/ Treatment	REQUIRED: • Physical exercise (with information on the type, amount, and duration of exercise performed) NOT REQUIRED (but provides greater accuracy or reliability): • Physical exercise sessions supervised by the researchers to ensure conformity of performance and adherence • Exercise protocols standardized for all subjects (*i.e.*, precludes personalization that could vary relative exertion)

Comparison/ Control	REQUIRED:
	• Includes at least one of the following:
	  ○ No intervention or treatment
	  ○ Planned crossover
	  ○ Other treatment (e.g., dietary modifications, lifestyle counseling, pharmacotherapy, electrical stimulation, etc.)
	  ○ Physical exercise combined with other treatment
	NOT REQUIRED (but provides greater accuracy or reliability):
	• Control group baseline characteristics highly similar to (*i.e.*, not significantly different from) those of the experimental group

Outcome	REQUIRED:
	• Evaluates changes in quantitative measurements of DSPN signs or symptoms (*i.e.*, neuropathic severity)
	  ○ QST to measure decreases in
	  ▪ Vibration perception threshold
	  ▪ Touch sensation (e.g., 10g monofilament, SWM)
	  ▪ Temperature threshold
	  ▪ Pinprick pain sensation
	  ▪ Ankle reflexes
	  ○ Posturography to measure abnormalities in proprioception
	NOT REQUIRED (but provides greater accuracy or reliability):
	• DSPN signs or neuropathic severity measured using validated clinical instruments or accessory methods recommended by the ADA [8]:
	  ○ Clinical instruments:
	  ▪ Michigan Neuropathy Screening Instrument
	  ▪ Modified Toronto Clinical Neuropathy Scale
	  ▪ Utah Early Neuropathy Scale
	  ▪ Neuropathy Disability Score
	  ○ Accessory methods:
	  ▪ Nerve Conduction Study
	  ▪ Corneal Confocal Microscopy
	  ▪ Skin Biopsy (for Nerve Fiber Density)

Study Type	REQUIRED: • Randomized and controlled NOT REQUIRED (but provides greater accuracy or reliability): • Randomization single- or double-blinded

Continued

(Report)	• Published within the last 8 years(January 1, 2012-April 20, 2020) • English language only • Snowballing references prohibited • Must obtain ≥10 eligible articles for thematic synthesis

Included studies fulfilled all of the required eligibility criteria based on PICOS. Qualitative analysis scores considered whether or not the selected studies satisfied criteria that, although not required, provided greater accuracy or reliability in study design and result interpretations. Acronyms: ADA = American Diabetes Association, DSPN = distal symmetric polyneuropathy, IDF = International Diabetes Federation, QST = quantitative sensory testing, SWM = Semmes-Weinstein Monofilament, T2D = type 2 diabetes.

more reliable criteria, and one point subtracted for each instance of bias or limitation.

2.3. Data Abstraction and Thematic Synthesis

Data abstracted for thematic synthesis included study location and duration, population source and total number of subjects (experimental, control, and dropout), demographics (sex distribution, average age and BMI, and duration of time pre-diagnosed with T2D and DSPN), main inclusion and exclusion criteria, exercise and control interventions, measurement time points, relevant outcomes involving DSPN, and results backed by statistical analyses (p-values).

Extracted data was thematically synthesized based primarily on relationships between interventions and corresponding outcomes to identify if exercise can effectively decrease DSPN neuropathic severity in T2D patients. Trends in population characteristics were also considered, whereas less emphasis was given to comparisons between clinical instruments (*i.e.*, the relative abilities of different measurement methods to detect significant or accurate outcomes). Proposed themes were supported by at least two separate studies by different research teams.

3. Results

Database searches yielded 379 unique records, which eligibility screening reduced to 15 randomized and controlled studies for undergoing thematic synthesis (**Figure 1**). Documentation of highlighted duplicates in the merged citation report before removal is provided in **Supplementary S2**. Refer to **Supplementary S3** for title, abstract, and full-title review results for each study. Four studies by Dixit *et al.* [27] [28] [29] [30] reported on different outcomes under the same RCT. Three studies—Ahmad *et al.* [31], Hung *et al.* [32], and Nadi *et al.* [33]—did not specify the type of clinically-diagnosed diabetes present within their populations, but they were nonetheless included with that caveat. Given the fact that T2D comprises 90% - 95% of all diabetes cases [4], these study populations likely consisted primarily of T2D.

Relative quality scores indicate the strength of PICO criteria fulfillment and, therefore, how much weight each article warrants in the thematic synthesis

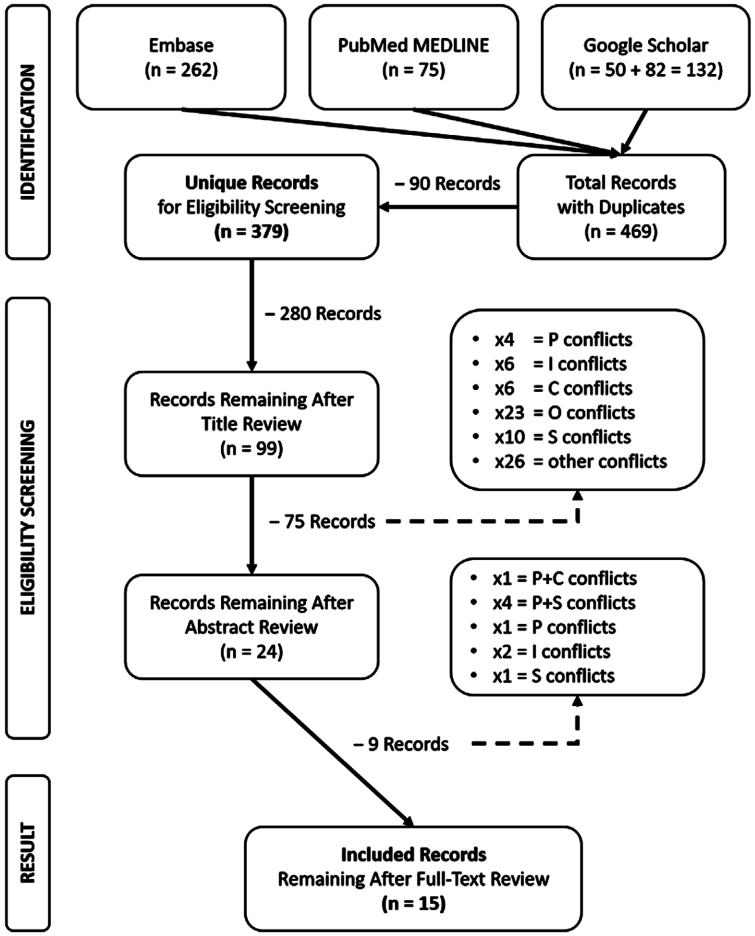

Figure 1. PRISMA flowchart of search results and eligibility screening.

interpretations (**Table S4**). Quality scores ranged from −5 to +5, and can be divided into quartiles with 0 as neutral (−5 to −4, −3 to −1, +1 to +3, and +4 to +5). Four of the 15 articles scored from +4 to +5, considered the highest quality. Another four scored from +1 to +3, or moderate quality. One scored a 0, or neutral quality. Two scored from −1 to −3, or low quality. The remaining four scored from −4 to −5, considered the lowest quality.

Data abstractions collated on study characteristics (**Table S5**) and results (**Table S6**) revealed a variety of measured outcomes, the use of several different exercise intervention modalities, and diverse population characteristics. All but one study—which was a randomized, planned crossover—were randomized controlled trials (RCT). Average ages ranged from 43- to 69-years-old, and average BMIs ranged from 24.8 to 32.6 kg/m^2. Outcomes of interest included MDNS (combines QST and nerve conduction studies), HbA1c levels, neurophysiological changes (nerve electrodiagnostics and density changes), posturography (static balance and proprioception), and QST of sensory perceptions (touch, vibration, and temperature). Exercise modalities included aerobic (treadmill and cycling), resistance (standard and isokinetic), balance and coordination (sensorimotor, ball, Frenkel, and IVGB), and mixed (involving some combination of range

of motion, stretching, balance, and muscle strengthening). Study population DSPN severity at baseline was undocumented in three studies, mild in one study, mild or worse in two studies, mild to moderate in seven studies, moderate in one study, and severe in one study. The following are major themes derived from qualitative syntheses of the study characteristics and results (also see **Table S7**), and are ordered from most to least reliable.

3.1. Aerobic Exercises Improve MDNS in T2D with DSPN

MDNS was evaluated in two studies: Dixit *et al.* [28] and Gholami *et al.* [34]. Both involved subjects with mild to moderate DSPN severity and a T2D duration (T2DD) of <10 years, and found total MDNS to significantly decrease (*i.e.*, improve) after eight and 12 weeks, respectively, of aerobic exercise. Dixit *et al.* [28] provided MDNS component scores, revealing significant improvements in motor and reflex scores in the exercise intervention group, whereas sensory score significantly improved in the control group only.

3.2. Exercise Reduces HbA1c Levels in Diabetic DSPN

HbA1c levels were compared at baseline and post-intervention in six studies: Gholami *et al.* [34], Gholami *et al.* [35], Nadi *et al.* [33], Stubbs *et al.* [36], Venkataraman *et al.* [37], and Win *et al.* [38]. Diabetes duration (DD) and DSPN severity varied and did not evince any noticeable patterns concerning the findings. Stubbs *et al.* [36] and Win *et al.* [38] observed insignificant changes in HbA1c levels after 24 and 16 weeks, respectively, of exercise interventions (to include aerobic, isokinetic, combined aerobic and isokinetic, or hand-and-foot). Venkataraman *et al.* [37] did not statistically evaluate the HbA1c level changes after mixed modality exercise intervention, thereby neutralizing this result for thematic synthesis purposes. Gholami *et al.* [34], Gholami *et al.* [35], and Nadi *et al.* [33] found HbA1c levels to significantly decrease after 12 weeks in the exercise intervention groups (aerobic and mixed modality, respectively) compared with the controls.

3.3. Exercise Increases Sural Sensory NCV in T2D with DSPN

Sural sensory NCV was analyzed in three studies: Dixit *et al.* [27], Gholami *et al.* [35], Stubbs *et al.* [36]. Dixit *et al.* [27] and Gholami *et al.* [35] involved subjects with DSPN severities ranging from mild to moderate and a T2DD of <10 years, and recorded significant increases in NCV (*i.e.*, improvements) after eight and 12 weeks, respectively, of aerobic exercise intervention. Stubbs *et al.* [36] involved subjects with unknown DSPN severity and a T2DD of >10 years, and did not find significant changes in sural NCV after 24 weeks of aerobic, isokinetic, or combined aerobic and isokinetic exercise interventions.

3.4. Balance Exercises Increase OLS/UST Times in Diabetic DSPN

OLS/UST times were measured in three studies: Ahmad *et al.* [31], Hung *et al.*

[32], and Rojhani-Shirazi *et al.* [39]. DD and DSPN severity varied and did not evince any noticeable patterns concerning the findings. All three studies found OLS/UST times to significantly increase (*i.e.*, improve) after balance and coordination exercise interventions lasting three, six, and eight weeks in duration, respectively.

3.5. Gaps in Knowledge

The following are potential themes involving outcome results that either conflicted between studies, derived from only one study, or involved different measurement methods.

Exercise may increase peroneal motor NCV in T2D with DSPN, but may not for several other nerves. Dixit *et al.* [27] measured significant increases in peroneal motor NCV after eight weeks of aerobic exercise. Gholami *et al.* [35] found the same outcome after 12 weeks; however, this difference was only significant within the exercise intervention group (*i.e.*, when comparing baseline to post-intervention) and not between the exercise and control groups. Additionally, changes in tibial motor NCV were found to be insignificant. Both of these study populations had a T2DD of <10 years, whereas it was >10 years in the Stubbs *et al.* [36] and Serry *et al.* [40] populations. These latter two studies found no significant changes in NCVs of medial plantar sensory [40] and peroneal motor, tibial motor, sural sensory, ulnar sensory, and medial sensory nerves [36] after eight and 24 weeks, respectively, of exercise interventions (to include aerobic, isokinetic, or combined aerobic and isokinetic).

Exercise may improve some sensory perceptions in T2D with DSPN. Three studies conducted QST to measure sensory perception outcomes: Dixit *et al.* [30]. Stubbs *et al.* [36], and Win *et al.* [38]. Dixit *et al.* [30] found significant improvements in vibration perception threshold (VPT) among three sites on both feet after eight weeks of aerobic exercise intervention involving a population with mild to moderate DSPN severity and a T2DD of <10 years, whereas Stubbs *et al.* [36] did not find such improvements in overall foot VPT after 24 weeks of aerobic, isokinetic, or combined aerobic and isokinetic exercise interventions involving a population with unknown DSPN severity and T2DD of >10 years. Win *et al.* [38] did not find a significant improvement in touch sensation threshold of either the hands or feet after 16 weeks of hand-and-foot exercises.

Exercise may not improve sway velocity in Diabetic DSPN. Three studies analyzed sway velocity: Ahmad *et al.* [31], Dixit *et al.* [29], and Venkataraman *et al.* [37]. All three studies involved different conditions and measured insignificant changes in sway velocity following sensorimotor, aerobic, and mixed modality exercise interventions, respectively, lasting eight weeks in duration.

Sensorimotor exercises may reduce center of pressure range and position angle differences in Diabetic DSPN. Ahmad *et al.* [31] measured significant decreases in center of pressure range and position angle differences (an estimation of proprioception) with eyes open on a firm surface after eight weeks of sensorimotor exercises.

Balance exercises may lessen center of mass, ankle, and hip sway in T2D with DSPN. Grewal *et al.* [41] measured significant decreases in center of mass (mediolateral), ankle, and hip sways with eyes open on a firm surface after four weeks of sensor-based interactive balance exercises. Ankle sway also decreased with eyes closed on a firm surface.

4. Discussion

To answer the question of whether or not and in what ways physical exercise reduces T2D DSPN severity, this systematic review utilized a comprehensive search and screening process involving multiple databases and robust queries highly specific and sensitive for relevant study identification. Qualitative analysis scoring criteria objectively mirrored PICO except for the bias and limitation score component, which—to maintain objectivity—assessed common markers of validity for randomized trials as specified in the PRISMA statement [19]. Only high-level evidence studies (*i.e.*, randomized and controlled) were selected; accordingly, the thematic synthesis results can be considered strongly substantiated.

Results of the thematic synthesis were provisionally in support of the alternative hypothesis: physical exercise may effectively improve certain aspects of T2D DSPN, but those effects may be limited by condition severity. Specifically, exercise may improve MDNS, reduce HbA1c levels, increase sural sensory NCV, and increase OLS/UST times in patients with mild to moderate DSPN severity (see **Table S7**). Except for reduced HbA1c levels, this is the first systematic review to acquire these results—and to do so within the context of DSPN severity—out of three others related to this subject [15] [16] [17]. There were no discernible correlations between improvements in DSPN or HbA1c levels and exercise modality, duration and intensity of exercise, BMI, or weight loss. However, when compared with Dixit *et al.* [29]—the one posturography study involving aerobic exercise—balance and coordination exercises were associated more often with improvements in static balance outcomes (see **Table S6**).

4.1. Aerobic Exercises Improve MDNS in T2D with DSPN

Although rated most valid of all the identified themes, this finding was only supported by two studies—one of highest quality and the other moderate. The MDNS is a screening instrument that evaluates several neuropathic signs and symptoms to diagnose DSPN and gauge severity. It consists of QST (pain, vibration, and light touch sensations) and nerve conduction measurements of five nerves—sural sensory, peroneal motor, median sensory and motor, and ulnar sensory [14]. Unlike the MNSI, the MDNS can be considered more objective in its analysis because it does not include a subjective questionnaire component. As discussed previously, however, nerve conduction studies display high interobserver variability [13]. Since the total number of nerves with conduction abnormalities directly determines the DSPN categorical severity on the MDNS, this

may significantly reduce its accuracy (especially when QST component scores are incongruous). Dixit *et al.* [28] and Gholami *et al.* [34] both measured total MDNS, but only the former provided sensory, motor, and reflex component scores. All three component scores significantly improved; however, sensory score improvement occurred in the control group only. Consequently, it is unclear to what degree QST or nerve conduction contributed to MDNS improvement.

4.2. Exercise Reduces HbA1c Levels in Diabetic DSPN

Four of the highest quality studies contributed to this theme, but one was unsupportive and reduced the overall validity. While ostensibly unrelated to the thesis, this theme is critical because it serves as a positive control that validates the systematic review protocol and also provides a potential mechanistic context for the other themes. Recall that elevated HbA1c levels directly correlate with prolonged hyperglycemia. Extensive research evidence (including meta-analyses) has established that routine exercise promotes modest but clinically significant reductions in HbA1c levels [6] [7]. Furthermore, glycemic control has been associated with decreased T2D neuropathic severity through reductions in VPT and nerve conduction abnormalities [42]. From these concepts, it may be inferred that exercise could ameliorate DSPN through glycemic control. However, exercise interventions have also yielded such improvements independently of glycemic control or weight loss [5], though this may reflect outcome attributes (*i.e.*, the degree in which a measured outcome directly or indirectly assesses DSPN severity).

Study populations in Gholami *et al.* [34] [35] were entirely male, whereas the population in Nadi *et al.* [33] was entirely female; regardless of sex, both studies yielded significant reductions in HbA1c levels after different exercise interventions. Nadi *et al.* [33] additionally measured pro-inflammatory marker level changes. Serum level increases in tumor necrosis factor-α and C-reactive protein have been associated with T2D and DSPN [2], and this study measured significant decreases in both factors following exercise intervention. Although unspecified, the population in Stubbs *et al.* [36] may have had severe DSPN (explained further in Theme 3 below), which may explain the insignificant changes in HbA1c levels found in that study. Perhaps HbA1c level reductions in response to exercise decrease proportionally with increasing severity of either or both T2D and DSPN. Exercise intensity and duration may also be contributing factors. For example, the Win *et al.* [38] study involved low-intensity hand-and-foot exercises. Mean compliance with this home-based (unsupervised) exercise routine was 65%, with only 45% showing complete compliance. These circumstances may explain why this study found insignificant changes in HbA1c levels.

4.3. Exercise Increases Sural Sensory NCV in T2D with DSPN

Two of the three studies contributing to this theme were of highest quality, but

one was unsupportive and reduced the overall validity. DSPN usually begins with injury to sensory SNFs, progressing to involve sensory and motor LNFs; this suggests that sensory nerves are more sensitive to hyperglycemic injury than motor nerves [5]. Endothelial dysfunction caused by hyperglycemia can impair vasodilation and subsequently compromise oxygen and nutrient supplies to nerve cells, causing damage [6] [43]. Conversely, improvements in microvascular blood flow correlate with increased NCV and function [44]. Therefore, the significant increases in sural sensory NCV following exercise interventions may be a result of either or both glycemic control and increased blood flow to the lateral foot (*i.e.*, enhanced oxygen and glucose uptake). Indeed, Dixit *et al.* [27] found that increases in sural sensory NCV occurred independently of medication use, but that insulin injections alone also had a minor beneficial effect. Recall that Gholami *et al.* [34] [35] found significantly reduced HbA1c levels following exercise interventions; these reductions were concomitant increases in sural sensory NCV [35] and improvements in MDNS and superficial femoral artery flow-mediated dilation [34].

Since unmyelinated SNFs have a greater capacity to regenerate than myelinated LNFs (especially motor nerves), differential nerve fiber involvement among DSPN patients may be a source of variation in responsivity to exercise interventions [5]. This may explain the absence of significant changes in motor NCVs observed in these studies; alternatively, exercise intervention duration may need to be extensively longer to achieve such a regenerative effect. Although Stubbs *et al.* [36] did not observe significant increases in sural sensory NCV, this may have been related to 82% of test subjects presenting at baseline without any conduction readings at all. Furthermore, composite electrodiagnostics of sensory nerves (sural, ulnar, and median) revealed a significant overall improvement in the exercise groups compared with the control, and lateral malleolus epidermal SNF density increased almost two-fold in 50% of biopsied exercise group subjects while worsening in 67% of controls. These findings suggest that increasing DSPN severity may inversely correlate with the restorative effects of exercise.

4.4. Balance Exercises Increase OLS/UST Times in Diabetic DSPN

Two of the three supporting studies were of the lowest quality, making this finding the least valid of all the identified themes. Prolonged hyperglycemia is associated with injury to LNFs, which may cause balance impairments—one of the most dangerous consequences of DSPN due to a considerably increased risk of falling and associated injuries [5] [8] [45]. Both groups in the Hung *et al.* [32] randomized crossover study showed significant improvements in OLS/UST times; however, most of this improvement occurred during the control phase for Group B. Since 1/3 of the subjects were regular exercisers (3/12 in Group A and 5/12 in Group B), this may have confounded the results and explain the contradictory Group B findings. Rojhani-Shirazi *et al.* [39] involved the shortest exercise intervention of all the thematic synthesis studies. OLS/UST times significantly improved despite only three weeks of balance exercises, although the ac-

tual times in seconds were much lower on average than those measured in the other supporting studies. Subjects in this study had MNSI scores of >2, or at least mild DSPN severity; however, the average MNSI score (*i.e.*, average DSPN severity) was not disclosed. If study subjects had severe DSPN, that could explain the relatively short OLS/UST times with eyes open (<10 seconds).

An advantage of the Ahmad *et al.* [31] study was its assessment of age as a contributing factor in balance improvement after sensorimotor exercise intervention. As would be expected, subjects in the ≥60-year-old group averaged longer DDs and, accordingly, greater DSPN severity than the <60-year-old group. OLS/UST times improved significantly in both age groups, but also more significantly in the older group versus the younger group. Indeed, OLS/UST times in the younger group were more than double that of the older group. If DSPN in the older group was characterized by greater LNF involvement, then perhaps partial restoration of LNF function due to exercise intervention yielded more substantial improvements in OLS/UST times. Alternatively, these balance improvements may merely be due to differences in average muscle strength between age groups and the fact that regular exercise—independently of disease states—can increase muscle mass and enhance muscle fiber recruitment [46].

5. Implications

Several theoretical models of DSPN pathogenesis explain how hyperglycemia alters metabolic pathways to provoke cellular dysfunction and damage, including one that involves direct injury to nerve cells via glucotoxins [47]. These glucotoxins may activate various metabolic pathways and pro-inflammatory processes that ultimately damage vascular endothelia, thereby triggering insulin resistance consequent defective endothelium-dependent vasodilation and glucose uptake. Ensuing blood flow abnormalities may generate hypoxic conditions leading to peripheral nerve injury and degeneration [42] [47]. Exercise may protect against damage to both nerve and vascular endothelial cells by stimulating angiogenesis and reducing hyperglycemia, insulin resistance, and lipotoxicity. Exercise could accomplish this by compensating for impaired insulin-mediated nitric oxide production and vasodilation, thereby partially restoring glucose uptake in peripheral tissues [2] [5]. Specifically, exercise could increase nitric oxide synthesis and bioavailability via flow-mediated dilation pathways [43]. Restored glucose uptake may then reinforce insulin sensitivity in peripheral tissues by preventing cyclical inflammation and damage to the vascular endothelia. Regardless, even in a background of insulin resistance, restoration of glucose uptake through exercise may quell inflammation related to hyperglycemia and hyperlipidemia, thereby slowing or preventing vascular and nerve tissue damage while maintaining nutrient supplies and supporting regenerative processes.

Healthcare providers should consider prescribing exercise regimens to their T2D DSPN patients alongside dietary interventions and medications for glycemic control and symptomatic relief. Before starting any exercise plan, however, patients should be physically evaluated to tailor the routine, modality, and

goals based on the extent of DSPN severity and identified risks (e.g., falling, foot ulceration, and respiratory or cardiovascular issues), and then reevaluated periodically. Guidance is available for implementing exercise regimens in patients with diabetes, including those with neuropathy [48] [49] [50]. Improved understanding of key physiological processes involved in DSPN pathogenesis will enable exercise prescription refinement to augment patient outcomes.

6. Limitations

Collaboration is considered a cornerstone of systematic literature reviews because it allows inter-rater reliability assessments—comparisons between reviewer perceptions that could reveal selection, exclusion, measurement, and analysis biases in study screening, quality scoring, and thematic synthesis. Since only one investigator conducted this research, there is the potential for blinded single-rater bias. To control for this, methodology was kept as transparent and objective as possible. Quality scoring criteria, although predominately objective (tared to the PICOS criteria), lacked standardization; this was solely due to a lack of expertise in using risk-of-bias analysis tools (e.g., Cochrane's RoB 2 tool for randomized trials). However, the qualitative analysis method devised and implemented for this systematic review offers one which can easily be adopted in other systematic reviews conducted by solo investigators.

Web of Science database inaccessibility and restricting years of publication from 2012-2020 may have inadvertently introduced publication bias by excluding studies highly influential to the thematic synthesis results. Since Tesfaye *et al.* [51] was the first study evaluating the effects of exercise on diabetic peripheral neuropathy, the protocol for this systematic review should be repeated to include studies published between 1992 through December 31, 2011 and April 20, 2020 through present time to capture the remaining literature.

As of December 31, 2021, database queries revealed seven studies (three older and four newer) satisfying eligibility criteria and suitable for thematic synthesis, and additionally identified four systematic reviews related to this subject matter (**Table S8**). Five of the seven eligible studies involved posturography, with only one of those solely involving T2D subjects rather than an unspecified diabetes type or a mixed population of T1D and T2D. Incorporating these studies in the thematic synthesis only has the potential to alter the posturography theme, which was the least valid of all the discovered themes; however, their absence may be precluding the discovery of additional posturography themes. Two of the seven eligible studies evaluated other DSPN severity outcomes, finding several improvements after intervention involving a home-based foot-ankle exercise program; however, both studies involved a mixed population of T1D and T2D.

Additional research is required to achieve external validity and avoid a potential type one error in the thematic synthesis results. Findings from each considered study must be viewed contextually; while internally valid, the results may not be extrapolatable into generalities. All future RCTs on this subject should

use validated clinical instruments (e.g., the MNSI) and measure HbA1c levels, relevant inflammatory markers, and a variety of DSPN-associated outcomes (e.g., QST, NCV, and posturography) in subjects pre- and post-exercise interventions to determine whether exercise effectively reduces DSPN severity while also reducing hyperglycemia and alleviating inflammatory pathways linked with insulin resistance. Such associations and findings would support a model whereby exercise rectifies manifestations of DSPN pathogenesis by modifying inflammation generated within a hyperglycemic state.

7. Conclusion

Through thematic synthesis, this systematic review provides evidence in support of physical exercise as an ameliorative treatment of T2D DSPN, one that can readily be incorporated into care plans at no cost. However, exercise treatment efficacy may be limited by DSPN severity and only improve some signs or symptoms. Other evidence suggests that exercise may even delay or altogether prevent DSPN onset [52]. Future research investigating the efficacy of exercise treatments for T2D DSPN may identify optimal combinations of exercise modalities and intensities and, additionally, highlight fundamental metabolic and physiologic divergences in T2D and DSPN etiologies that could guide reexamination and refinement of theoretical models and the identification of principal pharmacotherapeutic targets.

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Conflicts of Interest

This research did not receive any grants or data support. There are no conflicts of interest or preconceptions that could be perceived as influencing the objectivity of the reported research. Furthermore, the views and information presented are those of the author and do not represent the official position of the U.S. Army Medical Center of Excellence, the U.S. Army Training and Doctrine Command, or the Departments of Army, Department of Defense, or U.S. Government.

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Supplementary

Includes captions (for all supporting information), **Tables S1-S8**, **Files S1-S2**, and **Supplementaries S1-S3**. Also included for convenience is a list of acronyms and abbreviations used throughout the manuscript. All supporting information is available within a repository published on Zenodo (DOI 10.5281/zenodo.6944112): https://zenodo.org/record/6944112#.YuU-w3bMIuU.