Study Protocol for a Randomised Controlled Trial to Investigate the Enhancement of Diabetic Foot Ulcer Healing Using Low-Magnitude High-Frequency Vibration Treatment

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Title

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Abstract

Background:

Diabetes has a prevalence of 11.6% in China with diabetic foot ulcerations affecting over 30 million Chinese. 85% of these patients require amputation and 5-year mortality for diabetics is 70% when associated foot ulcers. Clinical trials have shown that standing on whole-body vibration platforms, specifically low-magnitude high-frequency vibration (LMHFV); promotes angiogenesis, enhances muscle bulk and accelerates epithelization. Investigation on diabetic rats with foot wounds found accelerated wound healing, increased perfusion and upregulation of factors such as VEGF, PECAM-1 and PCNA. Hypothesis: We postulate LMHFV will enhance diabetic foot ulcer healing.

Methods:

Prospective, single-centre, randomised control trial to treat 106 subjects with diabetic foot ulcers.

Interventions: The intervention group will stand on LMHFV whole-body vibration platforms for 20min on alternate days for 20 weeks, together with conventional dressing by a trained wound-care nurse as in the control group.

Main Outcome Measures: Ulcer size will be measured at multiple time points, the incidence of amputations/infections will be recorded, perfusion via ankle-brachial pressure index will be calculated and foot function via the foot and ankle outcome score will be analysed.

Data analysis: Repeated measure of ANOVA to analyze time-point differences and student's t-test for same time-point comparison.

Discussion:

This is the first clinical trial to investigate the effect of whole-body vibration on diabetic foot ulcers. It will show us if the results from animal studies will translate into clinically significant results. If positive effects are established, whole-body vibration can be a valuable treatment regime to tackle diabetic foot ulcers.

Trial registration: NCT04275804 clinicaltrials.gov (19 Feb 2020)

Keywords

Diabetic Foot, Whole Body Vibration, Low Magnitude High Frequency Vibration,

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62 ## Administrative information

63 'Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the
64 items has been modified to group similar items (see http://www.equator-network.org/reporting-
65 guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/)

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Title {1}	Study Protocol for a Randomised Controlled Trial to Investigate the Enhancement of Diabetic Foot Ulcer Healing Using Low-Magnitude High-Frequency Vibration Treatment
Trial registration {2a and 2b}.	Trial registration: NCT04275804 clinicaltrials.gov (19 Feb 2020)
Protocol version {3}	Version 01 (19 Feb 2020)
Funding {4}	The project has no external funding source.
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Name and contact information for the trial sponsor {5b}	n/a there is no trial sponsor
Role of sponsor {5c}	n/a there is no sponsor

Introduction

Background and rationale {6a}

Diabetic Foot Ulcers are a major problem.

Diabetes is a major non-communicable disease which affects has a prevalence of 11.6% in the Chinese, affecting over 110 million people. (1-3). Diabetics have more than doubled in our locality over the past 20 years, this has been attributed to many different factors including urbanization, genomic predisposition, dietary (rice is high in carbohydrates) and the generally sedentary lifestyles adopted in Hong Kong. (4-7) It is reported that 30% of diabetics have foot ulceration in which ~60% are non-healing. (8, 9) This creates a huge social-economic burden in society and utilizes 184 hospital bed days/1000 diabetic patients/year. (10)

Amputations are common.

Studies have reported that 20-85% of patients with diabetic foot ulceration eventually require an amputation (8, 9) and 70% of them die within 5 years. This is significantly higher (x 2.5 times) than diabetic patients without foot ulcerations. (3, 8, 11, 12) There are many confounding factors that contribute to the high mortality with decreased ambulation (or prolonged bed-rest) due to amputations being one of them. The aetiology is multifactorial with neuropathy, vasculopathy and decreased muscle bulk being the major factors. (8, 11) Current conventional treatment is surgical debridement in conjunction with revascularization and proper glycaemic control. (10, 13) However, unlike biophysical interventions such as whole-body vibration (14, 15), they are often less effective in improving the microcirculation and intrinsic foot muscle bulk. Limitations of conventional dressing are indirectly evidenced by the high amputation rates (13, 16-18) and the many ongoing studies to find a better solution to this widespread problem. Different modes of wound dressing are currently being investigated such as artificial skin and biologically augmented dressing material (e.g stem cells, concentrated platelets etc.) but most are one-off expensive interventions.

Whole-body vibration can modulate the healing response at a cellular level.

Whole-body vibration platforms (fig 01 and fig 02 in supplementary notes) are widely used by the public for exercise and weight loss regimes; there are two main types, the low-magnitude high-frequency vibration (LMHFV) platforms which vibrates in the vertical axis with a mild displacement (max 0.3g, displacement <0.1mm) and the side-to-side vibration platforms which have a larger displacement (max 22g, displacement

12.2mm). They are a relatively cheap, non-invasive biophysical intervention that vibrates the body when the subject is standing on top.

Previous clinical trials on whole-body vibration have found enhancement of healing and modulation of various hormonal factors for bone and muscles. (19-21) An RCT involving 710 participants showed that therapy with a Low-Magnitude High-Frequency Vibration platform (20min/day 5days/ week) significantly improved muscle strength, less bone loss and improved quality of life. (14) Over the years, clinical trials using low-magnitude high-frequency vibration platforms (LMHFV) have shown that it is a safe and effective treatment modality.

Vibration enhances DM ulcer healing.

Animal studies on low-magnitude high-frequency vibration showed improved circulation evaluated by doppler USG, micro-CT angiography and histology in a rat model. There was increased angiogenesis and expression of vascular endothelial growth factor (VEGF) as well as improved bone formation and mineralization. A study of 96 diabetic rats with foot wounds showed that LMHFV significantly accelerated wound healing and improved skin micro-circulation with upregulation of various healing markers. (15, 22) The wound size was significantly smaller, blood glucose levels were significantly lower and glucose transporter 4 expression (GLUT 4 immunoblotting) was significantly better in the vibration group. Perfusion in the wound, measured using laser Doppler, was also significantly better in the vibration group and more granulation and epithelial tissue were seen on histology. Platelet endothelial cell adhesion molecule-1 (PECAM-1), a signalling molecule that upregulates angiogenesis and endothelialization, was significantly higher in the vibration group. Proliferating cell nuclear antigen was also higher which signifies there was more cell proliferation in the vibration group. Vascular Endothelial Growth Factor (VEGF), which promotes bone formation, haematopoiesis, wound healing as well as angiogenesis was significantly elevated in the vibration group compared to the controls.

Clinical trials (14, 20) using low-magnitude high-frequency vibration (LMHFV) show that it is a safe intervention for human subjects, and laboratory findings on DM ulcer healing suggest that there is evidence whole-body vibration may enhance diabetic ulcer healing in our patients.

Objectives {7}

We postulate that Low-Magnitude High-Frequency Vibration (LMHFV) will enhance diabetic foot ulcer healing and decrease the need for major amputation.

Trial design {8}

Single Blind, Parallel group, 1:1 allocation, Superiority, Single centre, Randomised Controlled Trial.

Methods: Participants, interventions and outcomes

Study setting {9}

Participants will be recruited from the patients in the Orthopaedic & Traumatology department at a tertiary teaching hospital affiliated to CUHK.

Eligibility criteria {10}

Inclusion criteria:

- >18 years old (legally able to self-sign consent)
- Able to stand independently
- Biochemically confirmed Diabetes with a fasting plasma glucose ≥ 7.0 mmol/L, or a random plasma glucose ≥ 11.1 mmol/L or hemoglobin A1c (HbA1c) level ≥ 6.5%
- Ulcers will be below the level of the malleoli, excluding those confined to the interdigital web space
- Cross-sectional area of the index ulcer should be 50- 1000 mm2
- Wagner stage 2-3
- Not active infection according to the Infectious Diseases Society of America guidelines

Exclusion criteria:

- Severe cognitive impairment or severe comorbidity, which may impair the ability to adhere to intervention plan, e.g. severe dementia, poor cardiopulmonary reserve requiring home oxygen, daily hemodialysis etc.
- Evidence of active infection
- Recent revascularization procedure (<12 weeks)
- Recently received medication/intervention which might affect cell proliferation (eg chemotherapy, radiotherapy etc)
- Allergy to dressing, adhesives or antibiotics
- Incapable to understand the study protocol or provide written informed consent
- Presence of other foot deformities

Who will take informed consent? {26a}

Principal Investigator/ Research Assistant will obtain written consent from all participants.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

There are no plans for participant data to be used in ancillary studies

Interventions

Explanation for the choice of comparators {6b}

We did not include a sham vibration group because it is obvious to the participants if the vibration is present or not. For our previous investigations, we have attempted to ask participants to stand on a sham platform

for 20mins, but compliance was low. In some muscle studies, the control group can perform different exercises on a platform for 20mins, however there are no proven exercise regimes that help diabetic foot ulcer healing

- **Intervention description {11a}**

  Control group: conventional dressing

  - Alternate day dressing in a designated clinic by a trained nurse specialized in wound care
    - Dressing by a specialized wound-nurse is the current gold-stand of treatment for diabetic ulcers (13).
    - We did not include a sham vibration group because it is obvious to the participants if the vibration is present or not. For our previous investigations, we have attempted to ask participants to stand on a sham platform for 20mins, but compliance was low. In some muscle studies, the control group can perform different exercises on a platform for 20mins, however there are no proven exercise regimes that help diabetic foot ulcer healing.
    - The duration of dressing will last until participant's wound is healed. If it is not healed after the study period, PI will look into the case to see if other treatments are needed.

- Vibration group: conventional dressing + LMHFV
  - Alternate day dressing in a designated clinic by a trained nurse specialized in wound care (13).
    - The duration of dressing will last until participant's wound is healed. If it is not healed after the study period, PI will look into the case to see if other treatments are needed.
  - Alternate day 20-week course of whole-body vibration therapy
    - Alternate day 20min sessions on a self-designed vibration platform with low-magnitude high-frequency vibration (35Hz, 0.3g peak-to-peak displacement <0.1mm). Since the participants will return for dressing change on alternate days, the vibration group will also undergo the LMHFV during the same attendance.
    - Our previous study have shown that the dosage of LMHW at 20min/session 3 days/week is sufficient. (14)
    - 10 Low-Magnitude High-Frequency vibration platforms are available in our outpatient department at Prince of Wales Hospital; these machines are available to be used by

our patients. In addition, 150 community centres distributed around New Territories, Kowloon and HK Island are equipped with our LMHFV machines. They are open to the public either free-of-charge or with a nominal fee. Participants will be equipped with a personal NFC smart card that will log and record their usage of the platforms.

Criteria for discontinuing or modifying allocated interventions {11b}

Interim data analysis will be performed at 20weeks, the investigators will then decide on discontinuing/modifying the intervention based on the judgement of safety and benefits.
Participant may experience mild discomfort including itchiness and redness of the lower limb skin. The symptoms should resolve shortly after intervention. If these symptoms do not resolve/worsen after 30 minutes, it should be reported as an adverse event. PI will then look into the case and decide if the participant is suitable to continue the intervention for the rest of the study period.

Strategies to improve adherence to interventions {11c}

- Conventional dressing: Each attendance to wound dressing will be recorded by the clinic nurse.
- LMHFV Vibration: each participant in the vibration intervention group will be assigned a personal 'smart card'. This smart card will record each utilization of the vibration platform to ensure compliance.

Relevant concomitant care permitted or prohibited during the trial {11d}

The use of LMHFV vibration will not require alteration to usual care pathways (including use of any medication) and these will continue for both trial arms.

Provisions for post-trial care {30}

There is no anticipated harm and compensation for trial participation. Usual care pathways will be provided post-trial.

Outcomes {12}

Primary Outcome:

- **Ulcer size**: 0wk, 2wk, 8wk, 14wk, 20wk, 52wk
    - The baseline ulcer size will be measured at 0 weeks and a core interim measurement will be conducted at 20 weeks since 30% of ulcerations will heal at 20 weeks using conventional dressing. (13) A 1-year reassessment will help differentiate if the 20-week course of LMHFV therapy has created sustainable changes. Multi-ulcer will not be considered.

The early follow-up at 2 weeks will serve as a chance for the participant to voice out difficulties and for the investigator to provide early intervention if required. Subsequent 6-weekly documentation of the change in ulcer size will help decipher the ideal duration of LMHFV therapy.

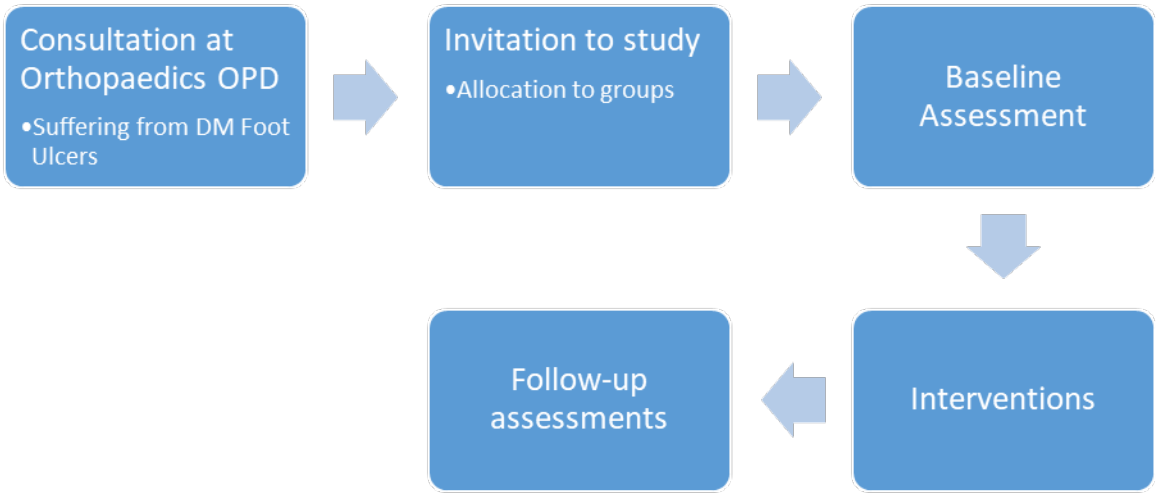
The ulcer area will be measured using a digital photograph with a standardized 10mmx10mm ruler square. The image will be sent to an independent, blinded researcher who will calculate the wound size by defining the wound edge using the colour differential in the skin and using the magnetic lasso tool in the Photoshop CS6 software. The ulcer size will be calculated in the photo imaging software SPOT 3.5.5 Window using those standardized squares.

Bonferroni tests are used for multiplicity adjustment.

Secondary Outcome:

1. **Time (days) to healing**
    - The day of complete wound closure will be documented during their alternate day dressings in the designated clinic. The participant will still be reviewed at 20 weeks and 1 year for the primary outcome.
    - Mean of time to healing will be recorded.
2. **Incidence of amputation**
    - The reason and day of below knee/above knee amputation will be recorded. Details will be retrieved from the Clinical Management System, the centralized electronic healthcare system utilized by public hospitals in Hong Kong.
3. **Incidence of secondary infection**: Defined by IDSA criteria of infection (23)
    - The number of hospitalized days and number of days of systemic antibiotic therapy will be documented. Details will be retrieved from the Clinical Management System, the centralized electronic healthcare system utilized by public hospitals in Hong Kong.
4. **Perfusion** via the Ankle-brachial pressure index (ABI): 0wk, 20wk
    - The measurement of the ABI will be standardized. (24) The subject will be at rest in supine position for 10mins, Doppler ultrasound to measure systolic blood pressure twice in the posterior tibial artery (If there is no obtainable signal in the posterior tibial artery, the dorsalis pedis will be used.), the average systolic blood pressure in the posterior tibial artery/dorsalis pedis divided by the higher of the SBP in the two arms will be used to calculate the ABI. (The higher SBP of the arm will be used in these calculations due to previous studies showing a strong association between peripheral arterial disease and subclavian stenosis)
5. **Foot function** via the Foot and Ankle Outcome Score (FAOS) (25): 0wk, 20wk
    - Foot function will be measured using the FAOS which is a variant of the Knee Injury and Osteoarthritis Outcome Score designed specifically for problems related to the foot and ankle region. The FAOS also has validated translations in English and Chinese; it is a questionnaire consisting of 5 Likert score subscales; Pain, Symptoms, ADL, Recreation and Foot related QOL. Answers are graded a score from 0-4 and a normalised score can be calculated for each subscale (100 is asymptomatic while 0 indicates extreme symptoms).

Participant timeline {13}



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Timeline:
Study Protocol for a Randomised Controlled Trial to Investigate the Enhancement of Diabetic Foot Ulcer Healing Using Low-Magnitude High-Frequency Vibration Treatment

	Months																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Recruit 50% (n=53) participants	x																							
Recruit 100% (n=106) participants							x																	
Intervention Control	x																							
Intervention Vibration	x																							
Analysis Interim																		x						
Analysis Final																								x

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283 **Sample size {14}**

284 106 subjects randomized 1:1 into the two treatment groups.
285 The sample size was calculated by using the primary endpoint of wound size in G*Power 3.1.9.4 (Germany).
286 Using a 1:1 randomization ratio a type I error rate (a-level) of 0.05 and power of 0.95. Our vibration study of
287 diabetic rat wounds showed an effect size d of 0.99. We estimate a tuned-down effect in human subjects, thus
288 using an effect size of 0.7 we calculated that we should recruit 90 participants with 45 in each group. (22) To
289 account for a dropout rate of 15%, we will recruit 106 participants.

Recruitment {15}

Participants will be recruited from the patients in the Orthopaedic & Traumatology department at the Prince of Wales Hospital, the tertiary teaching hospital affiliated to CUHK. All patients from the Orthopaedic and Traumatology department will be screened. Those who meet the inclusion and exclusion criteria will be recruited.

To ensure sufficient recruitment, patients can be recruited from affiliated hospitals such as Alice Ho Miu Ling Nethersole Hospital and North District Hospital.

Assignment of interventions: allocation

Sequence generation {16a}

There is no list of factors for stratification. Permuted block randomization is used.
Generation of the allocation sequence: Research Assistant

Concealment mechanism {16b}

Sequentially numbered. The opaque envelopes containing the treatment allocation are sequentially numbered and sealed. They are opened by the principal investigator on participant enrolment.

Implementation {16c}

Enrollment of participants: Principal Investigator
Assignment of participants to interventions: Principal Investigator or research assistant
Allocation sequence: Principal Investigator or research assistant

Assignment of interventions: Blinding

Who will be blinded {17a}

Single Blinded. Participants will know they are undergoing vibration therapy, but the assessors and data analysts will be blinded.

Procedure for unblinding if needed {17b}

The design is open label with only outcome assessors being blinded so unblinding will not occur.

Data collection and management

Plans for assessment and collection of outcomes {18a}

All collected personal data and medical information relevant to this study about the subjects will be strictly confidential. The data can be accessed only by the principal investigator, co-investigators and the research assistant(s) in charge. Subjects will only be identified by a study number and initials in the study database, and no personal identity will be disclosed when study results are being reported and/or published. The data will be kept for an additional 5 years for monitoring. Data that are related to future patient management will be stored in hospital CMS system.

Plans to promote participant retention and complete follow-up {18b}

n/a all participants are chronic disease patients with regular scheduled follow-up regardless of this trial.

Data management {19}

The nurse and research assistant (both reporting directly to the principal investigator) will be responsible for data collection and data entry while the principal investigator will be responsible for data analysis. The principal investigator himself will make decisions to terminate the trail trial if needed. Data quality is ensured by double data entry (the nurse and the research assistant). Electronic data entry will be used.

Confidentiality {27}

All collected personal data and medical information relevant to this study about the subjects will be strictly confidential. Subjects will only be identified by a study number and initials in the study database, and no personal identity will be disclosed when study results are being reported and/or published. Only the trial team including principal investigator and research assistant will have the right to access the data.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable as no biological specimens were collected as part of this trial

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Intention to treat population will be used. Repeated measures of ANOVA will be used to analyze the ulcer size groups and time points differences with be analyzed with post-hoc Bonferroni tests. Student’s t-test for two independent samples will be used to compare groups of the same time point. Non-parametric tests will be used if data are not normally distributeThe Kruskal-Wallies test and Matt-Whitney U test will be used

instead of ANOVA and t-tests in case the data are not normally distributed. A mixed-effect model will be used to analyse the primary outcome. ANOVA will be used for analysing the secondary outcomes. Statistical analyses will be performed using IBM SPSS 25 (IBM, Armonk, NY, USA), and statistical significance was considered at $p < 0.05$. This protocol will follow the CONSORT 2010 statement (BMC Medicine).

Interim analyses {21b}

PI will monitor the results and make final decisions. An interim analysis will be performed with week 20 data. Ulcer size, time to healing, incidence of amputation, incidence of secondary infection, perfusion and foot function will be used in the interim analysis.

Methods for additional analyses (e.g. subgroup analyses) {20b}

n/a, there are not current plans for subgroup analysis.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Missing data will be accounted for via listwise deletion.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

Principal investigator

- Design and conduct the study
- Preparation of protocol and revisions
- Organising trial steering committee meetings
- Publication of study reports

Trial steering committee

(Principal investigator and co-investigators)

- Agreement of final protocol
- Recruitment of patients
- Reviewing progress of study and if necessary agreeing changes to the protocol and/or investigators brochure to facilitate the smooth running of the study

the Principal and Co-investigators will oversee the entire trial.

Composition of the data monitoring committee, its role and reporting structure {21a}

Data monitoring will be from a committee made up of professorial-grade staff from the department. The data monitoring committee is independent of the study organisers and have no competing interests. During the period of recruitment to the study, interim analyses will be supplied, in strict confidence, to the DMC, together with any other analyses that the committee may request. This may include analyses of data from other comparable trials.

Adverse event reporting and harms {22}

The research assistant will contact the participants regularly (once per week) to record any adverse events. There should not be any potential harms caused to the participants. Minor adverse events such as itchiness and redness of the lower limbs may be observed. However, the discomfort will disappear shortly after the vibration treatment terminates. If such event occurs, it will be reported to DMEC and relevant regulatory bodies as required indicating expectedness, seriousness, severity, and causality.

Frequency and plans for auditing trial conduct {23}

Auditing will be performed as per the Joint CUHK-NTEC guidelines.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Principal Investigator will be responsible to update the clinical registry and ethics committee for any changes in the protocol.

Dissemination plans {31a}

Journal publication and abstract presentations are planned.

Discussion

Diabetic foot ulcers are a massive problem affecting 110 million in China alone; it is a large social-economic burden without a good treatment option.(1-3) Whole-body vibration is a safe, non-invasive, non-pharmacological intervention that is widely tolerated. Whole-body vibration can theoretically be an effective

means of non-invasive treatment of diabetic foot ulcers. The authors believe it will be embraced in diabetic ulcer treatment since inexpensive vibration machines are readily available commercially and small clinics and centres can easily equip themselves with one. Our study can help investigate the clinical effects of vibration therapy of diabetic ulcerations and also act as a foundation for further research to investigate the mechanistic pathways in which whole-body vibration modulates the body's response.

Trial status

Protocol version01, registered on clinicaltrials.gov as NCT04275804 (19 Feb 2020). Anticipated recruitment 1 Apr 2020 and anticipated completion 30 Mar 2023.

Abbreviations

- *ABI = Ankle Brachial Pressure Index*
- *CT = Computer Tomography*
- *DM = Diabetes Mellitus*
- *FAOS = Foot and Ankle Outcome Score*
- *GLUT4 = glucose transporter 4*
- *LMHFV = Low-Magnitude High-Frequency Vibration*
- *VEGF = vascular endothelial growth factor*
- *Wk = Week*

Declarations

Acknowledgements

The authors acknowledge Yuen-Man Wu for her help in the paperwork for this manuscript.

Authors' contributions {31b}

Authors' contributions: SKKL is the principle investigator who conceived the study and wrote the protocol.

NCLH updated and revised the manuscript. WHC significantly contributed to the methodology and design of the trial. PSHY contributed significantly to the study design and revisions of the manuscript.
All authors read and approved the final manuscript.

Funding {4}

The project has no external funding source.

Availability of data and materials {29}

Any data required to support the protocol can be supplied on request.

Ethics approval and consent to participate {24}

Ethics initial approval obtained from the Joint CUHK-NTEC CREC. Ref number 2020.068
Written consent will be obtained from all study participants in the trial.

Consent for publication {32}

Written consent will be obtained from all study participants. This is available from the corresponding author on request.

Competing interests {28}

The authors declares they have no competing interest.

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References

1. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. Jama. 2009;301(20):2129-40.
2. Chan JC, Zhang Y, Ning G. Diabetes in China: a societal solution for a personal challenge. The lancet Diabetes & endocrinology. 2014;2(12):969-79.
3. Chammas NK, Hill RLR, Edmonds ME. Increased Mortality in Diabetic Foot Ulcer Patients: The Significance of Ulcer Type. Journal of diabetes research. 2016.
4. Ramachandran A, Ma RC, Snehalatha C. Diabetes in Asia. Lancet. 2010;375(9712):408-18.
5. Yan BP, Zhang Y, Kong AP, Luk AO, Ozaki R, Yeung R, et al. Borderline ankle-brachial index is associated with increased prevalence of micro- and macrovascular complications in type 2 diabetes: A cross-sectional analysis of 12,772 patients from the Joint Asia Diabetes Evaluation Program. Diabetes & vascular disease research. 2015;12(5):334-41.
6. Ma RC, Lin X, Jia W. Causes of type 2 diabetes in China. The lancet Diabetes & endocrinology. 2014;2(12):980-91.
7. Chan JC, Ozaki R, Luk A, Kong AP, Ma RC, Chow FC, et al. Delivery of integrated diabetes care using logistics and information technology--the Joint Asia Diabetes Evaluation (JADE) program. Diabetes research and clinical practice. 2014;106 Suppl 2:S295-304.
8. Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. New Engl J Med. 2017;376(24):2367-75.
9. Khalifa WA. Risk factors for diabetic foot ulcer recurrence: A prospective 2-year follow-up study in Egypt. Foot (Edinb). 2018;35:11-5.
10. Egan AM, Dinneen SF. In-hospital metabolic regulation in patients with a diabetic foot ulcer: is it worthwhile? Diabetes-Metab Res. 2016;32:297-302.
11. Francia P, Gulisano M, Anichini R, Seghieri G. Diabetic Foot and Exercise Therapy: Step by Step The Role of Rigid Posture and Biomechanics Treatment. Current diabetes reviews. 2014;10(2):86-99.

12. Zarei F, Negahdari B, Eatemadi A. Diabetic ulcer regeneration: stem cells, biomaterials, growth factors. Artif Cell Nanomed B. 2018;46(1):26-32.
13. Margolis DJ, Kantor J, Berlin JA. Healing of diabetic neuropathic foot ulcers receiving standard treatment - A meta-analysis. Diabetes care. 1999;22(5):692-5.
14. Leung KS, Li CY, Tse YK, Choy TK, Leung PC, Hung VW, et al. Effects of 18-month low-magnitude high-frequency vibration on fall rate and fracture risks in 710 community elderly--a cluster-randomized controlled trial. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2014;25(6):1785-95.
15. Cheung WH, Sun MH, Zheng YP, Chu WC, Leung AH, Qin L, et al. Stimulated angiogenesis for fracture healing augmented by low-magnitude, high-frequency vibration in a rat model-evaluation of pulsed-wave doppler, 3-D power Doppler ultrasonography and micro-CT microangiography. Ultrasound Med Biol. 2012;38(12):2120-9.
16. Razzaghi R, Pourbagheri H, Momen-Heravi M, Bahmani F, Shadi J, Soleimani Z, et al. The effects of vitamin D supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: A randomized, double-blind, placebo-controlled trial. Journal of diabetes and its complications. 2017;31(4):766-72.
17. Snyder R, Galiano R, Mayer P, Rogers LC, Alvarez O, Investigators ST. Diabetic foot ulcer treatment with focused shockwave therapy: two multicentre, prospective, controlled, double-blinded, randomised phase III clinical trials. Journal of wound care. 2018;27(12):822-+.
18. Lavery L, Fulmer J, Shebetka KA, Regulski M, Vayser D, Fried D, et al. Open-label Extension Phase of a Chronic Diabetic Foot Ulcer Multicenter, Controlled, Randomized Clinical Trial Using Cryopreserved Placental Membrane. Wounds-a Compendium of Clinical Research and Practice. 2018;30(9):275-8.
19. Wong RMY, Ho WT, Tang N, Tso CY, Ng WKR, Chow SK, et al. A study protocol for a randomized controlled trial evaluating vibration therapy as an intervention for postural training and fall prevention after distal radius fracture in elderly patients. Trials. 2020;21(1):95.
20. Cheung WH, Mok HW, Qin L, Sze PC, Lee KM, Leung KS. High-frequency whole-body vibration improves balancing ability in elderly women. Archives of physical medicine and rehabilitation. 2007;88(7):852-7.

21. Wang J, Leung KS, Chow SK, Cheung WH. Inflammation and age-associated skeletal muscle deterioration (sarcopaenia). Journal of orthopaedic translation. 2017;10:94-101.

22. Yu COL, Leung KS, Jiang JL, Wang TBY, Chow SKH, Cheung WH. Low-Magnitude High-Frequency Vibration Accelerated the Foot Wound Healing of n5-streptozotocin-induced Diabetic Rats by Enhancing Glucose Transporter 4 and Blood Microcirculation. Scientific reports. 2017;7.

23. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJG, Armstrong DG, et al. 2012 Infectious Diseases Society of America Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections. Clinical Infectious Diseases. 2012;54(12):E132-U232.

24. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012;126(24):2890-909.

25. Ling SKK, Chan V, Ho K, Ling F, Lui TH. Reliability and validity analysis of the open-source Chinese Foot and Ankle Outcome Score (FAOS). Foot (Edinb). 2018;35:48-51.

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