

Benefits and Harms of Exercise Therapy for Patients With Diabetic Foot Ulcers: A Systematic Review

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Abstract

Aim. Exercise therapy is a core element in the treatment of diabetes, but the benefits and harms for patients with a diabetic foot ulcer (DFU) are unknown. We therefore aimed to systematically review the benefits on health-related quality of life (HRQoL) and harms of exercise therapy for patients with DFU. **Methods.** We searched 6 major databases. We performed citation and reference searches of included studies and contacted authors of ongoing trials. We included randomized controlled trials (RCTs) to assess potential benefits on HRQoL and harms of exercise therapy. Observational studies were included to identify potential harms of exercise therapy. **Results.** We included 10 published publications of 9 trials and results from 2 unpublished trials including a total of 281 individuals with DFUs receiving various forms of exercise therapy. Due to lack of HRQoL measurements and high heterogeneity, it was not possible to perform meta-analyses. Results on HRQoL was present in one unpublished study. Harms reported ranged from musculoskeletal problems, increased wound size, to amputation; however, no safe conclusions could be drawn from the available data due to high heterogeneity and risk of bias in the trials. **Conclusions/ Interpretation.** Protective strategies are often preferred over therapeutic exercise that might have unforeseen consequences for patients over time. Based on the current literature, no evidence-based recommendations can be provided on the benefits and harms of exercise therapy for patients with DFUs. Well-conducted RCTs are needed to guide rehabilitation including detailed description of adverse events and an exercise program in a semisupervised or fully supervised setting.

Keywords

diabetic foot ulcers, wound care, health-related quality of life assessments

One of the most feared complications of diabetes mellitus is diabetic foot ulcers (DFUs), as it can cause severe adverse consequences such as amputation or death.¹ The 5-year mortality rate is 2.5 times higher for patients with DFUs compared with patients with diabetes mellitus and no foot ulcer.¹ Of those who survive, 40% have been reported to have a new or recurrent DFU within 12 months.² Overall, healing rates of DFUs have been reported to vary from 65% to 77%,^{3–8} and while wound healing may take many months or years, unfortunately for some, wound closure is never achieved.⁹ According to the International Working Group on the Diabetic Foot guidelines of 2019, multiple interventions are typically required to heal a DFU. The most important are pressure off-loading, infection management, revascularization, and local wound management.¹⁰

Patients are often required to refrain from bearing weight on their affected limb,¹¹ leaving some patients immobile for weeks, months, or even years.¹² This is in direct contrast to guidelines for diabetes where exercise therapy and physical activity are core elements in rehabilitation and treatment of the disease.¹³ This leaves patients and caretakers with a paradox. If a DFU evolves, should patients continue following the

guidelines for diabetes? Even if these guidelines include recommendations of brisk walking and exercising at high intensity?

Inclusion of exercise therapy in the treatment of DFUs could be relevant, since it reduces hyperglycemia and

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visceral fat, and has been found to increase health-related quality of life (HRQoL) in patients with diabetes.¹⁴ The latter is of key relevance to patients with DFUs, as a DFU is associated with reduced mobility, depression, and overall low HRQoL.¹⁵⁻²² Patients report severely decreased HRQoL at initial presentation in the foot clinic²³ and further decreased if the DFU does not heal.²⁴ However, it remains unclear to what extent exercise therapy can affect this decline in HRQoL, and if exercise therapy is safe to perform for patients with DFUs.

Although, one previous systematic review from 2015²⁵ intended to evaluate the effectiveness of Buerger's exercise on DFU, they retrieved and included no studies on patients with DFUs. We therefore aimed to systematically review the benefits on HRQoL and harms of exercise therapy for patients with a DFU.

Methods

We conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.²⁶ The review protocol was registered at the International Prospective Register of Systematic Reviews on October 3 (<http://www.crd.york.ac.uk/prospero>; Registration number: CRD42020151933) prior to study commencement.

Database Searching and Search Strategy

We searched MEDLINE (via PubMed), EMBASE (via OVID), CENTRAL (via the Wiley InterScience portal), CINAHL (via EBSCOhost), Physiotherapy Evidence Database (PEDro), and Web of Science. We did not apply any language restrictions.

All databases were systematically searched from inception to October 2019 for studies on exercise therapy for patients with an active DFU. We used free text, keywords, Medical Subject Headings, and word variants for DFU such as "Diabetic foot ulcer," "Diabetic feet," "Diabetic foot wound," and combined these with terms for exercise such as "Physical activity," "Physical fitness," "Exercise therapy," and "Strength training" (Supplement Material: Search Strategy). To identify additional studies, the reference lists of all included full-text articles were screened and we performed a citation search in Web of Science of all included full-text articles.

Study Selection

One reviewer scanned titles and abstracts for potentially eligible studies. Two reviewers read the full-text version of potentially eligible studies and decided independently whether the study could be included. Disagreements were discussed with a third reviewer and resolved by consensus.

We included randomized controlled trials (RCTs) to assess both potential benefits and harms of exercise therapy and observational studies (ie, comparative studies [prospective or retrospective], case series, case studies, and pilot studies) to identify potential harms of exercise therapy.^{27,28} Eligible studies included patients with an active DFU receiving exercise therapy. We excluded studies with no original data (eg, editorial, commentary, or letter), duplicate data, and studies presented only as conference abstracts.

We defined exercise therapy as "a regimen or plan of physical activities designed and prescribed for specific therapeutic goals." Its purpose is to restore normal musculoskeletal function or to reduce pain caused by diseases or injuries.²⁹

Outcomes on benefits of exercise therapy were any generic or specific measures of HRQoL (ie, Medical Outcomes Study Questionnaire Short Form 36 [SF-36],³⁰ EuroQOL-5D [EQ-5D],³¹ The Diabetic Foot Ulcer Scale,³² and Wound-QoL³³).

Outcomes of harms included, but were not limited to, death; amputation (including major and minor lower extremity amputation); new or worsening of existing DFU formation; new pre-ulcerative lesion formations (including abrasions, hyperkeratosis, and blisters); acute Charcot foot; infection; and hospital admissions. Adverse events mentioned in the primary studies were registered as yes or no and registered separately for intervention and control groups.

Reports of adherence rates to the exercise program and number of dropouts were registered separately for the intervention and control groups since discontinuations and withdrawals could reflect patient's inability to tolerate the intervention.³⁴

Data Extraction and Quality Assessment

Two reviewers independently extracted data of included studies on study characteristics and results using a standardized form (Supplement Material: Standardized Form). Disagreements were discussed with a third reviewer and resolved by consensus. In cases of multiple publication of data from identical patients at different follow-ups, we summarized the development of and included data from the most recent follow-up.

One reviewer assessed the methodological quality of included studies. The methodological quality of each included RCT was assessed based on quality criteria specified by the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).³⁵

The risk of bias in observational studies were assessed according to predefined criteria^{36,37}: (1) the cohort was consecutively or randomly sampled; (2) dropouts or loss to follow-up were few (<15%); (3) classification procedure was adequate (ie, using Wagner's class scale, or measurements of

the wound in cm²); (4) outcome was blindly assessed; (5) no conflicts of interest; (6) we considered the cohort to be fairly representative for the “average” patient with a DFU.³ Case series including less than 10 patients were not assessed for risk of bias.

Data Synthesis and Analysis

We planned to conduct a meta-analysis on benefits of exercise therapy using any reported measures of HRQoL and a meta-analysis on the relative risk of adverse events in the groups receiving exercise therapy, if the included studies were homogeneous and presented the characteristics to enable a meta-analysis, otherwise the studies would be summarized qualitatively.

Study management and data extraction was performed using EndNote X9 and Microsoft Word 2019.

Results

Study Identification

From 6985 citations, we selected 31 for full-text evaluation (Figure 1). After a detailed assessment, we included 6 studies.³⁸⁻⁴³ We excluded 25 studies retrieved in full text due to the following reasons: inclusion criteria were not met ($n = 18$)⁴⁴⁻⁶¹; presented as a debate article, conference abstracts, trial registrations ($n = 5$)⁶²⁻⁶⁶; and duplicate data ($n = 2$).^{67,68}

A citation search in Web of Science of all 6 included studies yielded 3 additional studies. Huang et al⁶⁹ presented data for 3-month follow-up of the same population of patients as Chen et al,⁴⁰ Chang et al,⁷⁰ and finally Nwankwo et al.⁷¹ Authors of the 3 trial registrations⁶⁴⁻⁶⁶ were contacted by email in order to obtain unpublished data. Two replies were received: Jørgensen provided his PhD thesis⁷² including data from NCT02785198⁶⁵ and the same data from the conference abstract originally excluded.⁶³ S. Morgan provided unpublished data from their ongoing trial NCT03002155.⁶⁶

Characteristics and Quality of the Included Studies

In total, there were 3 RCTs,^{38,39,71} 3 prospective cohort studies in 4 publications,^{40,41,69,70} 1 pre-post designed feasibility study⁴² and 1 case series study,⁴³ and data from 2 unpublished studies (Jørgensen⁷² and S. Morgan, unpublished data, December 2019). Studies included 281 patients with DFUs in total. The studies varied widely in patient characteristics, mean age, setting where exercise therapy took place, the exercise intervention, duration, and frequency of

exercise. Characteristics of the included studies are provided in Tables 1 and 2.

In accordance with the RoB 2 Quality Assessment scale for RCTs, all 3 RCT studies were overall judged to be of high risk of bias (Table 3). Flahr³⁹ and Eraydin and Avşar³⁸ described their study design as both randomized and quasi-randomized and were therefore assessed as RCT studies. In both studies, the randomization process was on “the order of patient referral to the clinic,” whereas Nwankwo et al⁷¹ described a randomization method of pithers bowl, with no specification of it. All 3 studies had baseline differences in patient characteristics that suggested a problem with the randomization process. Flahr³⁹ described a difference between group, whereas Nwankwo et al⁷¹ reported a significant difference ($P < .00$) in ulcer area values at baseline, and Eraydin and Avşar³⁸ reported an almost twice as large ulcer area difference at baseline ($P < .05$). None of the 3 studies employed blinding. No studies stated that an intention-to-treat analysis was performed. No studies had a published trial protocol or trial registration to assess (Supplement Material: RoB 2 Template for Completion).

The risk of bias in the observational studies were considerable (Table 4). No studies were considered to have a low risk of bias according to all 6 criteria. Unclear reporting hampered the assessment. One study⁷⁰ was considered to have low risk of bias in 4 of 6 domains. Three studies^{40,41,69} complied with 3 out of 6 domains. One study⁴² complied with 1 out of 6 domains. Finally, one study⁴³ included 5 patients and was not assessed for risk of bias.

Benefits and Harms of Exercise Therapy

Assessing the benefits of exercise therapy on HRQoL or harms through meta-analysis was not possible. Hence, only one study reported results of HRQoL and studies reporting harms had high heterogeneity. Data are therefore summarized below.

No published studies included measurements of HRQoL. Both unpublished studies included measurement of HRQoL (Table 1). Although Jørgensen⁷² recorded SF-36 and EQ-5D at baseline and 16-week follow-up, they did not report baseline or change score on HRQoL. Morgan (unpublished data, December 2019) recorded HRQoL using PROMIS.⁷³ On PROMIS-Global, they reported reduced fatigue ($P = .06$) and on PROMIS-Physical Function improved physical function ($P = .009$). It is unclear if these significant changes were clinically relevant. No other significant findings were demonstrated (S. Morgan, unpublished data, December 2019).

Wound condition change was an outcome measure in all but one study, either reported in a dichotomous^{41,70} or

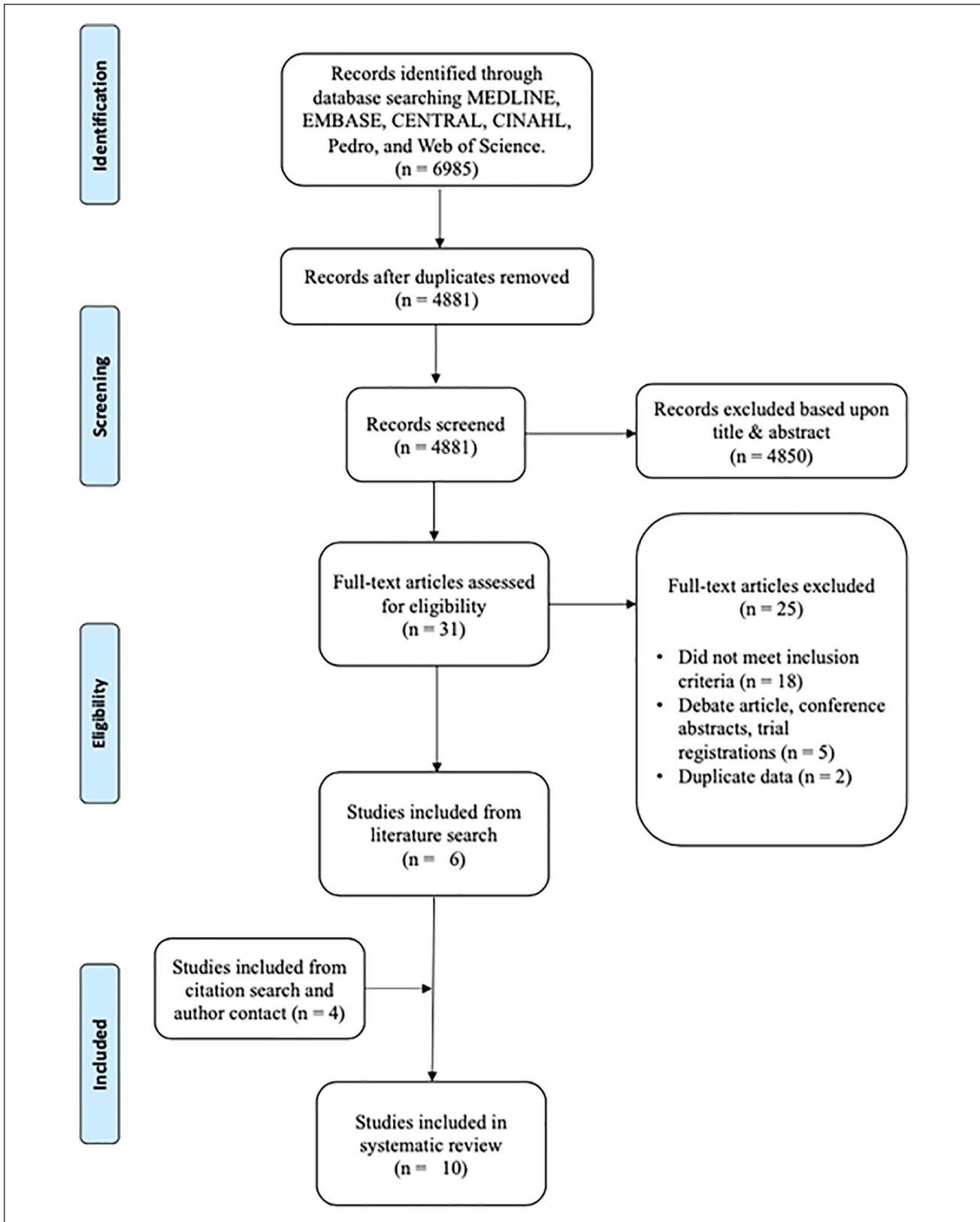


Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram presenting the process undertaken to identify eligible studies.

Table 1. Study Characteristics.

First author, country	Aim	Population enrolled/completed	Outcome measures	Wound condition/size results
<i>Randomized studies</i>				
Eraydin and Ayşar, ³⁸ Turkey	To examine the effect of foot exercises on wound healing in patients with type 2 diabetes with a DFU	65 patients hospitalized with DFUs enrolled Intervention group, n = 30 (mean age = 61.03) Control group, n = 30 (mean age = 65.76)	<ul style="list-style-type: none"> Wound size in cm² using a scaled transparent measurement paper Exercise log 	Comparison between groups after 12 weeks: Exercise group: Mean DFU area 3.29 cm ² (SD = 3.80) Control group: Mean DFU area 18.52 cm ² (SD = 21.49) P < .01
Flahr, ³⁹ Canada	To explore the effect of exercise on healing diabetic foot ulcers	19 patients with DFUs enrolled Intervention group: n = 10 (mean age = 62.2) Control group: n = 9 (mean age = 74.25) 61 patients with DFUs Intervention: n = 31 (mean age = 69.06 ± 4.79) Control: n = 30 (mean age: 68.50 ± 5.01)	<ul style="list-style-type: none"> Wound size in cm² traced onto an acetate grid Infection protocol Dartmouth COOP Functional Assessment Chart/WOCNA Wound size in cm² using a transparent ruler Fasting plasma glucose test Total cholesterol test 	90% experienced a reduction in wound size of 26% to 100% over the 12-week program
Nwankwo et al, ⁷¹ Nigeria	Investigate the effect of aerobic exercises on changes in biochemical profiles of diabetic subjects and rate of ulcer healing on patients with diabetic foot ulcers			Comparison between groups after 12 weeks: Exercise group: Mean DFU area 1.97 cm ² (SD = 4.17) Control group: Mean DFU area 7.93 cm ² (SD = 4.08) P < .01
<i>Observational studies</i>				
Chen et al ⁴⁰ and Huang et al, ⁶⁹ China	To investigate reliability and effectiveness of near-infrared spectroscopy on continuous peripheral circulation changes detection while asking the patients to do Buerger's exercise	30 patients with DFUs and 15 generally healthy populations A peripheral arterial disease group with DFUs: (A1 group) n = 21 (mean age = 70.62 ± 11.16) A non-PAD group with DFUs: (group A2) n = 9 (mean age = 57.78 ± 5.85) A generally healthy group (group B) n = 15 (mean age = 20.67 ± 1.89)	<ul style="list-style-type: none"> Oxygenated hemoglobin concentration Total tissue hemoglobin concentration 	Not relevant
Lin et al, ⁴¹ China	To investigate the Buerger's exercise effects in patients with vasculopathic DFU with a cohort follow-up and determine whether near-infrared spectroscopy system is an effective monitoring tool for this exercise in a rehabilitation program	14 patients with a DFU and absence (A1) or presence (A2) of previous percutaneous transluminal angioplasty A1: n = 8 (mean age = 68.2 [SD = 9.6]) A2: n = 6 (mean age = 72.8 [SD = 13.5])	<ul style="list-style-type: none"> Wound condition (healed/healing) Oxygenated hemoglobin concentration Total tissue hemoglobin concentration 	Wounds healed: 11/14 = 78.57% Wounds healing: 3/14 = 21.43% P = .539
Chang et al, ⁷⁰ China	Unclear	30 patients with unilateral or bilateral DFU n = 30 (mean age = 63.4 [SD = 13.7])	<ul style="list-style-type: none"> Wound condition (healed/healing) Skin perfusion pressure measured in mm Hg 	Healed: 9 (26.5%) Improving: 14 (41.2%) Stasis: 6 (17.6%) Progression: 3 (8.8%) Toe amputation: 2 (5.9%)

(continued)

Table 1. (continued)

First author, country	Aim	Population enrolled/completed	Outcome measures	Wound condition/size results
Otterman et al, ⁴² the Netherlands	To investigate the feasibility and preliminary effectiveness of an exercise program for patients with diabetic complications	25 patients with various diabetic foot complications. Two patients described with an active DFU—no specification of age	<ul style="list-style-type: none"> • Program adherence • Adverse events • Achievement of the target training intensity • Patient satisfaction on a numeric rating scale from 0 to 10 	Not reported
Lindberg et al, ⁴³ Denmark	To examine the feasibility and safety of an exercise program tailored for people with diabetes, severe peripheral neuropathy and an active foot ulcer	5 patients with DFUs n = 5; mean age (SD) = 68.2 (7.1)	<ul style="list-style-type: none"> • Wound size in cm² • 10 repetition maximum for knee flexor, knee extensor, hip abductor, low row • Patient-specific functional scale • Endurance cycling on stationary bike • Number of ankle dorsiflexion repetitions • Participant satisfaction measured by Numeric Rating Scale 	Wound size: Pre-exercise: median 1.9 cm ² (IQR = 1.1-7.3) Post-exercise: median 0.0 cm ² (IQR = 0.0-3.0)
<i>Unpublished studies</i> S. Morgan (2019), USA	To evaluate the effects of a seated exercise program on clinically meaningful outcomes in people with diabetic foot ulcers	34 patients with DFU enrolled; 18 completed Intervention: n = 7 (mean age 59.7) Control group: n = 11 (mean age 55.6)	<ul style="list-style-type: none"> • Wound size in cm² • Glycated hemoglobin • Chair Stand Test • Patient reported outcome measurement—PROMIS • Exercise self-efficacy scale • Retention, recruitment, adherence, and adverse event rates 	Not reported
T. S. Jørgensen, ⁷² Denmark	To evaluate the effect and feasibility of 8 weeks of passive movement exercise of both legs on wound healing in nonhealing diabetic foot ulcers	21 patients with DFUs Intervention: n = 11 (mean age 58 ± 1.7) Control group: n = 10 (mean age 64 ± 4.8)	<ul style="list-style-type: none"> • Wound size in cm² • Change in Wagner's wound classification • Perfusion of the lower extremity using Doppler • Skin perfusion pressure measured in mm Hg • Biochemical and histological changes • Patient reported outcome measurement—MOS SF36 and EQ-5D • 30-second Chair Stand Test • Maximum let extension test • Adverse event rates • Distal blood pressure 	Comparison between groups after 8 weeks: 40% reduction in wound area P = .062

Abbreviations: DFU, diabetic foot ulcer; PAD, peripheral arterial disease; IQR, interquartile range.

Table 2. Details of Intervention.

First author	Intervention	Control	Duration, frequency, and attendance rates of the exercise therapy intervention	Intervention supervised/not supervised and delivered individually/in a group
<i>Randomized studies</i>				
Eraydin and Avşar ³⁸	Instructions to patients with DFU were provided that included the following information: (1) avoid exercises that require weight bearing; (2) complete the exercise program in a sitting position at first and in a standing position after the wound heals; (3) exercises include range-of-motion movements of plantar flexion, dorsiflexion, inversion, eversion, circumduction, and plantar and dorsal flexion of toes.	Usual care—not specified	3.3% did exercises between 61 and 90 days, 50% between 31 and 60 days, and 26.7% between 0 and 30 days	Not supervised and delivered individually
Flahr ³⁹	Non-weight-bearing ankle exercises: Simple ankle inversion, eversion, flexion, and extension.	Usual care—not specified	Exercise frequency in the experimental group varied from “unknown” to 3 times per day for 80% of patients while 20% performed the exercises 2 times per day as requested	Not supervised and delivered individually
Nwankwo et al ⁷¹	Cycling on an ergometer bicycle with foot interaction kept constant with a standard gym pedal and a specialized off-loading insole padding to relieve pressure on the ulcer.	Usual care—normal wound dressing, diet control, counseling, and medication without any form of exercise	3 times a week for 12 weeks. Increased exercise by 5 minute each 2 weeks until 50 minutes exercise time was reached Initial aerobic exercise intensity was on 60% maximum; progressed to 85% over 12 weeks using Borg’s rating scale of perceived exertion	Supervised delivered individually
<i>Observational studies</i>				
Chen et al ⁴⁰ and Huang et al ⁶⁹	Buerger-Allen’s exercise	Not relevant	For 3 months; duration and frequency not reported	Supervised by a well-trained research assistant and delivered individually
Lin et al ⁴¹	Buerger-Allen’s exercise	Not relevant	Not relevant	Not supervised and delivered individually
Chang et al ⁷⁰	Buerger-Allen’s exercise	Not relevant	For 3 months; duration and frequency not reported	Not supervised and delivered individually

(continued)

Table 2. (continued)

First author	Intervention	Control	Duration, frequency, and attendance rates of the exercise therapy intervention	Intervention supervised/not supervised and delivered individually/in a group
Otterman et al ⁴²	Combined resistance and aerobic training: supervised training session consisted of a warm-up, resistance exercise, aerobic exercise, and cooling down. Resistance training (30 minutes) consisted of different forms of exercise addressing major muscle groups (eg, knee extensors, hip extensors, abdominal muscles, shoulder extensors, and elbow flexors).	Not relevant	2-week individualized exercise program consisting of 2 supervised group sessions Duration and frequency of 2 ulcer patients not reported	Supervised and not supervised and delivered individually
Lindberg et al ⁴³	A combination of aerobic and resistance training exercises including active dorsal/plantar ankle flexion exercises. Starting with up to 12-minute cycling on a stationary bike and ended with cooling down with active ankle movements.	Not relevant	10-week (attending biweekly) exercise program All patients completed the exercise program with a session attendance from 85% to 95%	Supervised in a group
<i>Unpublished studies</i>				
S. Morgan (2019)	Community-based seated exercise program (EnhanceFitness) with the following elements: Seated cardiovascular exercise (20 minutes), seated strength training (20 minutes), and seated stretching (10 minutes) + warm-up and cool down The training included the following: warm-up, aerobics, cool down, balance training, strength training, and stretching.	Usual care	1 hour, 3 times a week, for 12 weeks Attending rates in the exercise group = 67%	Supervised in a group
T. S. Jørgensen ⁷²	Passive movement training in a passive leg movement machine.	Usual care—not specified	Three times a week for 8 weeks; each session lasting for 60 minutes Adherence to the exercise protocol was 100%	Supervised and delivered individually

Abbreviation: DFU, diabetic foot ulcer.

Table 3. Quality of Included Randomized Studies (n = 3).

First author	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported results
Eraydin and Avşar ³⁸	–	–	–	–	?
Flahr ³⁹	–	–	+	–	?
Nwankwo et al ⁷¹	–	–	+	–	?

Abbreviations: +, low risk; –, high risk; ?, some concerns.

Table 4. Quality of Observational Studies (n = 4 in 5 Reports).

First author	The cohort was consecutively or randomly sampled	Dropouts or loss to follow-up were few (<15%)	We considered the classification procedure as adequate	Outcome was blindly assessed	No conflicts of interest	We considered the cohort to be fairly representative for the “average” patient with a diabetic foot ulcer
Chen et al ⁴⁰ and Huang et al ⁶⁹	–	+	–	?	+	+
Lin et al ⁴¹	–	+	–	?	+	+
Chang et al ⁷⁰	–	+	+	?	+	+
Otterman et al ⁴²	–	–	–	?	+	? ^a

Abbreviations: +, low risk; –, high risk; ?, unknown.

^aUnclear characteristics on duration of diabetes and age of diabetic foot ulcer patients.

numeric^{38,39,43,71,72} scale. Two studies included laboratory measures as primary outcomes^{40,69} (Table 1).

In total, 5 studies reported adverse events of various severity^{39,42,43,70,72} (Table 5). Adverse events ranged from musculoskeletal problems,⁴³ increased wound size,^{39,70,72} osteomyelitis,³⁹ to amputation.^{70,72} The latter was also present in the corresponding control group.^{70,72}

Otterman et al⁴² reported 52 adverse events in 18 patients but did not specify if these occurred in patients with or without the active DFU.

Dropout rates varied in the studies, with some due to health issues,^{38,72} and others due to relocation, lack of interest from patients, or planning issues.^{38,42} Although not reported as an adverse event, 1 patient in the study of Eraydin and Avşar³⁸ receiving exercise therapy dropped out of the study due to “general condition deteriorated.” Reasons for the deterioration was not specified (Table 5).

Discussion

To our knowledge, this is the first systematic review aimed at assessing the benefits and harms of exercise therapy for patients with a DFU. Despite using a comprehensive and structured search strategy, including RCTs and observational studies as well as unpublished material, very few studies were identified that investigated exercise therapy for patients with a DFU. None of the available studies had low risk of bias, and no published studies evaluated HRQoL.

This highlights the need for high-quality trials in order to inform clinical practice.

Benefits of Exercise Therapy

Exercise therapy is described as a core element in the treatment of various chronic conditions,^{13,14,74–78} and for patients with diabetes, it has been found to reduce hyperglycemia and visceral fat and increase HRQoL.¹⁴ The search yielded no published studies on exercise therapy for patients with DFU measuring HRQoL. Jørgensen⁷² used HRQoL measures of SF-36 and EQ-5D, yet reported no baseline or change results of these, whereas S. Morgan (unpublished data, December 2019) reported significant improvements in 18 patients on the Physical Function subscale of PROMIS, although unclear if these significant changes were clinically relevant.

Outcome measures used in the included studies were peripheral circulation change^{40,41,69,70} and reduction in wound size^{38,39,72} (Table 1). Although increasing peripheral circulation to the affected foot and ulcer is relevant, the outcome is a laboratory outcome measure and is not an essential outcome for clinical decision-making.⁷⁹ Reduction in wound size would be considered an important and meaningful outcome for patients, and together with HRQoL, probably the 2 most relevant outcomes for patients with DFUs. Yet, the casualty between exercise and wound healing has not been established. To our knowledge, only a few

Table 5. Results on Harms and Dropouts.

First author	Number of patients affected by adverse events	Adverse events (type and description)	Dropouts
<i>Randomized studies</i>			
Eraydin and Avşar ³⁸	Not reported	Not reported	Intervention group: 3 Reasons for withdrawal: general condition deteriorated, went out of city, and wanted to leave Control group: 2 Reasons for withdrawal: went out of city and unreachable
Flahr ³⁹	Intervention group: 1 Control group: 3	Intervention group: 1 diagnosed with osteomyelitis Control group: 3 wounds increased during study	Control group: 1 Reason for withdrawal not reported
Nwankwo et al ⁷¹	Not reported	Not reported	Not reported
<i>Observational studies</i>			
Chen et al ⁴⁰ and Huang et al ⁶⁹	Not reported	Not reported	0
Lin et al ⁴¹	Not reported	Not reported	0
Chang et al ⁷⁰	5	3 had a progression in wounds 2 had toe amputation	0
Otterman et al ⁴²	Overall adverse events recorded: 55 Not specified for patients with DFUs	Not specified for patients with DFUs	2 dropouts in total Reasons for dropout were: Start of an education that could not be combined with participating in the study, and transportation problems
Lindberg et al ⁴³	7	Low level of blood glucose during training: 2 Shoulder pain during cycling: 1 Delayed onset muscle soreness in their thighs and knee pain to an extent that compromised progression in cycling and resistance training loads for several weeks following start of the program: 3 Transient exudate from the foot ulcer during the first weeks of training: 1	0
<i>Unpublished studies</i>			
S. Morgan (2019)	0	Not relevant	16 dropouts in total Intervention group: 8 Control group: 8 Reasons for dropouts included: Scheduling challenges (exercise: 4 and control: 2) Ineligibility in baseline screen (exercise: 2 and control: 1) Lost interest (exercise: 2) Preference for the exercise group (control: 5)
T. S. Jørgensen ⁷²	4	Intervention group: 2 <ul style="list-style-type: none"> • Deep infection. One resulting in amputation of the first toe Control group: 2 <ul style="list-style-type: none"> • Deep infection resulting in above knee amputation for one and amputation of the toe for the other 	5 dropouts in total Intervention group: 2 <ul style="list-style-type: none"> • Due to infection and amputation Control group: 3 <ul style="list-style-type: none"> • 2 due to infection and amputation • 1 from the control group is unclear why

Abbreviation: DFU, diabetic foot ulcer.

animal and human studies have investigated the role of exercise on wound healing⁸⁰⁻⁸⁴ with results indicating that exercise may be able to play a supporting role in wound healing of healthy human adults and for patients with chronic leg wounds^{80,81} as long as the adherence rates to exercise are high.⁸⁵ Unfortunately, nonadherence to treatment is a widespread problem for patients with DFUs.⁸⁶ One such example is with the use of off-loading devices. Although the association between off-loading adherence and DFU healing is high, research has found adherence with a removable cast walker in patients with active DFU to be low.^{87,88} In fact, numerous intervention studies⁸⁹⁻⁹⁵ have been hampered by the fact that a large number of patients did not adhere to the recommended treatment.⁹⁶

In 3 studies,^{42,43,72} adherence rates to the exercise program exceeded 80% in either a semisupervised⁴² or fully^{43,72} supervised setting. Six studies^{38-41,69,70} used a home-based setting. Although, studies using a home-based setting argued that this program was easy to use and with low cost for patients, Eraydin and Avşar³⁸ and Flahr³⁹ both reported issues with low adherence to the exercise programs in a nonsupervised home-based setting with the other 4 studies suffering from unclear reporting of their adherence rates. This is not surprising, hence adherence has generally been found better in programs with supervision.⁹⁷ One possible explanation to this could be that direct supervision offers additional encouragement and motivation to patients.⁹⁸ So, it could be argued that in order to fully examine if exercise therapy has an effect on both wound healing and/or HRQoL, it should be examined in a semisupervised or fully supervised setting to ensure high adherence to treatment.

Harms of Exercise Therapy

Most newly introduced treatments usually report benefits, with little effort to balance these with the potential harms,^{27,99} and many trials across various medical areas do not report harms or report them in a fragmented or suboptimal way.^{99,100} This is in line with results from the included studies. Although some adverse events were reported (Table 5), the consensus of what would be considered a potential harm when introducing exercise therapy to this population of people already at a high risk of infection and amputation was neither described nor discussed in any included studies. A recent systematic review by Niemeijer et al¹⁰¹ including 378 studies comparing exercise therapy intervention with a nonexercising control treatment on participants with or without a medical condition did not find an increased risk ratio (RR = 0.96 [95% confidence interval (CI) 0.90-1.02]) of serious adverse events (ie, death, hospitalization, or a serious risk of deterioration in health). However, the study did find a risk ratio of 1.19 (95% CI = 1.09-1.30) for nonserious adverse events (ie, pain, fatigue, and edema) in studies of exercise therapy.¹⁰¹ It remains

unclear, if these results reflect the risk for patients with DFUs.

Introducing exercise therapy could be considered potentially dangerous; hence, the formation of new ulcers commonly occur due to repetitive stress over an area that is subject to high vertical or shear stress.^{86,102} Yet, usual care is not without risks as DFUs and amputations are associated with a reported 5-year mortality of 45%, 18%, and 55% for neuropathic, neuroischemic, and ischemic ulcers, respectively,¹ which are similar or worse than many common types of cancer.¹⁰³

The benefits and harms of exercise therapy should be investigated in well-conducted RCT studies as an add-on to the existing evidence-based guidelines from the International Working Group on the Diabetic Foot.¹⁰ Although included studies had limitations and the potential risk of bias was high, some key points should be considered in future studies: The exercise program used should be either in a semisupervised or fully supervised setting as used in 3 included studies.^{42,43,72} As reported by Lindberg et al,⁴³ a clear detailed description of adverse event, no matter the severity, is vital. Many patients with a DFU often have a history of diabetic peripheral neuropathy and have previously been asked to avoid weight-bearing activities, which severely affects their ability to participate in the exercise program.⁴⁵

Strengths and Limitations

The strength of this study is its comprehensive scope, the inclusion of all types of exercise therapy, the thorough search strategy applied, and the inclusion of unpublished data.

Due to lack of HRQoL outcomes and lack of reporting on adverse events in the studies included, it was not possible to perform meta-analysis on neither benefits nor harms. Including studies with a high risk of bias is a limitation in itself because the reported outcome effect is susceptible to bias and must be read with caution. Assessment of risk of bias in observational studies were based on common sense—so it should be regarded as tentative. As should the arbitrary limit of only including case studies with 10 or more patients, although case studies in general usually warrant rating down from low to very low quality evidence.¹⁰⁴

Conclusion

We found no high-quality evidence assessing HRQoL or harms of exercise therapy in patients with a DFU. The few RCTs and clinical studies found had high heterogeneity and high risk of bias.

Based on the current literature, no evidence-based recommendations can be provided on the benefits and harms of exercise therapy for patients with DFUs. Well-conducted RCTs are needed to guide rehabilitation including detailed

description of adverse events and an exercise program in a semisupervised or fully supervised setting.

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