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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 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Results We included 10 published publications of 9 trials and results from two unpublished trials including a total of 281 individuals with DFUs receiving various forms of exercise therapy.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 Results on HRQoL was present in one unpublished study.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 death[1]. The 5-year mortality rate is 2.5 times higher for patients with DFUs compared to 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 65-77 %[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 offloading, 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?

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 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 clinic[23] 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 2015[25] 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 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 injuries[29].

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 Scale[32], Wound-QoL[33]).

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 intervention[34].

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 cm^2); (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 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 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

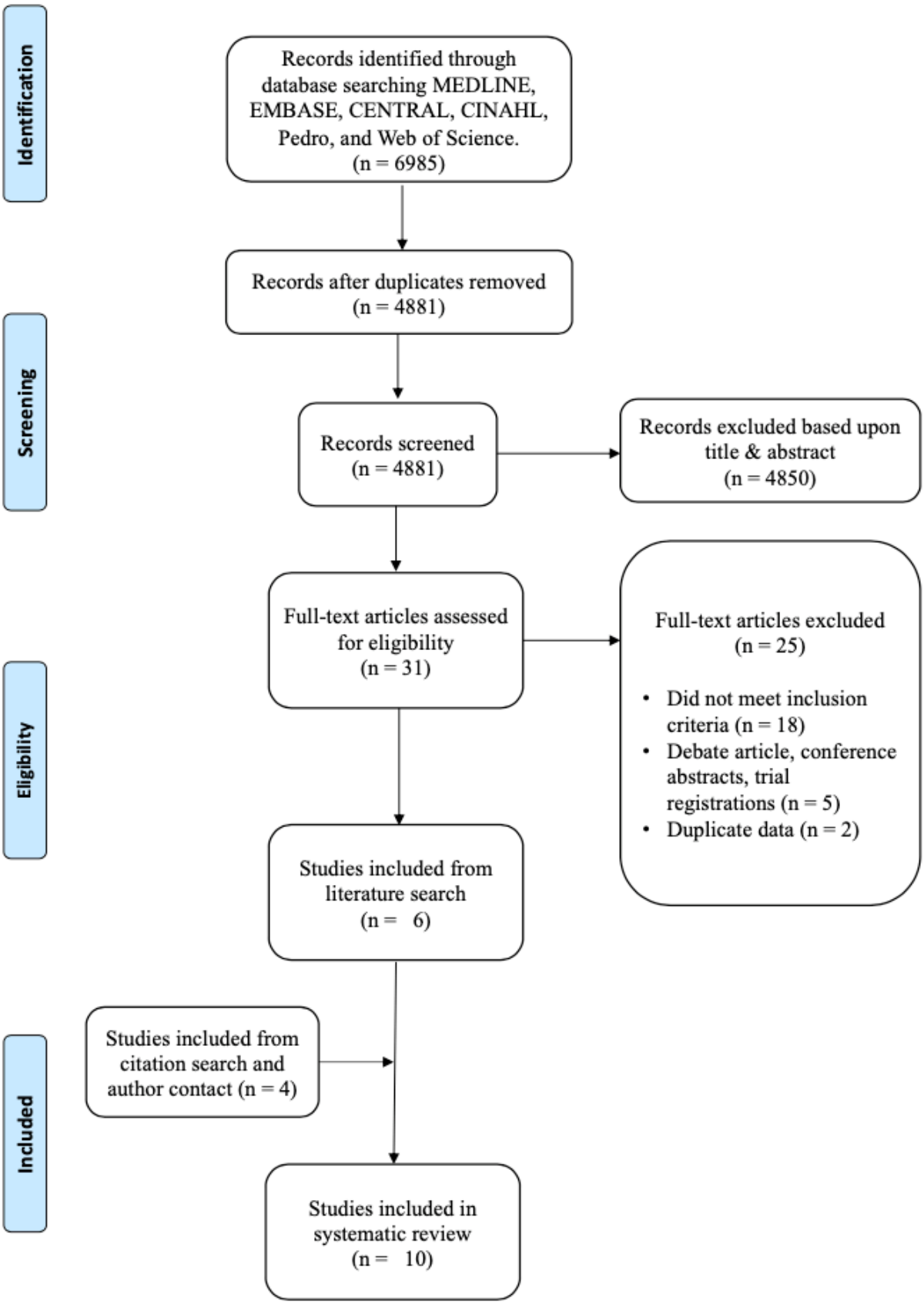

Figure. 1 – PRISMA diagram presenting the process undertaken to identify eligible studies.

Study identification

From 6985 citations, we selected 31 for full text evaluation (Fig. 1) After a detailed assessment, we included 6 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 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 registrations[64–66] were contacted by e-mail in order to obtain unpublished data. Two replies were received: Jørgensen TS. provided his PhD thesis[72] including data from NCT02785198[65] and the same data from the conference abstract originally excluded[63]. S. Morgan provided unpublished data from their ongoing trial NCT03002155[66].

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 study[42] and one case series study[43] 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). Flahr[39] 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 study[70] 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 study[42] complied with one out of six domains. Finally, one study[43] 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 PROMIS[73]. 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 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 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 HRQoL[14]. 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-making[79]. 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 healing[80–84] 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 have found adherence with a removable cast walker in patients with active DFU to be low[87,88]. In fact, numerous intervention studies[89–95] have been hampered by the fact that a large number of patients did not adhere to the recommended treatment[96].
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 Flahr[39] 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 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 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 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, neuro-ischaemic and ischaemic 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 semi- or fully supervised setting as used in three included studies[42,43,72]. As reported by Lindberg *et al*[43] a clear detailed describtions 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[105].

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.

References

1. Moulik PK, Mtonga R, Gill GV. Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. *Diabetes Care*. 2003;26(2):491-494.
2. Pound N, Chipchase S, Treece K, Game F, Jeffcoate W. Ulcer-free survival following management of foot ulcers in diabetes. *Diabet Med*. 2005;22(10):1306-1309. doi:10.1111/j.1464-5491.2005.01640.x
3. Prompers L, Schaper N, Apelqvist J, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. *Diabetologia*. 2008;51(5):747-755. doi:10.1007/s00125-008-0940-0
4. Gershater MA, Londahl M, Nyberg P, et al. Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. *Diabetologia*. 2009;52(3):398-407. doi:10.1007/s00125-008-1226-2
5. Oyibo SO, Jude EB, Tarawneh I, et al. The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. *Diabet Med*. 2001;18(2):133-138.
6. Jeffcoate WJ, Chipchase SY, Ince P, Game FL. Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures. *Diabetes Care*. 2006;29(8):1784-1787. doi:10.2337/dc06-0306
7. Gul A, Basit A, Ali SM, Ahmadani MY, Miyan Z. Role of wound classification in predicting the outcome of diabetic foot ulcer. *J Pak Med Assoc*. 2006;56(10):444-447.
8. Beckert S, Witte M, Wicke C, Konigsrainer A, Coerper S. A new wound-based severity score for diabetic foot ulcers: A prospective analysis of 1,000 patients. *Diabetes Care*. 2006;29(5):988-992. doi:10.2337/diacare.295988
9. Jeffcoate WJ. Wound healing--a practical algorithm. *Diabetes Metab Res Rev*. 2012;28 Suppl 1:85-88. doi:10.1002/dmrr.2235
10. International Working Group on the Diabetic Foot. IWGDF Guidelines on the prevention and management of diabetic foot disease. *International Working Group on the Diabetic Foot*. 2019. https://iwgdfguidelines.org/wp-content/uploads/2019/05/IWGDF-Guidelines-2019.pdf.
11. Sacco ICN, Sartor CD. From treatment to preventive actions: improving function in patients with diabetic polyneuropathy. *Diabetes Metab Res Rev*. 2016;32 Suppl 1:206-212. doi:10.1002/dmrr.2737
12. Kinmond K, McGee P, Gough S, Ashford R. "Loss of self": a psychosocial study of the quality of life of adults with diabetic foot ulceration. *J Tissue Viability*. 2003;13(1):6-8, 10, 12 passim. doi:10.1016/s0965-206x(03)80025-6
13. American Diabetes Association. Standards of Medical Care in Diabetes-2017 Abridged for Primary Care Providers. *Clinical diabetes : a publication of the American Diabetes Association*. 2017;35(1):5-26. doi:10.2337/cd16-0067
14. Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2006;(3):CD002968. doi:10.1002/14651858.CD002968.pub2
15. Ragnarson Tennvall G, Apelqvist J. Health-related quality of life in patients with diabetes mellitus and foot ulcers. *J Diabetes Complications*. 2000;14(5):235-241.
16. Brod M. Quality of life issues in patients with diabetes and lower extremity ulcers: patients and care givers. *Qual Life Res*. 1998;7(4):365-372.
17. Goodridge D, Trepman E, Sloan J, et al. Quality of life of adults with unhealed and healed diabetic foot ulcers. *Foot Ankle Int*. 2006;27(4):274-280. doi:10.1177/107110070602700408
18. Nabuurs-Franssen MH, Huijberts MSP, Nieuwenhuijzen Kruseman AC, Willems J, Schaper NC. Health-related quality of life of diabetic foot ulcer patients and their caregivers. *Diabetologia*. 2005;48(9):1906-1910. doi:10.1007/s00125-005-1856-6
19. Ribu L, Hanestad BR, Moum T, Birkeland K, Rustoen T. Health-related quality of life among patients with diabetes and foot ulcers: association with demographic and clinical characteristics. *J Diabetes Complications*. 2007;21(4):227-236. doi:10.1016/j.jdiacomp.2007.02.001
20. Vileikyte L, Peyrot M, Gonzalez JS, et al. Predictors of depressive symptoms in persons with diabetic peripheral neuropathy: a longitudinal study. *Diabetologia*. 2009;52(7):1265-1273. doi:10.1007/s00125-009-1363-2
21. Reiber GE, Lipsky BA, Gibbons GW. The burden of diabetic foot ulcers. *Am J Surg*. 1998;176(2A Suppl):5S-10S.
22. Ashford RL, McGee P, Kinmond K. Perception of quality of life by patients with diabetic foot ulcers. *Diabet Foot J*. 2000;3:150-155.
23. Siersma V, Thorsen H, Holstein PE, et al. Importance of factors determining the low health-related quality of life in people presenting with a diabetic foot ulcer: the Eurodiale study. *Diabet Med*. 2013;30(11):1382-1387. doi:10.1111/dme.12254

24. Ribu L, Birkeland K, Hanestad BR, Moum T, Rustoen T. A longitudinal study of patients with diabetes and foot ulcers and their health-related quality of life: wound healing and quality-of-life changes. *J Diabetes Complications*. 2008;22(6):400-407. doi:10.1016/j.jdiacomp.2007.06.006
25. Chang C-F, Chang C-C, Chen M-Y. Effect of Buerger's Exercises on Improving Peripheral Circulation: A Systematic Review. *Open Journal of Nursing*. 2015;5:120-128.
26. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1. doi:10.1186/2046-4053-4-1
27. Chou R, Aronson N, Atkins D, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the effective health-care program. *J Clin Epidemiol*. 2010;63(5):502-512. doi:10.1016/j.jclinepi.2008.06.007
28. Venning GR. Validity of anecdotal reports of suspected adverse drug reactions: the problem of false alarms. *Br Med J (Clin Res Ed)*. 1982;284(6311):249-252. doi:10.1136/bmj.284.6311.249
29. National Center for Biotechnology Information, U.S. National Library of Medicine. (2019). MESH database definition on Exercise Therapy. Available from https://www.ncbi.nlm.nih.gov/mesh/?term=exercise+therapy. Accessed 4 December 2019
30. Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. *BMJ*. 1993;306(6890):1437-1440. doi:10.1136/bmj.306.6890.1437
31. Sullivan PW, Ghushchyan VH. EQ-5D Scores for Diabetes-Related Comorbidities. *Value Health*. 2016;19(8):1002-1008. doi:10.1016/j.jval.2016.05.018
32. Abetz L, Sutton M, Brady L, McNulty P, Gagnon DD. The Diabetic Foot Ulcer Scale (DFS): a quality of life instrument for use in clinical trials. *Practical Diabetes International*. 2002;19(6):167-175. doi:10.1002/pdi.356
33. Blome C, Baade K, Debus ES, Price P, Augustin M. The "Wound-QoL": a short questionnaire measuring quality of life in patients with chronic wounds based on three established disease-specific instruments. *Wound Repair Regen*. 2014;22(4):504-514. doi:10.1111/wrr.12193
34. Ioannidis JPA, Evans SJW, Gotzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med*. 2004;141(10):781-788. doi:10.7326/0003-4819-141-10-200411160-00009
35. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898
36. Norris SL, Atkins D. Challenges in using nonrandomized studies in systematic reviews of treatment interventions. *Ann Intern Med*. 2005;142(12 Pt 2):1112-1119. doi:10.7326/0003-4819-142-12_part_2-200506211-00011
37. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. *Health Technol Assess*. 2003;7(27):iii-x, 1-173.
38. Eraydin S, Avsar G. The Effect of Foot Exercises on Wound Healing in Type 2 Diabetic Patients With a Foot Ulcer: A Randomized Control Study. *J Wound Ostomy Continence Nurs*. 2018;45(2):123-130. doi:10.1097/WON.0000000000000405
39. Flahr D. The effect of nonweight-bearing exercise and protocol adherence on diabetic foot ulcer healing: a pilot study. *Ostomy Wound Manage*. 2010;56(10):40-50.
40. Chen ML, Lin BS, Su CW, et al. The application of wireless near infrared spectroscopy on detecting peripheral circulation in patients with diabetes foot ulcer when doing Buerger's exercise. *Lasers Surg Med*. 2017;49(7):652-657. doi:10.1002/lsm.22667
41. Lin BS, Chang CC, Su CL, et al. The assessment of Buerger's exercise on dorsal foot skin circulation in patients with vasculopathic diabetic foot ulcer by using wireless near-infrared spectroscope: a cohort prospective study. *Lasers Med Sci*. 2018;33(5):977-982. doi:10.1007/s10103-017-2420-6
42. Otterman NM, van Schie CHM, van der Schaaf M, van Bon AC, Busch-Westbroek TE, Nollet F. An exercise programme for patients with diabetic complications: a study on feasibility and preliminary effectiveness. *Diabet Med*. 2011;28(2):212-217. doi:10.1111/j.1464-5491.2010.03128.x
43. Lindberg K, Moller BS, Kirketerp-Moller K, Kristensen MT. An exercise program for people with severe peripheral neuropathy and diabetic foot ulcers - a case series on feasibility and safety. *Disabil Rehabil*. 2018:1-7. doi:10.1080/09638288.2018.1494212
44. Chang CF, Chang CC, Hwang SL, Chen MY. Effects of Buerger Exercise Combined Health-Promoting Program on Peripheral Neurovasculopathy Among Community Residents at High Risk for Diabetic Foot Ulceration. *Worldviews Evid Based Nurs*. 2015;12(3):145-153. doi:10.1111/wvn.12091
45. Mueller MJ, Tuttle LJ, Lemaster JW, et al. Weight-bearing versus nonweight-bearing exercise for persons with diabetes and peripheral neuropathy: a randomized controlled trial. *Arch Phys Med Rehabil*. 2013;94(5):829-838. doi:10.1016/j.apmr.2012.12.015

46. Kruse RL, Lemaster JW, Madsen RW. Fall and balance outcomes after an intervention to promote leg strength, balance, and walking in people with diabetic peripheral neuropathy: "feet first" randomized controlled trial. *Phys Ther*. 2010;90(11):1568-1579. doi:10.2522/ptj.20090362
47. Brandon LJ, Gaasch DA, Boyette LW, Lloyd AM. Effects of long-term resistive training on mobility and strength in older adults with diabetes. *J Gerontol A Biol Sci Med Sci*. 2003;58(8):740-745. doi:10.1093/gerona/58.8.m740
48. Anichini R, Francia P, De Bellis A, Lazzeri R. Physical activity and diabetic foot prevention. *Diabetes*. 2005;54:A50-A50.
49. Ahn S, Song R. Effects of Tai Chi Exercise on Glucose Control, Neuropathy Scores, Balance, and Quality of Life in Patients with Type 2 Diabetes and Neuropathy. *Journal of Alternative & Complementary Medicine*. 2012;18(12):1172-1178. doi:10.1089/acm.2011.0690
50. Ahmad I, Noohu MM, Verma S, Singla D, Hussain ME. Effect of sensorimotor training on balance measures and proprioception among middle and older age adults with diabetic peripheral neuropathy. *Gait Posture*. 2019;74:114-120. doi:10.1016/j.gaitpost.2019.08.018
51. Ahrweiler F. Impact of physical activity on recurrent diabetic foot ulcer disease. [German]. *Diabetes und Stoffwechsel*. 1999;8(3):95-100.
52. Akbari M, Jafari H, Moshashaee A, Forugh B. Do diabetic neuropathy patients benefit from balance training? *Journal of Rehabilitation Research & Development*. 2012;49(2):333-338. doi:10.1682/JRRD.2010.10.0197
53. Allet L, Armand S, Aminian K, et al. An exercise intervention to improve diabetic patients' gait in a real-life environment. *Gait Posture*. 2010;32(2):185-190. doi:10.1016/j.gaitpost.2010.04.013
54. Allet L, Armand S, de Bie RA, et al. The gait and balance of patients with diabetes can be improved: a randomised controlled trial. *Diabetologia*. 2010;53(3):458-466. doi:10.1007/s00125-009-1592-4
55. Balducci S, Vulpiani MC, Pugliese L, et al. Effect of supervised exercise training on musculoskeletal symptoms and function in patients with type 2 diabetes: The Italian Diabetes Exercise Study (IDES). *Acta Diabetologica*. 2014;51(4):647-654.
56. Boyd BS, Nee RJ, Smoot B. Safety of lower extremity neurodynamic exercises in adults with diabetes mellitus: a feasibility study. *Journal of Manual & Manipulative Therapy*. 2017;25(1):30-38. doi:10.1080/10669817.2016.1180772
57. Fayed EE, Badr NM, Mahmoud S, Hakim SA. Exercise therapy improves planter pressure distribution in patients with diabetic peripheral neuropathy. *International Journal of PharmTech Research*. 2016;9(5):151-159.
58. Kanchanasamut W, Pensri P. Effects of weight-bearing exercise on a mini-trampoline on foot mobility, plantar pressure and sensation of diabetic neuropathic feet; a preliminary study. *Diabet Foot Ankle*. 2017;8(1):1287239. doi:10.1080/2000625x.2017.1287239
59. Monteiro RL, Sartor CD, Ferreira J, Dantas MGB, Bus SA, Sacco ICN. Protocol for evaluating the effects of a foot-ankle therapeutic exercise program on daily activity, foot-ankle functionality, and biomechanics in people with diabetic polyneuropathy: a randomized controlled trial. *BMC Musculoskelet Disord*. 2018;19(1):400. doi:10.1186/s12891-018-2323-0
60. Roaldsen KS, Rollman O, Torebjörk E, Olsson E, Stanghelle JK. Functional ability in female leg ulcer patients -- a challenge for physiotherapy. *Physiotherapy Research International*. 2006;11(4):191-203.
61. Otterman NM, van der Schaaf M, Busch-Westbroek TE, van Schie CH, Nollet F. The use and safety of combined resistance and aerobic training in a patient with complications related to type 2 diabetes: a case report. *Disabil Rehabil*. 2012;34(17):1495-1500. doi:10.3109/09638288.2011.650312
62. Dhatariya K, Fox M. Should patients with active foot ulcers be non-weight bearing or take exercise to improve cardiovascular fitness? *Diabetic Foot Journal*. 2014;17(3):92-99.
63. Smith Jorgensen T, Gottlieb H, Brorson S, Hellsten Y, Hoier B. Passive movement training as a treatment for non-healing diabetic foot ulcers: a microcirculatory perspective. *Microcirculation*. 2019;26(4). doi:10.1111/micc.12524
64. Chinese Clinical Trial Register [Internet]. Chengdu (Sichuan): Ministry of Health (China). 2007 Jun 27 - . Identifier ChiCTR-OOR-15006056, The effect of an exercise prescription in patients with diabetic foot ulcers and peripheral arterial disease; 2015 Mar 9 [cited 2019 Oct 10]. Available from: http://www.chictr.org.cn/showproj.aspx?proj=10533
65. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 -. Identifier NCT02785198, Passive Training as a Treatment for Diabetic Foot Ulcers; 2016 May 27 [cited 2019 Oct 10]. Available from: https://clinicaltrials.gov/ct2/show/NCT02785198
66. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 -. Identifier NCT03002155, Effects of a Exercise Program on Health Outcomes in People With Diabetic Foot Ulcers; 2016 Dec 23 [cited 2019 Oct 10]. Available from: https://clinicaltrials.gov/ct2/show/NCT03002155

67. Chang CC, Lin BS, Li JR, Chen ML, Chen MY, Huang YK. Buerger's exercise effects on improvement of dorsal foot skin circulation assessed by wireless near-infrared spectroscope in patients with vasculpathic diabetes foot ulcers: A cohort prospective study. *Lasers in Surgery and Medicine*. 2017;49 (Supplement 28):6-7.
68. Ahrweiler F, Chantelau E. Recurrent vs. non-recurrent diabetic foot ulcer disease: Impact of physical activity. *Diabetologia*. 1997;40:1912-1912.
69. Huang YK, Chang CC, Lin PX, et al. Quantitative Evaluation of Rehabilitation Effect on Peripheral Circulation of Diabetic Foot. *IEEE J Biomed Health Inform*. 2018;22(4):1019-1025. doi:10.1109/jbhi.2017.2726540
70. Chang CC, Chen MY, Shen JH, Lin YB, Hsu WW, Lin BS. A quantitative real-time assessment of Buerger exercise on dorsal foot peripheral skin circulation in patients with diabetes foot. *Medicine (Baltimore)*. 2016;95(46):e5334. doi:10.1097/md.0000000000005334
71. Nwankwo MJ, Okoye GC, Victor EA, Obinna EA. Effect of Twelve Weeks Supervised Aerobic Exercise on Ulcer Healing and Changes in Selected Biochemical Profiles of Diabetic Foot Ulcer Subjects. *International Journal of Diabetes Research*. 2014;3(3):41-48. doi:10.5923/j.diabetes.20140303.03
72. Jørgensen TS. Improvements in vascular function and angiogenesis to ameliorate blood supply and healing in non-healing diabetic foot ulcers. 2018.
73. Gruber-Baldini AL, Velozo C, Romero S, Shulman LM. Validation of the PROMIS((R)) measures of self-efficacy for managing chronic conditions. *Qual Life Res*. 2017;26(7):1915-1924. doi:10.1007/s11136-017-1527-3
74. Smidt N, de Vet HCW, Bouter LM, et al. Effectiveness of exercise therapy: a best-evidence summary of systematic reviews. *Aust J Physiother*. 2005;51(2):71-85. doi:10.1016/s0004-9514(05)70036-2
75. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports*. 2015;25 Suppl 3:1-72. doi:10.1111/sms.12581
76. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol*. 2012;2(2):1143-1211. doi:10.1002/cphy.c110025
77. Cooney GM, Dwan K, Greig CA, et al. Exercise for depression. *Cochrane Database Syst Rev*. 2013;(9):CD004366. doi:10.1002/14651858.CD004366.pub6
78. Taylor RS, Long L, Mordi IR, et al. Exercise-Based Rehabilitation for Heart Failure: Cochrane Systematic Review, Meta-Analysis, and Trial Sequential Analysis. *JACC Heart Fail*. 2019;7(8):691-705. doi:10.1016/j.jchf.2019.04.023
79. O'Connor D, Green S, Higgins JPT (editors). Chapter 5: Defining the review question and developing criteria for including studies. In: Higgins JPT, Green S (editors), Cochrane Handbook of Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2008.
80. Emery CF, Kiecolt-Glaser JK, Glaser R, Malarkey WB, Frid DJ. Exercise accelerates wound healing among healthy older adults: a preliminary investigation. *J Gerontol A Biol Sci Med Sci*. 2005;60(11):1432-1436. doi:10.1093/gerona/60.11.1432
81. Smith D, Lane R, McGinnes R, et al. What is the effect of exercise on wound healing in patients with venous leg ulcers? A systematic review. *Int Wound J*. 2018;15(3):441-453. doi:10.1111/iwj.12885
82. Pence BD, Woods JA. Exercise, Obesity, and Cutaneous Wound Healing: Evidence from Rodent and Human Studies. *Adv Wound Care (New Rochelle)*. 2014;3(1):71-79. doi:10.1089/wound.2012.0377
83. Goh J, Ladiges WC. Exercise enhances wound healing and prevents cancer progression during aging by targeting macrophage polarity. *Mech Ageing Dev*. 2014;139:41-48. doi:10.1016/j.mad.2014.06.004
84. Keylock KT, Vieira VJ, Wallig MA, DiPietro LA, Schrementi M, Woods JA. Exercise accelerates cutaneous wound healing and decreases wound inflammation in aged mice. *Am J Physiol Regul Integr Comp Physiol*. 2008;294(1):R179-184. doi:10.1152/ajpregu.00177.2007
85. O'Brien J, Finlayson K, Kerr G, Edwards H. Evaluating the effectiveness of a self-management exercise intervention on wound healing, functional ability and health-related quality of life outcomes in adults with venous leg ulcers: a randomised controlled trial. *Int Wound J*. 2017;14(1):130-137. doi:10.1111/iwj.12571
86. Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. *N Engl J Med*. 2017;376(24):2367-2375. doi:10.1056/NEJMra1615439
87. Crews RT, Shen B-J, Campbell L, et al. Role and Determinants of Adherence to Off-loading in Diabetic Foot Ulcer Healing: A Prospective Investigation. *Diabetes Care*. 2016;39(8):1371-1377. doi:10.2337/dc15-2373
88. Armstrong DG, Lavery LA, Kimbriel HR, Nixon BP, Boulton AJM. Activity patterns of patients with diabetic foot ulceration: patients with active ulceration may not adhere to a standard pressure off-loading regimen. *Diabetes Care*. 2003;26(9):2595-2597.
89. Bus SA, Waaijman R, Arts M, et al. Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial. *Diabetes Care*. 2013;36(12):4109-4116. doi:10.2337/dc13-0996
90. Lavery LA, Higgins KR, Lanctot DR, et al. Preventing diabetic foot ulcer recurrence in high-risk patients: use of temperature monitoring as a self-assessment tool. *Diabetes Care*. 2007;30(1):14-20. doi:10.2337/dc06-1600

91. Hamonet J, Verdie-Kessler C, Daviet J-C, et al. Evaluation of a multidisciplinary consultation of diabetic foot. *Ann Phys Rehabil Med*. 2010;53(5):306-318. doi:10.1016/j.rehab.2010.04.001
92. Armstrong DG, Harkless LB. Outcomes of preventative care in a diabetic foot specialty clinic. *J Foot Ankle Surg*. 1998;37(6):460-466.
93. Viswanathan V, Madhavan S, Rajasekar S, Chamukuttan S, Ambady R. Amputation prevention initiative in South India: positive impact of foot care education. *Diabetes Care*. 2005;28(5):1019-1021.
94. Calle-Pascual AL, Duran A, Benedi A, et al. Reduction in foot ulcer incidence: relation to compliance with a prophylactic foot care program. *Diabetes Care*. 2001;24(2):405-407.
95. Chantelau E, Haage P. An audit of cushioned diabetic footwear: relation to patient compliance. *Diabet Med*. 1994;11(1):114-116.
96. Bus SA, van Netten JJ. A shift in priority in diabetic foot care and research: 75% of foot ulcers are preventable. *Diabetes Metab Res Rev*. 2016;32 Suppl 1:195-200. doi:10.1002/dmrr.2738
97. Room J, Hannink E, Dawes H, Barker K. What interventions are used to improve exercise adherence in older people and what behavioural techniques are they based on? A systematic review. *BMJ Open*. 2017;7(12):e019221. doi:10.1136/bmjopen-2017-019221
98. Hageman D, Fokkenrood HJ, Gommans LN, van den Houten MM, Teijink JA. Supervised exercise therapy versus home-based exercise therapy versus walking advice for intermittent claudication. *Cochrane Database Syst Rev*. 2018;4:CD005263. doi:10.1002/14651858.CD005263.pub4
99. Ioannidis JPA. Adverse events in randomized trials: neglected, restricted, distorted, and silenced. *Arch Intern Med*. 2009;169(19):1737-1739. doi:10.1001/archinternmed.2009.313
100. Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. *JAMA*. 2001;285(4):437-443. doi:10.1001/jama.285.4.437
101. Niemeijer A, Lund H, Stafne SN, et al. Adverse events of exercise therapy in randomised controlled trials: a systematic review and meta-analysis. *Br J Sports Med*. 2019. doi:10.1136/bjsports-2018-100461
102. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Predictive factors for diabetic foot ulceration: a systematic review. *Diabetes Metab Res Rev*. 2012;28(7):574-600. doi:10.1002/dmrr.2319
103. Armstrong DG, Wrobel J, Robbins JM. Guest Editorial: are diabetes-related wounds and amputations worse than cancer? *Int Wound J*. 2007;4(4):286-287. doi:10.1111/j.1742-481X.2007.00392.x
104. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol*. 2011;64(4):407-415. doi:10.1016/j.jclinepi.2010.07.017

Table 1
Study characteristics

First author (Year) Country	Aim	Population enrolled / completed	Outcome measures	Wound condition/size results
Randomised studies				
Eraydin e*t al.* (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)	• 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)	• Wound size in cm^2 raced 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 *et al*. (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)	• 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 e*t al.* (2017) and Huang e*t al.* (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. • 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)	• Oxygenated hemoglobin concentration • Total tissue hemoglobin concentration	Not relevant

Lin e*t al.* (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))	• 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 *et al.* (2016), China	Unclear	30 patients with unilateral or bilateral DFU *n* = 30 (mean age 63.4 (SD 13.7)	• 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 e*t al.* (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.	• Programme adherence • Adverse events. • Achievement of the target training intensity. • Patient satisfaction on a numeric rating scale from 0 to 10	Not reported
Lindberg e*t al.* (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).	• 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) cm2.

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)	• 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)	• 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 e*t al.* (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 *et al*. (2014)	Cycling on an ergo meter bicicle 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 e*t al.* (2017) and Huang e*t al.* (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 e*t al.* (2018)	Buerger-Allen's exercise	Not relevant	Not relevant	Not supervised and delivered individually
Chang *et al* (2016)	Buerger-Allen's exercise	Not relevant	For 3-month. Duration and frequency not reported	Not supervised and delivered individually
Otterman e*t al.* (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 e*t al.* (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. Adherence to the exercise protocol was 100 %	Supervised and delivered individually

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 e*t al.* (2018)	–	–	–	–	?
Flahr D (2010)	–	–	+	–	?
Nwankwo *et al*. (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 e*t al.* (2017) and Huang e*t al.* (2018)	–	+	–	?	+	+
Lin e*t al.* (2018)	–	+	–	?	+	+
Chang e*t al.* (2016)	–	+	+	?	+	+
Otterman e*t al.* (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 e*t al.* (2018)	Non reported	Non reported	Intervention group: 3. Reasons for withdrawal • general condition deteriorated • went out of city • wanted to leave Control group: 2. Reasons for withdrawal • 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 *et al*. (2014)	Non reported	Non reported	Non reported
Observational studies			
Chen e*t al.* (2017) and Huang e*t al.* (2018)	Non reported	Non reported	0
Lin e*t al.* (2018)	Non reported	Non reported	0
Chang *et al* (2016)	5	3 had a progression in wounds. 2 had toe amputation.	0

Otterman e*t al.* (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: • Start of an education that could not be combined with participating in the study • Transportation problems
Lindberg e*t al.* (2018)	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
Unpublished studies			
Morgan S. (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)
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.