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PhD Thesis

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Exercise therapy for patients with diabetic foot ulcers

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List of papers and studies

This PhD thesis is based on the following papers:

1. Aagaard T, Moeini S, Skou ST, Madsen UR, Brorson S. Benefits and harms of exercise therapy for patients with diabetic foot ulcers: A systematic review. The International Journal of Lower Extremity Wounds. 2020 Sep 14:1534734620954066. *(Published)*

2. Aagaard T, Skou ST, Brorson S, Madsen UR. "Just a bump in the road" - A grounded theory study on patients' behaviour after referral to a wound care clinic with a diabetic foot ulcer *(In review)*

3. Aagaard TV, Lindberg K, Brorson S, Madsen UR, Skou ST. A 12-Week Supervised Exercise Therapy Program for Patients with Diabetic Foot Ulcers: Program Development and Preliminary Feasibility. The International Journal of Lower Extremity Wounds. 2023;0(0). doi:10.1177/15347346221149786 *(Published)*

Abbreviations

CERT – the Consensus on Exercise Reporting Template

CONSORT – Consolidated Standards of Reporting Trials

COVID-19 – Coronavirus disease-19

DFU – Diabetic Foot Ulcer

EQ-5D-3L – the European Quality of life - 5 Dimensions - Three-Level Scale

EQ-VAS – European Quality of life – Visual Analogue Scale

GUIDED – the Guidance for the reporting of intervention Development

GUREGT – the Guideline for Reporting and Evaluating Grounded Theory Research Studies

HRQoL – Health-related Quality of Life

ICMJE – the international committee of medical journal editors

IWGDF – International Working Group on the Diabetic Foot.

MDT – Multidisciplinary Team

MRC – Medical Research Council

PEDro scale –the Physiotherapy Evidence Database scale

PRISMA – the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROM – Patient-Reported Outcome Measures

PROMIS – Patient-Reported Outcomes Measurement Information System

RCT – Randomized Controlled Trial

SF-36 – The 36-Item Short Form Health Survey

TIDieR – the exercise therapy program adheres to the template for intervention description and replication

Wound-QoL – Wound-Quality of Life

English summary

The prevalence of diabetes mellitus is increasing worldwide, due to population growth, ageing, urbanization, and the increasing prevalence of obesity and physical inactivity. One of the most feared complications of diabetes is foot ulcers as they can result in severe adverse outcomes including amputation or death. For ulcers to heal, patients are often required to refrain from bearing weight on the affected limb for weeks or months. This is in direct contrast to guidelines for diabetes rehabilitation where exercise is highly advocated. Exercise is known to improve health-related quality of life, blood flow and blood sugar stabilization in other populations; however, little is known about the benefits and harm of exercise therapy in patients with diabetic foot ulcers. The goal of this thesis was to develop an exercise therapy intervention for patients with diabetic foot ulcers.

This thesis is based on the results of three studies. We found that no pre-existing evidence-based recommendations could be provided on the benefits and harms of exercise therapy intervention for patients with diabetic foot ulcers, given that no previously published studies assessed health-related quality of life. In addition, we found that patients with diabetic foot ulcers view their ulcer as "just a bump in the road". Patient's behaviour and underlying concerns after referral to a diabetic foot ulcer clinic can be described in four categories related to daily activities: *Restricting my freedom; Trusting or doubting the system; Feeling no pain or illness;* and *Receiving insufficient information.* And finally, we developed an aerobic and resistance exercise therapy program for patients with diabetic foot ulcers in a thorough evidence-based process with patients' and physiotherapists' involvement. Conclusions about the feasibility of the intervention were, however, limited by the low number of participants included.

Some of the issues evaluated in this thesis warrant further study. We suggest that further investigations should be made to improve recruitment rates in exercise studies of the diabetic foot ulcer population and that more feasibility exercise studies with amendments to the developed intervention are needed.

Danish summary

Diabetes mellitus-prævalensen er stigende på verdensplan grundet befolkningstilvækst, aldring, urbanisering og den stigende forekomst af fedme og fysisk inaktivitet. En af de mest frygtede komplikationer af diabetes er fodsår, da det kan resultere i alvorlige uønskede udfald såsom amputation eller død. For at sår skal heles, er patienter ofte forpligtet undgå vægtværing på den berørte fod i uger, måneder eller år. Dette er i direkte modsætning til retningslinjerne for diabetesrehabilitering, hvor motion er stærkt anbefalet. Motion er kendt for at forbedre sundhedsrelateret livskvalitet, blodgennemstrømning og blodsukkerstabilisering for andre befolkningsgrupper. Fordelene og ulemperne ved træningsterapi hos patienter med diabetiske fodsår er dog sparsomt undersøgt. Målet med denne afhandling var at udvikle en træningsterapi intervention til patienter med diabetiske fodsår.

Denne afhandling er baseret på resultaterne af tre undersøgelser. Vi fandt at der ikke kunne gives evidensbaserede anbefalinger om fordelene og ulemperne ved træningsterapi til patienter med diabetiske fodsår. Da ingen publicerede undersøgelser, vurderede sundhedsrelateret livskvalitet. At personer med diabetiske fodsår betragter deres sår som "et bump på vejen". At patientens adfærd og underliggende bekymringer efter henvisning til en diabetisk fodsårsklinik kan beskrives i fire kategorier relateret til daglige aktiviteter: *Begrænsning af min frihed*; *At stole på eller tvivle på systemet*; *Føler ingen smerte eller sygdom* og *Modtagelse af utilstrækkelig information*.

Nogle af de problemstillinger, der er vurderet i denne afhandling, kræver yderligere undersøgelser. Vi foreslår, at der bør foretages yderligere undersøgelser for at forbedre rekrutteringsraten i træningsstudier for den diabetiske fodsårspopulation, og at der er behov for flere gennemførlighedsundersøgelser af træning med ændringer til den udviklede intervention.

Background

Diabetic foot ulcers

The prevalence of diabetes mellitus is increasing worldwide, due to population growth, ageing, urbanization, and the increasing prevalence of obesity and physical inactivity,[1] and is projected to rise from 171 million in the year 2000 to 366 million in 2030.[1] Diabetes mellitus is a disease associated with multimorbidity (two or more chronic conditions)[2] with the commonest comorbidities being hypertension, cardiovascular disease,[3] back pain,[2] and depression.[4] In poorly managed diabetes mellitus, the frequently observed complications are retinopathy, nephropathy, neuropathy, and foot ulcers,[5] with one of the most feared complications being diabetic foot ulcers (DFUs), which often result in severe adverse outcomes including amputation or death,[6,7] with a mortality rate of nearly 50% within five years.[8] The risk of developing a DFU is estimated to be as high as 15–25%.[9,10] DFUs are sometimes due to trauma, they commonly occur in the forefoot and are caused by repetitive stress over an area that is subject to high vertical or shear stress.[11,12] The rate of DFU healing within 1 year is reported to be 77%,[13] with an overall expected healing rate reported to range between 65–77 %.[7,13–17] However, for some patients, wound closure is never achieved[18] and unfortunately, for those where wound closure is achieved, 40% will have a recurrent DFU within 1 year, almost 60% within 3 years, and 65% within 5 years.[11] Having a DFU is associated with reduced mobility, depression and an overall low health-related quality of life (HRQoL).[19] Low HRQoL has even been shown to be a contributor to the probability of major amputation and death of DFU patients,[20] and has been linked to a negative impact on treatment adherence.[2110] Patients often report severely decreased HRQoL at initial presentation in the foot clinic[22] and while foot ulcer healing is associated with an increase in HRQoL, a non-healing DFU is associated with a further decrease in HRQoL.[23]

Normal wound healing

The skin's primary function is to protect the body against the surrounding environment. To prevent bacteria and other substances from invading the body, the skin has regenerative properties which restore tissue integrity.[24] Normal wound healing has been suggested to consist of four overlapping phases: homeostasis, inflammation, proliferation, and remodelling.[25] The *homeostasis phase* begins within 30 minutes of injury and may last several hours.[26] The vessels constrict to control bleeding and form clots to provide a barrier against bacteria. The *inflammation phase* will last about 2–5 days, in which the inflammatory cells (neutrophils, macrophages, and lymphocytes) converge on the wound

site[26] A low level of inflammation is necessary for faster wound healing, whereas a high level of inflammation is destructive and can delay it.[27] The *proliferation phase* continues for 2–4 weeks after the inflammation stage. Inflammatory cells and factors are reduced, and fibroblast proliferation, collagen deposition, angiogenesis, tissue granulation, re-epithelialization, and wound closure restructure the wound.[27,28] The *remodelling phase* is the final stage of wound healing and begins 2–3 weeks after injury and may continue for a year or more.[26,29] This phase includes the restoration of tissue structure, strength, and function.[28]

For successful wound healing to happen, each stage must occur in the appropriate order. The phases are interdependent, and the later phases depend on success in the preceding phase.[28] Any disturbance in each phase delays wound healing or can lead to a chronic non-healing wound.[26,30] In patients with diabetes, the body has an abnormal inflammatory and immune response, resulting in a prolonged inflammation phase, decreased contraction of the wound, and an imbalance between the construction and decomposition of the extracellular matrix and its remodelling.[31] Other factors associated with poor healing include congestive heart failure, peripheral artery disease, or end-stage kidney disease requiring renal-replacement therapy and the inability to walk independently.[11,13]

DFU treatment

Within the Danish healthcare system, complex DFUs are referred to and treated in multidisciplinary teams (MDT) as recommended worldwide.[32–34] A DFU is defined as 'complex' when one or more of the following criteria is present: Suspected infection, inflammation, ischemia, foot deformities, gangrene, neuropathy, a history of DFU, a positive probe-to-bone test and/or considerable comorbidity and compliance issues.[35] Furthermore, patients with a non-complex DFU that has not shown improvement after 2–3 weeks of treatment by a general practitioner should also be referred to an MDT team.[35] The composition of MDT teams differs around the world[36–40] but usually includes, or has the possibility to refer to, specialists with skills in specific areas of diabetology, podiatry, diabetes specialist nursing, vascular surgery, microbiology, orthopaedic surgery, biomechanics and orthoses, casting, and wound care.

DFU treatment includes debridement (removing surface debris and necrotic tissue) of the wound, management of any infection, revascularization procedures when indicated, and off-loading of the

ulcer.[34,41] Off-loading with the purpose of relieving plantar pressure and shear stress from the DFU has been found to be of key importance.[42] Off-loading can be achieved by many mechanisms, including shoe modifications, boots, and orthotic walkers. Total contact casting or prefabricated removable walkers that are rendered irremovable are considered the offloading gold standard.[43] Historically, however, a common recommendation[44] and practice in some Danish hospital departments[40] has been the total physical off-loading of patients at hospital admission, with recommendations of bed rest and/or the use of a wheelchair. This action of recommending reduced weight-bearing activities is not uncommon for clinicians[45] but might be difficult to accomplish. Firstly, Najafi et al.[46] monitored physical activity in DFU patients using either removable or irremovable footwear and, in the removable footwear group, found a change in behaviour from week 4, where patients became more active compared to the baseline, indicating a potential diminishing of restriction adherence over time. This is not an unusual issue, as earlier studies have found both adherence to participating in research studies and adherence to the generally recommended treatment to be low.[11,47–49] It is unclear whether the reasons why patients do not comply with treatment can be ascribed to ignorance, forgetfulness, or an emotional reaction to their disease and treatments; or if patients are active in their non-compliance and only choose to comply when it makes sense to them according to their own beliefs and is also possible to carry out within the constraints of their everyday lives.[50,51] Secondly, the recommendation might indeed be counterproductive as some studies have found that individuals with diabetes who engage in more sedentary activities, and whose average daily activity is limited, present more vulnerable skin[52,53] and are at a higher risk of ulceration.[54–56]

Low physical activity

A sedentary lifestyle, low levels of physical activity or being physically inactive have been described as major risk factors for obesity, cardiovascular disease, type 2 diabetes, and various types of cancer.[57] Yet they are also recognized as among the most modifiable risk factors for these pathologies.[58,59] Reduced mobility is associated with a loss of muscle mass and muscular weakness,[60,61] and the general decline of muscle function has been found to be relatively slow between 20–50 years of age, yet increasing in pace after 50 years of age.[62] Muscle power decreases by about 3.5% every year for people between 65–89 years,[63] and by 6% annually over three years among adults aged 70–85 years.[64] Besides this general decline in muscle function seen in the elderly population, disuse is also an important cause of muscle deterioration. Disuse atrophy can be defined as “simple atrophy” in that

atrophy is intrinsic to the muscle(s) specifically exposed to the affected limb, i.e., muscles in the leg in a cast, or in the whole body due to bed rest regimes.[65]

Periods of muscle disuse can occur in healthy people as a consequence of injury or illness[66] and are frequently found in the elderly population.[67] Fixed joint methods of immobilization result in greater changes in strength and neuromuscular function than methods allowing for free joint movements.[68] Healthy elderly individuals showed reduced quadriceps femoris muscle activation and a decrease in rapid force capacity following two weeks of immobilization by unilateral, whole-leg casting.[69] This rapid force capacity is important for the patient's ability to counteract unexpected perturbations during walking and/or avoiding falling.[70–72]

Following periods of immobilization, muscular strength, muscle size and neuromuscular function decrease,[68] although muscle strength and mass loss can be effectively regained through high-intensity strength training in healthy young and older adults.[69,73–76] Studies on inactivity, with a subsequent rehabilitation phase in healthy adults on bed rest restrictions for 14 days[77] and unilateral leg suspension,[75] showed recovery of pre-inactivity conditions occurring more slowly in older people, emphasizing the importance of an active lifestyle in old age and of avoiding or minimizing periods of inactivity.[77]

In the older general population, a loss of muscle mass is associated with greater morbidity and mortality,[78,79] functional decline,[80] reduced independence, and a higher risk of falling and consequent hip fractures.[79] In the population of people with type 2 diabetes this decline has been found to be accelerated[81] and having diabetes has been found to be associated with a higher functional physical disability over time compared to healthy individuals.[81–83] Therefore, increased activity has for many years been one of the key elements of the rehabilitation of diabetes as it has been found to counteract the associations listed above and help improve glycemic control, insulin sensitivity, lipids, and blood pressure.[84–87]

Exercise and DFUs

People living with diabetes are recommended to take exercise and be physically active,[84] while people with DFUs either with or without diabetic peripheral neuropathy have historically been advised to avoid weight-bearing activities altogether[40,88,89] due to an increased risk of developing a DFU.[90] However, diabetic peripheral neuropathy results in impaired mobility and loss of muscle strength,[81,91–93] and avoiding weight-bearing activities may exacerbate neuropathy and skin sensation

loss.[94] Some studies have found that patients with diabetes and peripheral neuropathy who are less active are at greater risk of developing DFUs,[53,95,96] and for those with DFUs that do heal, some studies have found high re-ulceration rates when patients begin reloading plantar tissues, after a period of non-weight bearing.[97] As a result, some clinicians have called for a paradigm shift towards including weight-bearing exercises for patients with peripheral neuropathy.[90] Supporting these calls is the Physical Stress Theory framework, which states that the relationship between mechanical stress and tissue health is dynamic and that tissue adapts to increases in the physical stress placed on them.[90,94]

Including increased physical activity or exercise in DFU treatment could have many benefits. It would solve the paradox of whether to continue following the guidelines for diabetes if a DFU evolves, and it could help counteract the decline that prolonged peripheral neuropathy causes,[98,99] and potentially support the mechanisms needed for effective wound healing.[100,101] Doing exercise has been found to reduce systemic and local inflammation in obese and older individuals,[102] although dependent on the age and fitness level of each individual and the duration and intensity of exercise.[27] Exercise supports vascular growth[103] and increases the supply of blood and oxygen to peripheral wound tissue, which is vital because oxygen helps synthesize connective tissue and prevent wound infection.[104] Finally, exercise therapy could increase HRQoL in patients with DFUs, as it has been found to do in patients with diabetes without a DFU.[84]

While the benefits of exercise may be significant a scientific evaluation of the utility of exercise therapy for patients with a DFU is lacking. Armstrong et al[11] suggest, in an article from the New England Journal of Medicine, that future studies of DFUs and their recurrence should have a specific focus on patient behaviour and its role in adherence to, and outcomes of, therapy. It is important to include perspectives from patients themselves because the management of physical activity in patients with DFUs is poorly understood, and much prejudice from healthcare professionals on the importance of physical activity for patients exists[47,53,105]

Objectives

The overall aim of this PhD project was to develop an exercise therapy intervention, for patients with DFUs, that would be both accepted by and feasible for the patients.

The thesis is based on three papers with the aim of answering the following questions:

1. What are the benefits and harms of exercise therapy for patients with a DFU? (Study 1)

2. What are the main concerns about activity among patients with DFUs who attend a specialized outpatient clinic for follow-up treatment? (Study 2)

3. Is it possible to develop and feasibility test a 12-week exercise therapy program for patients with DFUs, focusing on the program's inclusion, adherence, and adverse event rates? (Study 3)

Methods

The following section provides a brief outline of the overall framework used to guide the development of the intervention, a brief outline of the methodological consideration of each study, and the ethical considerations. All the studies are described in detail in the accompanying manuscripts (Papers I-III).

Medical Research Council Framework

We followed the UK Medical Research Council (MRC) framework for researchers and research funders in developing and evaluating complex interventions. The framework was first published in 2000[106] with revised guidance in 2008[107] and most recently in 2021,[108] and aims to ensure that the interventions developed are empirically and theoretically founded.[109] The 2006 framework consists of four phases (Figure 1). The first phase is to develop the intervention to the point where it can reasonably be expected to have a worthwhile effect.[107,108] The second phase includes testing procedures for the acceptability of the developed intervention and estimating the likely rates of recruitment and retention of subjects and is assessed in a feasibility piloting design. The third stage includes the evaluation of the effectiveness of using a randomized controlled trial (RCT), where individuals are randomly allocated to receive either an experimental intervention (the developed exercise therapy program) or an alternative such as standard treatment.[107,108] The fourth and final stage is getting the findings translated into routine practice. Of importance at this stage is to make them available using methods that are accessible and convincing to decision-makers.[107,108] Although the evidence base for effective implementation remains limited[110] it usually includes conclusions published in systematic reviews, for example, the Cochrane Intervention reviews,[111] and/or finally national[112] and international guidelines.[34]

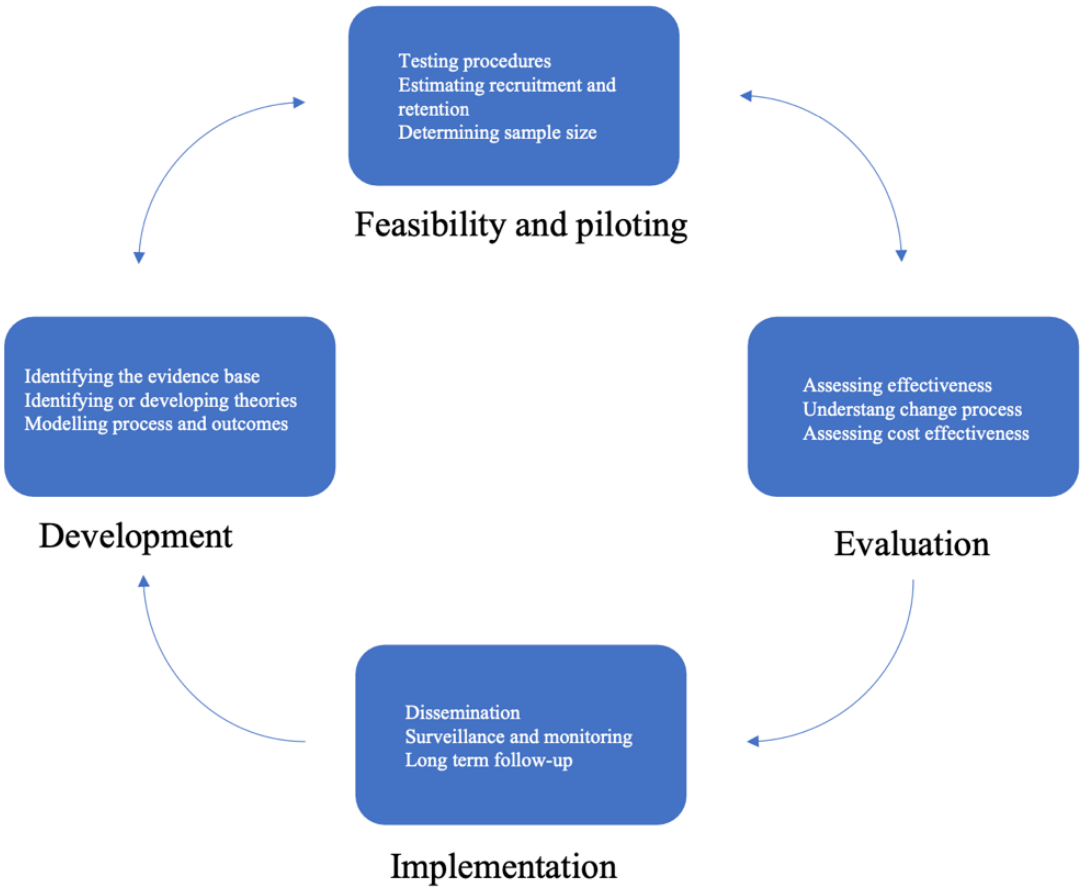

Figure 1 *- The four phases of the MRC framework*

The MRC framework (of 2006) was chosen as the overall framework in the PhD as it provides an iterative view on the development, implementation, and evaluation of complex interventions[113] (Figure 1). The choice of this framework was twofold. Firstly, exercise therapy, in general, could be described as a complex intervention as it has "several dimensions of complexity such as variations in the number of intervention components, a high degree of flexibility and is highly dependent on the behaviour of the individuals receiving the intervention."[107,109] With little knowledge of exercise for this population, we foresaw that developing an exercise therapy for DFU patients and the potential implementation into clinical practice would be complex. As depicted in Figure 2 the initially planned Studies 1 and 2 could inform and help the development of Study 3 which would eventually be used in the later RCT evaluation phase of Study 4.

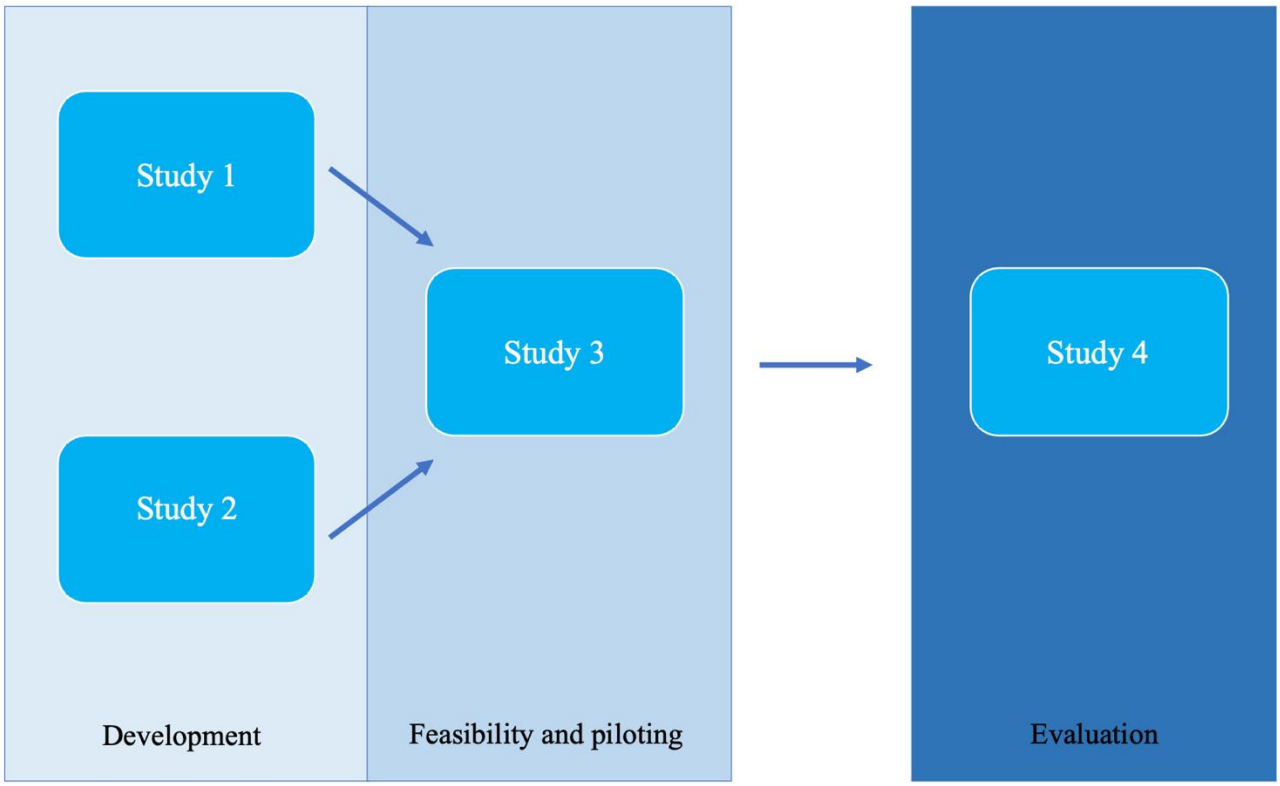

Figure 2 *- The planned PhD studies following the MRC framework*

Methodological considerations

Identifying the evidence base (Study 1)

In Study 1, we conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[113] and following the Cochrane methodology[111]

We included RCTs to assess both the potential benefits of exercise therapy and RCTs and observational studies (i.e., comparative studies [prospective or retrospective], case series, case studies, and pilot studies) to identify potential harms of exercise therapy.[114,115]

We chose to use a broad definition of exercise to ensure that we did not exclude potentially relevant trials. HRQoL as an outcome was chosen over ulcer healing or reduction in DFU size because the causality between exercise and wound healing has not been fully established, and only a few human and animal studies have investigated the role of exercise on wound healing.[27,102,116,117] Equally important were safety considerations of introducing exercise to this population. Despite most studies on new treatments reporting benefits, there was little effort to balance these with the potential

harm,[114,118] and this balance was key to investigate as protective strategies are often preferred in the clinic,[40] and an increase in HRQoL after exercise would not be beneficial if it resulted in amputation or death for the patient.

We planned to conduct a meta-analysis of the 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 studies included were homogeneous and presented characteristics that would then enable a meta-analysis to be performed.

Developing appropriate theory (Study 2)

In Study 2, we conducted a constructivist grounded theory study, reported according to the Guideline for Reporting and Evaluating Grounded Theory Research Studies (GUREGT).[119] The grounded theory study addressed the question of how meaningful patients with DFUs find exercise or activity in general, and its repercussions on everyday activities while attending a specialized outpatient clinic for follow-up treatment. A constructivist grounded theory approach was used[120] because of its ability to provide an abstract understanding of the life of the patients under study and a view of the analysis as located in time and place[120] Originally introduced by Glaser and Strauss,[121] as a reaction to criticism about qualitative research not being valid and reliable because of its apparently non-systematic methods, Charmaz[120] builds her understanding of the grounded theory method on a constructivist perspective based on the assumption that social reality is multiple, processual, and constructed. The grounded theory approach consists of systematic yet flexible guidelines for collecting and analysing qualitative data to construct theories from the data itself.

Data was collected from qualitative observations and interviews. The initial sampling consisted of two patients referred to an outpatient clinic for DFU care, and this formed the first set of data. Firstly, patients' reactions to the potential consequences of the DFU such as restrictions in activity, and the interaction between patients and healthcare professionals, were observed during scheduled meetings at the hospital's specialized DFU outpatient clinics. Each patient was followed over time and observed at each clinic visit and interviewed before and after their visit. The focus was the research question: ''What are the main concerns about activity among patients with a DFU who attend a specialized outpatient clinic for follow-up treatment and how do these evolve over time?'' An inductive interview approach was used, hence grounded theory studies begin with inductive data because this approach is characterized by the search for patterns by moving from the data to a theoretical understanding.[122] As the developed theory evolved the interview approach transitioned from an inductive to a more

abductive approach.[123] Abduction begins when a researcher discovers a surprising finding that neither fits the pattern of other findings nor can be theoretically explained[120]

Data collection, analysis and coding are performed simultaneously with the constant comparison method of the concept and incidents that emerge through data and not from pre-existing theory. All further inclusion thereafter was guided by the principle of theoretical sampling.[120] This method is a deductive process where the researcher seeks people, events, or information to illuminate and define the properties, boundaries and relevance of the theoretical categories that emerge through analysis.[120] [120]

The final product is the construction of a grounded theory explaining the main concerns and behaviour of patients with a DFU after referral to an outpatient clinic for DFU care.

Program development and feasibility testing (Study 3)

In Study 3, we conducted a development and pre-feasibility study. The development process followed the Medical Research Council guidance for the development of complex interventions[107] and was reported according to the Guidance for the reporting of intervention Development (GUIDED) recommendations.[124] Reporting of the feasibility study was conducted according to the Consolidated Standards of Reporting Trials (CONSORT) statement extension to randomized pilot and feasibility trials,[125] with research progression criteria based on a traffic light system of green (continue without changes), amber (apply changes to improve study design), and red (no RCT unless major changes are applied), instead of a simple stop/go approach.[126]

Exercise therapy program development phase

The development process included the integration of the results from Studies 1 and 2 and involved relevant stakeholders, including DFU patients, doctors, wound care nurses, podiatrists, and physical therapists to integrate their needs and perspectives.

Semi-structured interviews with included participants and physiotherapists were conducted at the end of the 12-week exercise program. Each interview lasted between 30 and 60 minutes and was conducted by the first author. The interview guide included open questions on the acceptability of assessment procedures, treatment experience, and feedback about the supervised sessions and potential adverse events. The themes brought up during the interviews were followed up by probing

questions. All interviews were conducted in Danish by the first author. Data was recorded with notes and descriptive field notes.

Pre-feasibility phase

The planned feasibility study was designed to evaluate a 12-week exercise program using research progression criteria in preparation for a definitive future RCT. The predetermined research progression criteria were as follows: The *recruitment rate* was analysed by dividing the number of participants included by the number of months it took to include them. *Participant retention* was evaluated by the number of participants showing up at the 12-week follow-up. *Adverse events* were registered at every exercise session based on patient-reported adverse events, and their relatedness to the index ulcer and to the exercise program.

The outcomes measurements included the Wound-QoL[127,128] the European Quality of life – 5 Dimensions – Three-Level Scale (EQ-5D-3L),[129] the 30-second chair-stand test,[130] the Tandem Test,[131] the 4 x 10-meter fast-paced walk test,[132] and change in ulcer size in cm^2 assessed on digital images with a standardized measuring tape.

Ethical considerations and approvals

Prior to the commencement of the systematic review (Study 1), a protocol of the intended systematic review was registered at the International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/prospero; Registration number: CRD42020151933).

The Grounded Theory study (Study 2) was approved by the Danish Data Protection Agency on April 22nd, 2021 (Region Zealand j.nr. REG-036-2021). The study was presented to the Regional Committees on Health Research Ethics for Region Zealand, who decided that it did not need further ethical approval according to Danish law (Region Zealand j.nr. 20-000013). This, however, did not mean that the researchers were less obligated to act with responsibility. The study was ethically guided by the principles of autonomy, beneficence, and non-maleficence.[133] To ensure autonomy, all participants were given verbal and written information prior to the study commencing. Beneficence refers to participants who have benefited from participating in research, whereas non-maleficence refers to any potential harm that participating might bring. While participating in research and having the opportunity to tell one's own story and help others is generally considered beneficial,[134] we did have some concerns about interviewing patients regarding their activities and the influence a DFU might have on this, given that the subject, to our knowledge, was not that well examined. It became

apparent early in the interviews that falling was not uncommon in DFU patients, perhaps due to their neuropathy or balance issues, and that this was not always shared with the healthcare professionals in the municipality or the MDT team. As a trained physiotherapist my ethical considerations were about when to step back as an observant researcher and when to potentially interfere and what that interference might look like. My conclusion was to steer interviews and influence participants to act on these issues themselves, resulting in one asking the municipal nurse for guidance and another buying a walking cane to use daily.

Before the initiation of the development and pre-feasibility study (Study 3), a protocol was registered on https://clinicaltrials.gov (reference ID: NCT05101473). The feasibility study was approved by the Danish Data Protection Agency on August 17th, 2021 (Region Zealand j.nr. REG-075-2021) and by the Danish Data Protection Agency, and the Regional Committees on Health Research Ethics for Region Zealand (Region Zealand j.nr. SJ-928).

The patients included were asked at every exercise session if they had experienced any adverse event since their last visit. They were also asked if consultations with their podiatrist, the municipality wound care nurses, or the MDT team had found any adverse event in their feet.

Serious adverse events covered life-threatening events, disability, or permanent damage,[135] whereas minor adverse events covered muscle soreness and post-exercise fatigue. Negative events were registered according to the foot ulcer. Serious adverse events were reported to The National Committee of Health Research Ethics within seven days from the time of the event.

Results

Identifying the evidence base (Study 1)

Ten studies met the eligibility criteria and were included in Study 1 (Figure 3): Three RCTs,[136–138] and three prospective cohort studies in four publications,[139–142] and one "pre-post designed" feasibility[143] study, and one case series study.[144] Data from 2 unpublished studies[145,146] were also included.

All three RCT studies were judged to be at high risk of bias. Two described the randomization process as "the order of patient referral to the clinic," and one[138] described the "pitcher bowl" randomization method, with no specification. All three studies had baseline differences in patient characteristics,

suggesting a problem with the randomization process. None of the three studies employed blinding at any level of the trial design and, although blinding of assignment of participants in exercise studies is nearly impossible,[147] neither data collectors (testing staff) nor statistical staff were blinded.[148]

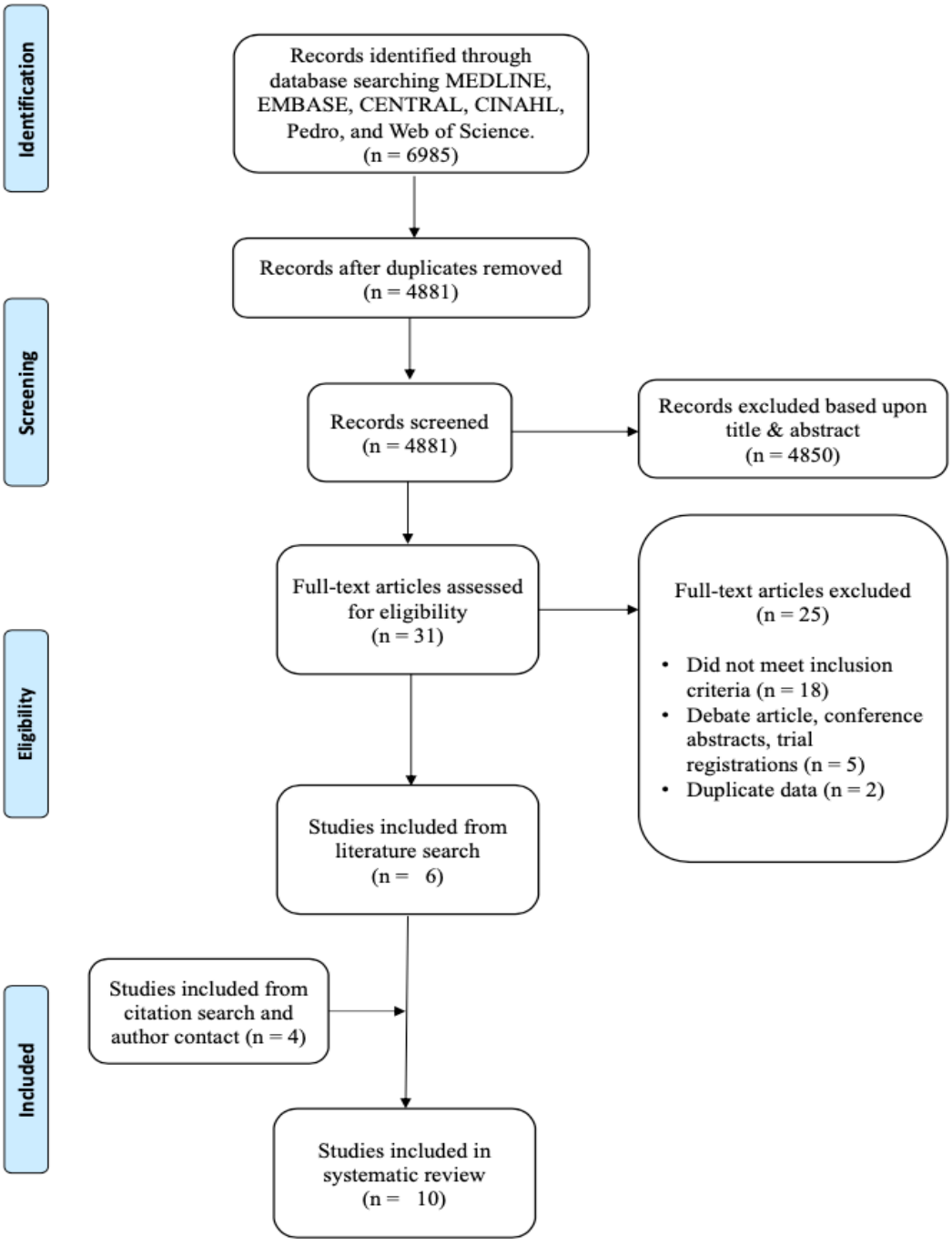

Figure 3 *- Flow diagram, from paper 1, figure 2.*

The risk of bias in the observational studies was also found to be considerable as unclear reporting hampered the assessment.

Only one[146] (unpublished data) study reported the results of HRQoL, and studies reporting harms had high heterogeneity and did not present the characteristics necessary to enable a meta-analysis. Hence, it was not possible to assess the benefits of exercise therapy on HRQoL or the harms through meta-analysis.

The conclusion of the study was that no evidence-based recommendations could be provided on the benefits and harms of exercise therapy for patients with DFUs. And that more studies are needed that include a detailed description of the exercise program and any adverse events and that focus on attaining a high adherence rate to exercise.

Developing appropriate theory (Study 2)

Participants were recruited from multidisciplinary outpatient DFU clinics at two hospitals in Denmark. All five participants we approached accepted participation. Three were male; and two were female, with ages between 49 and 78 years. Participants were followed throughout treatment for their DFU, beginning with their first visit to the outpatient clinic. For some, this meant weekly or biweekly observation and interviewing (each participant was interviewed 3–11 times, depending on the number of hospital visits). Data were collected from 33 interviews lasting between 30 and 180 minutes, field notes based on 18 observations, and memos of theoretical reflections and insights.

The grounded theory of "just a bump in the road" was constructed based on patients with DFUs' main concerns and behaviour after referral to an outpatient clinic for DFU care. "Just a bump in the road" means that a person with a DFU interprets the ulcer as a passing phase in their life. They actively strive towards what the individual considers normality. From entering the clinic, the patients have high hopes for wound healing and the return to their former life and activities. Each of the four categories outlines different aspects that either limit or reinforce the patient's perception of the wound as just being a bump in the road of their life. Figure 4 presents a visualization of the grounded theory and the embedded categories.

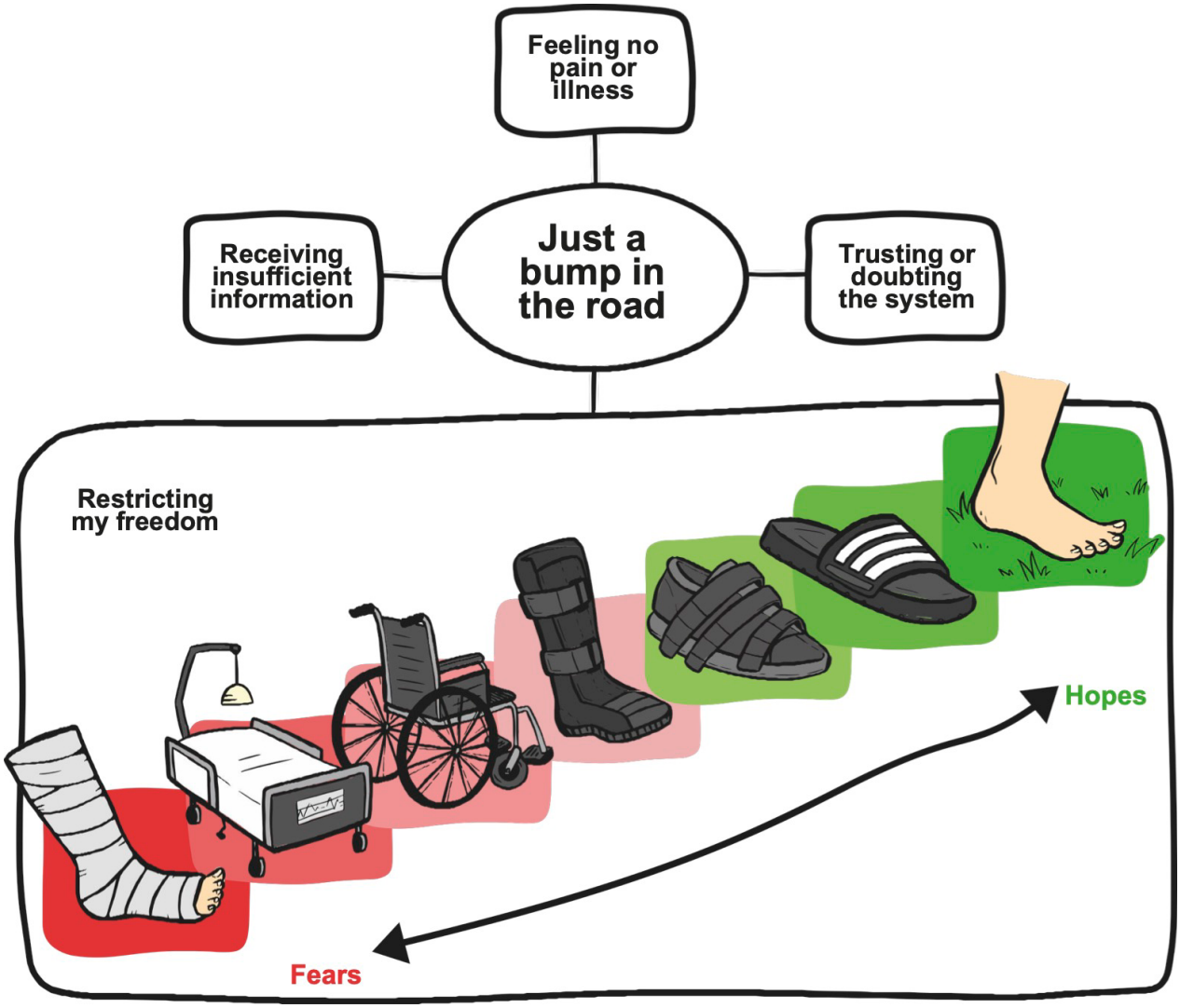

Figure 4 *- Grounded theory representation, from paper 2 (manuscript), figure 1.*

The grounded theory of "just a bump in the road" consists of four sub-categories, describing a patient´s behaviour and underlying concerns, related to daily activities.

The category *Restricting my freedom* expresses the participants' reactions to the off-loading regime prescribed by the DFU clinic. From one follow-up visit to the next, the participants described their hopes and fears relating to the level of restriction imposed. The lower left depicts the participant's most dreaded outcome of being put in a cast, which would make walking impossible. whereas images in the top right corner represent the participants' recollection of normal activities (e.g., walking barefoot or in slippers).

The category of *Receiving insufficient information* describes how participants felt that the information offered by the healthcare staff was insufficient. This included information on wound prognosis,

guidelines on movement restriction, or plans for visits to the clinic. For most, the information gap had been apparent from the very first visit. In some cases, information failed to be communicated; in other cases, it was phrased in ways that the participants found incomprehensible.

The category of *Feeling no pain or illness* captures the participants' perception of their feet and the ulcer as well as their behaviour after referral to the DFU clinic, when hospitalized or asked about the future, their expectations for wound healing, and the risk of amputation. In this category, all participants included had neuropathy (a well-known symptom in the DFU population, with rates of up to 79% reported).[13] The absence of pain or the sense of being ill appeared to make the participants describe their perception of their foot as the same, regardless of whether they had spent a whole day in bed or walked 10,000 steps.

The category of *Trusting or doubting the system* describes the participants' dilemma during their visits to the diabetic foot clinic. They said that even if the information provided was unclear, they always appeared for their hospital appointments, frequently out of respect for the physicians who had allotted time for them. Participants went from trusting the treatment regime to doubting it as their wounds failed to heal, which may have attenuated their treatment adherence and led them to focus on resuming their normal lifestyle.

In conclusion, the grounded theory of 'just a bump in the road' helps us understand patients' behaviour and underlying concerns when they are referred to outpatient DFU care. Adapting the treatment according to an improved understanding of their behaviour could ensure better compliance and more efficient treatment.

Program development and feasibility testing (Study 3)

The exercise program was planned as a group-based, supervised 12-week program with a combination of aerobic and resistance training exercises delivered by physiotherapists. The program consisted of 24 exercise sessions and the procedure for each session is outlined in Figure 5 and in more detail in Appendix 4. The sessions took place at the department of Physio- and Occupational therapy at Zealand University Hospital, Koege, Denmark.

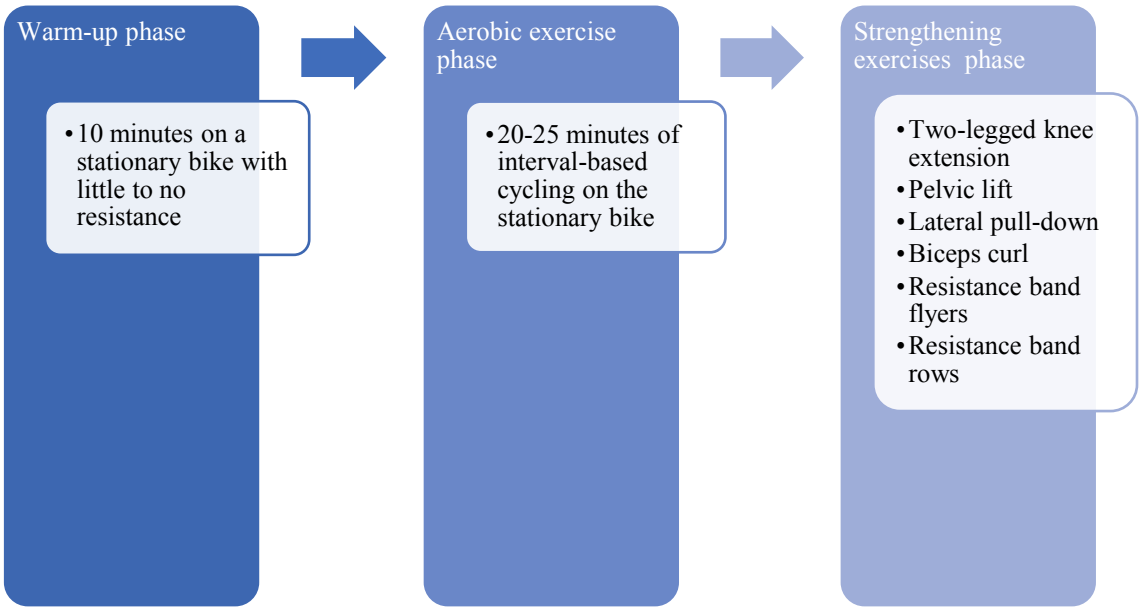

Figure 5 - *The exercise program phases*

Patient inclusion

Fifteen patients were assessed for eligibility from September 1, 2021, to April 1, 2022, of whom three male patients were included (Figure 6).

The main reason for not being included was the patient declining participation (n = 8). When asked to elaborate, one was already enrolled in municipality heart and post-surgery rehabilitation programs, five found the 24 planned exercise sessions and the travel time twice a week too burdensome, while two were in jobs that made participating during the daytime impossible.

Of the three male patients who participated in the exercise intervention, two received the planned 12 weeks while one received an intervention of eight weeks, after which he discontinued due to a prescribed Achilles tendon lengthening operation. All three were included in the analysis, respectively with 12-weeks and 8-week follow-ups.

The primary outcome levels of acceptance were met for the assessment of burdensomeness, adherence, and adverse events, but not for recruitment and retention rate (Table 1).

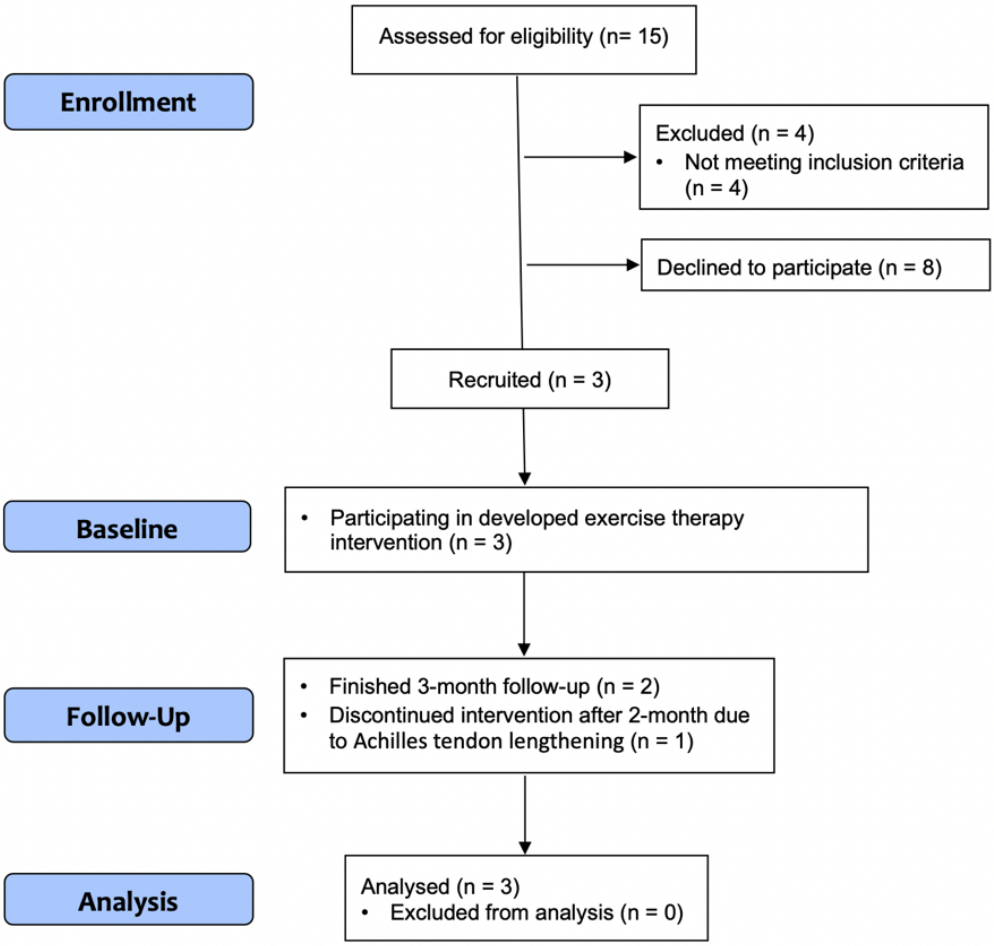

Figure 6 *- Flow diagram, from paper 3, figure 1.*

Table 1
Research progression criteria

Participation recruitment rate (*n*/month)	0.4/month, 3 in total	Red (do not proceed)
Patient retention		
Patients who completed the follow up (*n*, %)	2 (66 %) *	Amber (amend)
Adherence to exercise intervention		
Patients attending exercise program (*n*, %)	60/72 (83.3 %)	Green (go)
Patients that did not find the exercise program too burdensome (%)	100 %	Green (go)
Adverse events		
Minor	4	Green (go)
Serious	0	Green (go)

* Based on 3 patients

The results of the patients included are presented in Table 2. All patients had a reduction in DFU size. Results on the functional outcomes of the Sit-to-stand, Tandem test and 40m walk test were all inconclusive, as were the subjective questionaries of EQ-5D and Wound-QoL.

Table 2

Outcomes at baseline and follow-up

Variable	Patient 1		Patient 2		Patient 3	
	Baseline	Follow-up*	Baseline	Follow-up	Baseline	Follow-up
DFU size (cm^2)	2	0.7	2	0.5	3	0.7
Sit to stand	12	11	5	7	13	13
Tandem test (sec)	11	10	3	29.6	30	30
40m walk test (sec)	37.35	41.83	50.99	50.91	26.29	26.68
EQ-VAS, 0-100	60	60	55	70	80	75
EQ-5D						
Index score, < 0-1	0.858	0.83	0.826	0.427	0.874	0.806
Wound-QoL	1.647	1.411	1.058	0.764	1.176	1.235

*2-months follow-up

In interviews with participants, they described the exercises and progression as relevant and effective. They considered supervision from physical therapists important. Furthermore, they described finding pleasure and meaning in adopting exercise therapy in their weekly routine and stated that doing regular exercise twice a week gave them more energy and boosted their physical and mental capacity. However, participants also described how they would have liked the exercise therapy setting to be placed closer to their home and/or perhaps in the municipality instead. In conclusion, a 12-week supervised exercise therapy intervention was developed with positive feedback from the included patients. However, conclusions on feasibility are limited by the low recruitment rate, as are conclusions on acceptability from patients of the exercise setting used.

Discussion

Main findings

The main findings in Study 1 were that no evidence-based recommendations could be provided on the benefits and harms of exercise therapy for patients with DFUs. Despite a comprehensive search strategy and inclusion of published studies and unpublished data, the risk of bias, lack of studies focusing on HRQoL, and uncertainty of all the effect estimates were pronounced. That said, some key points worth considering were found in the intervention setting that was included in the development of Study 3.

The main findings in Study 2 were that patients with a DFU view their condition as "*Just a bump in the road"* after referral to an outpatient clinic for DFU care – a passing phase after which they will strive to regain what they consider a normal life. The grounded theory included four sub-categories; *Restricting my freedom, Receiving insufficient information, Feeling no pain or illness* and *Trusting or doubting the system,* each of which gave some insight that was later used in the development phase of Study 3.

The main finding in Study 3 was the development of a 12-week supervised aerobic and resistance exercise therapy program for people with DFUs from a hospital setting that can be adapted to other patient-important healthcare settings. Conclusions on feasibility, however, were limited by the low recruitment rate, and future studies should focus on trying to address this before the commencement of RCTs of exercise interventions for the DFU population.

Methodological considerations

This PhD project includes three studies with three different study designs, with individual methodological considerations discussed below.

Identifying the evidence base (Study 1)

At the time of Study 1's publication, this was the first systematic review assessing the benefits and harms of exercise therapy for patients with a DFU. As no early indicators of success existed this meant an inherent risk of producing an "empty review", defined as a systematic review that finds no studies eligible for inclusion.[149] These may be problematic for clinicians and decision-makers but, as

Lang et al.[149] point out, they have key relevance as they offer researchers the opportunity to 1) inform those who are interested in the topic, 2) highlight major research gaps, and 3) indicate the state of research evidence at a particular point in time. Empty reviews and reviews with few studies included may be the result of a new area of study that has not previously been examined. Hence, their publication might help stimulate appropriate future research.[150]

Due to the lack of studies including HRQoL outcomes, and the studies included that reported adverse events having high heterogeneity, it was not possible to perform a meta-analysis. While the term heterogeneity means that there is variability in the data, in research, there are different types of heterogeneity – clinical, methodological, and statistical.[151,152] The studies included had differences in participants and interventions (clinical heterogeneity) as well as differences in study design and risk of bias (methodological heterogeneity). The main bias in the RCT studies was the randomization process. Group allocation should be based on chance, thereby minimizing the risk of selection bias.[153] [152] If randomization is conducted properly, it reduces the risk of an imbalance between groups that could falsely influence the endpoints being assessed.[153,154] Dufour and Duhoux[155] point out this exact limitation in a letter to the editor of *The Journal of Wound, Ostomy and Continence Nursing,* regarding the RCT study by Eraydin and Avsar,[136] that the favourable effects observed in the experimental group could be attributed to the difference in groups at baseline rather than the relationship between exercise and ulcer healing.

Another issue in the studies was the choice of outcomes. Outcomes should be chosen with a clear theoretical or evidence-based rationale and guide the sample size estimation.[147] Healing or reduction of DFUs is a "hard" outcome, with obvious clinical and practical relevance.[147] However, to analyse such outcomes, large samples are usually needed; hence, no studies described a sample size estimation. This may have led to an overestimation of positive treatment effects (healing of DFUs) and an underestimation of negative treatment effects (adverse events).[156]

Developing appropriate theory (Study 2)

In qualitative research, no common vocabulary on the quality criteria that studies should aspire to has been agreed upon.[157] However, the "quality" term can usually be called trustworthiness or credibility, determined by the accuracy of the findings from the perspectives of the researchers, research informants or readers.[158] Study 2 was, therefore, evaluated according to the quality criteria for grounded theory studies on *credibility*, *originality*, *resonance*, and *usefulness,* as described by Charmaz.[120]

Credibility

The term credibility refers to confidence in the data and its interpretation.[157] One way of doing so in grounded theory is to become familiar with the study setting and collect rich data using different data collection methods and include a range of participants with various experiences of the topic under study.[120] The data collection included both observations and interviews where I, as a researcher, became intimately familiar with the participants and topic of interest. To ensure that the topic of interest was relevant to participants, a pilot study involved focus group discussion, and researchers that did not include the main author preceded this grounded theory study. Furthermore, patient information material and initial study queries were discussed with two patients, to validate the relevance of the study subject.

Researchers should question whether the data gathered is sufficient to merit the claims proposed.[120] In quantitative studies, sample size calculations guide the research to demonstrate the effect of an intervention. No similar standards for the assessment of sample size exist for qualitative interviews.[159] In grounded theory, the constant comparison method guided me until saturation was achieved.[120] Although the sample of included participants in Study 2 was small the study used multiple interviews and observations with the same participants, had a narrow focus and timeframe,[120,160] and aimed to generate a small micro-level theory on patients' behaviour after referral to an outpatient clinic for DFU care.[161] The analysis stopped when theoretical saturation was reached.[162–164]

In qualitative studies, the data collection and analysis are built upon a subjective process where preconceptions may compromise credibility.[120] This is not in line with the common misassumption of grounded theory studies that a researcher should enter the field without any knowledge of prior research.[165] What is important is to engage in reflexivity about preconceptions.[120] Thus, during the data collection, I tried to stay open-minded and wrote my reflection in a logbook after each observation and interview. For example, I reflected on my experience as a trained physiotherapist and the preconception that staying active is an important part of life, and how this doctrine could impose itself on me as a researcher in an interview setting, with participants not necessarily agreeing with this.

The procedure of Investigator triangulation was used to further reduce the risk of researcher bias.[166] My co-supervisor Ulla Riis Madsen assisted in the coding and analysis process, and we met regularly to discuss expansions and modifications of the emergent theory as it evolved.

Originality

The criteria of originality refer to the social and theoretical value of the work or theory developed: "*Does your analysis provide a new conceptual rendering of the data?"* and *"How does your grounded theory challenge, extend, or refine current ideas, concepts, and practices?"*[120 p. 337] Following the principles of grounded theory,[120] the existing literature was not searched and compared before the theory was written, thereby preventing preconceived ideas and theories from being forced on the data. The grounded theory of "*Just a bump in the road"* provided new insight into the behaviour and underlying concerns of patients living with DFUs, relating to daily activity. Part of the theory had similarities to the existing literature. Multiple studies have described how patients view their first DFU as an acute condition that would heal quickly.[167–171] Coffey et al.[172] found that participants were likely to take strategic risks to maintain as normal a life as possible. Barg et al.[173] found that patients with a DFU, or an amputation preceded by a DFU, described how their condition would not stop them from living their life.[173] Similar sentiments have been described by McCaughan et al.[174] in patients living with surgical wound healing. Here patients described limited physical mobility (and particularly being unable to drive) as frustrating and disruptive to their normal activities. This study however adds important detailed insight into adjusting to life and restrictions, or the lack thereof, for people with a DFU after referral to an outpatient clinic for DFU care.

Resonance and usefulness

The criteria of *resonance* questions whether the theory makes sense to the participants or to people who share their circumstances. Charmaz proposes the use of member-checking as a way of confirming ideas and theories.[120] However, as the purpose of this study, was the behaviour and underlying concerns of people living with DFUs, related to daily activity after initial referral to an outpatient clinic for DFU care, it was unclear whether the findings persisted or changed over time, so another approach was used. After the write-up of the manuscript of Study 2, I started recruiting for Study 3 and talked to new patients in the outpatient clinic and people with recurrent ulcers. Here I presented the findings from Study 2 and heard patients describe their own experiences with activity while living with a DFU. Realizing that the results had resonance and usefulness with patients, the theory has been presented to nurses, doctors and podiatrists working with this population. Although many of these health professionals have displayed prejudice towards patients, sometimes describing

them as being lazy and unintelligent, the theory and underlying categories resonated with them regarding the usefulness of good communication and proper off-loading guidance.

Program development and feasibility testing (Study 3)

Several objective and subjective measurements were included in Study 3. Unfortunately, outcomes reported in DFU research are heterogeneous[175–178] and no recommended set of outcomes is available. Therefore, the focus for us was outcomes with little or no risk of harm to the participants' feet, employing the gross motor bodily functions, which would be easy to implement in the clinic. This meant the inclusion of the 30-second chair-stand test,[130] the Guralnik Tandem Test,[131] and the 4 x 10-meter fast-paced walk test[132] rather than the tests recommended by the American Heart Association (AHA)[179] for cardiorespiratory fitness assessment, which is a maximal cardiopulmonary exercise with concomitant gas exchange analysis, or the submaximal assessment using the 6-minute walk test. Although the tests are all widely used their psychometric properties for validity and reliability in people with a DFU have not been evaluated. Wound-QoL is disease-specific for people with hard-to-heal wounds[128,129,] and measures changes in HRQoL over time or with treatment, which is impossible with generic measures.[180] It is not widely used in research and has only recently been translated into Danish (by Knudsen et al.[128]), which limits the comparability of results across studies. Results from Study 1 showed no published studies including measurements of HRQoL in studies on exercise intervention, and unpublished data are varied, with the use of the generic SF-36 and EQ-5D in Jørgensen,[145,181] and the Patient-Reported Outcomes Measurement Information System (PROMIS) in Morgan.[146] A published study protocol by McCarthy et al. 2020[182] on an arm exercise intervention that includes the Cardiff Wound Impact Schedule has also been validated in a DFU population. This lack of agreement on which HRQoL tests to choose highlights that further development and use of patient-reported outcome measures (PROM) on HRQoL for people with a DFU in general treatment, and in exercise studies, are vital.

Main findings in relation to other studies

Choice of developing methods.

Early in the planning of this PhD project, my supervisors and I had questions about exercise for people with DFUs. Although conducting an RCT with an exercise intervention versus usual care was discussed, it quickly became apparent that some questions needed answering first. Knowledge of the safety of exercise for people with DFUs was limited. What should an exercise intervention include?

Would the population take exercise – did being active have meaning for people with a DFU? Where should an exercise intervention be situated in both place and time? Was it even possible to recruit patients on a small scale for an exercise intervention?

The MRC Framework for developing and evaluating complex interventions was chosen to guide the process, and although the MRC framework has been ongoingly revised in 2000,[106] 2008[107] and 2021,[108] this is not in itself enough to produce successful health interventions. O'Cathain et al.[183] describe the evidence base in the field of health as sparse on whether following a specific published approach or undertaking a specific action, results in effective interventions.

In retrospect, an argument could be made that we applied a mixed-method design without acknowledging it. This approach would also sit well within the multiphase model of the MRC framework,[106,107,184] yet mixed method studies intentionally use one data source with another, to triangulate their results. In contrast, a multiple-method approach uses different data collection strategies in the same program, with no intention to combine them.[185] While the sub-studies were complementary and did build upon each other, their success also relied upon each other, with a substantial risk that the planned latter parts would not be possible to initiate. For example, the possibility that the systematic review would not identify studies looking into this area, or that it might even describe the harms of exercise in people with DFUs in such a way that a continuation of any exercise regime would be deemed unethical. Or, if results from the grounded theory study showed that being physically active meant nothing to people living with a DFU and that they welcomed the possibility of sitting passively with open arms, waiting for their DFU to heal, then an intervention study with exercise would be unrealistic.

The art of interpreting discordant SRs

Some systematic reviews with various focuses on exercise therapy for patients with DFUs have since been published.[186,187] The evidence base is the same as in Study 1, yet some debate on the confidence of the results has emerged.[188] Brousseau-Foley et al.[187] suggest that additional research is needed and that the most desirable attributes of a program would be improvements in wound-healing, cardiorespiratory, and metabolic health parameters, and reducing disease-related morbidity and mortality. Tran and Haley[189] concluded that there is insufficient evidence to conclusively support exercise as an intervention to improve the healing of DFUs, but in the subsequent sentence write "*the results demonstrate some degree of wound size reduction and there were no negative consequences of the intervention for the participants".* This conclusion and encouragement of exercise surprised

Brousseau-Foley and Blachette[188] who, in a letter to the editors of The International Journal of Lower Extremity Wounds journal, addressed some key issues with the systematic review by Tran and Haley[189] in that the authors present a lack of correlation between exercise performed and wound healing achieved, a lack of discussion on the adverse events reported in the studies, and finally, uses the PEDro scale[190] for the risk of bias assessment in the RCTs, instead of the Cochrane RoB tool.[111,191] This lack of agreement on core methodological elements in the development of a systematic review has been described as a challenge in health research.[192] Unfortunately, the question of interpreting different results from similar SRs is not new,[193] and is not uncommon in different medical disciplines.[194,195] But as described by Puljak et al.[196] it may lead to the dissemination of inconsistent recommendations, slowing the transfer of research evidence into practice, or in the case of exercise for people with a DFU, it might do more harm than good.

Integrating patient knowledge

The grounded theory of "*Just a bump in the road"* provided new insight into patients living with DFUs' behaviour and underlying concerns, related to daily activities in the early stages after their referral to the clinic; and as previously described in the *Credibility* caption, in accordance with the existing literature. The individual categories themselves, however, also provided insight into the planning phase of Study 3.

Participants were originally only planned to be interviewed at the end of the 12-week exercise period regarding the program parts, and whether they had any suggestions for improvements. However, the categories *Receiving insufficient information* and *Trusting or doubting the system* underlined patients' need for communication on the progression of their condition as also described by McCaughan et al,[174] who found that positive feedback from healthcare professionals boosted morale and sustained patients' hopes for healing. At the same time, negative remarks adversely affected the patients' general outlook. Conflicting information from different nurses regarding the condition of their wounds or their management was particularly troubling for patients. The reasoning was that a lack of communication might potentially influence participants' attitudes towards the system or treatment. As a result, a greater participant involvement in the development of Study 3 was welcomed than initially planned. For example, one participant asked if he could share the exercise program and study protocol with his private physician, who was sceptical of the concept of the exercise, and requests and feedback from participants led to the aerobic exercise phase being expanded from 10 to 20 minutes, and to the inclusion of biceps curls in between other planned exercises.

The grounded theory of "*Just a bump in the road"* highlighted a need to check participants included in Study 3's general daily activity since their last exercise visit. Coffey et al.[172] describe that people with a DFU have alternative interpretations of the condition that can significantly influence their behavioural choices. For example, without focusing on daily activity, participants could have gained more energy as their health improved, resulting in increased daily activities and the risk of DFU enlargements or an increased probability of falls.

The category *Feeling no pain or illness* emphasized to the research team that a fully supervised setting was necessary. The fear was that participants over time had become complacent about their feet, due to the lack of visible symptoms and gradual onset of this "silent disease," as described by Coelho et al.[197] Participants doing exercises might cause adverse events during the exercise session and not notice it, a concern also mentioned in studies on exercise for people with diabetes and peripheral neuropathy.[100,198] Injuries might include accidentally tripping or falling during the exercise session. Furthermore, questions before and after the exercise session on the status of the patient's feet were emphasized, partly due to the previously mentioned communication focus, but also to reinforce to participants that since their sensory system provides them with few cues for action and they feel no pain, their sight and vision must "take over" and help them.

Insights from the category *Restricting my freedom* indicated a transition in activity behaviour for patients. When patients over time transitioned to a prescribed therapeutic shoe in the clinic, their response was to resume more normal activities, and they saw this footwear as the least hindrance in their daily life. This, in combination with results from Lindberg et al.,[144] and their issues with having people with a prescribed boot take cardiovascular exercise on a bike, and the fact that multiple studies have found that DFU patients display an increased level of activity over time,[46,168,172,199–201] have resulted in the inclusion criteria in Study 3 of only including people with a prescribed therapeutic shoe. The hope was that patients would be more capable of participating in an exercise intervention at this stage in their DFU treatment and that it would have the least influence on their ability to participate in the developed intervention. However, the inclusion criteria limited the number of people eligible for inclusion in the clinic.

Recruiting difficulties

The inclusion of participants in Study 3 did not meet the predetermined goal of 15 participants and could be the reason why the individual outcome measures were inconclusive and did not reach the smallest detectable change or the minimal clinically important difference.[128,131,132,202] Similar

recruitment issues have been found in other exercise studies on DFU patients[144–146,203,204]. Molsted et al.[203] and Nielsen et al.[204] found a higher risk of drop-out and low adherence to exercise in diabetes patients with risk stratification level 3 and low functional level due to impaired balance, being severely overweight, or DFUs.[203]

One or more reasons could explain this issue. Negative experiences from eligible participants could result in barriers to engaging in an exercise intervention. A study by Stuij et al.[205] on negotiating exercise as medicine for people with type-2 diabetes showed that nearly all respondents talked about rather negative experiences with 'physical activity care,' despite considering it a useful means to manage blood glucose levels and postponing possible complications. Interviews with those agreeing to be contacted but declining to participate showed barriers due to long transportation to training facilities in a hospital setting, and the lack of the physical and psychological resources to participate in the intervention setting of exercise two times a week. Both these reasons were also identified in people living with multimorbidity by Jäger et al.[206]

Potential scepticism about an exercise intervention from healthcare professionals might also have affected the inclusion potential.[207] Scepticism might have resulted in healthcare professionals not approaching all potentially eligible participants. Unfortunately, statistics on how many participants they approached, that then declined to be contacted by me, still need to be generated. This might give insight into healthcare professionals' "success rate" and people's initial reaction when presented with exercise as an offer.

Finally, in 2018 during the planning phases of the PhD, the exercise intervention was planned to be carried out in one or more municipalities in Region Zealand. Yet, as COVID-19 entered Denmark, with face masks and social distancing restrictions, these plans changed to a hospital intervention. For people with diabetes, COVID-19 made adherence to exercise recommendations challenging,[208] with the pandemic resulted in nonadherence to physical activity for 73.6% of those previously following the recommendations.[209] Changing to a hospital setting in Study 3 had the advantage that the flow of patients with a DFU was higher, and restrictions in the hospital were limited when recruitment began in late 2021. The disadvantage, however, was that participants had to enter the hospital for exercise sessions two times a week, and while all eligible participants were asked whether declining to participate was due to fear of catching COVID-19, which they denied, this could psychologically have put some eligible participants off agreeing to participate in the first place.

Current evidence and suggestions for future research

The MRC framework of 2008 described key elements in the development and evaluation process of complex interventions in a cyclical sequence,[107] where feasibility and piloting are directly followed by an evaluation in the form of an RCT. However, it would be premature to go forward with an RCT study given the results of low recruitment in Study 3.

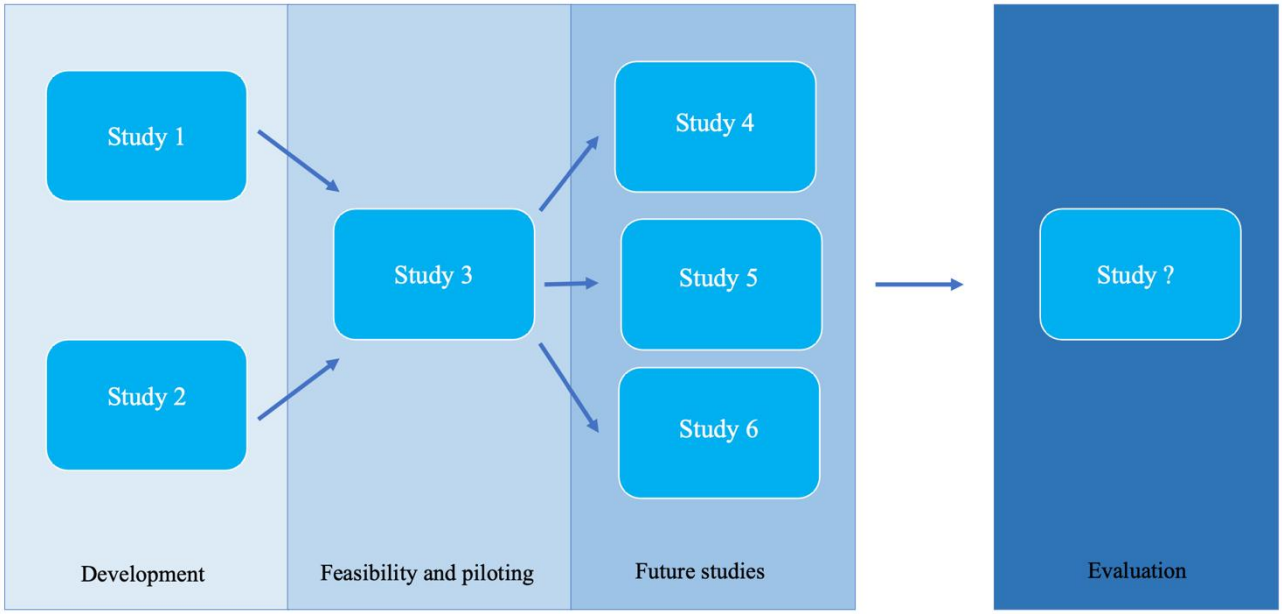

***Figure** 7 - Future studies following the MRC framework*

Figure 7 depicts how knowledge gained from the PhD project could be included in future studies and potential evaluations following the MRC framework. Further investigations and amendments should be made to improve recruitment rates in exercise studies for the DFU population, and future studies should seek to clarify any barriers to exercise interventions from nurses, doctors, or podiatrists. Potential barriers could be in the form of written local guidelines, recommendations or verbal communication from health professionals advocating a sedentary lifestyle during the DFU treatment period.

More studies are needed to assess important patient-centred outcomes for the DFU population. For example, future studies should investigate the physical limitations of patients with a DFU, as information on this might help guide the choice of measurement outcomes in exercise studies and show what body functions an exercise intervention should have a key focus on.

More feasibility studies are required in settings closer to where patients live, for example in the municipality. Given that many patients already have contact with the municipality for wound care

such an exercise intervention setting could reduce their transportation burden. Again, a key focus should be on attaining a high recruitment rate and reporting both benefits and harms of exercise. Hopefully, results might reveal or indicate if the next logical step after this is an RCT evaluation, more feasibility exercise studies with further amendments, or if a reconsideration and a change of course on exercise as a concept in general for the DFU population is needed.

Conclusions

This PhD project provided contemporary data on the developing process of exercise therapy intervention for patients with DFUs, to answer the following questions:

1. *What are the benefits and harms of exercise therapy for patients with a DFU?*

No evidence-based recommendations could be provided on the benefits and harms of exercise therapy intervention for patients with DFUs, given that no published studies assessed HRQoL, and that all studies included had high heterogeneity and a high risk of bias.

2. *What are the main concerns about activity among patients with DFUs who attend a specialized outpatient clinic for follow-up treatment?*

People with a DFU view their ulcer as "*Just a bump in the road*". The four subcategories of the grounded theory describe the patient's behaviour and underlying concerns as they relate to daily activities: *Restricting my freedom; Trusting or doubting the system; Feeling no pain or illness* and *Receiving insufficient information.*

3. *Is it possible to develop and test for the preliminary feasibility of a 12-week exercise therapy program for patients with DFUs, focusing on the program's inclusion, adherence, and adverse event rates?*

An aerobic and resistance exercise therapy program for patients with DFUs was developed thoroughly, including results from Study 1 and Study 2, and patient and physiotherapist involvement. However, conclusions on the feasibility of the intervention are limited by the low number of participants included.

The studies that were included suggest that exercise therapy for the DFU population may be beneficial and present a developed exercise therapy program. However, further investigations and studies are necessary to improve recruiting rates and enable potential future evaluations.

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Paper 1

Original Article

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

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Abstract

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

Keywords

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

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

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

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

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visceral fat, and has been found to increase health-related quality of life (HRQoL) in patients with diabetes.[14] The latter is of key relevance to patients with DFUs, as a DFU is associated with reduced mobility, depression, and overall low HRQoL.[15-22] Patients report severely decreased HRQoL at initial presentation in the foot 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," and "Strength training" (Supplement Material: Search Strategy). To identify additional studies, the reference lists of all included full-text articles were screened and we performed a citation search in Web of Science of all included full-text articles.

Study Selection

One reviewer scanned titles and abstracts for potentially eligible studies. Two reviewers read the full-text version of potentially eligible studies and decided independently whether the study could be included. Disagreements were discussed with a third reviewer and resolved by consensus. We included randomized controlled trials (RCTs) to assess both potential benefits and harms of exercise therapy and observational studies (ie, comparative studies [prospective or retrospective], case series, case studies, and pilot studies) to identify potential harms of exercise therapy.[27,28] Eligible studies included patients with an active DFU receiving exercise therapy. We excluded studies with no original data (eg, editorial, commentary, or letter), duplicate data, and studies presented only as conference abstracts.

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

Outcomes on benefits of exercise therapy were any generic or specific measures of HRQoL (ie, Medical Outcomes Study Questionnaire Short Form 36 [SF-36],[30] EuroQOL-5D [EQ-5D],[31] The Diabetic Foot Ulcer Scale,[32] and Wound-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; and hospital admissions. Adverse events mentioned in the primary studies were registered as yes or no and registered separately for intervention and control groups.

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

Data Extraction and Quality Assessment

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

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

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

the wound in cm^2); (4) outcome was blindly assessed; (5) no conflicts of interest; (6) we considered the cohort to be fairly representative for the "average" patient with a DFU.[3] Case series including less than 10 patients were not assessed for risk of bias.

Data Synthesis and Analysis

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

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

Results

Study Identification

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

A citation search in Web of Science of all 6 included studies yielded 3 additional studies. Huang et al[69] presented data for 3-month follow-up of the same population of patients as Chen et al,[40] Chang et al,[70] and finally Nwankwo et al.[71] Authors of the 3 trial registrations[64-66] were contacted by email in order to obtain unpublished data. Two replies were received: Jørgensen 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]

Characteristics and Quality of the Included Studies

In total, there were 3 RCTs,[38,39,71] 3 prospective cohort studies in 4 publications,[40,41,69,70] 1 pre-post designed feasibility study[42] and 1 case series study,[43] and data from 2 unpublished studies (Jørgensen[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 Tables 1 and 2.

In accordance with the RoB 2 Quality Assessment scale for RCTs, all 3 RCT studies were overall judged to be of high risk of bias (Table 3). Flahr[39] and Eraydin and Avşar[38] described their study design as both randomized and quasi-randomized and were therefore assessed as RCT studies. In both studies, the randomization process was on "the order of patient referral to the clinic," whereas Nwankwo et al[71] described a randomization method of pithers bowl, with no specification of it. All 3 studies had baseline differences in patient characteristics that suggested a problem with the randomization process. Flahr[39] described a difference between group, whereas Nwankwo et al[71] reported a significant difference ($P < .00$) in ulcer area values at baseline, and Eraydin and Avşar[38] reported an almost twice as large ulcer area difference at baseline ($P < .05$). None of the 3 studies employed blinding. No studies stated that an intention-to-treat analysis was performed. No studies had a published trial protocol or trial registration to assess (Supplement Material: RoB 2 Template for Completion).

The risk of bias in the observational studies were considerable (Table 4). No studies were considered to have a low risk of bias according to all 6 criteria. Unclear reporting hampered the assessment. One study[70] was considered to have low risk of bias in 4 of 6 domains. Three studies[40,41,69] complied with 3 out of 6 domains. One study[42] complied with 1 out of 6 domains. Finally, one study[43] included 5 patients and was not assessed for risk of bias.

Benefits and Harms of Exercise Therapy

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

No published studies included measurements of HRQoL. Both unpublished studies included measurement of HRQoL (Table 1). Although Jørgensen[72] recorded SF-36 and EQ-5D at baseline and 16-week follow-up, they did not report baseline or change score on HRQoL. Morgan (unpublished data, December 2019) recorded HRQoL using PROMIS.[73] On PROMIS-Global, they reported reduced fatigue ($P = .06$) and on PROMIS-Physical Function improved physical function ($P = .009$). It is unclear if these significant changes were clinically relevant. No other significant findings were demonstrated (S. Morgan, unpublished data, December 2019).

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

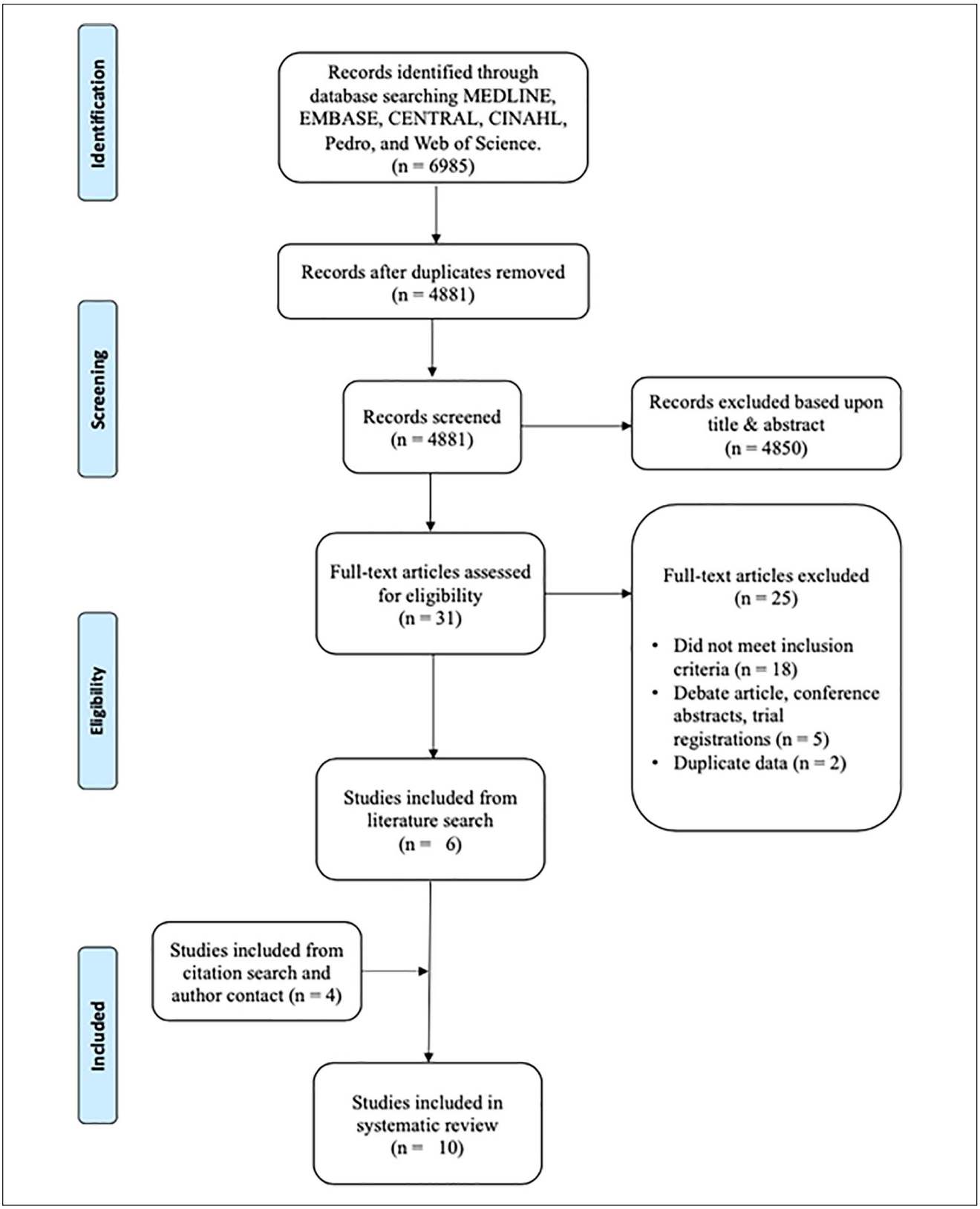

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram presenting the process undertaken to identify eligible studies.

Table 1. Study Characteristics.

First author, country	Aim	Population enrolled/completed	Outcome measures	Wound condition/size results
Randomized studies				
Eraydin and Avşar,[38] Turkey	To examine the effect of foot exercises on wound healing in patients with type 2 diabetes with a DFU	65 patients hospitalized with DFUs enrolled Intervention group, n = 30 (mean age = 61.03) Control group, n = 30 (mean age = 65.76)	• 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) $P < .01$
Flahr,[39] Canada	To explore the effect of exercise on healing diabetic foot ulcers	19 patients with DFUs enrolled Intervention group: n = 10 (mean age = 62.2) Control group: n = 9 (mean age = 74.25)	• 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,[71] Nigeria	Investigate the effect of aerobic exercises on changes in biochemical profiles of diabetic subjects and rate of ulcer healing on patients with diabetic foot ulcers	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 glucose test • 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) $P < .01$
Observational studies				
Chen et al[40] and Huang et al,[69] China	To investigate reliability and effectiveness of near-infrared spectroscopy on continuous peripheral circulation changes detection while asking the patients to do Buerger's exercise	30 patients with DFUs and 15 generally healthy populations A peripheral arterial disease group with DFUs: (A1 group) n = 21 (mean age = 70.62 ± 11.16) A non-PAD group with DFUs: (group A2) n = 9 (mean age = 57.78 ± 5.85) A generally healthy group (group B) n = 15 (mean age = 20.67 ± 1.89)	• Oxygenated hemoglobin concentration • Total tissue hemoglobin concentration	Not relevant
Lin et al,[41] China	To investigate the Buerger's exercise effects in patients with vasculopathic DFU with a cohort follow-up and determine whether near-infrared spectroscopy system is an effective monitoring tool for this exercise in a rehabilitation program	14 patients with a DFU and absence (A1) or presence (A2) of previous percutaneous transluminal angioplasty A1: n = 8 (mean age = 68.2 [SD = 9.6]) A2: n = 6 (mean age = 72.8 [SD = 13.5])	• Wound condition (healed/healing) • Oxygenated hemoglobin concentration • Total tissue hemoglobin concentration	Wounds healed: 11/14 = 78.57% Wounds healing: 3/14 = 21.43% $P = .539$
Chang et al,[70] China	Unclear	30 patients with unilateral or bilateral DFU n = 30 (mean age = 63.4 [SD = 13.7])	• Wound condition (healed/healing) • Skin perfusion pressure measured in mm Hg	Healed: 9 (26.5%) Improving: 14 (41.2%) Stasis: 6 (17.6%) Progression: 3 (8.8%) Toe amputation: 2 (5.9%)

(continued)

Table 1. (continued)

First author, country	Aim	Population enrolled/completed	Outcome measures	Wound condition/size results
Otterman et al,[42] the Netherlands	To investigate the feasibility and preliminary effectiveness of an exercise program for patients with diabetic complications	25 patients with various diabetic foot complications. Two patients described with an active DFU—no specification of age	• Program adherence • Adverse events • Achievement of the target training intensity • Patient satisfaction on a numeric rating scale from 0 to 10	Not reported
Lindberg et al,[43] Denmark	To examine the feasibility and safety of an exercise program tailored for people with diabetes, severe peripheral neuropathy and an active foot ulcer	5 patients with DFUs n = 5; mean age (SD) = 68.2 (7.1)	• 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)
Unpublished studies				
S. Morgan (2019), USA	To evaluate the effects of a seated exercise program on clinically meaningful outcomes in people with diabetic foot ulcers	34 patients with DFU enrolled; 18 completed Intervention: n = 7 (mean age 59.7) Control group: n = 11 (mean age 55.6)	• 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
T. S. Jørgensen,[72] Denmark	To evaluate the effect and feasibility of 8 weeks of passive movement exercise of both legs on wound healing in nonhealing diabetic foot ulcers	21 patients with DFUs Intervention: n = 11 (mean age 58 ± 1.7) Control group: n = 10 (mean age 64 ± 4.8)	• 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 $P = .062$

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

Table 2. Details of Intervention.

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

(continued)

Table 2. (continued)

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

Abbreviation: DFU, diabetic foot ulcer.

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

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

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

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

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

Abbreviations: +, low risk; −, high risk; ?, unknown.
[a]Unclear characteristics on duration of diabetes and age of diabetic foot ulcer patients.

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

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

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

Dropout rates varied in the studies, with some due to health issues,[38,72] and others due to relocation, lack of interest from patients, or planning issues.[38,42] Although not reported as an adverse event, 1 patient in the study of Eraydin and Avşar[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 hyperglycemia and visceral fat and increase HRQoL.[14] The search yielded no published studies on exercise therapy for patients with DFU measuring HRQoL. Jørgensen[72] used HRQoL measures of SF-36 and EQ-5D, yet reported no baseline or change results of these, whereas S. Morgan (unpublished data, December 2019) reported significant improvements in 18 patients on the Physical Function subscale of PROMIS, although unclear if these significant changes were clinically relevant.

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

Table 5. Results on Harms and Dropouts.

First author	Number of patients affected by adverse events	Adverse events (type and description)	Dropouts
Randomized studies			
Eraydin and Avşar[38]	Not reported	Not reported	Intervention group: 3 Reasons for withdrawal: general condition deteriorated, went out of city, and wanted to leave Control group: 2 Reasons for withdrawal: went out of city and unreachable
Flahr[39]	Intervention group: 1 Control group: 3	Intervention group: 1 diagnosed with osteomyelitis Control group: 3 wounds increased during study	Control group: 1 Reason for withdrawal not reported
Nwankwo et al[71]	Not reported	Not reported	Not reported
Observational studies			
Chen et al[40] and Huang et al[69]	Not reported	Not reported	0
Lin et al[41]	Not reported	Not reported	0
Chang et al[70]	5	3 had a progression in wounds 2 had toe amputation	0
Otterman et al[42]	Overall adverse events recorded: 55 Not specified for patients with DFUs	Not specified for patients with DFUs	2 dropouts in total Reasons for dropout were: Start of an education that could not be combined with participating in the study, and transportation problems
Lindberg et al[43]	7	Low level of blood glucose during training: 2 Shoulder pain during cycling: 1 Delayed onset muscle soreness in their thighs and knee pain to an extent that compromised progression in cycling and resistance training loads for several weeks following start of the program: 3 Transient exudate from the foot ulcer during the first weeks of training: 1	0
Unpublished studies			
S. Morgan (2019)	0	Not relevant	16 dropouts in total Intervention group: 8 Control group: 8 Reasons for dropouts included: Scheduling challenges (exercise: 4 and control: 2) Ineligibility in baseline screen (exercise: 2 and control: 1) Lost interest (exercise: 2) Preference for the exercise group (control: 5)
T. S. Jørgensen[72]	4	Intervention group: 2 • 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

Abbreviation: DFU, diabetic foot ulcer.

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 has 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 3 studies,[42,43,72] adherence rates to the exercise program exceeded 80% in either a semisupervised[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 and Avşar[38] and Flahr[39] both reported issues with low adherence to the exercise programs in a nonsupervised home-based setting with the other 4 studies suffering from unclear reporting of their adherence rates. This is not surprising, hence adherence has generally been found better in programs with supervision.[97] One possible explanation to this could be that direct supervision offers additional encouragement and motivation to patients.[98] So, it could be argued that in order to fully examine if exercise therapy has an effect on both wound healing and/or HRQoL, it should be examined in a semisupervised or fully supervised setting to ensure high adherence to treatment.

Harms of Exercise Therapy

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

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

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

Strengths and Limitations

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

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

Conclusion

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

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

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

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Paper 2

“Just a bump in the road” - A grounded theory study on patients’ behaviour after referral to a wound care clinic with a diabetic foot ulcer

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Keywords: Diabetes, Diabetic Foot Ulcers, Rehabilitation, Exercise, DFU.

ABSTRACT

Aim: The aim of this study was to construct a grounded theory on patient's activity behaviour over time after referral to an outpatient clinic for DFU care.

Methods: A constructivist grounded theory approach was used. Data from observations and interviews with 5 participants were collected and analysed using the constant comparative method and a grounded theory constructed.

Results: The participants considered their DFU as 'just a bump in the road' in their life. The grounded theory consists of four sub-categories, describing the patient´s behavior and underlying concerns, related to daily activities: *Restricting my freedom; Trusting or doubting the system; Feeling no pain or illness;* and *Receiving insufficient information*

Conclusion: A person with a DFU sees the ulcer as something that needs to pass and actively strives towards what they consider normality. Results from this study could help explain why and perhaps prevent treatment recommendations from sometimes ending up being discarded by patients.

Keywords

Diabetes, diabetic foot ulcers, qualitative, semi-structured interviews, grounded theory.

As one of the most serious complications of diabetes mellitus, a diabetic foot ulcer (DFU) constitutes a substantial burden for patients[1,2] and is often seen as the end stage of diabetes. The major cause of amputation in diabetes healthcare, ulcers may take months or years to heal[3–8] and result in repeated hospitalizations.[9–11] Slow-healing chronic wounds are associated with a high death rate,[12] its five-year mortality rate is similar to or worse than those of many common types of cancer.[13,14] Often requiring patients to refrain from bearing weight on the affected limb[15,16] and leaving some patients immobile for weeks, months, or even years.[17] Immobility contravenes diabetes guidelines, which have physical activity as a core element of rehabilitation and treatment.[18]

Patients' experience of DFUs is associated with a range of negative emotions, such as anger, fear, and depression, often accompanied by low overall health-related quality of life (HRQoL),[19] and a negative impact on patients' lifestyle.[20–22] Research associates decreased HRQoL with a range of parameters that could affect ulcer healing, such as poor glycemic control, low physical activity, avoidance of help, and poor adherence to the treatment regime.[23–26] Meric et al. found that most of the interviewed DFU patients' wounds had developed during daily activity and that they had attempted to heal the developing wounds by dressing them before seeking medical help. Expecting the healthcare personnel to show awareness and understanding of their individual characteristics, the interviewees called for clearer information, saying they disliked being met as "just another ulcer patient."[27] When Kinmond et al. investigated the lived experience of 24 individuals with a DFU, they found that living with a DFU had a detrimental effect on the participants' daily lives. Compared to their situation before the foot ulceration, the participants reported a sense of lost opportunities. A life challenged by the practicalities of taking a shower, shopping, or cooking was felt as a restricted life.[17] The complexity of remaining active with a DFU requires that patients' lives are considered in their social context. Previous research has indicated a gap in our understanding of life with a DFU and its repercussions on everyday activities, whether short- or long-term. Closing this gap could help health professionals to have a better understanding of patients' behavior.

AIM

Aim

The aim was to construct a grounded theory of the activity behavior of people with a DFU after referral to an outpatient DFU care clinic.

Research questions: What are the main concerns of people with a DFU regarding their physical activity? How do patients' concerns change during their time as outpatient DFU patients?

METHOD

Design

This study used a constructivist grounded theory approach as described by Kathy Charmaz.[28] It was reported according to the Guideline for Reporting and Evaluating Grounded Theory Research Studies (GUREGT).[29] Remaining active while living with a DFU is a complex and difficult challenge for patients. The constructivist grounded theory approach was chosen because of its ability to study and analyze complex phenomena in their social context. Assuming that researchers, like everyone else, create mental constructions of the realities in which they participate, the method acknowledges the inherent subjectivity of any research endeavor. Grounded theory explicates the process under study while it attempts to demonstrate its causes and the conditions under which it emerges and varies.[28]

Setting

The study was performed from February 2020 to March 2021. The participants were recruited from specialized multidisciplinary outpatient DFU clinics at two hospitals in Denmark with multidisciplinary teams including orthopedic surgeons, endocrinologists, wound care nurses and certified podiatrists.

Participants

Consistent with methods of constructivist grounded theory,[28] the initial sampling of participants included two participants who had been referred to the specialized multidisciplinary outpatient DFU clinics. To investigate patients' concerns about their physical activity, the researchers invited participants who met the following inclusion criteria: Danish-speaking, no previous amputation, no current wheelchair use, and no diagnosis of dementia. In line with the constructivist grounded theory methodology, a study sample and data sources were not set a priori to initiation[29] and further recruitment of participants was guided by the principles of theoretical sampling, while a search was conducted for data to expand the emerging categories and concepts.[28]

We conducted repeated cycles of recruitment among participants initiating treatment at the DFU clinic as we focused on the patient's long-term behavior after referral to a DFU clinic. All of the five

participants we approached accepted participation. Three were male; two were female, with ages ranging between 49 and 78 years. Two participants had no previous history of ulcers, one had a history of multiple ulcers, one had previously had a single ulcer, and one had an ulcer that had failed to heal properly for two years. Common for those with a history of, or an active DFU was that they had not received previous treatment in the multidisciplinary team that they were now referred to. Due to rapidly increasing infection and fever, one of the patients was toe-amputated between the first and the second interview. The participants all had at least one comorbidity, a diabetes history of more than 10 years, and severe neuropathy. Three participants lived with their spouses; two lived on their own.

Data collection

Data collection, coding and analysis were performed simultaneously. The data were comprised of individual interviews and ethnographic observations.[30] The first author followed the participants throughout their treatment for DFU, beginning with their first visit to the outpatient clinic, where they were observed and interviewed. For some, this meant weekly or biweekly observation and interviewing (each participant was interviewed 3–11 times, depending on the number of hospital visits). All visits to vascular surgeons, prosthetists, and wound surgeons took place within weeks of the initial referral. Some participants were also seen three times a week for bandage changes by a hospital wound nurse. The many encounters between the researcher and the participants, combined with the intimacy of intensive interviewing, provided a deep understanding of the participants' lives compared with what a single structured or informational interview would provide.[28,31]

The semi-structured interviews were audio recorded and took place either in person or by phone. Throughout the data collection period, follow-up interviews were scheduled as needed for theoretical development. Interviews occurred in the participants' homes, at the hospital bedside, in the waiting room in connection with the follow-up visit to the clinic, or in an undisturbed room at the hospital.

In all initial interviews, the project was introduced by the phrase: "I'm interested in knowing how your everyday activities are affected by your diabetic foot ulcer." The participants' responses revealed their concerns. Further questions elicited information about their daily routines and relationships and whether and how they were affected by the restrictions caused by the DFU. In accordance with the theoretical sampling method, the interview guide was customized as the analysis developed from one interview to the next.[28] The short-term ethnographic observations[32] were conducted in the outpatient clinic, focusing on the participant's behaviour and the contexts in which they took place. Observations

were short and closely linked to a 30–45-minute appointment in the outpatient clinic followed by an interview with the participant. The combination of observations and interviews aimed at comparing the observed behaviour with the participants' narratives, thereby gaining analytic direction to pursue in the study.[28] For instance, observing participants' reactions and interactions when faced with wearing offloading shoes enabled concrete focus and the opportunity to dig beneath the surface in the following interviews.[28] Observations were performed by the first author who focused on the participant's behaviour when interacting with the multidisciplinary team. Although the observations included the entire multidisciplinary team, the doctors were sometimes out of the room, as were podiatrists for fitting and manufacturing the offloading shoes. Observations followed the grounded theory methods and were without the use of a checklist and unstructured yet concentrated on the basic social process of participant interactions. This helped to gain a more complete picture of the whole setting and to follow up on emergent patterns and problems in real-time.[28] Field notes included observations of informal conversations between participants and health professionals. Memos were written throughout the analysis process to document thoughts and ideas on the definition of subcategories. Data from field notes and transcribed interviews were analyzed together.

The first author is responsible for the data collected in the 33 interviews, each lasting between 30 and 180 minutes, the field notes based on 18 observations, and memos of theoretical reflections and insights. Following the digital recording, the interviews were transcribed verbatim and managed using NVivo 12 software (http://www.qsrinternational.com), as were the memos and field notes.

Data analysis

Before coding, the interview transcripts and field notes of observations were read multiple times to understand the nuances of the participants' narratives.[28] The first coding involved line-by-line coding using gerundial constructions[33] to characterize behavior related to the research questions: "What are the main concerns of people with a DFU regarding their physical activity?" and "How do patients' concerns change during their time as outpatient DFU patients?" The first author identified and assigned gerunds to the data using in vivo codes where possible. The codes help preserve the participants' intended meanings as expressed in speech and action.[28] This strengthened theory development and the credibility of findings by accurately representing the participants' meanings. The use of in vivo codes to capture the participants' exact words or phrases also reduced the risk of researcher bias by importing existing theories or preconceived opinions into the analysis.[34] As an example, the code "Limiting my freedom to drive" was based on the words of Participant 3, "It limits

my freedom because I can't go for a drive." Further data were collected, line-by-line coded, and compared using the constant comparison method until four subcategories were constructed: *Restricting my freedom; Trusting or doubting the system; Feeling no pain or illness;* and *Receiving insufficient information (table 1)*. In line with the constructivist grounded theory methodology, theoretical sampling ceased when the constructed subcategories were saturated and further data appeared not to contribute any new knowledge to the emerging theory.[35,36] Through continuous and systematic comparison of categories during memo writing, the analytic conceptualizations reached higher levels of abstraction, as shown in Figure 1. The construction of the grounded theory "just a bump in the road" was based on observations of the participants' behaviors regarding activity after referral to an outpatient clinic for DFU care.

Table 1. The process of analysis and coding.

Code	Category	Grounded theory
Staying positive, I am not feeling sick Feeling no pain Walking on a broken foot without pain Having a lot of diabetes	Feeling no pain or illness	Just a bump in the road
Being a patient expert Doing what I am tolled Having little faith in nurses Being loyal to the hospital	Trusting or doubting the system	
Being overwhelmed Refraining from walking as much Nobody tells me anything Failing to understand restrictions.	Receiving insufficient information	
Limiting my freedom Keeping high spirits Fearing not being able to walk Loving being barefooted	Restricting my freedom	

Ethical considerations

The study complies with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (approval number: REG-036-2021). The study was presented to the Regional Ethics Committee, which decided that we did not need further ethical approval to proceed with the study according to Danish law (approval number: 20-000013). All participants received oral and written information on the study and were informed of their right to withdraw from the study at any time. Participants provided written consent before data collection commenced. All data were deidentified and coded, and a pseudonym was allocated to each participant during data analysis.

Qualitative rigor

Initial data collection and analysis were undertaken by the first author, followed by the last author's independent review of the procedures. Any differences concerning coding and theme identification were overcome through discussion, further improving the rigor of the study.[37]

The two researchers met regularly to discuss expansions and modifications of the coding framework as it evolved during the initial phases of data analysis. At each meeting, the first author introduced to the last author cases he believed to represent emerging categories. Based on their reflective notes to help clarify both established and new themes, the authors reached a consensus.

Patient involvement

Contributions from patient partners were included at several stages of the research process. A pilot study involved focus group discussion with several people with either a history of a DFU or an active ulcer convinced us of the importance of this grounded theory study (unpublished data). Patient information material and initial study questions were discussed with two patients to validate the relevance of the study and ensure successful recruitment. A draft interview guide received crucial feedback from two patients and their families. One visited the clinics with a healed ulcer after three to four years of regular controls and one patient with his wife was referred to the clinics for the first time. They agreed on the key importance of maintaining everyday routines, such as driving.

FINDINGS

"Just a bump in the road"

The construction of the grounded theory "just a bump in the road" was based on the main concerns and activity behavior of people with a DFU after referral to an outpatient clinic for DFU care. The phrase was used to indicate that people with a DFU interpreted their ulcer as a passing phase or something that they needed "to get done with", which testifies to their strong efforts to resume a normal life.

The four subcategories of the grounded theory describe patient's behavior and underlying concerns as they related to daily activities: *Restricting my freedom; Trusting or doubting the system; Feeling no pain or illness* and *Receiving insufficient information.* Each category outlines a different aspect that either limits or reinforces patients' perception of the wound as merely a passing phase in their lives. Figure 1 illustrates the grounded theory and its embedded categories.

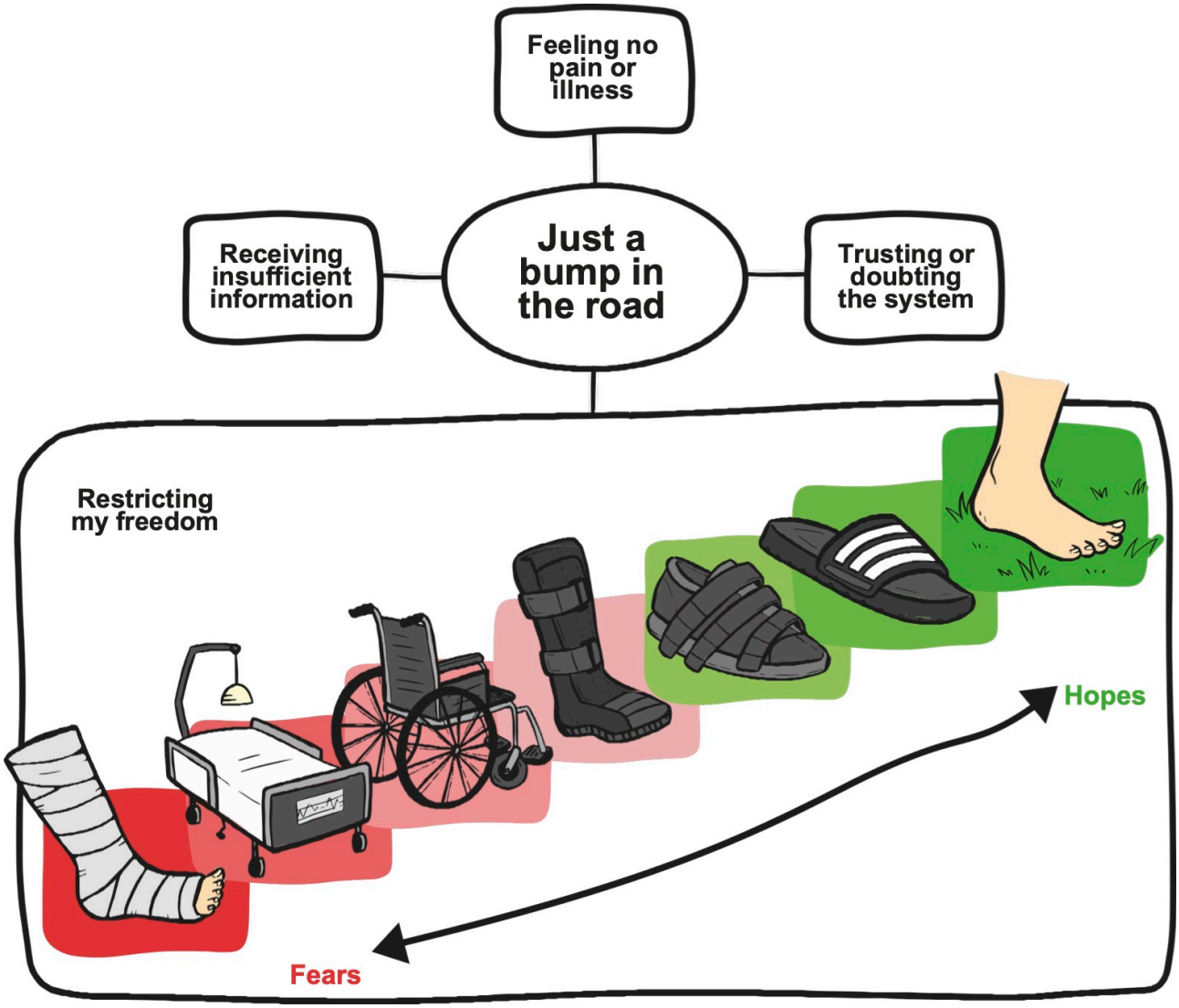

Figure 1: A visual representation of the grounded theory "Just a bump in the road". The figure both describes categories and their relationships while highlighting through images the lived representation of hopes and fears that participants meet.

Restricting my freedom

The in vivo coded subcategory *Restricting my freedom* expresses the participants' reactions to the offloading regime prescribed by the DFU clinic. Figure 1 illustrates their perception of escalating restrictions and that, although their experience of the problem varied, they shared many hopes and fears. The participants' descriptions of their expectations before follow-up visits were surprising; for example, while the lower left extreme of the continuum might be expected to show a bedridden person, being put in a cast that would make walking impossible was the most dreaded outcome. From one follow-up visit to the next, the participants described their hopes and fears relating to the imposed

level of restriction. The images in the top right corner represent the participants' recollection of normal activities (e.g., walking barefoot or in slippers).

Participant 3 said, "I just hope they won't put me in a cast. I'd rather they didn't, because then I can't walk… I can't move." Immobilization in a wheelchair or bed was acceptable only if walking was perceived as impossible. The same participant continued, "I'd stay in the wheelchair if I was unable to walk. Otherwise… heck, I'd walk a little. That's what I'm thinking!" A walker boot severely restricted the person's freedom of movement. Questioning the purpose of the prescribed boot, some participants spontaneously refused to wear it as they found it too extreme. Despite their difficulties with walking using the boot, they reported that they had resumed their normal daily lives, which had caused Participant 3 to fall on two occasions: "Being a smart-aleck, I tried to walk in some reeds on a bathing pier […] so I fell. I could hardly get up again, but I had to see them [the grandchildren] sail off, you know."

For most participants, the ability to drive an automobile was closely associated with a sense of freedom. As the boot made this impossible, some chose to discontinue using it in situations where they felt forced to drive, while others relied on help from family and friends for visits to municipal offices or the hospital. This created a feeling of being a burden to others. The boot caused physical restrictions as well as emotional burdens. The stigma associated with the boot or the therapeutic sandal was sometimes experienced as worse than the physical restrictions. Participant 5 said, "I look like someone with a disability. That's not how I perceive myself." This made Participant 5 take off the prescribed shoes and immediately order a pair of ordinary shoes from an orthopedic shoemaker while placing the prescribed shoes in a closet. The participants consistently expressed their wish to return to normality and followed it up by resuming their accustomed activities. One participant with a newly formed foot wound described having walked barefooted "quite a bit" at home. Ignoring the risk of developing a new wound, Participant 5 spontaneously rejected the idea of throwing out his entire collection of normal sports shoes, saying, "I've been a [US] size 10 for the past many years. I will return to that again." The participants' descriptions of returning to their former behavioral selves, with no acceptance of the prescribed offloading regime, support the link between the Restricting my freedom subcategory and the grounded theory of "just a bump in the road".

<u>Feeling no pain or illness</u>

The subcategory named *Feeling no pain or illness* captures the participants' perception of their feet and the ulcer as well as their behavior after referral to the DFU clinic, when hospitalized or asked about the future, the expectations for wound healing, and the risk of amputation.

The sensory loss related to neuropathy was a prominent symptom in all included participants. Some had received the diagnosis on their recent first visit to the clinic, others had lived with it for several years. We found no association, however, between a neuropathy diagnosis and the participants' consideration of their condition. Like most of the patients, Participant 4 had continued his previous level of activity, explaining that "as long as the ulcer is not painful, I have no sense at all of being ill." Even when faced with hospitalization due to an infected foot ulcer, the participants struggled to grasp the potential severity of the situation. As Participant 1 argued, "But I don't feel ill … I know this may sound rude but lying here [in the hospital] feels kind of a waste of time." Like everyone else, Participant 2 excluded the possibility of hospital admission and tended to be unaware of the ultimate consequences of an ulcer: "Oh no. No, I don't suppose they'll admit me just because of that [the ulcer]." Ignoring the risk of amputation or death, Participant 3 said that losing her leg "would probably [make me] worry, but that's not going to happen, not unless the wound gets bigger. […] I won't die because of my foot. It's not like it's cancer or anything like that." The absence of pain or the sense of being ill appeared to make the participants describe their perception of their foot as the same, whether they had spent a whole day in bed or walked 10,000 steps. This reinforced the patients' notion that the DFU was truly "just a bump in the road".

<u>Receiving insufficient information</u>

The participants felt that the information offered by the health care staff was insufficient, whether this concerned wound prognosis, guidelines on movement restriction, or plans for visits to the clinic. For most, the information gap had been apparent from the very first visit. In some cases, information failed to be communicated, in other cases, it was phrased in ways that the participants found incomprehensible. The participants felt at a loss about how to use the prescribed offloading device. Participant 3 said, "I'm not allowed to walk that much, but what does *as much* mean?*"* In practice, this led patients such as Participant 1 to create their own rules: "I was given these therapeutic sandals. I interpret this as though I'm allowed to walk again". One participant had reduced his daily walking from 4–5 km to 1–2 km. This was felt as a great sacrifice in his daily life as walking energized and kept him fit and sane enough to face his five weekly dialysis sessions.

Others said they had received no information from health professionals on the risk of amputation or death caused by DFU, yet participants did not actively try to get information from the healthcare staff. Observations supported this, as the dynamics of physician-patient relationships and communication were seen as one-way only. In the subsequent interview, Participant 3 expressed her sentiment by saying: "You don't want to cause trouble, do you?" Describing the dilemma between wanting to hear the truth about the severity of their situation and sensing that such a conversation would be taboo.[38] Participant 4 expressed it this way: "If they don't take it seriously, why should I?" As the severity was toned down, the participant's perception of the wound as "just a bump in the road" was reinforced.

Trusting or doubting the system

Trusting or doubting the system describes the participants' experience of facing a dilemma during their visits to the diabetic foot clinic. They said that even if the information was unclear, they always appeared for hospital appointments, frequently out of respect for the physicians who had allotted time for them. As Participant 3 said, "I faithfully show up because they set aside time for me, you know." Over time the loyalty turned into doubt in the system as the wound failed to heal. Participant 3 continued, "I think it's pretty much a waste of time, but I guess it's also because I believe they can perform miracles up here – but of course, they can't." This distrust led some participants to assume care of the wound themselves, occasionally with catastrophic outcomes, as described by Participant 4. After one week, his toe had grown in size and become red with infection. Desperate and hoping for the best, he had doused the wound with alcohol but finally had to call the outpatient clinic, where the wound care nurse told him to either seek his family physician or come to the emergency room if he was worried. The reaction led him to reason that, "if the nurse was no more worried than that, then I thought it would be okay." The patients went from trusting the treatment regime to doubting the system as their wounds failed to heal, which may have attenuated their treatment adherence and led them to focus on resuming their normal lifestyle.

DISCUSSION

This study provides a unique insight into the concerns of participants with a DFU after referral to care in an outpatient clinic. Documenting the participants' view of their DFU as "just a bump in the road", the relationship between subcategories describes how wound healing is inhibited as patients become oblivious of or ignore the severity of the situation.

Highlighting some of their concerns about the prescribed orthopedic boot or shoes, our study offers detailed insight into DFU patients' struggle to continue a normal active life. Our results corroborate those of Beattie et al., who studied people remaining at high risk of re-ulceration despite a healed ulcer.[39] The participants of our study described changing their clothes as the orthopedic shoes were unattractive and drew attention to their foot problems and suggested that risking what they called "a little ulcer" was preferable to wearing orthopedic shoes.[39] Kinmond et al. have reported similar concerning behavior by a male patient after 3.5 years with a non-healing DFU. In an attempt to regain a feeling of normality, he had ignored professional advice to rest his ulcerated foot in a wheelchair and decided to become mobile again regardless of the risk.[17] Although our findings are similar to those of previous research, our study offers an extension by showing that their longing for a normal life leads people to ignore restrictions at a much earlier stage of treatment than previously believed. Their motivations are expressed through the subcategories entitled *Feeling no pain or illness* and *Receiving insufficient information,* which may lead to what Campbell et al. have characterized as "strategic non-compliance". In the authors' synthesis of qualitative research on diabetes and diabetes care, they noted the patients' attempts to attain a balanced life with diabetes as "the thoughtful and selective application of medical advice rather than blind adherence".[40]

The experience of DFU patients distinguishes them from others with disabling conditions in that they are forced to deal with a DFU after having lived a relatively healthy life with diabetes for many years. The transition from being healthy to becoming ill offers a "before and after" experience that enables them to compare their present capability with what they could previously do.[41] The experience of being ill relates to both lived and objective bodily aspects, such as feeling pain from an open ulcer or a fractured foot. It relates to the body's objective and biological dysfunction[42]. Yet, the participants in our study did not describe their experience with a DFU as a bodily experience of pain or objective dysfunction. In fact, we are tempted to argue that people with a DFU judge the importance of their illness solely according to its physical noticeability and the degree to which it interferes with their life.[43] Meric et al. reported that although their participants had noticed a small wound developing on their foot, they had failed to associate it with diabetes.[27] This could likewise explain why the participants of our study missed the significance of their DFU and considered themselves fortunate that they had not contracted cancer. While it is not uncommon, the comparison with another disease may seem surprising, as has been previously reported by participants with diabetic polyneuropathy and a DFU.[43,44]

Our findings provide important additional insights into the experience of being a patient with a DFU and receiving professional healthcare. Although consulting diabetes health professionals is a familiar experience for many DFU patients, for most of them the condition involves a day-to-day life with self-managing "homework"[45,46] such as self-administration of glucose measurements, medication and/or insulin injection, and diet and exercise. Focusing on normality is key in the treatment of diabetes, which requires the "good patient" to make the medically recommended decisions in terms of diabetes self-management.[46] Considering it as abandoning normal life, health professionals view diabetes patients' passivity as unacceptable.[44] For participants with a DFU, this is in direct contrast with what is expected. Although the amount of expected self-managing homework is rarely specified, health professionals expect participants to take no part in the DFU treatment and leave the changing of bandages to them. Likewise, highly restrictive protective footwear is handed out with little guidance on usage. Prescription footwear is often prescribed to protect participants' feet, but According to Tan et al., the patient often views the effect of protective footwear as uncertain.[47] The many contradictory messages conflict with the norms and freedom that defined participants' lives before the DFU. The wish of being seen as a patient expert could explain patients' behavior categorized under the subcategory *Trusting or doubting the system* as the response from participants to maintain their former role.

The "just a bump in the road" theory helps us understand patients' behavior and underlying concerns when they are referred to outpatient DFU care. The theoretical concepts could prove useful when professionals support patients in coping with their situations. As the ranking of an illness by participants can influence how much attention and treatment it receives, this could go some way in explaining the widespread problem of nonadherence to treatment which has been established by previous studies of people with DFUs.[24,48–51] The results of our study indicate that since they are given no clear or meaningful recommendations on the amount of activity with the restrictive footwear, patients find the term adherence (or nonadherence) meaningless.

The grounded theory of "just a bump in the road" could shed new light on the behavior of DFU patients. Adapting the treatment according to the improved understanding of their behavior could ensure better compliance and more efficient treatment. As argued by Toombs,[52] if "therapeutic goals are to be optimally effective—and suffering is to be relieved—attention must be directed to the patient's perceived lived body disruption rather than being exclusively directed towards the objective pathophysiology of the disease state''. It is to be hoped that a more efficient overall treatment would result from a shift in focus – from seeing patients as simply their wounds to seeing them as people.

Healthcare staff professionals should be aware that there might be an information asymmetry between healthcare professionals and patients.[53,54] Living with diabetes involves having homework daily, sometimes for many years and although many have been given information on diabetes complications for years, they might still be unaware of the dangers that a DFU might cause over time. People living with a DFU, do not always actively express the need for information and guidance on why restrictions sometimes might be relevant. What consequences restrictions might have for the individual? And how these should be implemented in the person´s life.

This study has some limitations. Its sample size was small and based on the inclusion of only two hospitals. A larger sample and the inclusion of multiple hospitals may have yielded greater variation in participants' ages and physical, social, and cultural backgrounds. This study used multiple interviews with the same participants and included participant observations to gather more in-depth data,[55] and had a narrow focus on participants' behaviour in the first treatment period[28,56] thus developing a micro-level theory[57] and the analysis indicated that the point of theoretical saturation was reached.[58–60] To increase the study's validity, data were collected from a heterogeneous sample of patients the first author, who became intimately familiar with the settings through a combination of observation and interviews. In qualitative studies, preconceived ideas may influence data collection and analysis. To minimize this risk and increase validity, the last author assisted in the analysis of data and read all coded data.

On their first visit to the clinic, the study participants either had been diagnosed with neuropathy or received the diagnosis on that occasion. Although neuropathy is a well-known symptom of long-term diabetes with population rates of up to 79%,[8] the results of this study may not be valid for patients without neuropathy or those with painful neuropathy. Furthermore, as the participants were included after their referral to outpatient DFU care, the data are transferable [28] only to the first treatment period, and it remains unclear whether the findings of this study persist or change over time with a DFU and/or would be the same for patients with recurrent DFUs treated in the same outpatient clinic.

CONCLUSION

Supported by its grounded theory based on the "'bump in the road" epithet, this study provides a unique insight into the concerns and behaviors of people with a DFU after referral to an outpatient clinic for the care of their diabetic ulcer. The phrase indicates the patients' view of their condition as merely a passing phase after which they will strive to regain what they consider a normal life. We show the usefulness of the theory's subcategories to health professionals whose job it is to support

people with a DFU and hope that this contribution to explaining patients' reasoning can help prevent professional advice from being disregarded.

Declaration of Conflicting Interests

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Authors' contributions

The study was designed by TAA, URM, STS and SB. Data collection was performed by TAA. Analysis and draft of the manuscript was performed by TAA, supervised by URM. Critical revisions for important intellectual content were provided by URM, STS and SB and all authors agreed on the final version of the manuscript.

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Paper 3

Case Report

A 12-Week Supervised Exercise Therapy Program for Patients with Diabetic Foot Ulcers: Program Development and Preliminary Feasibility

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Abstract

Exercise therapy helps improve glycaemic control and insulin sensitivity and may be relevant in treating patients with diabetic foot ulcers (DFUs). This study describes the development of a 12-week exercise therapy program for patients with DFUs and the preliminary feasibility of the program focusing on the program's inclusion, adherence, and safety. The development process is built on knowledge from a published systematic review on exercise for people with DFUs and a grounded theory study on the main concerns of people with DFUs regarding physical activity. The development involved doctors, wound care nurses, podiatrists, and feedback from patients and physical therapists using semi-structured interviews. The program was designed as a combination of aerobic and resistance training exercises. The aerobic exercise phase on the stationary bike of 30-minute duration was aimed at a moderate intensity. Resistance exercises were conducted with a 15-repetition maximum approach (four to five sets per trial) throughout the 12-week period. Three patients were included and received the exercise intervention. Except for recruitment and retention rates, acceptance levels were met for all other research progression criteria. Patients found the intervention relevant, wanted further guidance on continuing exercising, and would have liked the intervention closer to their home for example, a municipality setting. Although the exercise therapy program for patients with DFUs was developed in a thorough process with the inclusion of available evidence and the involvement of patients and other stakeholders conclusions on feasibility are limited due to the low recruitment rate. A reconsideration of the setting is needed in future exercise intervention studies.

Keywords

diabetic foot ulcers, lower extremity wounds, health-related quality of life assessments, wound assessment

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Background

Diabetes mellitus is associated with retinopathy, nephropathy, peripheral artery disease, heart disease, neuropathy, and diabetic foot ulceration (DFU). DFU is the most common and feared complication of diabetes and is associated with amputation and death.[1,2] Patients living with a DFU are often required to refrain from bearing weight on their affected limb,[3] leaving some patients immobile for weeks, months, or even years.[4] Such immobility contradicts diabetes guidelines, where exercise therapy is a cornerstone of treatment.[5] Living with restrictions on activity and movement is hard to accept by patients[4,6] who might ignore the severity of the situation and thus regard having a DFU as a "bump in the road" in their life (Aagaard 2021, unpublished manuscript, August 2022).

Guidelines for treating and preventing diabetic foot complications from the International Working Group on the Diabetic Foot (IWGDF) include the management of diabetes, integrated foot care, patient education, and self-management of foot care.[7] These guidelines do not include physical activity and exercise, despite their importance in the treatment of diabetes.[8] On a biological level periods of exercise have been found to lead to a significant improvement of important ulcerative risk factors,[3,9,10] and play a supporting role in wound healing of healthy human adults and patients with chronic leg wounds[11–13] as long as the adherence rates to exercise are high.[14] Including exercise therapy in the treatment of a DFU could be relevant since it helps improve glycaemic control and insulin sensitivity, blood pressure, cardiovascular events, and mortality rates[15,16] and has been found to increase health-related quality of life (HRQoL) in people with diabetes.[8] The latter is of key importance to people with DFUs, as living with DFU has been reported to be associated with reduced mobility, depression, and overall low HRQoL.[17–19] Nonetheless, recent systematic reviews published on the benefits and harms of exercise therapy for patients with a DFU[20,21] conclude that the safety profile of exercise in the management of DFUs is unclear since the current quality of evidence is low and based on randomized controlled trials with a high risk of bias. Moreover, different exercise regimens have previously been prescribed and adherence to exercise is low or unclear.[20] This diversity and lack of consensus on the optimal exercise prescription is not surprising given a historical DFU treatment recommendation of bed rest and/or wheelchair use[22] and avoidance of weight-bearing in general.[3] This study aimed to describe the development of a 12-week exercise therapy program for patients with DFUs and the preliminary feasibility of the program focusing on the program's inclusion, adherence and safety.

Methods

Study Design

The development process followed the Medical Research Council guidance for the development of complex interventions[23] and was reported according to the Guidance for the reporting of intervention Development (GUIDED) recommendations.[24]

A feasibility study with pre-determined progression criteria based on recommendations for designing high-quality feasibility studies[25] was planned. However, we only succeeded in including three patients, limiting any conclusions on feasibility. Hence, in this paper, we only report on the methods and results of the semi-structured interviews with patients and physical therapists. To increase transparency, the methods of the planned feasibility study and the preliminary results from this are presented in appendix 1

Exercise Therapy Program Development

The development process included a systematic review of existing literature on exercise for people with a DFU,[20] a qualitative grounded theory study on the main concerns of people with a DFU regarding physical activity (Aagaard 2021, unpublished manuscript, August 2022), and involved relevant stakeholders including DFU patients, doctors, wound care nurses, podiatrists, and physical therapists to integrate their needs and perspectives.

An initial 12-week supervised exercise program aiming to increase the blood flow and thereby oxygenation to the

Table 1. Expected Mechanisms of Action.

Aim	Mechanisms of action	Expected outcomes
To improve health-related quality of life with concurrent positive effects while not negatively influencing the size of the DFU.	Physical factors: improving blood flow to the DFU, balance, cardiorespiratory fitness, strength, and flexibility Psychological factors: encouraging adherence to an exercise routine and supporting activities of daily living and physical functioning.	Improved health-related quality of life Improved blood flow to extremities Improved muscle strength Improved physical function Improved self-rated health Reduced burden of illness

Abbreviation: DFU, diabetic foot ulcer.

peripheral tissue through cardiovascular fitness, strength, and endurance training[26,27] with as little weight bearing on foot soles as possible, as recommended by local wound care nurses, doctors, and Danish physicians[28] was developed in close collaboration with the authors and four clinical physical therapists with 3–21 years of experience in the treatment of post-operative and acute orthopedic rehabilitation, joint injury, and musculoskeletal disorders.

Based on physical therapists' discussions and pre-testing at the first intervention session, the two-legged knee extension was changed from using an elastic band to a weight manchet due to discomfort from the elastic band, and the fear of shear damage to the patients. Other than that, the exercise program was not changed from the initial version. Table 1 shows the expected mechanisms of action of the 12-week exercise therapy program.

Recruitment of Patients

The staff (doctors, nurses, and podiatrists) at the multidisciplinary outpatient wound care clinic screened patients with DFUs. Potential patients were contacted by the first author and invited to a physical meeting.

Inclusion Criteria. Patients with diabetes above 18 years of age with chronic DFUs located distal to the malleoli were considered for inclusion. Patients had to be prescribed a therapeutic sandal, or an orthopedic specialist shoe (see appendix 2) adapted to foot deformities with stiff outsoles and customized insoles offloading the DFU made by an orthopedic technician.

Exclusion Criteria. Patients were excluded if they had (1) dementia or other cognitive impairments; (2) gangrene, osteomyelitis, infection, or acute phase Charcot arthropathy in the index extremity; (3) were wheelchair-bound; (4) were prescribed with or using a walker boot; (5) were unable to understand Danish.

Infection was defined according to the criteria of the Infectious Diseases Society of America and IWGDF.[29,30]

The Number Needed to Recruit

Because effectiveness was not evaluated, a formal power calculation was not performed. Julious[31] recommend including 12 patients in feasibility studies based on the rationale for a feasibility study, regulatory considerations, and statistical considerations about a precise and representable mean and variance. However, to make sure that enough patients were included, a total of 15 patients were planned to be recruited.

Patient and Physiotherapist Interviews

Semi-structured interviews with the patients were conducted at the end of the 12-week exercise program. An interview topic guide with open questions on the acceptability of assessment procedures, treatment experience, and feedback about the supervised sessions and potential adverse events was used. The themes that emerged during the interview were followed by probing questions and if needed, the interviewer made the open-ended question more focused, for example, "Which changes in your daily life (if any) have you experienced after finishing 12 weeks of exercising?." Physiotherapists were continuously interviewed after each exercise session and at the end of the 12-week exercise program. Their interview response covered whether specific exercises were applicable to this population, including handling the progression of exercise intensity and exercise and load modification. Finally, both patients and physiotherapists were asked whether they would participate in an exercise therapy program again and asked to suggest potential improvements to the study design and procedures. All physiotherapist and patient interviews were conducted in Danish. Data was recorded through notes and descriptive field notes and qualitative content analysis[32] was used to analyse the data. Each interview was conducted behind closed doors and lasted between 30 and 60 minutes. All interviews were conducted by the first author.

Results

The Final Exercise Therapy Program

The description of the exercise therapy program adheres to the template for intervention description and replication checklist[33] and the Consensus on Exercise Reporting Template items[34] (appendix 3).

The exercise therapy program was a 12-week group-based, supervised exercise therapy program (2 exercise sessions per week of 60 minutes each). Present at each exercise session for supervision was the principal investigator and one physical therapist member of the team. The program was designed as a combination of aerobic and resistance training exercises. Each exercise session started with a warm-up phase (10 minutes on a stationary bike with little to no resistance), followed by an aerobic exercise phase (20–25 minutes of interval-based cycling on the stationary bike) and finally strengthening exercises (two-legged knee extension, pelvic lift, lateral pull-down, biceps curl, and resistance band flyers and resistance band rows; appendix 4). The aerobic exercise phase on the stationary bike of 30 minutes duration aimed at a moderate intensity (Heart rate intensity 40%–60% or rating of perceived exertion: somewhat hard) as recommended to people with peripheral neuropathy.[35,36] To measure dyspnoea and perceived exertion during the stationary bike session the Dalhousie Dyspnoea and Perceived Exertion Scales[37] were used due to their additional pictorial scale to depict leg exertion/fatigue, which was key since some DFU patients undergo surgical

treatment with Achilles' tendon lengthening and gastrocnemius recession[38] and the effect of stationary cycling after this treatment is unclear. Resistance exercises were conducted with a 15-repetition maximum approach (four to five sets per trial) throughout the 12-week period. Since the patients were untrained and novices in the exercises, light loads coupled with higher repetitions to increase aerobic power and muscular endurance were used.[39,40] During the exercise sessions, the physical therapist gave the patients feedback to ensure proper performance of the exercises and to maintain their motivation. Patients were encouraged to increase speed and/or resistance on the stationary bikes as well as to progress training loads during the strengthening exercises while maintaining proper technique as assessed by the physical therapist.[40] Any adverse events were registered at the start of each exercise session and patients were instructed to check their feet on the night after the exercise session. Feedback on the 12-week period from patients covered municipality podiatrist's visits, outpatient visits at the hospital, home nurse visits and self-monitoring from patients.

Patient Inclusion

Fifteen patients were assessed for eligibility from September 1, 2021, to April 1, 2022, and three male patients were included (Figure 1).

The main reason for not being included was patients declining to participate ($n = 8$). When asked to elaborate, one was enrolled in municipality heart and post-surgery rehabilitation programs, five found the planned 24 exercise sessions and the travel times twice a week, too burdensome whereas two were in jobs that made participating during daytime impossible.

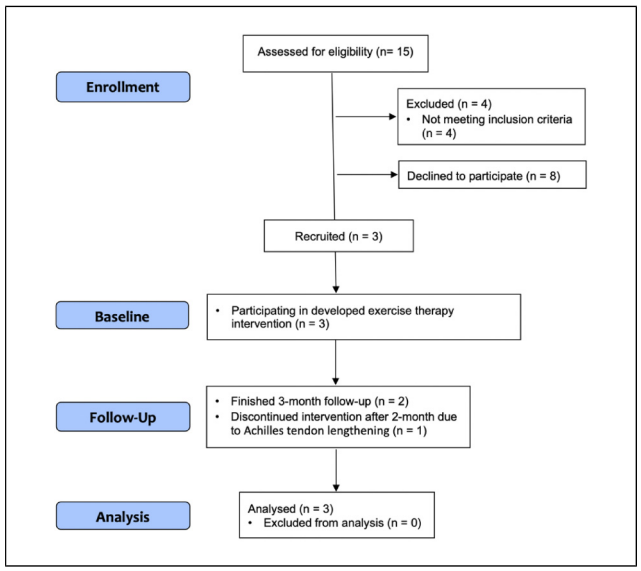

Figure 1. The CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

The demographic characteristics of the three included patients are presented in Table 2 and the preliminary feasibility outcomes can be found in appendix 1.

Patient and Physiotherapist Interviews

None of the patients had been offered exercise therapy throughout their time with a DFU before this study, and although some patients found the exercise therapy demanding, they all found it relevant. All three patients found exercise therapy two times a week appropriate but would have liked the exercise period to span for more than 12 weeks. At the end of the study, all three asked for advice on how and where to continue their exercise routines. When asked, all patients agreed that they would have preferred that the intervention took place closer to their home for example, a municipality setting.

When asked about the timing of the exercise intervention and their DFU history and treatment, all patients stated, that they were more mentally ready to participate in exercise now, than at the DFU debut. They reported somewhat negligence regarding what bodily consequences a DFU might give them over time, hence they had high hopes for complete healing after initial representation in the clinic.

All patients stated that doing regular exercise twice a week, gave them more energy and boosted their capacity. One patient resumed his passion for bowling 6 weeks into the study, whereas one decided to spend one-weekend cycling 10 km to test his bodily "limits" resulting in delayed muscle soreness for one week thereafter. He later stated that he would have only done so, after regular cycling on a stationary bike, and ongoing progression in the study.

The patients described that the physical therapists were supportive and ensured that the exercise therapy program was pro- and regressed the individual patient when needed. The patients considered the individual exercises feasible, relevant, and effective. The ongoing supervision was found important by patients, hence physical therapists could adjust the exercises if performed incorrectly. Although, physiotherapists described the patients: "as any other untrained geriatric patient with little exercise motivation and technique." They described patients' neuropathy and fear of inflicting a new wound on patients as a key focus in exercise situations. One described that she had to be "the patient's extra set of eyes" when performing exercises to ensure that patients did not accidentally fall or bump into things.

Discussion

This paper outlines the process undertaken to develop and evaluate the preliminary feasibility of a 12-week exercise

Table 2. Demographic Characteristics.

Variable	Pt. 1	Pt. 2	Pt. 3
Gender	Male	Male	Male
Age, years	78	63	70
Body mass index, kg/m^2	28.4	33.2	24.8
Diabetes type	2	2	2
Duration of diabetes, months	300	252	192
Duration of DFU, months	29	4	3
History of DFU, numbers/healed	3/3	3/3	3/3
Disease history	Diabetic peripheral neuropathy Hypertension Hyperlipidemia Erysiphales Skin cancer	Diabetic peripheral neuropathy Atrial fibrillation Hypertension Apoplexy cerebri	Diabetic peripheral neuropathy Hypertension Orthostatic hypotension
Prior surgery of index foot/leg	2 × Achilles tendon lengthening Percutaneous tenotomy of facia plantaris	1 × Achilles tendon lengthening Percutaneous tenotomy of facia plantaris	2 × Achilles tendon lengthening Percutaneous tenotomy of facia plantaris
Exercise history	No	Apoplexy cerebri rehabilitation	No

therapy program for patients living with a DFU. The developed exercise therapy program included a combination of aerobic and resistance training exercises. However, conclusions on feasibility are very limited by the low recruitment rate, a reconsideration of the setting is therefore needed in future exercise intervention studies.

The recruitment rate in this study did not meet the predetermined progression criteria. Similar recruitment issues have been found in other exercise studies on DFU patients.[41,42] One potential reason for the low recruitment rate might be due to "gatekeeping" from the healthcare professionals identifying and approaching patients.[43] Skepticism from the recruiting healthcare staff on the safety of exercise for DFU patients might have restricted access to patients who were potential trial patients. A way to identify if healthcare professionals engage in gatekeeping is through qualitative research. Hence, this can help develop information to guide recruiting practices and address inappropriate "over caution."[43] Another reason could be the hospital setting far from patients' homes and the time of day offered for the exercise intervention. Feedback from included patients, eligible patients declining to participate and research on people living with multimorbidity[44] indicates that these are barriers to engaging in exercise. Further testing is required to explore the best possible exercise setting for patients with a DFU and ways to improve inclusion rates.

Even though the interviews and ongoing feedback from patients and physiotherapists did not result in many changes to the exercise therapy program, they contributed key information and perspective on the program and future feasibility. First, individual exercises and progression were found relevant and effective. Second, supervision from physical therapists was considered important. Third, patients described finding pleasure and meaning in adopting exercise therapy in their weekly routine which, in turn, may have reduced the DFU burden by improving capacity as similarly reported in type-2 diabetes patients.[45] Fourth, physiotherapists' lack of knowledge in exercising the patient population indicates an educational need. And finally, the interviews highlighted the problem of the setting and thereafter recruitment issues and reinforced a need to rethink the setting in which exercise should be provided to this patient population.

A strength of the study is the standardized, transparent, and precisely described exercise therapy program for patients with a DFU that can easily be adapted for other settings[46] as well as the level of engagement and involvement from physiotherapists and supervision of patients during exercise interventions. As is the iterative development of the intervention with much discussion, questioning and refinement of individual components before they were brought together as a single coherent intervention. Although the development process is seldom reported[47] it is highly important to be able to understand the success (or failure) of an intervention and to enable potential replication.

The study has some limitations. The most important was that this study did not reach the target sample size due to challenges with recruitment limiting conclusions on the feasibility of the intervention developed. Considerations on improving this and including exercise in a more flexible setup to account for work hours or transport times should be a key focus in future studies as it will influence the future real-life implementation of exercise for this population. Secondly, only men with similar DFU complications were included in the study. DFU complications and comorbidities might

physically affect patients differently and thereby their ability to participate in exercise therapy as such, it is important to include individualized modifications to an exercise program. Thirdly, only patients using a therapeutic sandal or orthopaedic specialist shoe were included in this study. While the walker boot or total contact cast is considered the preferable method of off-loading in DFU parents. This inclusion criterion was guided by results from a qualitative grounded theory study on the main concerns of people with a DFU regarding physical activity (Aagaard 2021, unpublished manuscript, August 2022). Where patients describe their ability and willingness to participate in physical activity increased after using these off-loading devices.

Lastly, are the outcomes chosen in the study, hence no recommended set of outcomes was available for DFU patients and with the results being inconclusive further studies including qualitative research with patients[48] will be required to identify the outcomes most relevant for patients before future feasibility testing.

Conclusions

This study developed an aerobic and resistance exercise therapy program for patients with DFUs in a thorough process building upon a systematic review, a qualitative study and involving patient- and therapist feedback and other relevant stakeholders. Conclusions on feasibility are limited by the low recruitment rate, which calls for a rethink of future exercise intervention setups in the population. Future feasibility trials are required in which the developed program is adapted and tested in other settings to understand if exercise is feasible and relevant in the rehabilitation of patients with a DFU.

Ethical Considerations

The study complied with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (Region Zealand j.nr. REG-075-2021), the Regional Committees on Health Research Ethics for Region Zeeland (Region Zealand j.nr. SJ-928), and prospectively registered in clinicaltrials.gov (reference ID: NCT05101473).

Patients provided both oral and written informed consent before inclusion and the International Committee of Medical Journal Editors' Recommendations for the Protection of Research Patients were followed.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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Appendix

Appendix 1

Preliminary feasibility methods

Progression criteria

The preliminary feasibility programme included pre-determined a research progression criteria approach based on a traffic light system of green (continue without changes), amber (apply changes to improve study design) and red (no RCT unless major changes are applied) instead of a simple stop/go approach.[1]

The recruitment procedure was evaluated by comparing the number of patients at pre-screening with patients eligible for inclusion to identify reasons for exclusion, and the numbers needed to screen and optimize the eligibility criteria. The recruitment rate was analysed by dividing the number of included patients (n = 15) by the number of months it took to include them (calculated from the study start until the 15th patient was recruited). Patient retention was evaluated by the number of patients showing up at the 12-week follow-up. To evaluate exercise adherence, exercise logs completed at each session by the physiotherapist covering load and intensity were screened. Adherence was calculated by counting the number of exercise sessions completed in the exercise log, divided by 24 planned sessions, presented in percentage. Adverse events were registered at every exercise session based on patient-reported adverse events, and their relatedness to the index ulcer and the exercise program. Minor adverse events covered muscle soreness or post-exercise fatigue. Whereas serious adverse events covered all serious care-related adverse events.[2] Based on these research progression criteria (table 1), the feasibility and safety of the exercise program were evaluated, and decisions were taken on which amendments (if any) needed to be made.

Table 1
Progression criteria

Proceed with RCT	**Proceed, but changes to the protocol need to be discussed**	**Do not proceed with main trial unless the problem can be solved**
Recruitment of 15 patients with an active diabetic foot ulcer within 3 months	Recruitment of 15 patients with an active diabetic foot ulcer within 3-5 months	15 patients with an active diabetic foot ulcer within 5-7 months
At least 75% retention of patients through follow up	50-75% retention of patients through follow-up	Less than 50% retention of patients through follow up

Appendix 1

At least 75% complete more than half of the exercise therapy sessions	50-75% complete more than half of the exercise therapy sessions	Less than 50% complete more than half of the exercise therapy sessions and
Less than 20 % of patients find the exercise program so burdensome that they do not want to participate in the study again	20-40 % of patients find the exercise program so burdensome that they do not want to participate in the study again	More than 40 % of patients find the exercise program so burdensome that they do not want to participate in the study again
No serious care-related adverse events during follow up	Less than five serious care-related adverse events during follow up	Five or more serious care-related adverse events during follow up

Outcomes

Outcomes reported in diabetic foot research are heterogeneous[3–6] and no recommended set of outcomes is available. We, therefore, choose outcomes with little to no risk of harm to the patient's feet that would be easy to use in the clinic covering the gross motor bodily functions that could be affected by diabetes and the DFU.

The outcomes measurements included the 30-second chair-stand test[7] to test leg strength and endurance, the Guralnik Tandem Test[8] to evaluate standing balance, the 4x10-meter fast-paced walk test[9] for short-distance walking speed and change in ulcer size in cm^2 assessed on digital images with a standardized measuring tape.

The trial included two self-reported outcome measures. The Wound-QoL is a valid and reliable patient-reported outcome measure for assessing aspects of health-related quality of life in patients with hard-to-heal wounds.[10,11] The Wound-QoL consists of 17 items that can be combined into three individual multi-item domains: Body, Psyche and Everyday life.[5] The European Quality of life is a 5 Dimensions, Three-Level Scale (EQ-5D-3L).[12] The measure gives a score between 0 and 1, with 1 equalling full health and 0 equalling death. In addition, the EQ-5D- 3L includes the European Quality of life visual analogue scale (EQ-VAS) where the patient's health 'today' is rated between 0 (worst imaginable health) and 100 (best imaginable health).[12]

Appendix 1

Statistics

Baseline patient characteristics and wound characteristics are reported descriptively. Of the progression criteria outcomes, recruitment rate, retention rate, and rate of missed trial visits are reported in percentages (%). Self-reported and objective outcomes are reported descriptively and discussed in relation to the smallest detectable change and the minimal clinically important difference.[8,9,13,14]

Preliminary feasibility results

All three included patients participated in the exercise intervention. Two participated in the planned 12-week, whereas one participated in 8-weeks, after which he discontinued due to a prescribed Achilles tendon lengthening and was prescribed a total cast for 6-weeks. All three were included in the analysis, two with 12-weeks follow-up and one with 8-week follow-up.

Progression criteria outcomes

Except for recruitment and retention rate level of acceptance was met for all other research progression criteria (assessment of burdensome, adherence, adverse events) (table 2). During the first month, all three patients were recruited, but the recruitment rate stopped thereafter.

Combined, the three patients had an 83 % adherence to the prescribed exercise sessions. This was highly influenced by one patient discontinuing after 8 weeks; hence he had a completion adherence at 8 weeks of 88 % and both patients that completed the 12-week program had a 96 % completion adherence.

All three patients reported minor adverse events of short-lasting soreness in their Achilles tendon when cycling on the stationary bike, at the incision place of their previous Achilles tendon lengthening operation. One patient had an orthostatic hypotension episode in the first exercise week after transitioning to the standing position in the pelvic raise exercise.

Table 2
Research progression criteria

Participation recruitment rate (*n*/month)	0.4/month, 3 in total	Red (do not proceed)
Patient retention		

Appendix 1

Patients who completed the follow up (*n*, %)	2 (66 %) *	Amber (amend)
Adherence to exercise intervention		
Patients attending exercise program (*n*, %)	60/72 (83.3 %)	Green (go)
Patients that did not find the burden (%)	100 %	Green (go)
Adverse events		
Minor	4	Green (go)
Serious	0	Green (go)

* Based on 3 patients

The results of the included patients are presented in Table 3. All patients had a reduction in DFU size. Results on the functional outcomes of Sit-to-stand, Tandem test and 40 m walk test were all inconclusive, as were the subjective questionaries of EQ-5D and Wound-QoL.

Table 3
Changes in outcomes from baseline to follow-up

Variable	Pt. 1		Pt. 2		Pt. 3	
	Baseline	Follow-up*	Baseline	Follow-up	Baseline	Follow-up
DFU size, cm^2	2	0.7	2	0.5	3	0,7
Sit to stand	12	11	5	7	13	13
Tandem test, sec	11	10	3	29.6	30	30
40 m walk test, sec	37,35	41,83	50,99	50,91	26,29	26,68
EQ-VAS, 0-100	60	60	55	70	80	75
Index score, < 0-1	0,858	0,83	0,826	0,427	0,874	0,806
Wound-QoL	1.647	1.411	1.058	0.764	1.176	1.235

*2-months follow-up

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Appendix 2

Therapeutic shoe

Picture 1 - Used with permission from New Feet Medical footwear

Orthopedic specialist shoe

Picture 2 - Used with patient permission

Appendix 3

The Template for Intervention Description and Replication (TIDieR) and the Consensus on Exercise Reporting Template (CERT) checklist.

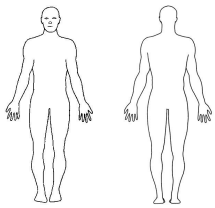
Item	Description
1. Brief name	Diabetic foot ulcer exercise therapy program
2. Why	The program will build on available evidence on exercise therapy(25) for people with a diabetic foot ulcer and through interviews with people, clinicians and other stakeholders.
3. What-materials	The intervention group will receive an exercise training programme developed for participants with a diabetic foot ulcer. This will in cooperation with the individual participant be tailored to any challenges that the participant might have. Precise details of both intervention content and the training programme will be developed in collaboration with physiotherapists at the Zealand University Hospital and people with a diabetic foot ulcer. The material will be made publicly available, when finalized and evaluated in a RCT.
4. What-procedures	The program will consist of 24 exercise sessions (two per week) during the 12 weeks. The 12-week program will be supervised to ensure that the participants learn a certain skill set to avoid adverse events when exercising. Furthermore, this will support them in understanding how and why they should continue exercising and being physically active. The exercise therapy programme will combine aerobic and strengthening exercises and will consist of a warm-up phase (e.g., on a stationary bike), a focused exercise phase and a cool-down phase. At the end of the 12 weeks, a strong focus will be on sustaining the motivation for continuous exercise and other behaviour change and activities and future goals will be discussed.
5. Who-provided	The exercise therapy will be delivered by physiotherapists.
6. How	Delivered face to face in groups and/or individually.
7. Where	At the physiotherapy department at Zealand University Hospital

Appendix 3

	The program will only require exercise equipment available in most gyms of hospitals and municipalities, ensuring feasibility of the future implementation of the intervention.
8. When and how much	24 supervised exercise therapy sessions will be delivered, each with a duration of around 60 minutes. Dosage (e.g., frequency, duration, intensity, level of severity) of the exercises will be adapted to the participant's abilities throughout the program to support progression and continuous improvements in symptoms during the 12 weeks. The progression will be guided using established tools such as the Borg scale(33) of perceived exertion for aerobic exercise and the +2 principle, i.e., when the participant is able to perform two additional repetitions in the last set, more weight is added and fewer repetitions per set are performed.
9. Tailoring	The program will be tailored to the conditions, characteristics and progression and improvements of the individual participant.
10. Modifications	Modifications will be reported (if any).
11. How well (planned)	Clinicians delivering the program will attend group discussions on the participant population and their characteristics throughout the intervention period to ensure program fidelity.
12. How well (actual)	This will be reported in the primary paper and focus on compliance and adherence to the program during the 12 weeks.

1. Stående cykel, siddende

OPVARMNINGEN BESTÅR AF 10 MINUTTERS CYKLING.
Opvarmningen består af 10 minutters cykling. Belastningen ind- stilles individuelt og må gerne øges gradvist undervejs. Målet er at opnå anstrengelse der svarer til ”nogenlunde hårdt”. Sadel- højden bør være indstillet, så knæene ikke strækkes helt. Du kan forvente at komme bedre igennem din træning, hvis du har varmet op.



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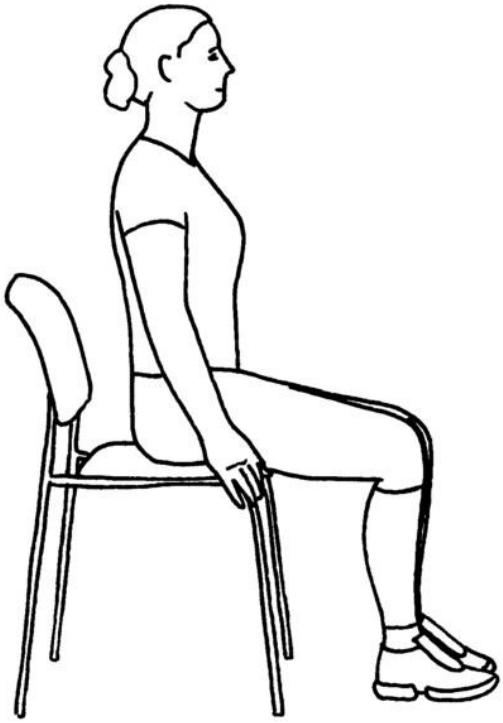
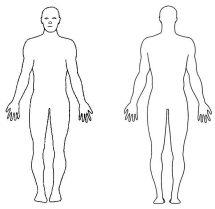


2. Siddende knæstræk

Sid på en stol/ bænk. Stræk knæene ud, et ad gangen så meget som muligt indtil smertegrænsen.



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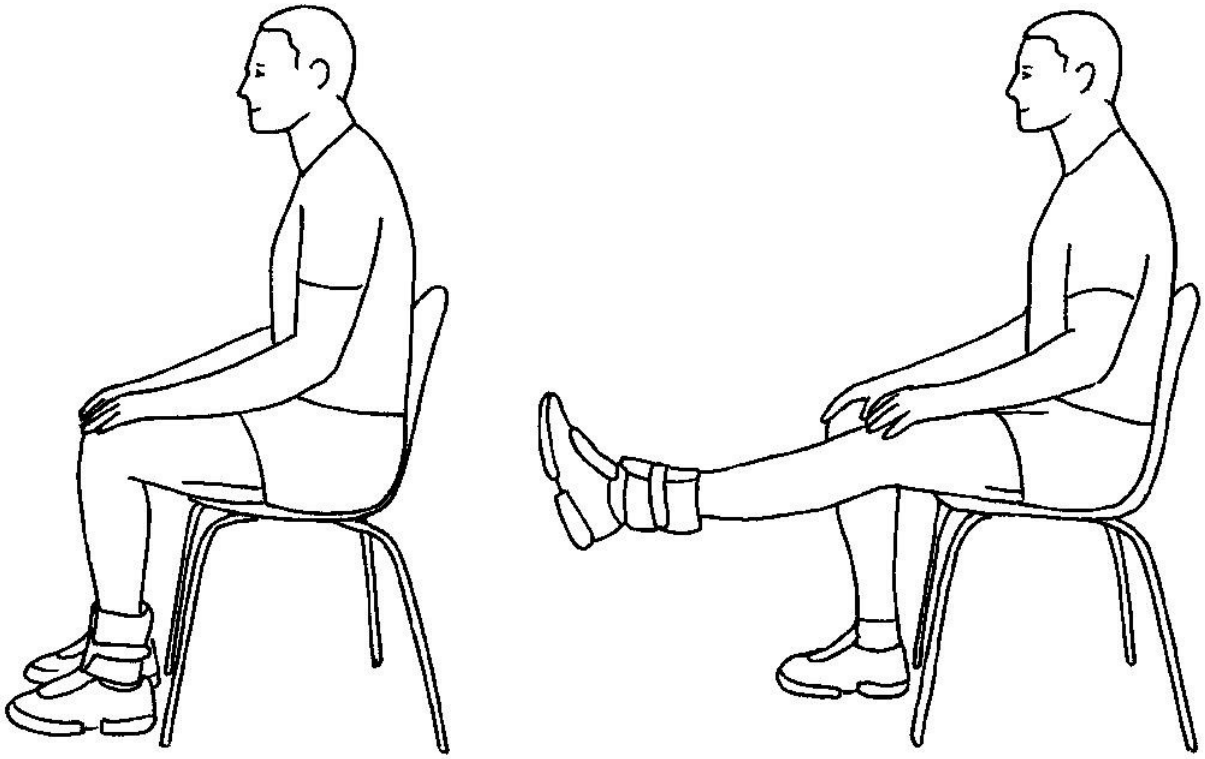
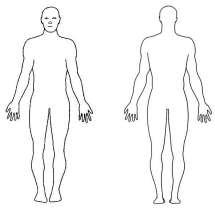


3. Siddende knæstræk med vægtmanchet

Sid på en stol med ret ryg og en vægtmanchet rundt om ankelen. Stræk ud i knæet. Sænk langsomt ned igen.



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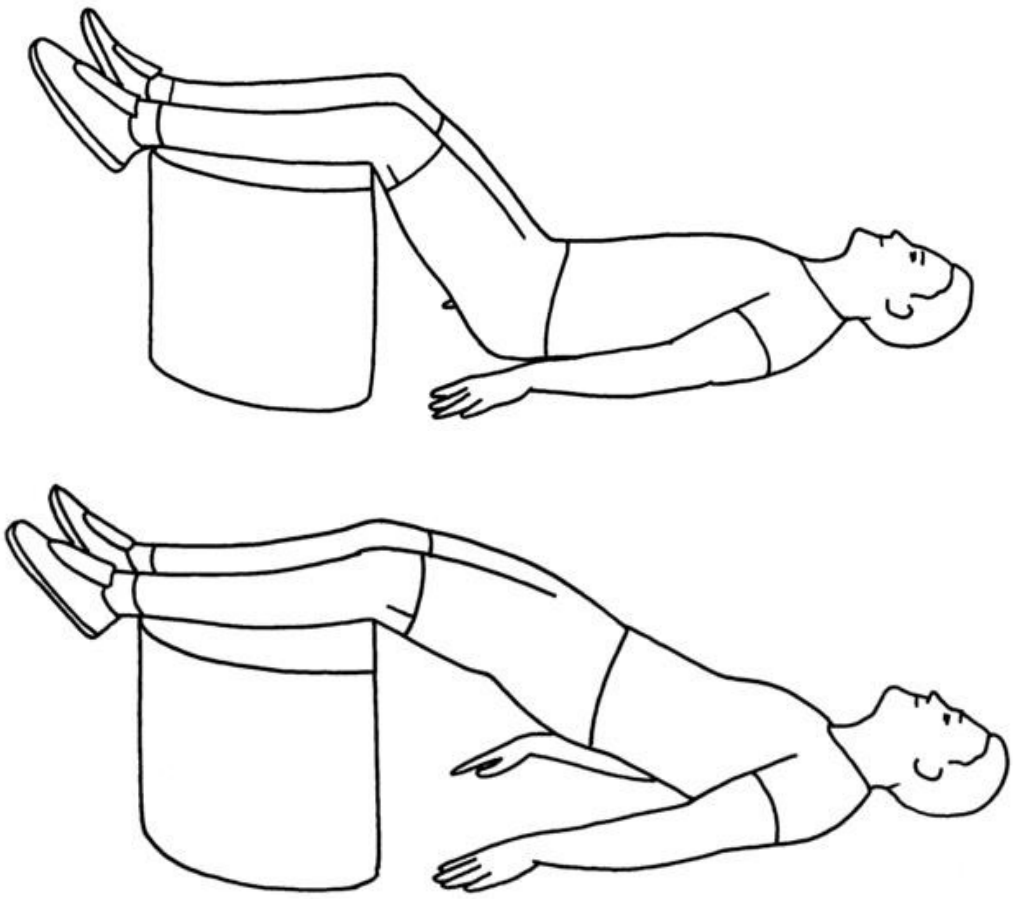
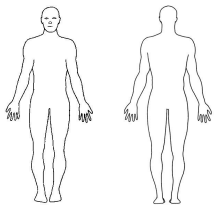


4. Rygliggende bækkenløft på psoaspude

Lig på ryggen med benene på en psoaspude. Hænderne ligger på måtten langs kroppen. Aktiver mavemusklerne. Løft bagdelen væk fra underlaget og stræk ud i hofteleddet. Sænk kontrolleret ned igen.



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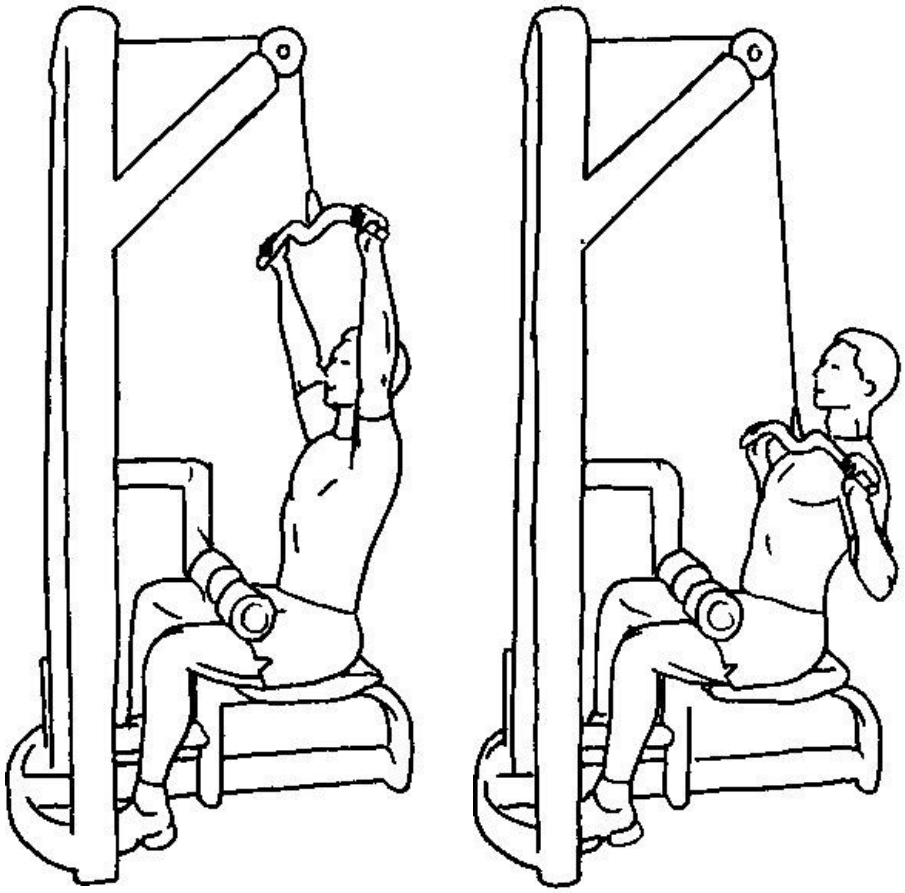
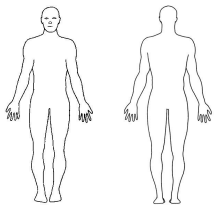


5. Træk til bryst

Tag et bredt greb, læn dig lidt bagud og kig skråt op. Skyd brytskassen frem og træk stangen ned til brystet. Vend roligt tilbage til udgangspositionen og gentag.



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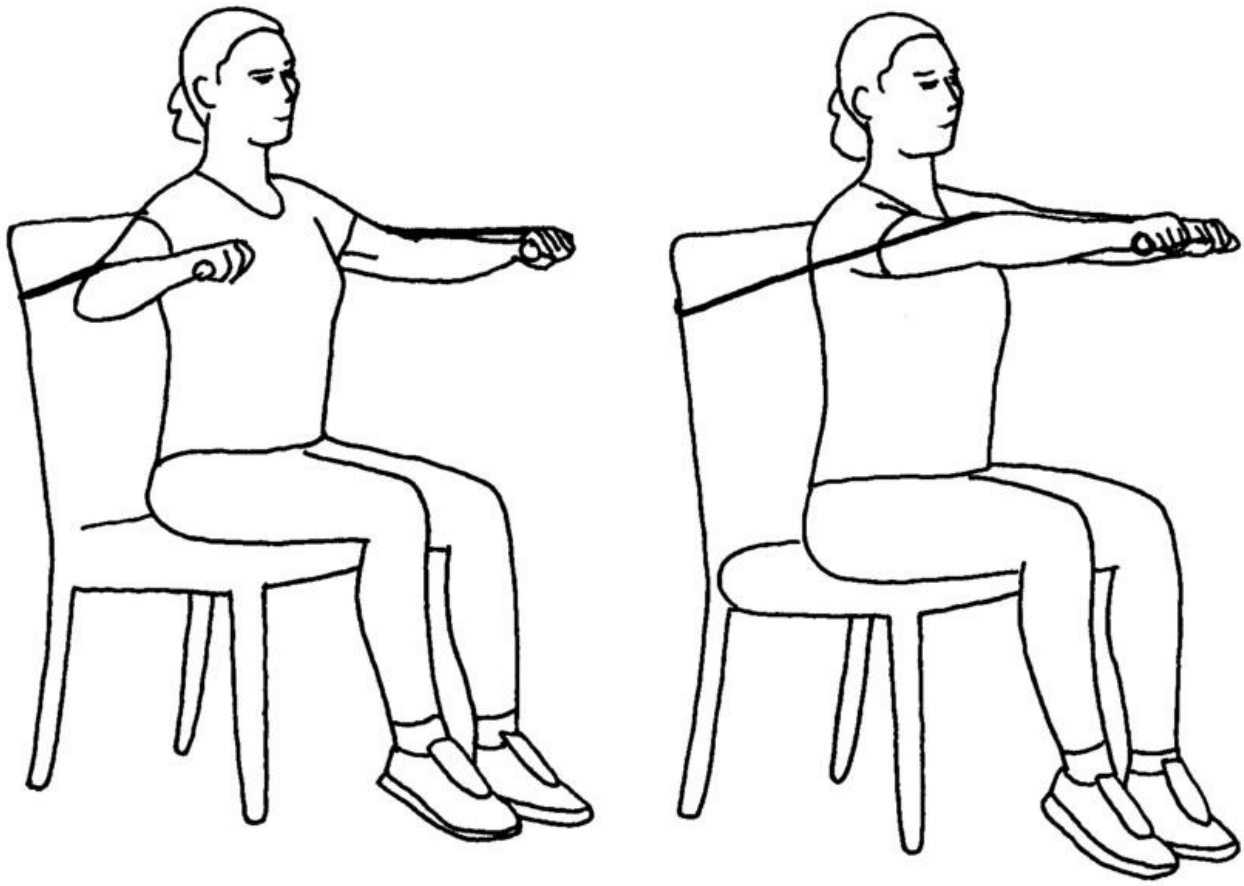
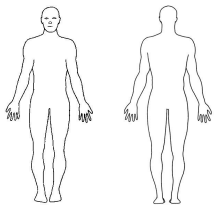


6. Siddende brystpres med elastik

Placer en elastik rundt om ryglænet af en stol. Sid på kanten af stolen med enderne af elastikken i hver hånd. Begynd med armene løftet ud til siden med albuerne bøjet 90°. Dine knoer skal pege fremad. Fra denne position, stræk albuerne og flyt dine arme lige fremad i brysthøjde. Vend langsomt tilbage til udgangsstillingen.



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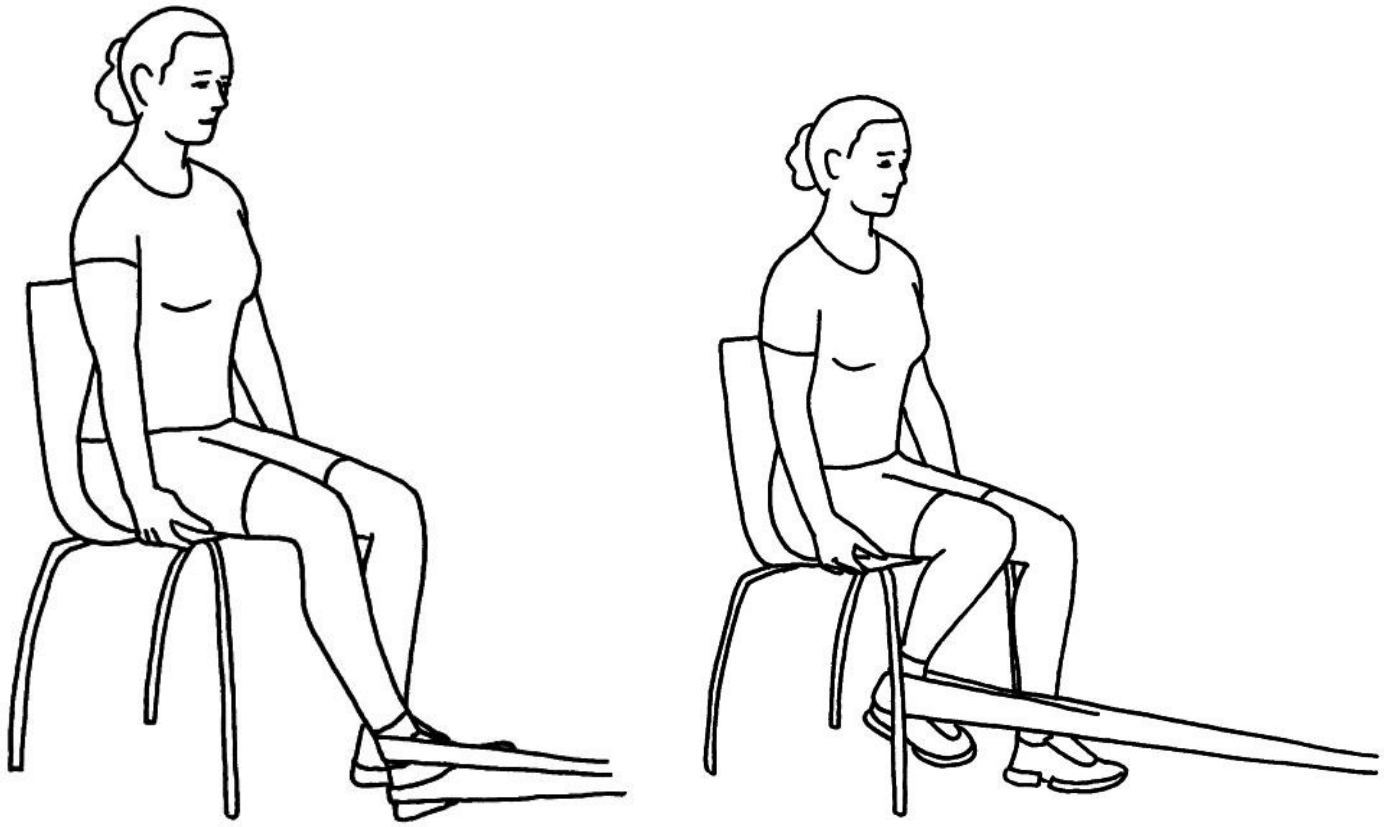
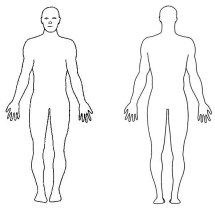


7. Siddende lårcurl m/ elastik

Fastgør elastikken over ankelhøjde og sid med ansigtet vendt mod det sted hvor elastikken er fastgjort. Sørg for at du har god støtte i lænderyggen og tag fat i sædet for støtte. Med elastikken rundt om hælen føres benet bagud og ind under stolen.
Før langsomt benet tilbage til udgangsstillingen og gentag.



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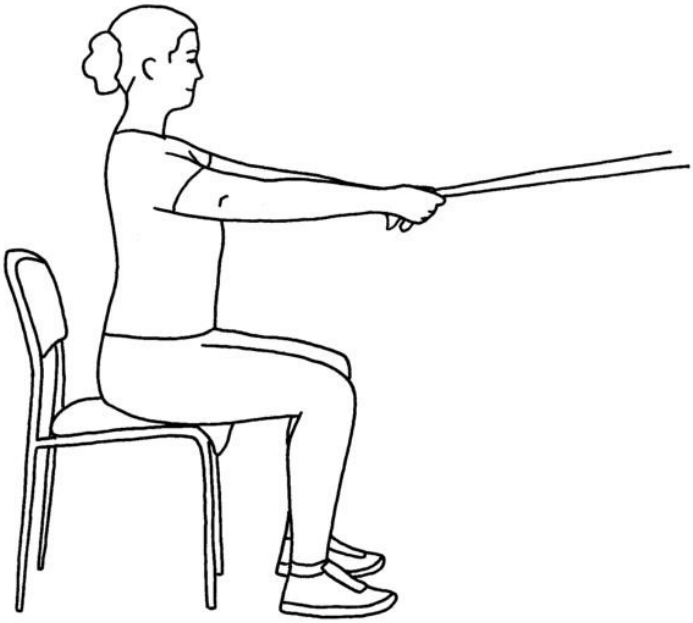
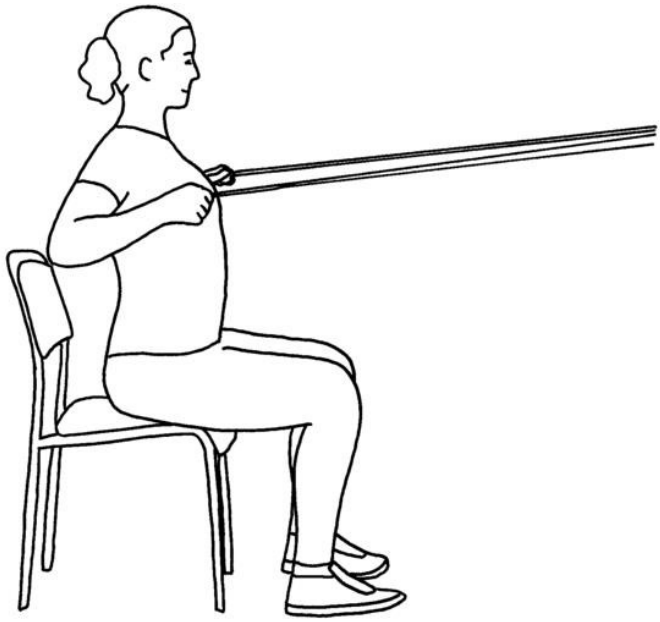
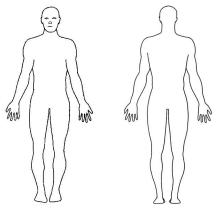




8. Siddende høj roning med elastik

Hav elastikken fastgjort til en vægbarre eller noget lignende. Sid på stolen med ansigtet mod fastgørelsen. Hold enderne af elastikken i dine hænder og træk dem mod brystet ved at bøje i albuerne og samle skulderbladene. Dine albuer skal være i skulderhøjde under hele øvelsen.



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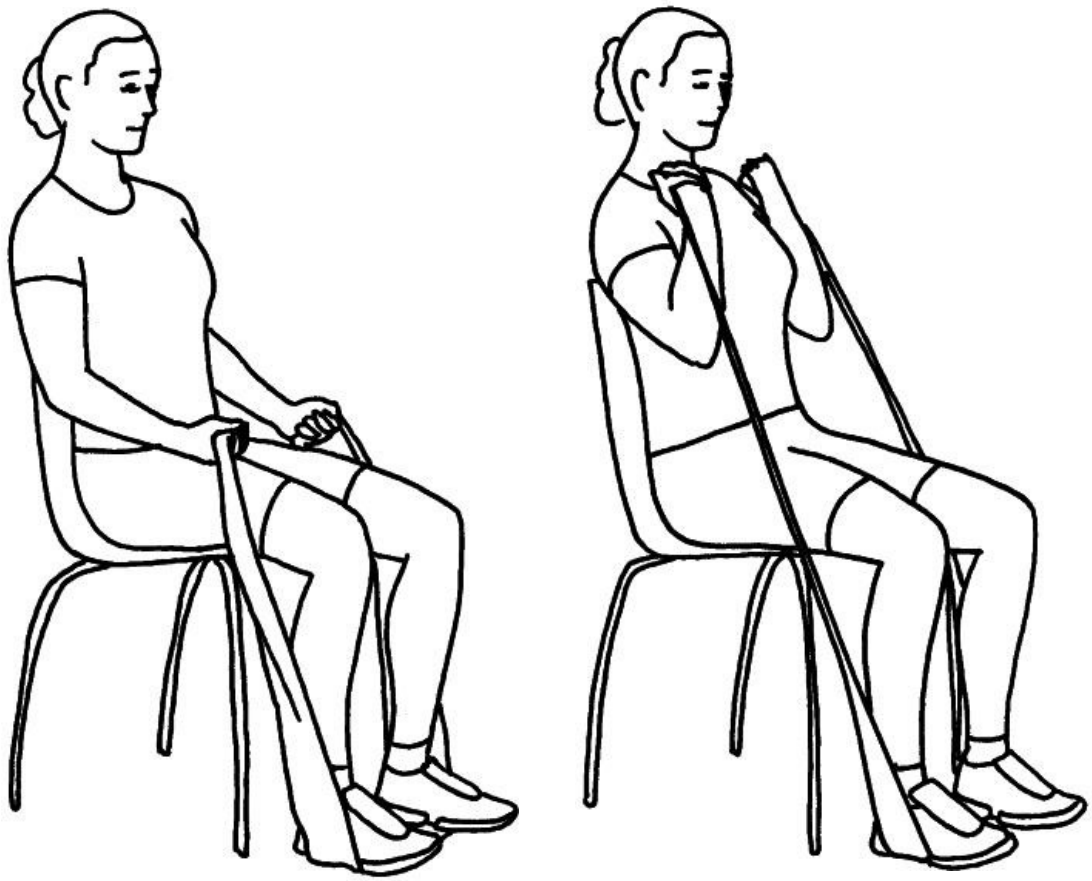
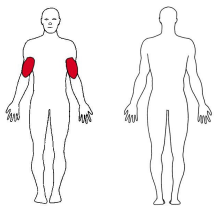


9. Siddende albuebøj m/elastik

Placer midten af elastikken under fødderne. Sid med armene langs lårene og tommelfingrene pegende fremad. Bøj albuerne samtidigt med at du drejer tommelfingrene udad. Sænk langsomt tilbage til udgangsstillingen og gentag.



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cykel	sæde- højde									
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træk til bryst	belastning									
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Siddende knæstræk	Vægt									
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Sidende albuebøj	belastning									
	antal									

		Dato	Dato	Dato	Dato	Dato	Dato	Dato	Dato	Dato
cykel	sæde- højde									
	Interval	5 x 2/1 min	5 x 2/1 min	5 x 2/1 min	5 x 2/1 min	5 x 2/1 min	5 x 2/1 min	5 x 2/1 min	5 x 2/1 min	5 x 2/1 min
træk til bryst	belastning									
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