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Can Weight Bearing Aerobic Exercise be Done Safely with an Active Diabetic Plantar Foot Ulcer and Can It Improve Healing Time

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ABSTRACT

Introduction

Diabetic foot ulcer (DFU) is a huge economic burden on the National Health Service (NHS). Research on the benefits of aerobic exercise on the vascular system in diabetics is vast, however research on the benefits of aerobic exercise on diabetics with active plantar DFU is slim. The purpose of this review is to determine whether weight bearing aerobic exercise can be safely undertaken with an active plantar DFU and whether exercise can in fact improve ulcer healing time.

Method

Five papers that included patients with active DFU taking part in weight bearing or semi weight bearing aerobic exercise programmes >10-weeks were found and reviewed.

Findings

Non weight bearing or semi-weight bearing exercise in the presence of DFU alongside severe diabetic neuropathy (DN) is safer and more feasible in the aim to try and stop the regression of diabetic complications. It has not been concluded whether aerobic exercise improves ulcer healing time.

Proposal

A pre-test, post-test randomized controlled trial (RCT), 30 participants (15 male, 15 female) with type 2 diabetics (T2D) and active plantar DFU, recruited from the Peter Mount Diabetes and Endocrine clinic at the Manchester Royal Infirmary, randomized into an evenly split intervention group/control group. Intervention group will take part in fully supervised 12-week semi weight bearing aerobic/resistance-based exercise programme: 3×per week working at 40-60% heart rate reserve (HRR) (Karvonen method) at the rehabilitation gym, Manchester Royal Infirmary (MRI). Participants will wear a removable air cast walker or equivalent. Monthly motivational interviewing and bi-weekly foot checks will be undertaken. Control group will continue usual wound care plan from the diabetic clinic. Outcome Measures: Baseline, 6, 12-weeks: transparent ruler measurement, toe brachial pressure index (TBPI) toe pressures, SPO_2, ankle brachial index (ABI), fasting blood glucose (FBG), blood cholesterol levels, Semmes monofilament test, blood pressure (BP), body mass index (BMI). Statistically analysed by statistical package for social sciences (SPSS) version 28 at $p<0.05$.

Keywords

Diabetic foot ulcer (DFU); Diabetic neuropathy (DN); Type 2 diabetics (T2D); Heart rate reserve (HRR); Body mass index (BMI).

INTRODUCTION

The diabetic foot (DF) is one of the most feared complications of diabetes due to its devastating effects; caused by a combination of diabetic neuropathy (DN) and peripheral arterial disease (PAD) which results in diabetic foot ulcers (DFU's), critical ischemia, and infection.[1] The economic burden of the DF on the National Health Service (NHS) in the UK is rising, with an estimated expenditure of over £837 million being cost on ulcer treatment and amputation during 2014-2015[2] to nearly one billion in 2022.[3]

DFU's are one of the leading causes of lower limb amputation (LLA) in the UK[4] with up to 85% of amputations caused by diabetes preceded by a DFU.[3] DFU's often arise due to infrequent

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foot checks by specialist physicians[5] and/or due to the symptoms of DF being hard to recognise by the patient due to sensory loss combined with being under educated on what to look out for at home during a personal foot check.[6] Recurrence of DFU's is common; Armstrong et al[7] states that 'around 40% of DFU patients have a recurrence within 1-year after ulcer healing, almost 60% within 3-years, and 65% within 5-years' and Moulik et al[8] categorises the reported 5-year mortality rate as 45%, 18% and 55% for neuropathic, neuroischemic and ischemic ulcers, respectively.

Many diabetics have vascular complications and co-morbidities[9] and in general lead sedentary lives, which leads to the worsening of these co-morbidities.[10] Research on the benefits of aerobic exercise on the vascular system in diabetics is vast with many studies indicating a reduced mortality rate and improved quality of life from exercising.[11] However, research on the benefits of aerobic exercise on diabetics with active DFU's is slim, making it difficult to assess whether aerobic exercise can be done safely in these patients. The general guidelines from the International Working Group on the DF is to offload the foot and make weight bearing minimal whilst recovering from a DFU[12] but this therefore worsens the sedentary behaviour and contributes to the already bleak outcome of having a DFU,[10] with between 15-20% of patients with DFU getting worse, leading to amputation.[1] Staggeringly, 70% of people with DFU's die within 10-years, with most of these deaths being vascular related.[13]

Study Selection

A total of 22 studies were found with keywords "active foot ulcer" AND "aerobic physical activity" AND "diabetic ulcer healing" *via* search databases PubMed, Elsevier, Academia and ResearchGate. After careful deselection of studies lasting less than 10-weeks and those that exclude PAD; 5 papers were included in the review (Table 1) (Appendix Table 2).

Table 1. *Papers in Question*

Author	Title
Lindberg et al[18]	An exercise program for people with severe peripheral neuropathy and diabetic foot ulcers – a case series on feasibility and safety.
Nwankwo et al[16]	Effect of Twelve Weeks Supervised Aerobic Exercise on Ulcer Healing and Changes in Selected Biomechanical Profiles of Diabetic Foot Ulcer Subjects.
Nwankwo et al[17]	Effect of Twelve Weeks Supervised Aerobic Exercise on Ulcer Healing and Changes in Selected Biomechanical Profiles of Diabetic Foot Ulcer Subjects.
LeMaster et al[15]	Effect of Weight-Bearing Activity on Foot Ulcer Incidence in People With Diabetic Peripheral Neuropathy: Feet Frist Randomized Controlled Trial.
Suryani et al[14]	Effect of foot-ankle flexibility and resistance exercise in the secondary prevention of plantar foot diabetic ulcer.

CRITIQUE OF THE LITERATURE

Participants

Suryani et al,[14] LeMasters et al[15] and Nwankwo et al[16,17] included between 50-80 mixed gender participants split into an invention group and control, whereas Lindberg et al[18] only included 5 male participants with no control. Holdcroft[19] found that studies with mixed gender have been shown to be more accurate and states that 'research funding for coronary artery disease in men is far greater than for women, yet the at-risk population of women, which is an older age group, suffers more morbidity and mortality'. Suryani et al[14] and LeMasters et al[15] used randomised selection methods but Nwankwo used own clinical judgement to recommend the participants, which has proven to increase bias.[20]

Age was slightly lower in the Suryani et al[14] study with an average of 55-years, compared to other papers average of between 65-69-years, which coincides with the average age of most diabetes patients in the UK today.[21] Lower age at disease onset correlated with participants having the longest duration of diabetes. Nwankwo's et al[16,17] average duration was considerably higher than other papers at 21.77-years. Song[22] found that duration of diabetes has been shown to be an indicator of progression of diabetic co-morbidities with 'stroke and peripheral vascular disease levels becoming significantly higher in type 2 diabetics (T2D) after 20-years duration' and Brownrigg et al[23] found that increased peripheral vascular disease has a diminishing effect on the rate of healing.

Lindberg's et al[18] participants had a prevalence of 80% T2D, whereas LeMaster et al[15] had T2 prevalence of 95% in the experimental group and 93.5% in both groups. Sunyani only included T2D and Nwankwo et al[16,17] failed to mention which type the participants were. T2D is more heavily associated with obesity and peripheral vascular disease than T1, therefore excess plantar pressures and dyslipidaemia may be more prevalent in this study.[24,25] However, recent findings are suggesting that obesity is a major predictor of T1D in children due to the 'accelerator hypothesis' by Wilkins.[26]

Body mass index (BMI) was higher for participants in LeMasters[15] study, with an average BMI of 36.55 (SD), putting these patients in the obese class 2 category.[27] Obesity has been proven to delay healing time due to vasculogenic impairment.[28] In the experimental groups, Lindberg's et al[18] average BMI was 28.7 and Nwankwo's et al[16,17] 27.66 but Nwankwo's et al[16,17] non-experimental group was 22.96, indicating a significant difference amongst the control and intervention group in this study. BMI was slightly lower in Suryani's et al[14] at 24.5, putting this group of participants in normal BMI range.[27]

Blood pressure (BP) allowance to participate in the exercise programmes also differed, whereby Lindberg et al[18] did not signify the systolic/diastolic value but referred to advice from the responsible physician. However, Nwankwo's et al[16,17] systolic inclusion value was <165 mmHg and LeMasters et al[15] <200 mmHg to take part; this is a significant difference and above the recommended BP value of <180/110 mmHg for completing light-moderate exercise in which no further evaluation is needed.[29]

Lindberg et al[18] had a 60% non-smoker statistic, LeMasters et al[15] had a 95% non-smoker statistic in the intervention group and a 91% accumulative percentage including control, but Nwankwo et al[16,17] and Suryani et al[14] failed to identify which par-

ticipants were smokers. Smoking increases the risk of diabetic foot amputation and is the leading cause of PAD (Appendix Table 3).[30]

Method

All papers were randomized controlled trials (RCT) apart from Lindberg' et al[18] which was a research paper. RCT's have been proven to be more accurate than research papers.[31] Duration of exercise programmes ranged from 10-weeks to 12-months. Lindberg et al[18] LeMaster et al[15] and Suryani et al[14] were mixed aerobic and resistance-based, whereas Nwankwo et al[16,17] solely aerobic. A mixture of aerobic/resistance exercise has been proven to have more benefits on the cardiovascular system and overall fitness than one category alone.[32]

Lindberg et al[18] and Nwankwo et al[16,17] were fully supervised trials, whereas LeMaster et al[15] was supervised for only the first 3-months and thereafter home based. Suryani et al[14] was entirely home based with tri-weekly monitoring over the phone and exercises recorded in a logbook. Regular monitoring improves adherence and inaccuracy's have been found when recording home exercise diaries.[11] Adherence has been noticeably poor in diabetics when asked to exercise, supervision has been known to increase adherence and enhance the benefits of an exercise programme.[33]

Sessions during Lindberg's et al[18] study were not progressive and there was no pre-scheduled programme with an aim to encourage self-management and improve adherence, therefore it is impossible to determine the number of sessions each individual patient took part in per week. The study included a patient satisfaction survey form report (PSSF) but no motivational interviewing or counselling. Counselling and motivational interviewing have proven to improve patient adherence to exercise.[34] Patients wore a removable air cast walker or orthopaedic shoe, completed 12-minute cardiovascular exercise plus light-moderate elastic band resistance exercises but many sessions were not completed due to adherence issues. Ulcer wound was evaluated by Wilcoxon Signed Ranks test, but the study did not mention if the wound was evaluated during the programme or just pre and post programme.

Nwankwo et al[16,17] included counselling in a structured, progressive exercise programme. A systematic review by Irvine et al[35] showed that progressive exercise programmes help increase adherence, motivation and reduce pain amongst diabetics. Variation in a programme can also have great purpose in motivating the participant.[36] Nwankwo's et al[16,17] experimental group wounds were checked bi-weekly by the nurse, measured with a transparent ruler. Regular checks from the diabetic nurse improve patient ulcer outcome rates.[37]

LeMaster et al[15] was the only full weight bearing walking programme that included at home daily living activity monitoring *via* accelerometer at 3, 6 and 12-month intervals. The patients performed 3×30 minute aerobic sessions per week in orthotic prescribed footwear, steps were recorded *via* pedometer throughout. The type of terrain the exercise was performed on was not mentioned. Even with the correct shoes, different terrain can cause sheer stresses and pressure[38] and although patients had access to an ongoing dermatologist if needed, they self-managed footcare at home. Home examinations have proven poor in diabetic patients due to being uneducated on what to recognise as potential harm.[6]

Statistics amongst all papers were analysed to a $p<0.05$ significance using statistical package for social sciences (SPSS) or statistical analysis system (SAS) software. SPSS has been found to be more commonly used amongst RCT's, with over 52.1% of studies using this software. However, SAS can be more useful for comparison graphs but can be time consuming (Appendix Table 4).[39]

Results

Lindberg showed that no DFU's worsened during the programme, proving safety and feasibility towards this variable. However, there were many adverse events with delayed onset muscle soreness (DOMS) being reported in 3 out of 5 participants. DOMS is partly due to a build-up of lactic acid accumulating when tissues become oxygen deprived during exercise,[40] which can be detrimental to diabetics because of their risk of lactic acidosis, often due to taking the popular medication metformin.[41] Progression of the programme was halted amongst individuals suffering from DOMS. However, patient satisfaction survey scores (PSSF) and performing daily living activities improved following the programme which is highly beneficial in a diabetic patient who is depressed due to pain.[42] One patient's ulcer increased in size during a holiday where he was walking regularly, highlighting that weight bearing may increase ulcer size.

Nwankwo et al[16] proved at 12-weeks there was a reduction in fasting plasma glucose. Exercise has shown to reduce fasting glucose levels in diabetics, decreasing the risk of cardiovascular disease.[11] Wound size percentage reduction was larger in the intervention group, however there was a large difference between baseline wound size in both groups, whereby the experimental groups size was 26.45+9.46 mm and the control 17.70+7.23 mm, indicating that results may be influenced by this. There was no difference in cholesterol levels at 12-weeks.

Nwankwo et al[17] showed an increase in SPO_2 in both groups, with greater increase in experimental group than the control. In the experimental group, ankle brachial index (ABI) levels also increased, wound size decreased with no correlation to BMI after 4-weeks but had a large connection to BMI level at 12-weeks, indicating that BMI is a large indicator in the duration of ulcers.[23] However, there was no correlation between BMI, wound size and SPO_2 in the control group.

LeMaster et al[15] suggested there was no additional risk in weight bearing exercise on DFU's in diabetics with DN. However, although he proved that there was no additional risk in plantar only ulcers, there was a significant increase in other types of lesions in the intervention group. Lesions on the dorsal toes or other areas of lower limb are associated with poor outcome in diabetics due to infection.[43] Healing time was slower in the intervention group indicating that weight bearing exercise may have an adverse outcome on healing. Step count increased in the intervention group for the first 6-months but not in the control, however, both groups' steps declined by 12-months, indicating a poorer adherence rate as time went on.

Suryani et al[14] proved there was less reoccurrence of ulcers overall in the intervention group but on the contrary to Nwankwo et al[16,17] ABI levels did not significantly improve. However, DN scores decreased in the intervention group and walking speed increased, even after 24-weeks, indicating that improved strength/ flexibility has an influence on walking speed.[44] HBA1C remained unchanged after this study correlating with Nwanko's et al[16,17] study (Appendix Table 5).

Discussion

The level of bias in Nwankwo's et al[16,17] study was high, ulcer size was higher in the intervention group at baseline than the control, leading to obscured results. Suryani et al[14] was less biased, with even parameters, making for a more viable outcome[20] but only included seated exercises therefore less pressure was applied to the foot. Lindberg et al[18] had no comparison control group and adherence was poor, therefore making conclusions on the relevance of the study is difficult. LeMasters et al[15] ulcer healing time and non-plantar lesions were much greater in the intervention group than the control, indicating that weight bearing exercise on diabetic patients with DN is perhaps not the best intervention to reduce diabetic complications.

Outcome measures varied amongst these papers with no identical testing strategies or assessments. However, it is acceptable to predict that Hemoglobin A1C (HBA1C) is not a viable assessment tool due to it remaining unchanged in 2 of the studies. HBA1C is a percentage of glucose levels over an 8-12-week time frame,[45] therefore changes in HBA1C level may not have changed for up to 3-months following an exercise programme. There was a contradiction between ABI measurement significance, however Nwankwo et al[16,17] devised a more aerobic programme, which may indicate that aerobic exercise has a more significant effect on ABI measures than resistance-based exercise such as Suryani's et al[14] programme. These papers did not indicate smoking status, smoking alone is a major cause of PAD which can lower ABI levels. Smoking also influences a person's ability to reach maximal cardiovascular benefits through hypercoagulation and respiratory distress.[46] Cholesterol levels may also be influenced by this; therefore, cholesterol may still be a viable tool in assessing the benefits of a short-term 12-week exercise programme.[47]

A raised BMI is a huge indicator in recurrence of DFUs[23] and aerobic exercise can decrease BMI. Flexibility exercises can improve cutaneous perfusion response.[48] Resistance exercises can improve neuropathy sensation,[14] which in turn increases balance, walking stability[44] and may also increase healing.[23]

Based on this review it is fair to say that non-weight bearing or semi-weight bearing exercise in the presence of DFU alongside severe DN is safer and more feasible in the aim to try and stop the regression of diabetic complications. It has not been concluded whether aerobic exercise improves ulcer healing time.

PROPOSAL

Specific Aims

The purpose is to devise a safe and feasible aerobic/resistance exercise programme for diabetics with an active plantar DFU associated with PN and/or mild to moderate ischemia, to increase healing time, improve cardiovascular health and ultimately reduce amputation/mortality rates. The proposal aims to increase adherence and sustainability of exercise by not exhausting participants interest and keeping participants motivated, in the hope of improving quality of life and encouraging better lifestyle choices following the programme.

The study will be a RCT, comprised of a 12-week exercise programme which will be individually tailored to the patient including two types of semi weight bearing aerobic methods alongside a variety of non-weight bearing resistance exercises to keep the participants engaged. Patients with mild-moderate PAD will be allowed to participate, on the contrary to other related studies whereby PAD is amongst the exclusion criteria,[49,50] in a bid to improve patient's circulation and oxygenise lower extremities. The programme will be gradually progressive to avoid any adverse effects caused by excess pressure which can be predicted under the physical stress theory[51] which will avoid any extreme muscular fatigue following exercise.

Background and Significance

Statistics by Mottolini[3] report that '7957 major diabetic LLA were reported in England between 2017-2020'. Prognosis is poor for diabetics with PAD who have undergone first minor amputation, with 23% of patients undergoing subsequent major amputation approximately 1-year later.[52] Quality of life following this loss is reduced markedly.[53] Aerobic exercise can decrease the devastating effects of cardiovascular associated problems in diabetics, lower glucose levels[54] and improve quality of life, which is of the upmost importance as 1 in 4 of the diabetic population suffer from depression.[55] Recent studies on diabetic ulcers, using near infrared spectroscopy show that peripheral HbO_2 and total Hb levels are increased following resistance-based exercise resulting in reduced ischemia.[56] However, there are few studies on aerobic combined with resistance-based exercise amongst patients with an active DFU.

The current guidelines on treatment of an active DFU are to offload the foot, reducing weight bearing activity to a minimum for the ulcer to heal.[12] However, being more sedentary worsens PAD, raises HBA1C levels and increases BMI, which has a negative effect on healing.[23] It seems that a greater amount of time is spent on treating the DF, rather than preventing the co-morbidities. For patients with stable ischemic heart disease, exercise programmes are currently prescribed; Boden et al[57] has shown that these programmes 'reduce total mortality by 20%, cardiac mortality by 26%, and non-fatal myocardial infarction by 21%', yet there is no current exercise prescription in place for diabetics when they share many of the same problems.

RESEARCH DESIGN

Participants

Participants are to give written informed consent and the study is

to be approved by Manchester University Foundation Trust and Ethical approval given by the NHS research Ethics Committee (REC). Thirty (30) participants, 15 male, 15 female with T2D, active plantar DFU will be recruited to the study from the Peter Mount, Manchester Royal Infirmary Diabetes and Endocrine clinic. Prior to the trial, the participants will be signed off by their primary physician and randomized using simple randomisation software into an evenly split intervention group/control group. The intervention group will take part in the exercise programme whereas the control group will continue to have the usual wound care from the diabetic clinic (Appendix Table 6).

Pre-programme Assessments

Participants will complete a pre activity level form, however due to the progressive nature of the programme – any level of pre activity will be accepted. Participants will be asked to record their morning resting heart rate before rising on 3 consecutive days before the study begins to determine mean resting heart rate, from this maximum heart rate and heart rate reserve levels will be calculated *via* the Karvonen method,[58] giving an indicator of patient's fitness level. Workload will be set to 40-60% HRR to avoid patients undertaking physical exercise challenges that cannot be achieved wearing a removable cast walker such as the Astrand cycle test[18] and follows the recommended cardiovascular guidelines of moderate exercise for diabetes with PAD complications (Appendix Table 7).[59]

Method

The programme will be fully supervised by Register for Exercise Professionals (REPs) Level 4 Advanced Exercise Trainer at the rehabilitation gym at Manchester Royal Infirmary (MRI). The trainer will provide monthly motivational interviewing. A band 7 diabetic nurse will complete foot checks biweekly. A band 5 Orthotist will prescribe new diabetic footwear for the participant once ulcer heals and will monitor removable walker's condition.

Baseline, 6 and 12-weekly assessments include transparent ruler measurement, toe brachial pressure index (TBPI) toe pressures, SPo_2, ABI, fasting blood glucose (FBG), blood cholesterol levels, Semmes monofilament test, BP, BMI. A polar heart rate monitor will be worn during exercise. Adverse events will be recorded. 2222 will be phoned for emergency care. An ankle pedometer will be worn by both groups to monitor steps at home to provide comparisons on activity levels and determine any correlation between higher activity/ulcer healing times outside of the programme. Whilst at home the guidelines on offloading devices will be advised.[60] Results will be statistical analysed by SPSS version 28 with an accuracy of $p<0.05$ (Appendix Tables 8 and 9).

Limitations and Difficulties

Claudication may occur because of ischemia; breaks need to be taken and exercise restarted once pain subsides. Patient needs to be reassured that the pain experienced is not dangerous and the pain should subside further into the programme as fitness level improves.[61] Hypoglycaemia should be managed appropriately with juice and snacks onsite if symptoms do occur. However, pre-exercise blood sugar checks will be taken prior to exercise; if levels are below 90 mg/dL, guidelines by Zaharieva et al[62] will be followed (Appendix Table 1).

Adherence to the participant wearing the removable walker at home may be a problem, with patients choosing not to wear their walkers. However, the motivational interviewing is to encourage participants to follow the guidelines because removable walkers have a better outcome on healing when used appropriately.[60]

BUDGET AND JUSTIFICATION

Budget and Justification (Appendix Table 10). Total expenditure is £29413.09. However, costs of treatment/amputation are reaching nearly £1billion.[3] Preventing the cause will be more cost effective in the long run.

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DECLARATION OF CONFLICT OF INTEREST

The author declares that there are no potential conflicts of interest with respect to the research and authorship of this article. If the proposal is to be undertaken as a study, it would need permission from the Manchester Foundation Trust and would need ethical approval from the Health Research Authority's (HSA) NHS RECS.

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APPENDICES

Table 1. *Carbohydrate Intake Strategies Based on Pre-Exercise Blood Glucose Level*[62]

Pre-Exercise Blood Glucose Concentration Author	Requirements
<90 mg/dL	Ingest 15-30 g of fast-acting carbohydrates before the onset of exercise, depending on the size of the individual. Follow with extra carbs throughout exercise.
90-149 mg/dL	Start consuming extra carbs at the onset of exercise (~0.5-1.0 g/kg body mass/hour of exercise), depending on the energy expenditure and the amount of circulating insulin at the time of exercise.
150-249 mg/dL	Initiate exercise and delay consumption of extra carbs until blood glucose levels drop to <150 mg/dL.
250-349 mg/dL	Test for ketones: do not perform any exercise if moderate amounts of ketones are present[58]; contact your health care team. Initiate mild- to moderate-intensity exercise. Intense exercise should be delayed until glucose levels drop to <250 mg/dL because intense exercise may exaggerate the huperglycemia.
≥350 mg/dL	Test for ketones: do not perform any exercise if moderate to large amounts of ketones are present[58]; contact your health care team. If ketones are negative (or trace), consider conservative insulin correction (e. g., 50% correction) before exercise, depending on current "on board" (active) insulin status. Initiate mild to moderate exercise and avoid intense exercise (aerobic of anaerobic) until glucose levels drop.
Blood glucose concentrations should always be checked before exercise, and if glucose is dramatically elevated (≥350 mg/dL), the urine or blood should also be tested for ketones. The target range for blood glucose before exercise is 90-250 mg/dL. Carbohydrate intake should depend on the glucose concentration at the start of exercise. Regardless of their initial blood glucose concentration, patients should continue to monitor blood glucose regularly during exercise (every 30-45-minutes) using an accurate glucose meter and to adjust insulin and carbohydrate intake accordingly. In general, adjusting insulin doses before exercise will reduce the need for increased carbohydrate intake. Adapted from Holt[55], Ignaszewski et al[58]	

Table 2. *Study Selection*

Study Selection	Requirements
Population	Human participants with type 1 or 2 diabetes with peripheral neuropathy and peripheral arterial disease and an active or recently healed plantar foot ulcer at time of study.
Intervention	Aerobic exercise combined with resistance-based exercises or solely aerobic exercise programme lasting longer than 10 weeks in duration.
Outcomes	Cardiorespiratory, glycaemic control, cholesterol and lipids, wound-healing, ankle brachial index, circulatory toe pressures, patient satisfaction scores.

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Table 3. *Participant Compatibles Nr*=Non-recorded*

Author	Participant Intervention Group	Control	M %	Age	Type 2 Prevalence %	Duration of Diabetes yrs	BMI	Baseline Wound Area Size cm^2	Duration of Ulcer Weeks	BP Inclusion Criteria	Offloading Device Used	Non Smokers %	Exclusion Criteria
Lindberg et al[18]	5	0	100	68.2	80%	14.4	28.7	1.9	38	nr	Removable air-cast/ half shoe	60	Critical limb ischemia >40mm Hg at toe level HbA1c<12% Beta blockers
Nwankwo et al[16,17]	31	30	50	69	not specified	21.77	27.66	2.65	>30	<165/ mmHg	Specialised off loading insole	nr	Congestive heart failure, uncontrollable cardiac arrhythmias, severe valvular heart disease, uncontrolled BP, extreme claustrophobia. Haematological disease affecting mobility or knee flexion of <1900, severe illness.
LeMaster et al[15]	41	38	50	65.7	93.5	11	36.5	No ulcers	n/a	<200/ mmHg Systolic <120/ mmHg Diastolic	n/a	91	Uncontrolled Blood Pressure Myocardial infarction or unstable angina in previous year Lower limb amputation of >1 digit or an unhealed ulcer in past month
Suryani et al[14]	25	25	50	55	100	9.38	24.5	Recently healed ulcers <12-months	n/a	nr	n/a	nr	Active plantar ulcer Inability to walk Osteomyelitis history Parkinsons Contracture

Nr=non-recorded*

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Table 4. *Methods*

Author	General Purpose	Study Type	Supervised	Equipment	Type of Exercise	Assessments /Outcome Measures	Duration/Frequency/ Delivery	Wound Evaluation	Statistical Analysis
Lindberg et al[18]	Examine feasibility and safety of a non-weightbearing program for severe PN and diabetic foot ulcer	Research Paper	Yes – outpatient rehabilitation centre	Stationary bike Resistance elastic band	Aerobic and resistance Ankle dorsiflexion and plantarflexion exercises	10mm Semmes-Weinstein monofilament Vibrometer-VPT threshold 50V Maximum 6 rep RM test Isometric Commander Muscle Testing 8LB005_A 12 min Astrand bicycle test Tandom test Patient Specific Function Scale Satisfaction scale (NFS) No of sessions attended	10 weeks – pre and post assessment 12 mins cycling followed by cooling down ankle exercises Resistance exercises – knee extension and flexion, hip abductio n and low row for upper body – 3x15 reps weeks 1-3 3x10 reps weeks 4-10 Dorsiflexion exercises conducted to exhaustion 3 times per session – non weight bearing	Wilcoxon Signed Ranks Test (median 25-75% quartiles) Removable air cast or orthopaedic shoe	SPSS version 22 (IBM Corp, Armonk, NY, USA) <0.05%
Nwankwo et al[16]	Evaluate the effect of aerobic exercise of diabetic ulcer healing and changes in biochemical profiles of diabetics	Randomized controlled trial	Yes – diabetic clinic	Bicycle ergometer Specializes off-loading insole padding ACU CHEK ROCHE ACCUTECH CholesTrak	Aerobic	Stress test Folstein mini-mental status Fasting plasma glucose Total cholesterol Borgs perceived exercise scale Diet control Counselling	12 weeks pre and post assessment 3xper week warm up 5 mins – 10 mins initial – 60% max HR Increase by 5 mins biweekly to reach 50 mins by 9th week 85% max HR by week 12.	Transparent ruler -biweekly reviews	Pearsons moment correlations SPSS version 15 $p<0.05$
Nwankwo et al[17]	Evaluate the effect of aerobic exercise on vascular blood perfusion and capillary oxygen tension associated with wound healing on diabetic foot ulcer patients	Randomized controlled trial	Yes – diabetic clinic	Bicycle ergometer Specializes off-loading insole padding	Aerobic	Stress test Folstein mini-mental status Borgs perceived exercise scale Diet control Counselling Ankle brachial index SPO2	12 weeks pre and post assessment 3xper week warm up 5 mins – 10 mins initial – 60% max HR Increase by 5 mins biweekly to reach 50 mins by 9th week 85% max HR by week 12.	Transparent ruler – biweekly reviews	Pearsons moment correlations SPSS version 15 $p<0.05$

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LeMaster et al[15]	Determine the effects of a lower-extremity exercise and walking intervention on weight bearing activity and foot ulcer incidence in diabetes and PN	Randomized controlled trial	Yes in months 1-3 – 8 sessions 3 home based aerobic sessions per week for 18-months	Waist worn pedometer – Accusplit Eagle 170 Therapeutic footwear StepWatch water-resistant computerised accelerometer	Strengthening lower leg exercises months 1-3 Aerobic Walking programme	6-minute walk test 3, 6, 12-month intervals – StepWatch accelerometer recordings for 2 weeks Motivational interviewing by nurse bi-weekly	12 months 30-minute aerobic sessions – 3 x per week	Ongoing dermatologist When?	SAS version 9.0 or Stata version 10 p value<0.05
Suryani et al[14]	Evaluate the effects of foot ankle flexibility and resistance exercises on recurrence of plantar foot diabetic ulcers	Randomized controlled trial	No - Home based	ABI – Handheld doppler – 8NHz probe Elastic resistance band–0.5 mm first 12-weeks and 0.65 mm in second 12-weeks	Foot-ankle flexibility and resistance exercises sat down Aerobic - Foot tapping to symbolise walking	5 m straight line walk test on smooth, indoor floor – ratio of distance to time Diabetic neuropathy examination HbA1c levels ABI levels	24-weeks 3xweek – Flexibility 30 reps Resistance reps to exhaustion Foot tapping 30 times in-between exercises Evaluations at 12 and 24 weeks - HbA1c levels repeated until plantar ulcer occurred or until 12 and 24 weeks.	Monitored every 3-weeks by phone Exercises completed recorded in logbook	Chi-square test Independent t-test Man-Whitney U test

Table 5. *Results*

Authors	Adverse Reactions	Adherence	Results
Lindberg et al[18]	1 participant suffered from frozen shoulder pain and needed breaks. 3 out of 5 participants suffered from DOMS which compromised programme. 2 participants had extubate of ulcer. 2 participants had habitual back pain.	All patients completed programme – 92% average attendance.	**At 10 weeks** • 3 of 5 ulcers had healed and all had decreased in size. • Ability to complete daily living activities improved. • NRS score median 10. • Patient satisfaction score had improved. • All muscle groups had improved strength, mostly in hip abduction. • Tandem and HBA1c inconclusive.
Nwankwo et al[16]		No participants absconded or died.	**At 12 weeks** • Decrease in fasting plasma glucose in experimental group. • No difference in total cholesterol blood levels. • Wound size percentage reduction larger in experimental group.
Nwankwo et al[17]		No participants absconded or died.	**At 12 weeks** • Increase in SPO_2 in both groups but more in experimental group. • Increase in ABI in experimental group. • Wound size reduction with no correlation to BMI after 4-weeks in experimental group.5 • Wound size reduction at 12 weeks in experimental group with a connection to BMI. • In control group no connection between BMI, wound size and SPO_2.
LeMaster et al[15]	57 lesions detected in total. 4 ulcers in intervention group >1cmsq 1 ulcer in control group >1cmsq Average duration of ulcer in intervention–74 days Average duration of ulcer in control – 51.5 days. 1 participant suffered proximal phalangeal great toe fracture due to osteoporosis	1 person died from unrelated cause. Average sessions during first 6 months in intervention group – 3×per week. Average sessions during first 6 months in control – 1.5-days per week. At 12-months average sessions per well for both groups was 1.5 sessions.	**At 6 months** • Steps increased during 30-minute sessions by 14% in intervention group. • Overall steps increased by 2.5% in intervention group. • Overall steps decreased by 6% in control group. **At 12 months** • Steps decreased between 6-12 months for intervention groups during 30-minute exercise and overall daily steps. • Overall steps decreased for control group.
Suryani et al[14]		6 participants did not complete programme. No participants died. According to logbook, very good compliance in the intervention group.	**At 12 weeks** • Ulcers in 2 patients (4%) in intervention group. • Ulcers in 17 patients (68%) in control group. • DNE decreased in intervention group. • Walking speed increased in intervention group. • HBA1C level unchanged in both groups. • ABI no significant difference in both groups but did increase gradually in intervention group. **At 24 weeks** • Ulcers in 4 patients (16%) in intervention group. • Ulcers in 17 patients (72%) in control group. • DNE decreased in intervention group. • Walking speed increased in intervention group. • ABI no significant difference in both groups but did increase gradually in intervention group.

Table 6. *Participant Criteria*

Inclusion Criteria	Exclusion Criteria
Aged 40-70-years Male or Female Non-smoking status Diagnosed peripheral neuropathy Mild to Moderate Ischemia (ABI levels 0.6 hmm and above combined with TBPA toe pressure of 40-59 hmm[12] Controlled blood pressure < 180/110 mmHg[29] Active plantar foot ulcer classification of grade 2 or below on the Wagner scale. Infection level of <1 and below[12] Cognitive function will be predicted to be sufficient by their primary physician based on MiniCog assessment tool[63] Patients wear a removable offloading walker on the affected foot	ABI <0.6, toe pressure <40 hmm Presence of gangrene, osteomyelitis, serious illness. Wagner score >2, Infection level >1[12] Unstable blood pressure or BP >180/11 mmHg. Unstable cardiovascular angina[64] Cognitive function predicted to be insufficient based on Mini Cog assessment tool by primary their primary physician.

Table 7. *Participant Criteria*

Karvonen Example Method
(220)-(your age)=MaxHR (MaxHR)-(mean resting heart rate)=HRR (HRR)x(60% to 80%)=training range % (Training range %)+(mean resting heart rate)=(target training zone)

Table 8. *Outcome Measures*

Baseline	6-Weeks	12-Weeks
Pre-activity level questionnaire	Patient Satisfaction Survey	Patient Satisfaction Survey
Semmes monofilament test	Semmes monofilament test	Semmes monofilament test
SPO_2 levels	SPO_2 levels	SPO_2 levels
TBPI toe pressures	TBPI toe pressures	TBPI toe pressures
ABI levels	ABI levels	ABI levels
Blood Pressure	Blood Pressure	Blood Pressure
Height	Height	Height
Weight	Weight	Weight
BMI	BMI	BMI
Wound size–transparent ruler	Wound size – transparent ruler	Wound size – transparent ruler
Fasting blood glucose	Fasting blood glucose	Fasting blood glucose
Blood cholesterol	Blood cholesterol	Blood cholesterol
Removable walker check	Removable walker check	Removable walker check

Table 9. *Programme Timetable to be Provided by the Physician*

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Week 1	2 minute warm up – 20-30% HRR 5 mins rowing - 30-40% HRR 2x30 reps – Leg extension Hamstring curl Adductor Abductor *Stretching programme		2 minute warm up – 20-30% HRR 5 mins cycling - 30-40% HRR 2x30 reps – Chest press Shoulder press Abdominal crunch *Stretching programme		2 min warm up -20-30% HRR 8 mins rowing - 30-40% HRR *Stretching programme		
Week 2	2 minute warm up - 20-30% HRR 8 mins cycling - 30-40% HRR 2x30 reps – Leg extension Hamstring curl Adductor Abductor *Stretching programme		2 minute warm up –20-30% HRR 10 mins rowing - 30-40% HRR 2x30 reps – Chest press Shoulder press Abdominal crunch *Stretching programme		2 minute warm up – 20-30% HRR 10 mins cycling -30-40% HRR Diabetic nurse review and motivational interviewing *Stretching programme		
Week 3	3 minute warm up – 30-40% HRR 10 mins rowing - 40-50% HRR 2x30 reps – Leg extension Hamstring curl Adductor Abductor *Stretching programme		3 minute warm up – 30-40% HRR 10 mins cycling - 40-50% HRR 2x30 reps – Chest press Shoulder press Abdominal crunch *Stretching programme		3 minute warm up – 30-40% HRR 12 mins rowing 40-50% HRR *Stretching programme		
Week 4	3 minute warm up – 30-40% HRR 12 mins cycle 40-50% HRR 2x30 reps – Leg extension Hamstring curl Adductor Abductor *Stretching programme		3 minute warm up – 30-40% HRR 15 mins rowing - 40-50% HRR 2x30 reps Chest press Shoulder press Abdominal crunch *Stretching programme		3 minute warm up – 30-40% HRR 15 mins cycling - 40-50% HRR Diabetic nurse review *Stretching programme		
Week 5	4 minute warm up 30-40% HRR 18 mins rowing - 40-50% HRR 2x15 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme		4 minute warm up 30-40% HRR 18 mins cycling - 40-50% HRR 2x15 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme		4 minute warm up 30-40% HRR 18 mins rowing 40-50% HRR *Stretching programme		
Week 6	4 minute warm up 30-40% HRR 20 mins cycling - 40-50% HRR 2x15 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme		4 minute warm up 30-40% HRR 20 mins rowing - 40-50% HRR 2x15 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme		4 minute warm up 30-40% HRR 20 mins cycling 40-50% HRR *Stretching programme Diabetic nurse review and motivational interviewing Assessments		

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Week 7	5 minute warm up 30-40% HRR 20 mins rowing - 40-60% HRR 2x15 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme	5 minute warm up 30-40% HRR 20 mins cycling - 40-60% HRR 2x15 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme	5 minute warm up 30-40% HRR 20 mins rowing 40-60% HRR *Stretching programme
Week 8	5 minute warm up 30-40% HRR 22 mins cycling - 40-60% HRR 2x15 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme	5 minute warm up 30-40% HRR 22 mins rowing - 40-60% HRR 2x15 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme	5 minute warm up 30-40% HRR 22 mins cycling 40-60% HRR Diabetic nurse review *Stretching programme
Week 9	5 minute warm up 30-40% HRR 25 mins rowing - 40-60% HRR 2x12 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme	5 minute warm up 30-40% HRR 25 mins cycling - 40-60% HRR 2x12 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme	5 minute warm up 30-40% HRR 25 mins rowing 40-60% HRR *Stretching programme
Week 10	5 minute warm up 30-40% HRR 28 mins cycling - 40-60% HRR 2x12 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme	5 minute warm up 30-40% HRR 28 mins rowing - 40-60% HRR 2x12 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme	5 minute warm up 30-40% HRR 28 mins cycling 40-60% HRR Diabetic nurse review and motivational interviewing *Stretching programme
Week 11	5 minute warm up 30-40% HRR 30 mins rowing - 40-60% HRR 2x12 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme	5 minute warm up 30-40% HRR 30 mins cycling - 40-60% HRR 2x12 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme	5 minute warm up 30-40% HRR 30 mins rowing 40-60% HRR *Stretching programme
Week 12	5 mins warm up 30-50% HRR 30 mins cycling - 50-60% HRR 2x12 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme	5 minute warm up 30-50% HRR 30 mins rowing - 50-60% HRR 2x12 reps Leg extension Hamstring curl Adductor Abductor Chest press Shoulder press Abdominal crunch *Stretching programme	5 mins warm up 30-50% HRR 30 mins cycling 50-60% HRR *Stretching programme Diabetic nurse review Assessments

HRR=Heart Rate Reserve

**Stretching programme – sat on exercise mat, hold each stretch for 30 seconds, repeat on both sidesx2.*

Seated hamstring stretch, seated inner thigh stretch, kneeling quadricep stretch, kneeling hip flexor stretch, seated triceps stretch, seated deltoid stretch

Table 10. *Budget and Justification*

Personnel	**Hours/ Amount**	**Cost**
Level 4 Advanced Exercise Trainer	139.5 hours at £25	£3487.50
Band 5 Orthotist plus allowance for prescribed diabetic shoes	19 hours at £11.23	£213.37
Band 7 Diabetic nurse/ wound specialist	50 hours at £16.83	£841.50
Researcher		
Band 2 Porter to transport pa-tients around hospital	150 hours at £8.61	£1291.50
Rehabilitation Gym Hire To be included in clinic hire costs: Recumbent bike Rowing machine Leg press machine Hamstring curl machine Abdominal crunch machine Chest Press machine Shoulder press machine Exercise mats Stadiometer Digital weighing scales	144 hours at £50	£5400.00
Diabetic Clinic room	7-days estimated costs at £200	£1400.00
Equipment	**Make/Model**	**Cost**
Handheld – 8mHz doppler in-strument	Hi Dop Vascular Doppler with 8 MHz Probe	£233.99
SPO_2 pulsometer	MediSupplies Finger Pulse Oximeter MD300C2	£34.44
10 g Monofilament instrument	Bailey Retractable Monofila-ment 10 g	£17.50
Glucometer/ Ketometer	Glucomen Areo Glucometer and Ketometer	£47.34
Glucose testing strips – 2x50	Glucomen - 2x50 at £14.29	£28.58
Ketone testing strips – 2x10	Glucomen - 2x10 at £14.29	£28.58
Cholesterol meter	GlucoRx X6 Multi Parameter Meter	£19.95
Cholesterol strips	GlucoRx X6 Total Cholester-ol Testing Strips 10x10 at £29.95	£299.50
Polar heart rate monitor chest strap	Polar H10 H HR Sensor BLE BLK M-XXLx5 at £66	£330.00
Transparent wound ruler	McKesson Wound measuring guide 5x7 inch clear plastic disposable–100 packx2 at £10.99	£21.98
Blood Pressure machine	Reister RBP–100 Blood Pressure Monitor Mobile De-vice	£234.12
Lenovo Yoga Laptop	7 Pro X 14.5 inch slim	£999.00
SPSS software (version 28)	6 months subscription	£38.00
Sphygmomanometry	Atys SysToe	£2495.00
Pedometer	Besportable 3D Digital Pe-dometer–30x£13.59	£407.70
Stopwatch	Kalenji Onstart 110 Stop-watch	£9.99
Supplies	**Amount**	**Cost**
Water from water machine Glucogel 3xtubes Carbohydrate snacks Apple juice Paper towels Disinfectant Logbook to document adverse events and attendance rates Pens Print out of exercise programme		Estimate allowance of £200.00
Travel	**Hours/ Amount**	**Cost**
Patient travel allowance – ambulance or taxi collection and drop off up to 5 miles distance from hospital	Allowance of £15 per person per day	£9000.00
		Total cost: £27079.54 Total cost adding 40% margin to staff costs: £29413.09