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Lepesis, V

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REVIEW ARTICLE

Systematic review and meta-analysis of the effects of foot and ankle physical therapy, including mobilisations and exercises, in people with diabetic peripheral neuropathy on range of motion, peak plantar pressures and balance

Vasileios Lepesis[1] | Jonathan Marsden[1] | Alec Rickard[1] | Jos M. Latour[2] | Joanne Paton[1]

[1]School of Health Professions, Faculty of Health, University of Plymouth, Plymouth, UK

[2]School of Nursing and Midwifery, Faculty of Health, University of Plymouth, Plymouth, UK

Correspondence
Vasileios Lepesis, School of Health Professions, Faculty of Health, University of Plymouth, Plymouth PL4 8AA, UK.
Email: vasileios.lepesis@plymouth.ac.uk

Abstract

To evaluate the effects of foot and ankle physical therapy on ankle and first metatarsophalangeal joint range of motion (ROM), peak plantar pressures (PPPs) and balance in people with diabetes. MEDLINE, EBSCO, Cochrane Database of Systematic Reviews, Joanna Briggs Institute Database of Systematic Reviews, PROSPERO, EThOS, Web of Science and Google Scholar were searched in April 2022. Randomised Controlled Trials (RCT), quasi-experimental, pre-post experimental design and prospective cohort studies were included. Participants were people with diabetes, neuropathy and joint stiffness. Interventions included physical therapy such as mobilisations, ROM exercises and stretches. Outcome measures focused on ROM, PPPs and balance. Methodological quality was assessed with Critical Appraisal Skills Programme RCT and Risk-of-Bias 2 tool. Meta-analyses used random-effects models and data was analysed using the inverse variance method. In total, 9 studies were included. Across all studies, participant characteristics were similar; however, type and exercise dosage varied greatly. Meta-analysis was performed with four studies. Meta-analysis showed significant effects of combined exercise interventions in increasing total ankle ROM (3 studies: MD, 1.76; 95% CI, 0.78–2.74; $p = 0$; $I^2 = 0\%$); and reducing PPPs in the forefoot area (3 studies; MD, −23.34; 95% CI, −59.80 to 13.13; $p = 0.21$, $I^2 = 51\%$). Combined exercise interventions can increase ROM in the ankle and reduce PPPs in the forefoot. Standardisation of exercise programmes with or without the addition of mobilisations in the foot and ankle joints needs further research.

KEYWORDS
diabetes, exercises, mobilisations, peak plantar pressures, range of motion balance

1 | INTRODUCTION

Type 2 diabetes is a global pandemic set to affect 700 million adults by 2045.[1] Diabetes and hyperglycaemia trigger microvascular changes leading to nerve damage and loss of foot sensation, known as diabetic peripheral neuropathy (DPN).[2] DPN together with foot deformity and elevated peak plantar pressures (PPPs) increase the risk of diabetic foot ulceration (DFU).[3]

Another factor towards the multi-factorial pathogenesis of DFU is limited joint mobility syndrome (LJMS).[4] LJMS is the most common musculoskeletal complication in diabetes, presenting as stiffness in the ankle and big toe joints.[5] Segmental stiffness in these joints alters the gait biomechanics and leads to further increases in PPPs, a precursor to skin breakdown and eventually ulceration.[6] DFU is linked to poor quality of life, with 5-year mortality rates ranging between 42% and 44%.[7] In the United Kingdom (UK) alone, the cost of treating DFU and subsequent lower limb amputation is also set to increase to £15.1 billion pounds.[8] Therefore, preventing and managing DFU has become a major clinical priority with guidelines produced by the UK's National Institute of Clinical Excellent[9] advising on footcare, callus debridement and provision of off-loading orthoses and footwear. However, these management options fall short in taking into consideration the foot and ankle biomechanical deficits secondary to LJMS.[10]

Physiotherapy management could be a way forward in addressing these by increasing the available range of motion (ROM) and normalising foot and ankle biomechanics during walking. Previous systematic reviews by the International Working Group on the Diabetic Foot[11,12] have reported weak, but favourable, outcomes of the effects of foot-and-mobility related exercises in increasing foot and ankle ROM, but less so in reducing PPPs. However, an effective physiotherapy management programme, including specific manual therapy techniques combined with exercises, has not been established in the literature for people with diabetes. Manual therapy has been employed in randomised controlled trials (RCTs) for people with chronic ankle instability[13–16] or with stroke.[17,18] The information gained from this review will aid the development of a physiotherapy treatment protocol designed to increase foot and ankle segmental mobility and decrease PPPs in people with DPN.

The aim of this review is to investigate the effectiveness of foot and ankle mobilisations and home stretches when compared to standard care on increasing ankle and big toe joint ROM, reducing PPPs and improving balance in people with DPN.

2 | METHODS

The systematic review was prospectively registered with PROSPERO (reg. no: CRD42022322552, available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022322552). The standardised Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) were followed.[19]

Studies were selected for inclusion into the review based on the following criteria: (a) published from the inception of the databases to April 2022, (b) included data from participants with diabetes and peripheral neuropathy, (c) interventions that included stretching exercises and/or mobilisations of the foot and ankle or other joints/muscles of the lower limb. These interventions had to be delivered on their own or as an adjunct to other types of exercises such as strengthening, balance and gait rehabilitation, (d) exercises that were either prescribed by a qualified physiotherapist in a group setting or were carried out independently by the participants at home. No limitations were applied in terms of exercise duration, intensity, volume and frequency, (e) control was used as a comparator, (f) reported outcome measures that captured changes in foot function including dynamic or static ROM in the ankle and/or hallux joint, peak plantar pressures in the forefoot and/or the rearfoot and lastly balance outcome measures (postural sway) and (g) included types of studies which were RCTs, quasi-experimental, uncontrolled studies with a pre-post experimental design, prospective cohort studies or single-case studies.

Studies were excluded from the review when: (a) research was carried out in non-humans, (b) interventions did not include either stretching or mobilisations in the foot and ankle, (c) employed outcome measures that did not measure either kinematic data (ankle and big toe ROM, postural sway) or kinetic data (PPPs) or both and (d) book chapters, conference abstracts, reviews and study protocols. Qualitative studies and systematic reviews were also excluded.

The Population, Intervention, Comparison, Outcome and Study design (PICOS) question[20] was defined as follows: Does foot and ankle mobilisations (I) increase foot and ankle ROM, reduced PPPs and/or postural sway (O) in people with DPN (P)?

2.1 | Information sources

Databases included MEDLINE (including PubMed), EBSCO (including AMED and CINHAL), Cochrane Database of Systematic Reviews, Joanna Briggs Institute Database of Systematic Reviews and PROSPERO. The search of grey literature was undertaken in EThOS, Web of Science and Google Scholar. Searches included manual searches of reference lists within articles.

2.2 | Search strategy

The search used English Medical Subject Headings (MeSH) terms and the search strategy was carried out in stages using Boolean operators. The search strings were conducted with assistance from an information technologist. Independent searches for Title/Abstract on patient population (Search #1) and patient problem (Search #2) were then combined, giving rise to search #3. Subsequently, Title/Abstract searches for the intervention (Search #4) and outcome measures (Search #5) were carried out individually. The final search, search #6, comprised of the combined searches #3, #4 and #5.

2.3 | Data collection process

Data extraction, including the main characteristics of the studies, was carried out by Vasileios Lepesis and independently confirmed by Jonathan Marsden. Information was presented in a tabulated format and included details on two main domains: study information (authors, study design/sample size, population, sample characteristics, type of randomisation) and overview of intervention and outcome measures (intervention content, length and number of sessions, timing and number of follow up, treatment issued by, control condition, treatment fidelity and outcome measures).

2.4 | Risk of bias assessment

The methodological quality of the included studies was carried out by two independent reviewers (Vasileios Lepesis and Jonathan Marsden). A consensus method was adopted to resolve any potential disagreement in scores between the reviewers. The methodological quality of the included studies was assessed using the Critical Appraisal Skills Programme (CASP) RCT Standard checklist,[21] which screens four main aspects of the RCT: (a) the validity of the study design, (b) the methodological quality, (c) the results and (d) the applicability of the results to the local population.

The Cochrane risk-of-bias (RoB) tool version 2, which is considered a vital component of a systematic review when assessing the effects of an intervention[22], was also carried out. In this updated version proposed by Sterne and authors, the RoB 2 tool is categorised into five main domains: (1) Bias arising from the randomisation process, (2) Bias due to deviations from intended interventions, (3) Bias due to missing outcome data, (4) Bias in the measurement of the outcome, (5) Bias in the selection of the reported result,[22] with each domain also including signalling and/or supplementary questions to help the researchers reach their decision. The overall judgement of the risk of bias for the result (Domain 6) was mapped as suggested by Sterne et al., (2019) (Supplemental Table S1).

The CASP checklist for Cohort studies and the Risk of Bias in non-randomised studies - of interventions (ROBINS-I) assessment tool was used for non-RCT studies.

2.5 | Data synthesis

The pooled study effects were analysed quantitatively in a meta-analysis using the Joanna Briggs Institute (JBI) System for the Unified Management, Assessment and Review of Information (SUMARI).[23] To establish the magnitude of treatment effects, the mean and standard deviations of baseline and follow-up or pre- and post-treatment data of each study were inserted in a spreadsheet and the Hedge's g effect size was determined.

Meta-analysis was performed using random-effects models for continuous variables. Data was analysed using the inverse variance method where the relative weighting of each paper is inversely proportional to its variance.[24] Effect sizes were presented alongside 95% confidence interval (CI)[25] and explained based on the following threshold criteria: <0.2, trivial; 0.2–0.6, small; >0.6–1.2, moderate; >1.2–2.0, large; >2.0–4.0, very large; >4.0, extremely large. Statistical heterogeneity was quantified using the I^2 statistic (I^2).[26] Thresholds for the interpretation of I^2 were taken as follows: 0/% to 40%: might not be important; 30%–60%: may represent moderate heterogeneity; 50%–90%: may represent substantial heterogeneity and 75%–100%: considerable heterogeneity. At this stage, we did not come to a decision about the degree of heterogeneity that would exclude studies from the meta-analysis.

3 | RESULTS

3.1 | Study selection

The initial database search revealed 124 articles (Figure 1). 40 articles were removed due to duplication, leaving 89 articles needed to be screened for eligibility. This step was carried out with the assistance of the online application Rayyan (https://rayyan.ai). Rayyan is a free online web tool which helps researchers with the screening process when conducting systematic reviews and is thought to assist in the quality of the reviewing process.[27] The EndNote referencing manager was used to upload the search results to Rayyan and Vasileios Lepesis invited a member of the research team (Jonathan Marsden) to review the titles and abstracts of the 89 articles. This was done independently by selecting the 'Blind ON' tab on Rayyan that ensured that decisions about inclusion/exclusion of studies were not visible to collaborators. After the first phase of independent screening was completed, Vasileios Lepesis changed the blind mode to 'Blind OFF' and was able to see the decisions made by Jonathan Marsden. There was one conflict between reviewers (a study using an unrelated intervention), which was resolved by discussion and identified 23 potentially relevant articles. Two independent reviewers screened all 23 full text articles against the inclusion criteria. A total of nine papers meeting the criteria were included in the review and data extraction (Figure 1). Reasons for excluding full text articles were (a) study design was a case study and not an RCT ($n = 1$), (b) an unrelated intervention was used ($n = 11$) and (c) an unrelated outcome measured was recorded ($n = 2$).

3.2 | Study characteristics

The characteristics of the studies are presented in Table 1. Samples ranged from 11 to 117 study participants. All studies included participants with a diagnosis of Type 2 DM, except one study[28] that included both DM Type 1 and 2 participants. Diagnosis of Type 2 DM ranging between a minimum of five to 15 years. None of the studies included provided a risk category for ulceration of their participants. One study did not specify whether participants were diagnosed with DPN[29] and in another study[28], just over half (54.4%) of participants had neuropathy. The remaining studies[30–36] included participants

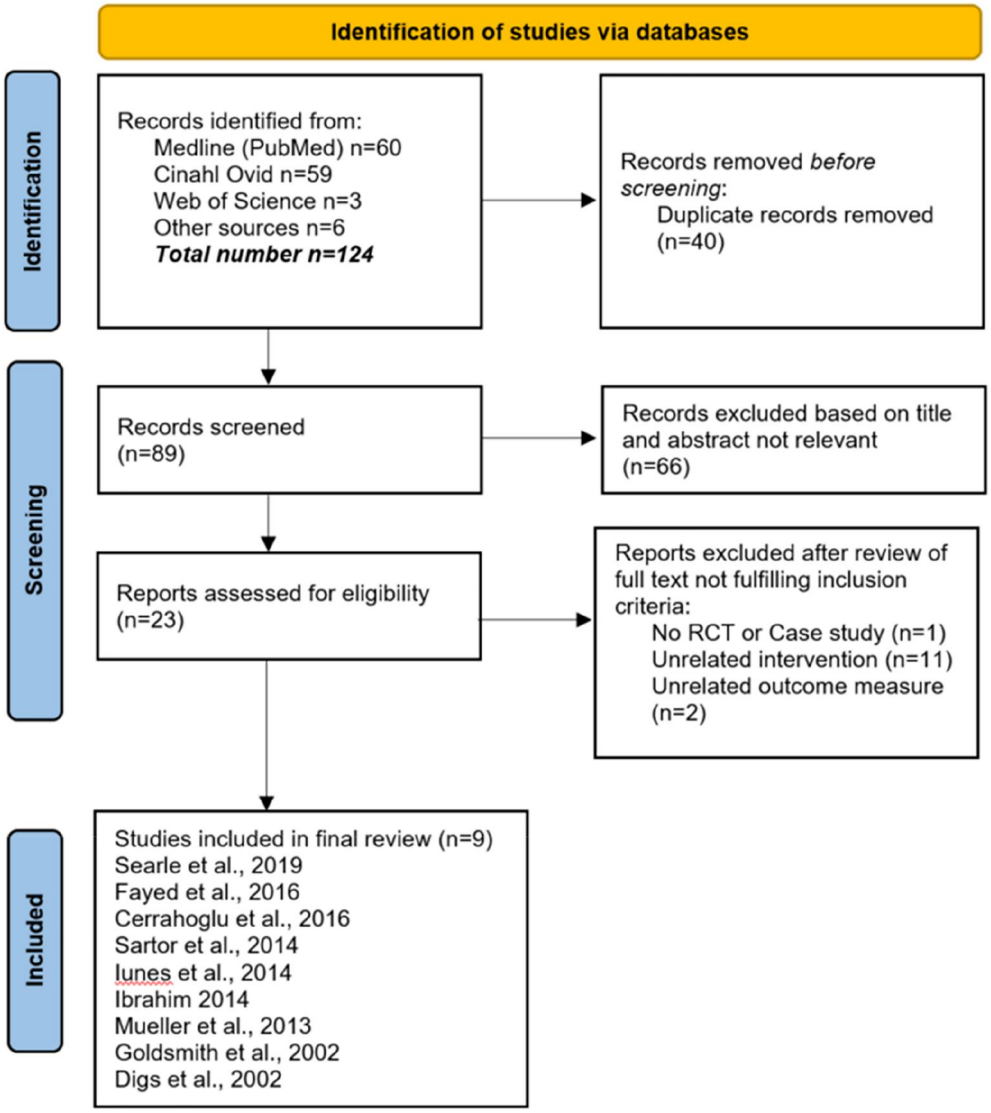

FIGURE 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart describing the study selection process.

with DPN (n = 342). Participants with DPN and LJMS were only specified in two studies,[28,31] even though one study[29] measured ankle and big toe stiffness quantified with a force by a dynamometer.

3.2.1 | Description of interventions

Interventions used in the included studies (Table 2) lasted between 4 weeks,[29,30] 8 weeks,[28,33] and up to 12 weeks.[35,36] In one study,[34] the duration of the intervention was not described. Sessions ranged between two times per week lasting between 40 and 60 min,[36] and three times per week for 40–60 min.[29,32,33,35] In one study,[28] the intervention was carried out 5 times per week for 4 min. The number and duration of sessions were not specified in two studies.[30,34] One study[31] delivered a manual therapy intervention between five to 10 weeks (two sessions per week accounting to overall 10–20 mobilisation sessions).

Exercises were performed by participants on their own[28–30,34] or in groups led by physiotherapists.[33,35,36] Exercises were performed either daily by individuals at home[28–30] or in a group setting for a minimum of two sessions per week.[32,36] Only one study[31] used manual therapy as an intervention on its own, or stretches[28] on its own. The remaining studies used stretching exercises combined with strengthening, and balance and functional exercises[30,32–36] or stretching with functional exercises.[36]

3.3 | Risk of bias

Based on the CASP RCT standard checklist,[21] the included studies addressed a well-defined research question (Supplemental Table S2). All studies randomly assigned participants to interventions except one.[32] Additionally, all participants who took part in the studies were accounted for in their conclusion, except in one study.[30] Adequate

TABLE 1 Study information, outcome measures and results.

Authors	Study design Sample size	Population	Sample characteristics (mean/SD)	Type of randomisation	Outcome measures	Result
Searle et al. (2019) Australia	Two-arm parallel RCT, $n = 68$	Type I or II DM and ankle equinus (≤5° ankle DF). Excluded participants with current ulceration, previous amputation, surgery, neurological conditions, inability to walk 8 m unaided, pregnancy.	Age (mean years [SD]) 67.4 (10.9), $M = 44$ (64.7%)/ $F = 24$ (35.3%), BMI (mean kg/m^2(SD) 32.8 (6.8), Type 2 DM $n = 60$ (88.2%), diabetes duration (means yrs. (SD) 14 (20.8), Neuropathy $n = 37$ (54.4%)	Subjects randomly assigned to stretching exercises ($n = 34$) and control ($n = 34$).	Change in ankle DF in WB and NWB, forefoot PPPs, forefoot pressure time integrals and adherence to stretches	No change in ankle ROM or PPPs
Fayed et al. (2016) Saudia Arabia, Giza, Egypt	RCT, $n = 40$	Participants with Type 2 diabetes and DPN, diabetes duration 5–15 years, BMI ranged from 25 to 29.9, and no Hx RA, previous foot surgery, current ulcers or Charcot arthropathy.	$F = 40$, 45–55 years/o, intervention $n = 20$, control $n = 20$	Subjects were divided into two groups: But no information on randomisation process given.	PPP rearfoot and forefoot	PPPs decreased
Cerrahoglu et al. (2016) Turkey	Prospective, randomised and controlled, $n = 80$	Participants with Type 2 medically controlled diabetes. Excluded type I DM, pregnant, inflammatory disease, Hx foot surgery and foot ulceration.	With neuropathy $n = 38$: Sex: Male = 14/Female = 24 Age: 56.87 ± 9.42 Dur.: 11.18 ± 6.86 BMI: 31.92 ± 5.20 Without neuropathy $n = 38$: Age: 53.66 ± 9.36 Dur.: 9.58 ± 7.07 BMI: 31.84 ± 6.38	Patients were divided into two groups: Neuropathic ($n = 40$) and non neuropathic ($n = 40$). Both groups were randomised into exercise ($n = 20$ each) and control ($n = 20$ each) groups.	ROM ankle and 1st MTPJ, peak plantar pressures	Exercises increased ROM and decreased PPPs in the forefoot
Sartor et al. (2014) Brazil	Two-arm parallel group RCT ($n = 55$) with blinded assessor. Due to high non-adherence of CG, cross-over intervention could not be implemented.	Participants with DM and DPN, diabetes duration min. 7 years, BMI ranging 18.5–29.9 kg/m^2, ability to walk independent in lab, no current plantar ulceration no partial or total foot amputation, not receiving physio or offloading devices.	$M = 31/F = 24$, 45–65 years/o, intervention $n = 26$, control $n = 29$	Randomisation software Clinstat used by independent researcher, who was not aware of group codes. A numeric block randomisation sequence, varying randomly in size from one to eight, was kept in sequentially numbered, opaque envelopes. After meeting eligibility criteria, patient enrolment was conducted by a physical therapist who also performed all the blind assessments. If a patient	PPPs, ankle kinematics and kinetics, MNSI and ABC questionnaire, muscle function, ankle and toe flexion/extension	No increase in ROM or reduction in PPPs

(Continues)

TABLE 1 (Continued)

Authors	Study design Sample size	Population	Sample characteristics (mean/SD)	Type of randomisation	Outcome measures	Result
				agreed to participate in the study, allocation to a group was made by a second independent researcher, unaware of group codes. Only the physio was not blind to the intervention.		
Iunes et al. (2014) Brazil	Prospective cohort, quasi- pre and post experimental, $n = 117$	Type 2 DM for >5 years, medically controlled. Excluded: Those with ulcers and/or previous limb amputation, clinical diagnosis of hemiplegy, paraplegy, or Parkinson's disease.	$N = 97$, mean age 62.12 ± 11.31 years, $M = 44\%/F = 56\%$, duration of diabetes 13.89 ± 7.57 years, DPN $n = 69$, BMI 17.64 ± 3.80 kg/m2, HbA1c 7.9 ± 1.0%	Not randomised, all participants received intervention.	Foot alignment, peak plantar pressures	No change in PPPs
Ibrahim (2014) Egypt	RCT, $n = 30$	Type 2 DM for >7 years, score higher than 2 out of 13 in the Michigan Neuropathy Screening Instrument, ability to walk independently. Excluded if unstable glycaemic control, malignancy, active/untreated thyroid disease, other neurological or orthopaedic impairments.	$M = 13/F = 17$, DPN, age range 50–65 years/o, BMI 25 and 34.9 kg/m^2 Intervention $n = 15$, control $n = 15$	Subjects randomised into two groups.	Walking velocity, cadence, step time, double support time, dynamic ankle ROM	Increase in ROM
Mueller et al. (2013) USA	Prospective RCT, $n = 29$	Type 2 DM with DPN, 2000 to 9000 steps per day, currently active. Excluded participants weighed >136 kgs, had a severe foot deformity with custom therapeutic footwear, or had a comorbidity or took a medication that would interfere with ability to exercise.	$M = 17/F = 12$, DPN mean age ± SD, 64.5 ± 12.5; mean body mass index (kg/m^2) ± SD, 35.5 ± 7.3),	Subjects randomly assigned to WB ($n = 15$) and NWB ($n = 14$) exercise groups.	6-min walk distance, daily step count, foot and ankle ability measure, ankle DF ROM	No change in ROM

TABLE 1 (Continued)

Authors	Study design Sample size	Population	Sample characteristics (mean/SD)	Type of randomisation	Outcome measures	Result
Goldsmith et al. (2002) USA	RCT, $n = 19$	Hx of DM with no ulceration, amputation, OA, osteoporosis or pregnant.	DM, $n = 10$ men, $n = 9$ women	Subjects randomly assigned to intervention ($n = 9$) or control ($n = 10$).	Ankle joint stiffness, peak plantar pressures	Reductions in PPPs
Dijs et al. (2002) Belgium	Prospective cohort, experimental pre-post, pilot study, $n = 11$	Hx of DM with LJMS and DPN. Excluded participants with Dupuytren's, foot ulceration or amputation, ankle fracture, PVD.	DPN and LJMS, $n = 10$ men, $n = 1$ woman, age (years) mean 56.6, range 38–66 years/o, diabetes duration (years) mean 26, range 5–38	None, but 11 participants matched with control groups (17 normal, 11 diabetic controls, 9 with DPN).	Ankle, STJ, 1st MTPJ and first ray ROM	Increase in ROM

blinding was achieved only in three studies[28,35,36] and not in four studies.[29,30,32,33] Baseline data for study groups were similar amongst all studies included in this review. Furthermore, each study group received the same level of care, in addition to the intervention, in all the studies. In all but one study,[30] the effects of the interventions were reported comprehensively. Treatment effect size was reported in three studies[28,35,36,] but it was not included in four studies.[28–30,32,33] Three studies found no difference between the intervention and the control group,[28,35,36] and for this reason these studies were judged as not benefitting or causing harm to the participants. None of the included studies reported harm or adverse events to the participants. It was also felt that the results of all the studies could be applied to the local population of people with diabetic peripheral neuropathy. Lastly, the final question of the CASP tool which states '*Would the experimental intervention provide greater value to the people in your care than any of the existing interventions*?' was difficult to answer with certainty due to the variability of existing interventions in clinical practice. The CASP cohort appraisal tool for the non-randomised studies[31,34] was used (Supplemental Table S3).

The overall RoB 2 judgement was high in three studies,[28,35,36] low in two studies[30,32] and unclear in further two studies[29,33] (Supplemental Table S4). The Risk of Bias in non-randomised studies - of interventions (ROBINS-I) assessment tool was used for two studies (Supplemental Table S5). The overall ROBINS-I judgement scored 'low to moderate' for one study[34] and at 'serious risk' for the second study.[31]

3.4 | Meta-analysis

When pooling together all the results from the studies, nine studies were included in this review, but a meta-analysis could not be performed in four of them. These four studies[30,31,34,35] did not include a definite control group (no treatment) in their experimental design when comparing the effects of their intervention (either single or multi-intervention). Specifically, two studies[31,34] did not include a control group in their pre- and post- experimental study design and therefore these were excluded. One study[30] presented data comparing ROM and PPP values before and after exercises in participants with and without neuropathy. However, they did not compare the data between the non-exercise control group and the home exercise group. This omission of data is reflected in both CASP and RoB tools. Lastly, another study[35] compared WB versus NWB type of exercises in their groups, so effectively both groups received an intervention.

3.4.1 | Effects of combined exercise intervention programmes on total ankle ROM

The results of a single intervention study[28] and multi-intervention studies[33,36] were pooled together for further analysis. The results demonstrate a significant effect of exercises in increasing total ankle

TABLE 2 Study intervention.

Authors	Intervention content	Length and number of sessions	Timing and number of f/u	Rx issued by	Control condition	Rx fidelity
Searle et al. (2019) Australia	Stretching programme: Standing calf stretch with knee extended.	One stretching session per day consisting of calf stretch x4 times, held for 30 s (2 min of stretching per leg). Stretches carried out 5 days a week for 8 weeks.	Both groups assessed at baseline and 8 weeks post intervention.	Self	Continue with normal physical activity	Stretch diary completed at home by participants
Fayed et al. (2016) Saudi Arabia, Giza, Egypt	Strengthening and stretching exercises to ankle and feet, balance exercises and gait training.	3 sessions per week, lasting for 60 min, for 8 weeks.	No f/u.	Physio	Continued with medical Rx	No formal evaluation
Cerrahoglu et al. (2016) Turkey	Home exercise programme (warm up walk, ABC foot exercises, ankle strengthening and gastrosoleus and big toe stretches) for self-care education and had motivational phone calls. Home exercise programme of ROM, stretching, and strengthening exercises for the ankle and MTP joints.	Exercises daily, weekly phone calls about home exercise programme and progression.	Both groups assessed at baseline and 1-month f/u.	Self	Does not specify	No formal evaluation
Sartor et al. (2014) Brazil	Physical therapy consisting of passive exercises, progressed to active ones, and finished with walking and functional skills. Also instructions to perform home exercises.	2 sessions per week, lasting between 40 and 60 min, for 12 weeks.	Both groups assessed at baseline and 12 weeks. IG also assessed at week 24 f/u.	Physio	Customised medical care including pharmacology and foot care advice	No formal evaluation
Iunes et al. (2014) Brazil	Self care foot protection advice and foot/ankle and hip exercises (AROM, strengthening, stretching and proprioceptive).	Return once per month, does not mention frequency.	Baseline measurements and at 10-month f/u.	Self	Not relevant	No formal evaluation
Ibrahim (2014) Egypt	Therapeutic sessions were divided into four types of exercises: (1) ROM exercises, (2) muscle strengthening exercises, (3) balance exercises, and (4) gait training exercises.	3x times a week, for 8-week, 45–60 min per session.	Both groups assessed at baseline and 8 weeks post-intervention.	Self/ physio	Continued with medical Rx	No formal evaluation
Mueller et al. (2013) USA	Group-specific progressive balance, flexibility, strengthening, and aerobic exercise conducted sitting or lying (NWB) or standing and walking (WB) group.	3x times week, for 12 weeks, 1xhour group sessions.	Both groups assessed at baseline and 12 weeks post intervention.	Self/ group by physio	Does not specify	No formal evaluation

TABLE 2 (Continued)

Authors	Intervention content	Length and number of sessions	Timing and number of f/u	Rx issued by	Control condition	Rx fidelity
Goldsmith et al. (2002) USA	Intervention involved active and passive ankle and toe stretches.	3x times per day, every day of the week for 4 weeks.	Both groups assessed at baseline and 3 weeks post intervention.	Self	Does not specify	No formal evaluation
Dijs et al. (2002) Belgium	Intervention involved: Passive mobilisation of ankle, STJ, midfoot joints and MTPJs/IPJs.	2 mobilisation sessions per week, up to 10 and 20 sessions.	Baseline, after 10 and 20 sessions of therapy and at 3,6,9 and 12 months post intervention—measurements compared against 17 healthy controls, 11 DM controls, 9 DPN control without LJMS.	Physio	Does not specify	No formal evaluation

ROM; $p = 0$, 95% CI (Figure 2). Heterogeneity was $I^2 = 0$ which in principle is indicative of no variability in the results obtained from these three studies. The potential of a misleading I^2 result observed in this subgroup due to the small number of studies is explored further in the discussion section.

3.4.2 | Effects of combined exercise intervention programme on forefoot PPPs

The results of single[28] and combined exercise programmes[32,36] were pooled together for further analysis. The results are indicative of the significant effects of exercises in reducing PPPs in the forefoot area, which includes the area in the hallux; $p = 0.21$, 95% CI (Figure 3). The heterogeneity score was $I^2 = 51$ which may represent moderate heterogeneity.

4 | DISCUSSION

This systematic review and meta-analysis were carried out to systematically explore the evidence of physical therapy management interventions (manual therapy and stretches) in improving ROM in the ankle/hallux, reducing PPPs under the plantar aspect of the foot and postural sway in people with diabetes.

Based on the CASP and RoB checklist assessment tools for both RCT and non-RCT studies, most studies presented with methodological weaknesses affecting both internal and external validity of their results. One study was a small sample pilot study[31] and another study a prospective quasi-experimental study.[34] Both studies lacked a control group and therefore, it is not possible to establish the causal effect of their intervention.[37]

4.1 | Range of motion

Exercises increased ankle ROM in three studies[30,33,36] whereas mobilisations increased ankle ROM in one study.[31] Ibrahim[33] used an extensive rehabilitation programme including ROM, foot and ankle muscle strengthening, balance and gait training exercises over a period of 8 weeks, three times a week for 45–60 min per session. Even though the authors mentioned that these exercises were made progressively difficult, it is not clear how variation in exercise intensity between participants was measured. Dynamic ankle ROM significantly increased, which correlates with the increases also found in walking velocity and cadence. However, it is debatable how well people with diabetes will adhere to such an intense exercise programme in the long term.

Cerrahoglu[30] utilised a similar exercise programme consisting of ROM, stretching, and strengthening exercises but did not use balance or gait retraining exercises as above.[33] Exercises were carried out daily for a period of 4 weeks, which again raises questions on the expectation of treatment adhesion. The authors mentioned that they

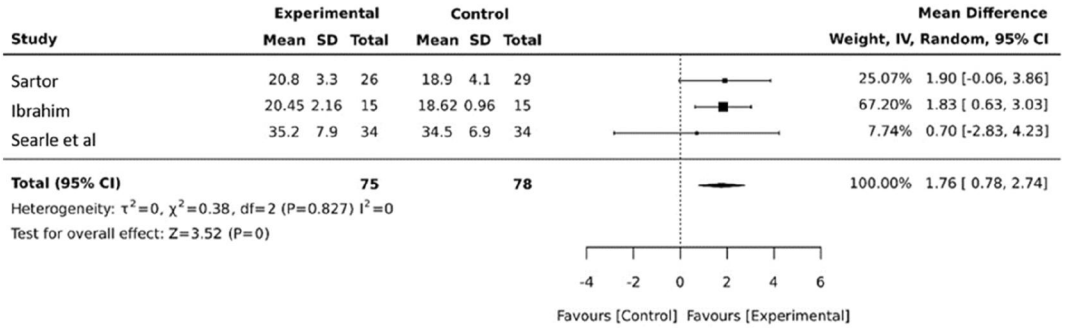

FIGURE 2 Meta-analysis forest plot of the effects of exercises in total ankle range of motion (ROM).

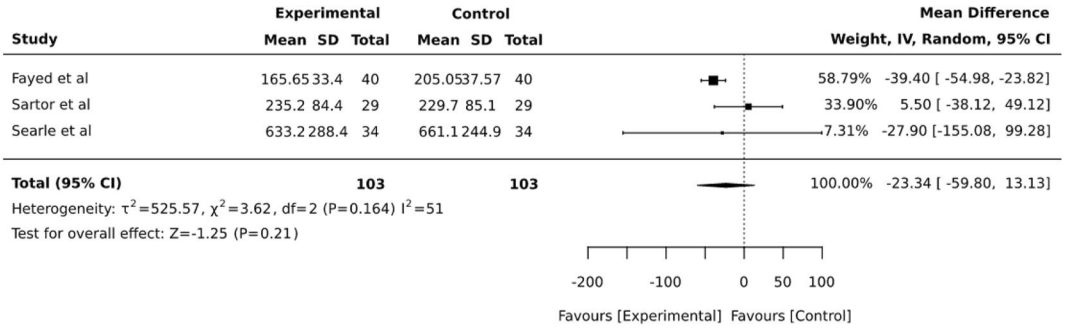

FIGURE 3 Meta-analysis forest plot of the effects of exercises in reducing peak plantar pressures (PPPs) in forefoot.

employed an exercise and a control group, but the results were presented based on neuropathy versus non-neuropathy group. Their findings supported that exercises increased ankle ROM, but this measurement was carried out statically with a goniometer rather than dynamically. This poses another limitation since static ROM does not always correlate nor predict dynamic ROM.[38,39]

Sartor[36] included foot and ankle strengthening, stretching and functional training exercises for 12 weeks, twice a week for 40–60 min per session and reported an increase in ankle dorsiflexion ROM even though the reported effect size was small (Cohen's $d = 0.02$). Dijs[31] was a pilot study who used manual therapy as their intervention rather than exercises. However, Dijs et al. did not specify the treatment dosage (i.e., duration of mobilisation and number of sets per joint) and they executed the treatment to all the foot and ankle joints (ankle, subtalar, midfoot joints, and 1st MTPJ and IP joints) which lacks specificity. For instance, in real practice, a physiotherapist would not choose to mobilise a joint unless it is restricted. The study found that mobilisations increased the ROM in all the foot and ankle joints, but this improvement plateaued after 6 months.

Exercises did not increase ankle ROM in two studies.[28,35] Mueller[35] used a progressive balance, flexibility, strengthening and aerobic exercise in sitting or lying and standing or walking, three times a week for 12 weeks. However, all participants received the intervention and comparisons were carried out between weight bearing and non-weight bearing groups. No difference was reported in ankle ROM between groups, but one could argue that this was to be expected since both groups received exercises. Searle[28] used a standing static calf stretch which was held for 30 s and repeated four times on each leg during each session (2 min of stretching per leg per session), 5 days a week for 8 weeks. They reported no significant increase of ankle ROM in the intervention group. This programme might benefit for being more acceptable to patients; however, it does not compare to the previous physical therapy interventions in terms of volume of exercise (8 minutes of exercise vs. 60 min). Also, stretching on its own might not be enough to produce a change in ankle ROM, which was measured statically and not dynamically.

The meta-analysis for change in ankle ROM included three studies[28,33,36] with the results indicating that exercises are statistically effective in increasing ROM and no heterogeneity (Figure 2). This is in agreement with previous systematic reviews[12] that support the notion that ankle ROM increases following physical therapy. However, the results of this analysis need to be regarded with caution as these results are based on a combined number of 153 participants with one study (Ibrahim, 2014) scoring poor to moderately on the CASP and RoB checklists. It is also unclear whether this statistical increase in ankle ROM is clinically meaningful. Even though a relationship between ankle ROM restriction and high PPPs exist[40,41] more robust evidence is needed. However, these studies showed that the difference in ankle ROM between participants who went on to ulcerate and participants who did not was only small (2°–4°). This is important when interpreting the results of this review and when recommending foot and ankle mobility exercises to patients.

4.2 | Peak plantar pressures

Exercises were effective in decreasing PPPs in three studies.[29,30,32] Goldsmith et al.[29] prescribed a 4 week exercise programme carried out daily, three times per day. Exercises included warm up and cool down and seven stretching exercises repeated 5 times, which totals to 105 exercises per day, which again cast doubts on acceptability. Dynamic barefoot PPPs were recorded during different periods of the gait cycle with the greatest change reported in the terminal stance, which is when you would expect elevated pressures on the forefoot, and therefore these findings are clinically meaningful. However, the authors chose not to present their findings in a graph and did not include numerical values of means and SDs, which is a considerable limitation.

Another study by Fayed et al.[32] employed a physiotherapeutic intervention of foot and ankle ROM, strengthening, balance, gait retraining and advice exercises with each session lasting for 60 min, and carried out 4 times per week, for a total of 8 weeks. As mentioned previously, adhesion rates might prove challenging in the real world. The authors reported statistically significant decreases in forefoot PPPs and attributed this to increases in foot and ankle ROM even though their study did not directly measure ROM. Cerrahoglu[30] intervention procedures described earlier also found significant decreases in dynamic PPPs but again their results compared groups between patients with neuropathy and without neuropathy. This is of limited value as observational studies have shown that people with diabetes and neuropathy present with higher PPPs than people with diabetes without neuropathy.[42]

On the other hand, no change in PPPs was reported in further three studies.[28,34,36] Sartor[36] described earlier found no significant change in PPPs with exercise therapy, even though they reported an increase in ankle ROM. This is important to consider since limitations in ankle ROM due to glycosylation tend to be associated with elevated PPPs and ulceration risk in people with diabetes and neuropathy.[43] This study does not support this hypothesis; however, the reason for this could be that they only reported a small effect size of their intervention on ankle ROM. Searle and authors[28] described above also found no reduction in PPPs with the application of calf muscle stretching. As discussed earlier, they also found no increase in ankle ROM following the stretching exercises; therefore, this fits the assumption that no change in ankle ROM should translate to no change seen in PPPs. Lastly, a non RCT carried out by Iunes and authors[34] reported no reduction in PPPs following an exercise programme that included self care foot protection advice and foot/ankle and hip exercises (AROM, strengthening, stretching and proprioceptive). The dosage, intensity, and frequency of the exercises were not adequately described, with all participants receiving the intervention. Due to the study design, it is difficult to establish the causal effect, the intervention might have on PPPs.

The meta-analysis for change in forefoot PPPs included three studies. The results pooled 206 participants and showed that exercises were statistically effective in reducing PPPs in the forefoot (Figure 3). However, the appraisal tools used to assess their methodological rigour in these studies found high risk of bias in one trial.[32] The heterogeneity score for the forefoot PPPs measurement was moderately significant $I^2 = 51$ and should be judged with an element of caution.[44,45]

4.3 | Limitations

The main limitation of this systematic review is the large heterogeneity of study designs and the different types of interventions used under the umbrella of 'exercise'. Even though heterogeneity is expected in systematic reviews,[46] it can still limit the interpretation of the results[47] Moreover, the point estimate I^2 can introduce its own bias when a small number of studies are included in the meta-analyses.[48,49]

Overall, there was very little agreement between studies as to what is the acceptable duration of treatment and exercise dosage (repetitions, intensity, and frequency). Similar issues were noted in the reliability and validity of outcome measures used, which differed considerably across the studies. Adhesion rates were not always noted by the authors and therefore it is difficult to conclude whether the intervention was ineffective because it was not carried out as prescribed. This large diversity of study design features and even study population limits the generalisability of the results.

Another limitation of this review was the predefined set of interventions which excluded studies that used gait training[50,51] or functional training[52] as an intervention. Similarly, our limited set of outcome measures excluded articles that measured improvements in physical activity,[53] foot ulcer incidence[54,55] and neuropathy signs.[52,53] However, the purpose of this review was to inform the intervention design of a proof-of-concept RCT which investigated the effects of mobilisations combined with stretches on ankle ROM, PPPs and balance.[56]

Lastly, the effects of exercise interventions on balance in people with diabetes have not been investigated.

5 | CONCLUSION

Overall, the studies included in this systematic review showed that exercises could have a positive effect in increasing ankle AROM and reducing forefoot PPPs. However, methodological flaws, heterogeneity of study designs and lack of a gold standard of physical therapy intervention or treatment protocol meant that firm conclusions are not easy to reach.

Future studies need to design their exercise programmes in partnership with PPI that are pragmatic and acceptable to participants and healthcare providers. The literature also needs to strive towards a universally recognised language when it comes to exercise prescription as the variability of terminology used generates poor evidence for the effectiveness of exercise in people with DPN. Long-term studies also need to be carried out with a shift of focus on patient reported outcome measures that are meaningful to patients.

Ultimately, the effectiveness of exercise therapy needs to be measured against the incidence or prevention of DFU.

AUTHOR CONTRIBUTIONS

Vasileios Lepesis carried out the initial database search screening for eligible articles. Vasileios Lepesis and Jonathan Marsden independently screened the eligible full text articles for inclusion in the study. Vasileios Lepesis carried out the data extraction of the included articles, which was subsequently independently confirmed by Jonathan Marsden. Vasileios Lepesis and Jonathan Marsden carried out methodological quality screening for all the included articles. Joanne Paton, Jos M. Latour and Alec Rickard reviewed and edited the manuscript. All authors approved of the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interest.

ETHICS STATEMENT

Ethical approval was granted by the Faculty Research Ethics Committee of the University of Plymouth (Ref: 17/18–866). The study protocol (IRAS, project ID: 228115) also received approval from NHS Health Research Authority and Southwest - Exeter Research Ethics Committee (Ref: 17/SW/0170).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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ORCID

Vasileios Lepesis https://orcid.org/0000-0003-0404-4636

PEER REVIEW

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