Study Protocol and Statistical Analysis Plan

Title: Effects of an exercise program for people with diabetic foot ulcers: A feasibility study with outcomes

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Aim of study:

This research aimed to address the concerning cycle of deconditioning and disablement in people with DFUs by introducing a seated exercise intervention to improve meaningful health and quality of life outcomes. We examined the feasibility of conducting a randomized controlled trial to assess the effects of 12-weeks of seated exercise in people with DFUs compared to peers who did not exercise. We also assessed physical, physiological, and psychosocial health outcomes in both groups. The exercise intervention in this study was EnhanceFitness,[1] an community-based group exercise program appropriate for people with weight-bearing restrictions due to wound-healing protocols. Numerous studies have been conducted that provide evidence of health benefits associated with participation in EnhanceFitness in older adults, including participants with diabetes.[2-7] We hypothesized that people with DFU who engaged in the fitness program would report high levels of satisfaction, adherence and participation, and a low frequency of adverse events. We also hypothesized that participation in the exercise program would be associated with improvements in key health outcomes as compared to a standard-care control group, who were instructed not to engage in regular exercise (i.e., not to change their current habit of no regular exercise).

Materials and methods

A pilot randomized controlled trial was conducted. Study participants were randomly assigned to a group-based exercise program with a seated option for participation (the EnhanceFitness intervention, described below) or to the control group. Participants in the exercise group attended fitness classes for a 12-week period; those in the control group received standard care, which did

not include exercise. Both groups of participants were assessed at two time points, baseline and 12-week follow-up.

Participants

Participants (target n=40) were enrolled and randomly assigned to either the intervention or control group. A randomization schedule was created using random number generator in Microsoft Excel (Microsoft Corporation, Redmond, USA). The study research coordinator created the randomization schedule for 40 potential participants prior to any study enrollment. Group assignment was placed in sealed envelopes to blind study investigators to randomization allocation. Corresponding envelopes were not opened until the participant was enrolled into the study.

Eligibility criteria for this study included: (1) 18 or more years of age, (2) diagnosis of diabetes, (3) current or recently-healed DFU (in the last six months), (4) and able to attend regular exercise classes and two data collection sessions. Exclusion criteria included: (1) medical conditions where aerobic or resistance exercise was contraindicated[8] (e.g., uncontrolled cardiovascular problems), (2) a score of less than 18 on the Montreal Cognitive Assessment indicating moderate cognitive impairment,[9] (3) response from primary physician requesting that the participant not engage in exercise, (4) current participation in a regular exercise program (more than 30 minutes, more than 2 times a week).

Study participants were recruited from podiatry and wound care clinics in the metro area using posted recruitment materials. Potential participants were also identified through targeted

mailings to patients in the University of Washington medical system with ICD-10 codes that indicate the presence of a DFU. Interested patients were screened by telephone for initial eligibility and, if eligible to participate, were enrolled and randomized to either the exercise group or the control group. For those randomized to the exercise group, we sent a letter to each participant's primary physician to inform them of participation in the EnhanceFitness program. Physicians were asked to respond if their patient should not engage in moderate, non-weight bearing exercise. Informed consent was obtained from all participants prior to their involvement in the study.

Outcomes

Feasibility Outcomes. We assessed feasibility outcomes to inform future, large-scale RCT research in this area. The feasibility of conducting a RCT to assess effects of seated exercise in people with DFUs was evaluated using the following parameters: (1) recruitment and retention; (2) adherence to the exercise protocol; (3) participant satisfaction with the exercise program; and (4) presence of serious adverse events. Retention was quantified as the percent of participants that completed the study (i.e., attended both the baseline and 12-week follow up appointments), as well as percent of those who withdrew during the study or were lost to follow-up in each arm. Adherence was quantified as percent of exercise sessions attended by those randomized to the exercise group (out of 36 possible sessions). Satisfaction with EnhanceFitness was quantified as a continuous score on a measure of satisfaction, ranging from 0 (not at all satisfied) to 5 (very satisfied). Finally, presence of serious adverse events (SAEs: adverse outcomes, related or unrelated to the study, such as hospitalizations, emergency room visits, increase in wound size,

and infection, over the course of the study) was quantified as the total number of SAEs reported by participants in each trial arm.

Health Outcomes. We anticipated that exercise might affect many aspects of health and health-related quality of life in people with current or recently-healed DFUs. The following health outcomes were assessed: (1) glycated hemoglobin (HbA1c[10]); Five-times sit-to-stand test (5xSTS, a measure of lower extremity strength[11]); Timed-up-and-go (TUG, a measure of functional mobility[12]); and 30-second biceps curls (a measure of upper extremity strength). We also asked participants to complete a survey comprised of standardized self-reported health measures, including the Patient-reported Outcome Measurement Information System measures of global health (PROMIS-Global 10-item short form),[13] depression (PROMIS-Depression 4-item short form),[14] fatigue (PROMIS-Fatigue 8-item short form), and physical function (PROMIS-Physical Function 11-item short form).[15] The Activities-Specific Balance Confidence Scale was used to assess balance confidence.[16]

Additional variables. Participant characteristics (e.g., age, sex, body-mass index, duration of diabetes) were collected at baseline to characterize the sample and evaluate the comparability between the exercise and control groups.

Procedures

Participants were asked to come to the University of Washington for two data collection sessions. All study procedures were reviewed and approved by a University of Washington institutional review board (IRB). The study was also registered with clinicaltrials.gov

(registration number NCT03002155). Participants were compensated for their time and participation in the study.

Exercise intervention. EnhanceFitness, an existing, evidence-based exercise program, was the intervention for this study. These group classes were offered at no cost to participants. EnhanceFitness classes were designed specifically for older adults at all fitness levels and may be performed in a seated position. Classes were offered at multiple locations across the Seattle metropolitan region, including community and senior centers, making them a convenient option for participants in the study. Each hour-long EnhanceFitness class incorporated cardiovascular exercise (20 minutes), strength training (20 minutes), and stretching (10 minutes). Evidence suggests that EnhanceFitness improves strength,[7] and reduces depression[3] and falls[5] in older adults. Participants in the exercise group attended EnhanceFitness classes three times a week for 12 weeks and were contacted regularly to remind them to attend their classes.

Control. Participants in the control group were contacted regularly to remind them to not change their exercise habits (self-reported as less than 30 minutes of activity, less than 2 times a week) while enrolled in the study. They were asked not to start new exercise regimens, or begin a regular exercise program. Any changes in their exercise routines were noted by researchers.

Baseline data collection session. At the baseline session, a study investigator explained the study to participants and obtained informed consent. We then administered a baseline survey and obtained performance measurements. The baseline survey included all self-reported health outcomes as well as demographic and health questions. Following the baseline survey, we

administered the 5xSTS, TUG, and biceps curls to assess each participant's baseline strength and mobility. At the end of the session, participants went to a hospital-based laboratory to have their blood drawn to test for HbA1c.

12-week data collection session. At the 12-week session, we administered a follow-up survey to assess changes in the previously listed self-reported health outcomes. The survey also included questions to assess satisfaction with the EnhanceFitness intervention for participants in the exercise group. Following the survey, we asked participants to perform the 5xSTS, TUG, and biceps curls. At the end of the session, the participant returned to the laboratory to have their blood drawn and tested for HbA1c.

Analysis

Sample Characteristics. Descriptive statistics (mean, standard deviation, frequency distributions) were calculated for variables used to characterize the sample (e.g., participant characteristics). Student *t*-tests (numeric data) and Chi-square tests (nominal data) were used to compare the intervention and control groups based on participant characteristics. The alpha level for these tests was set at $\alpha=0.05$ and significant findings for sample variables indicate that there are differences in demographic or clinical characteristics (e.g., age, sex, duration of diabetes) between the exercise and control groups.

Feasibility Outcomes. The ability to meet recruitment targets (20 participants per group, 40 total) was assessed. Retention (or percent of participants that completed the study) and percent attrition was calculated and reported separately for the intervention and control groups. Pre-intervention

characteristics were compared between participants who did and did not complete the study to determine if there was a biasing effect. Adherence to the protocol was assessed in the intervention group to quantify the extent to which participants attended exercise classes. Satisfaction with EnhanceFitness was assessed in the intervention group to ensure that participants reported a minimum of 4 on a 5-scale measure of satisfaction with the exercise intervention.

Health Outcomes. Descriptive statistics were calculated for all physical, physiological, and psychosocial outcomes. Separate repeated measures analyses of variance (ANOVA) were performed for each health outcome. The ANOVA models included two factors, each with two levels (group: intervention, control; time: pre-intervention, post-intervention). The alpha level was set at $\alpha=0.10$ for health outcomes and was not adjusted for multiple comparisons. A less conservative statistical approach is warranted for this pilot study so that effects of the intervention could be recognized and, if results suggested that the intervention was beneficial, the results could be used to power and inform a larger RCT. Significant interactions of group x time (with corresponding evidence of improved outcomes in the intervention group) would indicate that the exercise program improved physical, physiological, and psychosocial outcomes in the exercise group compared to the control group.

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