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Benefits and harms of exercise therapy for patients with diabetic foot ulcers: A systematic review

Msc Thomas Vedste Aagaard^{1,2,3}, MD Sahar Moeini³, Professor Søren T. Skou^{4,5}, PhD Ulla Riis Madsen^{2,6}, Professor Stig Brorson^{3,7}

¹ Department of Physiotherapy and Occupational Therapy, Holbaek Hospital

² Department of Orthopaedic Surgery, Holbaek Hospital.

³ Department of Orthopaedic Surgery, Zealand University Hospital

⁴ Department of Physiotherapy and Occupational Therapy, Naestved-Slagelse-Ringsted Hospitals

⁵ Research Unit for Musculoskeletal Function and Physiotherapy, Department of Sports Science and Clinical Biomechanics, University of Southern Denmark

⁶ The Danish Knowledge Centre for Rehabilitation and Palliative Care. University of Southern Denmark

⁷ Department of Clinical Medicine, University of Copenhagen

Corresponding author:

Thomas Vedste Aagaard, Department of Physiotherapy and Occupational Therapy and Department of Orthopaedic Surgery, Holbaek Hospital.

Address: Smedelundsvej 60, 4300 Holbaek, Denmark

E-mail: thva@regionsjaelland.dk

Telephone: +45 93567835

ORCID ID: <https://orcid.org/0000-0002-5098-5982>

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 six major databases. We performed citation and reference searches of included studies and contacted authors of ongoing trials. We included randomized controlled trials 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Results We included 10 published publications of 9 trials and results from two unpublished trials including a total of 281 individuals with DFUs receiving various forms of exercise therapy.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 Results on HRQoL was present in one unpublished study.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 which 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 semi- 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 (DFU), as it can cause severe adverse consequences such as amputation or death¹. The 5-year mortality rate is 2.5 times higher for patients with DFUs compared to patients with diabetes mellitus and no foot ulcer¹. Of those who survive, 40% have been reported to have a new or recurrent DFU within 12 months². Overall, healing rates of DFUs have been reported to vary from 65-77 %³⁻⁸ and while wound healing may take many months or years, unfortunately for some, wound closure is never achieved⁹. 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 offloading, infection management, revascularization and local wound management¹⁰.

Patients are often required to refrain from bearing weight on their affected limb¹¹, leaving some patients immobile for weeks, months or even years¹². This is in direct contrast to guidelines for diabetes where exercise therapy and physical activity are core elements in rehabilitation and treatment of the disease¹³. 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?

Including exercise therapy in the treatment of DFUs could be relevant, since it reduces hyperglycaemia and visceral fat and has been found to increase health-related quality of life (HRQoL) in patients with diabetes¹⁴. The latter is of key relevance to patients with DFUs, as a DFU is associated with reduced mobility, depression and overall low HRQoL¹⁵⁻²². Patients report severely decreased HRQoL at initial presentation in the foot clinic²³ and further decreased if the DFU does not heal²⁴. 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) statement²⁶. 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 feet wound' and combined these with terms for exercise such as 'Physical activity', 'Physical fitness', 'Exercise therapy', 'Strength training' (Supplement material: Search strategy). To identify additional studies, the reference lists of all included full-text papers were screened and we performed a citation search in Web of Science of all included full-text papers.

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 (i.e. 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 (e.g. 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 injuries²⁹.

Outcomes on benefits of exercise therapy were any generic or specific measures of HRQoL (i.e. Medical Outcomes Study Questionnaire Short Form 36 (SF-36)³⁰, EuroQOL-5D (EQ-5D)³¹, The Diabetic Foot Ulcer Scale³², 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; 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 drop-outs were registered separately for the intervention and control groups since discontinuations and withdrawals could reflect patient's inability to tolerate the intervention³⁴.

Data extraction and quality assessment

Two reviewers independently extracted data of included studies on study characteristics and results using a standardised form (Supplement material: Standardised 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 pre-defined criteria^{36,37}: (a) the cohort was consecutively or randomly sampled; (b) drop-outs or loss to follow-up were few (<15%); (c) classification procedure adequate (i.e. using Wagner's class scale, or measurements of the wound in cm²); (d) outcome was blindly assessed; (e) no conflicts of interest; (f) we considered the cohort to be fairly representative for the 'average' patient with a DFU³. 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 homogenous 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

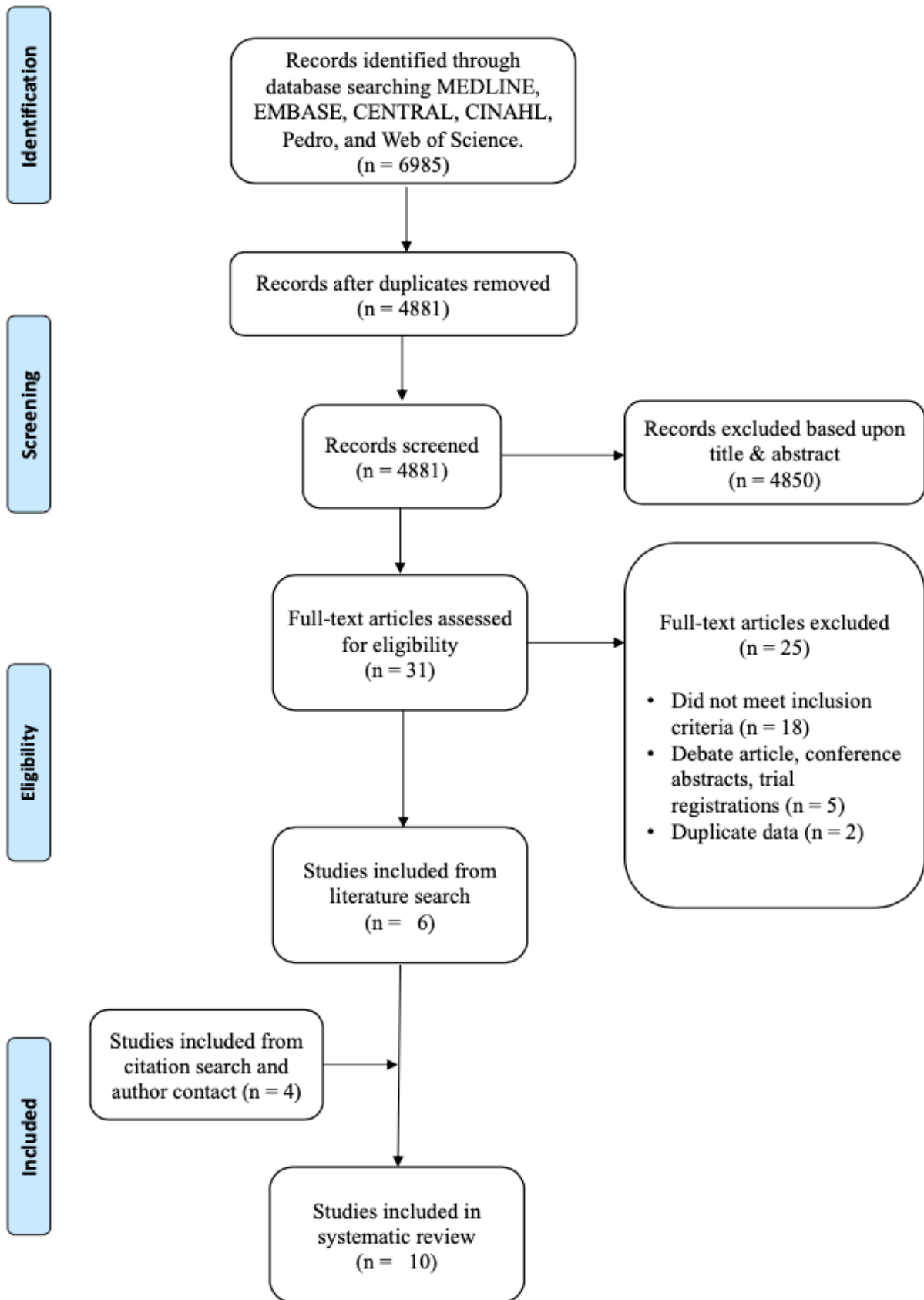


Figure. 1 – PRISMA diagram presenting the process undertaken to identify eligible studies.

Study identification

From 6985 citations, we selected 31 for full text evaluation (Fig. 1) After a detailed assessment, we included 6 studies³⁸⁻⁴³. 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 six included studies yielded three additional studies. Huang *et al*⁶⁹ presenting data for three-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 three trial registrations⁶⁴⁻⁶⁶ were contacted by e-mail in order to obtain unpublished data. Two replies were received: Jørgensen TS. provided his PhD thesis⁷² including data from NCT02785198⁶⁵ and the same data from the conference abstract originally excluded⁶³. S. Morgan provided unpublished data from their ongoing trial NCT03002155⁶⁶.

TABLE 1 + 2

Characteristics and quality of the included studies

In total, there were three RCTs^{38,39,71}, three prospective cohort studies in four publications^{40,41,69,70}, one pre-post designed feasibility study⁴² and one case series study⁴³ and data from two unpublished studies (Jørgensen TS.⁷² 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 Table 1+2.

In accordance with the RoB 2 quality assessment scale for RCTs, all three RCT studies were overall judged to be of high risk of bias (Table 3). Flahr³⁹ and Eraydin *et al*³⁸ described their study design as both randomised and quasi-randomised 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 al*⁷¹ described a randomization method of *pithers bowl*, with no specification of it. All three studies had baseline differences in patient characteristics that suggested a problem with the randomization process. Flahr described a difference between group, whereas Nwankwo *et al* reported a significant difference (P < .00) in ulcer area values at baseline and Eraydin *et al* reported an almost twice as large ulcer area difference at baseline (P < .05). None of the three 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)

TABLE 3

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 six criteria. Unclear reporting hampered the assessment. One study⁷⁰ was considered to have low risk of bias in four of six domains. Three studies^{40,41,69} complied with three out of six domains. One study⁴² complied with one out of six domains. Finally, one study⁴³ included 5 patients and was not assessed for risk of bias.

TABLE 4

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 Jørgensen TS.⁷² recorded SF-36 and EQ-5D at baseline and 16-week follow-up, they did not report baseline or change score on HRQoL. S. Morgan (S. Morgan, unpublished data, December 2019) recorded HRQoL using PROMIS⁷³. On PROMIS-Global they reported reduced fatigue (p=0.06) and on PROMIS-Physical Function improved physical function (p=0.009). 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 numeric^{38,39,43,71,72} scale. Two studies included laboratory measures as primary outcomes^{40,69}. (Table 1)

TABLE 5

In total, five studies reported adverse events of various severity^{39,42,43,70,72}. (Table 5) Adverse events ranged from musculoskeletal problems⁴³, increased wound size^{39,70,72}, osteomyelitis³⁹ to amputation^{70,72}. The latter was also present in the corresponding control group^{70,72}.

Otterman *et al*⁴² reported 52 adverse events in 18 patients but did not specify if these occurred in patients with or without the active DFU.

Drop-out 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, one patient in Eraydin *et al*³⁸ 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 hyperglycaemia and visceral fat and increase HRQoL¹⁴. The search yielded no published studies on exercise therapy for patients with DFU measuring HRQoL. Jørgensen TS.⁷² used HRQoL measures of SF-36 and EQ-5D, yet reported no baseline or change results of these, whereas S. Morgan (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-making⁷⁹. Reduction in wound size would be considered an important and meaningful outcome for patients, and together with HRQoL, probably the two 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 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 high⁸⁵. Unfortunately, nonadherence to treatment is a widespread problem for patients with DFUs⁸⁶. One such example is with the use of off-loading devices. Although the association between off-loading adherence and DFU healing is high, research have 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 treatment⁹⁶.

In three studies^{42,43,72} adherence rates to the exercise program exceeded 80 % in either a semi-⁴² 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 *et al*³⁸ and Flahr³⁹ both reported issues with low adherence to the exercise programmes in a non-supervised home-based setting with the other four studies suffering from unclear reporting of their adherence rates. This is not surprising, hence adherence has generally been found better in programmes with supervision⁹⁷. One possible explanation to this could be that direct supervision offers additional encouragement and motivation to patients⁹⁸. 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 semi- 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 al*¹⁰¹ including 378 studies comparing exercise therapy intervention with a non-exercising control treatment on participants with or without a medical condition did not find an increased risk ratio (RR = 0.96 (95% CI 0.90-1.02)) of serious adverse events (i.e. death, hospitalisation 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 non-serious adverse events (i.e. pain, fatigue and oedema) in studies of exercise therapy¹⁰¹. 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, neuro-ischaemic and ischaemic ulcers, respectively¹, which are similar or worse than many common types of cancer¹⁰³.

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 Foot¹⁰. 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 semi- or fully supervised setting as used in three included studies^{42,43,72}. As reported by Lindberg *et al*⁴³ a clear detailed descriptions 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 program⁴⁵.

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 evidence¹⁰⁵.

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 semi- or fully supervised setting.

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Table 1
Study characteristics

First author (Year) Country	Aim	Population enrolled / completed	Outcome measures	Wound condition/size results
Randomised studies				
Eraydin <i>et al.</i> (2018), 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 cm^2 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) $p < 0.01$
Flahr D. (2010), 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)	<ul style="list-style-type: none"> Wound size in cm^2 traced onto an acetate grid Infection protocol Dartmouth COOP Functional Assessment Chart/ WOCNA. 	90% experienced a reduction in wound size of 26% to 100% over the 12-week program.
Nwankwo <i>et al.</i> (2014), 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.	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 cm^2 using a transparent ruler. Fasting plasma glucosetest Total cholesterol test 	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) $p < 0.01$
Observational studies				
Chen <i>et al.</i> (2017) and Huang <i>et al.</i> (2018), 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. <ul style="list-style-type: none"> 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 <i>et al.</i> (2018), 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: $3/14 = 21.43\%$ $p = 0.539$
Chang <i>et al.</i> (2016), 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 %)
Otterman <i>et al.</i> (2011), The Netherlands	To investigate the feasibility and preliminary effectiveness of an exercise programme 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"> • Programme adherence • Adverse events. • Achievement of the target training intensity. • Patient satisfaction on a numeric rating scale from 0 to 10 	Not reported
Lindberg <i>et al.</i> (2018), 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 cm^2 • 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) cm^2 .

Unpublished studies

Morgan S. (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 cm^2• Glycated Hemoglobin• Chair Stand Test• Patient reported outcome measurement – PROMIS• Exercise self-efficacy scale• Retention, Recruitment, Adherence and Adverse event rates,	Not reported
Jørgensen T.S. (2019), Denmark	To evaluate the effect and feasibility of 8 weeks of passive movement exercise of both legs on wound healing in non-healing 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 cm^2• 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 $p = 0.062$

Table 2
Details of intervention

First author (Year)	Intervention	Control	Duration, frequency and attendance rates of the exercise therapy intervention.	Intervention supervised / not supervised and delivered individually / in a group.
Randomised studies				
Eraydin <i>et al.</i> (2018)	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 61-90 days, 50 % between 31-60 days and 26.7 % between 0-30 days.	Not supervised and delivered individually
Flahr D. (2010)	Nonweight-bearing ankle exercises: Simple ankle inversion, eversion, flexion, and extension.	Usual care – not specified	Exercise frequency in the experimental group varied from “unknown” to three times per day for 80 % of patients while 20 % performed the exercises two times per day as requested.	Not supervised and delivered individually
Nwankwo <i>et al.</i> (2014)	Cycling on an ergo meter 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, counselling and medication without any form of exercise	3 times a week for 12 weeks. Increased exercise by 5 minute each two weeks until 50 minutes exercise time was reached. Initial aerobic exercise intensity was on 60% of max. Progressed to 85% over 12weeks using Borg’s rating scale of perceived exertion	Supervised delivered individually
Observational studies				
Chen <i>et al.</i> (2017) and Huang <i>et al.</i> (2018)	Buerger-Allen’s exercise	Not relevant	For 3-month. Duration and frequency not reported	Supervised by a well-trained research assistant and delivered individually

Lin <i>et al.</i> (2018)	Buerger-Allen's exercise	Not relevant	Not relevant	Not supervised and delivered individually
Chang <i>et al.</i> (2016)	Buerger-Allen's exercise	Not relevant	For 3-month. Duration and frequency not reported	Not supervised and delivered individually
Otterman <i>et al.</i> (2011)	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 (e.g. knee extensors, hip extensors, abdominal muscles, shoulder extensors and elbow flexors).	Not relevant	2-week individualized exercise programme consisting of two supervised group sessions Duration and frequency of two ulcer patients not reported	Supervised and not supervised and delivered individually
Lindberg <i>et al.</i> (2018)	A combination of aerobic and resistance training exercises including active dorsal/plantar ankle flexion exercises. Starting with up to 12 min 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
Unpublished studies				
Morgan S. (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: warm up, aerobics, cool down, balance training, strength training,	Usual care	1 hour, 3 times a week, for 12 weeks. Attending rates in the exercise group = 67 %	Supervised in a group.

and stretching.

Jørgensen T.S. (2019)	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.	Supervised and delivered individually
			Adherence to the exercise protocol was 100 %	

Table 3

Quality of included randomised studies ($n=3$)

First author (Year)	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 <i>et al.</i> (2018)	–	–	–	–	?
Flahr D (2010)	–	–	+	–	?
Nwankwo <i>et al.</i> (2014)	–	–	+	–	?

+, low risk; –, high risk; ?. Some concerns.

Table 4
Quality of observational studies (*n*=4 in 5 reports)

First author (Year)	the cohort was consecutively or randomly sampled	drop-outs 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 <i>et al.</i> (2017) and Huang <i>et al.</i> (2018)	–	+	–	?	+	+
Lin <i>et al.</i> (2018)	–	+	–	?	+	+
Chang <i>et al.</i> (2016)	–	+	+	?	+	+
Otterman <i>et al.</i> (2011)	–	–	–	?	+	?*

+, low risk; –, high risk; ?, Unknown.

*Unclear characteristics on duration of diabetes and age of DFU patients.

Table 5
Results on harms and drop-outs

First author (Year)	Number of patients affected by adverse events	Adverse events (type and description)	Drop-outs
Randomised studies			
Eraydin <i>et al.</i> (2018)	Non reported	Non reported	Intervention group: 3. Reasons for withdrawal <ul style="list-style-type: none"> • general condition deteriorated • went out of city • wanted to leave Control group: 2. Reasons for withdrawal <ul style="list-style-type: none"> • went out of city • unreachable
Flahr D. (2010)	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 <i>et al.</i> (2014)	Non reported	Non reported	Non reported
Observational studies			
Chen <i>et al.</i> (2017) and Huang <i>et al.</i> (2018)	Non reported	Non reported	0
Lin <i>et al.</i> (2018)	Non reported	Non reported	0
Chang <i>et al.</i> (2016)	5	3 had a progression in wounds. 2 had toe amputation.	0

Otterman <i>et al.</i> (2011)	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: <ul style="list-style-type: none"> • Start of an education that could not be combined with participating in the study • Transportation problems
Lindberg <i>et al.</i> (2018)	7	<ul style="list-style-type: none"> • 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
Unpublished studies			
Morgan S. (2019)	0	Not relevant	16 dropouts in total. Intervention group: 8 Control group: 8 Reasons for dropouts included: <ul style="list-style-type: none"> • 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)
Jørgensen T.S. (2019)	4	Intervention group: 2 - Deep infection. One resulting in amputation of the first toe. Control group: 2 - Deep infection resulting in above knee amputation for one and amputation of the toe for the other.	5 dropouts in total Intervention group: 2 - due to infection and amputation. Control group: 3 - 2 due to infection and amputation. - 1 from the control group is unclear why.