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Study Protocol and Statistical Analysis Plan

Official Study Title:

Use of a Smartphone App Versus Motivational Interviewing to Increase Walking Distance and Weight Loss in Overweight/Obese Adults with Peripheral Artery Disease: Pilot Randomized Trial

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Use of a Smartphone Application versus Motivational Interviewing to Increase Walking Distance and Weight Loss in Overweight/Obese Adults with Peripheral Artery Disease: A Pilot Randomized Trial

Materials and Methods

Participants

We conducted a two-arm, pilot randomized trial. Inclusion criteria were age 50 years or older, overweight/obese (BMI $\geq$ 27), and symptomatic PAD – leg symptoms were captured by a validated survey and PAD was confirmed with the use of the ankle-brachial index (ABI) which is the ratio of the systolic blood pressure in the ankle to that in the arm. Our cut-point for the ABI was <0.9.

Individuals were excluded if they demonstrated at least one of the following conditions: intolerance to fruits, vegetables, fiber, and/or a low-fat diet, restricted water intake, pregnant, prior major ischemia or critical leg ischemia, use of 24-hour supplemental oxygen, heart attack within the last 3 months, inability to walk for exercise, or currently walking at least 3 days per week for at least 30 minutes each day. The University of Kansas Medical Center Institutional Review Board (KUMC IRB) approved this study and participants gave informed consent. The clinical trial registration for this study is NCT03694652.

Recruitment

We recruited study participants using a variety of modalities which included both the University of Kansas hospital system as well as unaffiliated health centers and community-based clinics.

Area clinicians and administrators voluntarily distributed flyers and mailings to eligible patients. We obtained KUMC IRB approval—as well as permission from participating hospitals and clinics--prior to each phase of the recruitment process.

Interventions

Motivational Interviewing (MI)

Participants randomized to MI participated in an initial one-hour, face-to-face session. Following the initial visit, we conducted four, 20-minute telephone calls; one call every two weeks for one month followed by two monthly phone calls.

Author KR provided MI counselor training through a series of workshops. The counselor was a medical school graduate and a student in the master's in public health program at KU School of Medicine-Wichita who was also applying for residency in primary care. Although the counselor had no experience in MI prior to this trial, author KR has trained multiple research staff in the delivery of MI. There were standardized patients and ongoing review of sessions through direct observation. The counselor's goals were to elicit and reinforce change talk about increasing walking behavior and healthy dietary habits.

During each counseling session, the counselor assessed participants' willingness to walk for exercise using the Patient-centered Assessment and Counseling for Exercise survey (PACE), which assesses readiness to exercise.[20, 21] Following a discussion of their current PACE score, the counselor queried patients about the importance of exercising and their current

motivation to increase walking behavior. The counselor concluded each session by offering patients the option to set a walking goal for the next two weeks.

The counselor followed a similar process with respect to the nutritional portion of the interview. She guided patients to choose one of six nutritional options to work on in the following two weeks: (1) reducing sodium, (2) increasing fruits, (3) increasing vegetables, (4) decreasing sugary drinks, (5) increasing whole grains, or (6) mindful eating. Similar to the exercise therapy, the counselor discussed the importance of change, patients' confidence levels, and individual values. After patients established exercise and nutritional goals, counselors would arrange for subsequent follow-up sessions at two-week intervals.

Smartphone Application

Development

We created the PAD Mobile App with support from the Center for Excellence in Health Communication to Underserved Populations at the University of Kansas School of Journalism and Mass Communication. Author MG supervised the design, operational functionality, and development of the App. We employed iterative feedback from experts and research team members to design the user interface, content, and functionality.

The App was designed for use with Android OS smartphones—patients without this type of phone received it as part of the study. We tailored nutritional content for clarity and lower health literacy levels. We designed the mobile app to allow users to input walking plans, track walking intervals, and record episodic pain. We designed in-app notifications to encourage patient use as well as diet and exercise management.

The App was completely automated and adaptive to patient use. The study team was available to troubleshoot and answer questions as needed. Safeguards permitted recovery of previously saved data in the event of accidental malfunction. Participant data was encrypted and saved locally to the phone. Once initialized, the App sent secure, de-personalized data to an online backup server via the internet.

Table 1. Behavior Change Techniques – Nutrition and Physical Activity

Technique	MI	App
1.1 Goal Setting (behavior): agreed on weekly walking goals	✓	✓
1.2 Problem solving: identifying triggers to eating unhealthy foods or avoiding walking for exercise	✓	✓
1.4 Action planning: setting aside time to exercise and planning meals in advance	✓	✓
1.6 Discrepancy between current behavior and goal: recorded walking goals or self-reported dietary goals were not met		✓

Table 1. Behavior Change Techniques – Nutrition and Physical Activity (cont'd)

Technique	MI	App
3.1 Social Support (unspecified):participants received recommendations on the value for having a buddy to walk with	✓	✓
4.1 Instruction on Walking Therapy to Improve Walking Distance	✓	✓
4.3 Re-attribution: if a participant attributed their desire for food to boredom, we provided guidance on mindfulness eating		✓

5.1 Information about health consequences: participants were provided information about the potential for disease progression in the absence of a walking intervention	✓	✓
5.4 Monitoring of emotional consequences: participants were queried about satisfaction with their weekly dietary and walking goals		✓
8.2 Behavior substitution: participants were provided with guidance on substituting unhealthy dietary choices with healthy dietary choices		✓
9.1 Credible source: participants viewed videos in which the Principal Investigator, who is board certified in internal and vascular medicine, shared the importance of walking for exercise for persons with PAD		✓
9.2 Pros and cons: participants were queried regarding the pros and cons of eating a healthy diet as well as walking for exercise	✓	✓
10.4 Social reward: participants were congratulated for achieving their weekly goals		✓

Table 1. Behavior Change Techniques – Nutrition and Physical Activity (cont'd)

Technique	MI	App
13.2 Framing/reframing: participants were provided with cognitive structuring to think of tasks to reduce sedentary behavior	✓	✓
15.1 Verbal persuasion about capability: participants were told they can walk for exercise despite leg discomfort	✓	✓

Michie et al, 2013

Implementation

We developed the PAD Mobile App specifically for this pilot study based on the PACE and MI principles described above. The PAD Mobile App had two distinct components: a nutritional component and a walking component. Similar to the MI group, the nutritional component of the mobile App contains six modules, with each of the six topics designed to be completed over a two-week time period. We designed each module to reflect nutritional issues specific to PAD patients. Of these modules, patients were permitted to choose the order of completion—yet, this completion was self-initiated. The App employed identical measures for assessing patients' perceptions of the importance of change, confidence levels, and individual values. The App utilized the PACE format to set exercise goals, and self-assessment to set nutritional goals over a 12-week period. Similar to the MI group, nutritional modules were further divided into six, two-week cycles.

On the first day of the study, patients installed the App, and it prompted them to enter their demographic, health, and identity information. The App then presented patients with six possible nutritional changes that they could choose to address during the first two-week cycle (Figure 1). Once participants chose one of the six dietary modifications, they were prompted to perform a self-assessment; the App would then adjust goals according to patients' responses.

We made explicit efforts to ensure that patients would not have trouble installing, using, or interacting with the application. Several safeguards were installed to provide patients with continuous support and resources. The App provided extensive exercise tracking (Figure 1) as well as a comprehensive reporting menu with information about patient progress (Figure 1).

Automatic reminders prompted participants to engage with the App and to select their next PAD intervention cycle at two-week intervals.

Measures

Ankle-Brachial Index (ABI)

The ABI was used to define the presence or absence of PAD. During this assessment, a participant rested for 5 minutes and a 5 MHz hand-held Doppler with an attached stethoscope was used to measure systolic blood pressures in both brachial arteries and in both ankles (i.e., the dorsalis pedis and posterior tibial arteries).[22]

Medical History

The PI and colleagues developed the Lifestyle and Clinical Survey (LCS) to obtain patients' medical history—including smoking status—sociodemographic, and comorbidity data. It has a summary k-statistic for reliability of 0.81 (95% confidence interval [CI] 0.78, 0.84) and a summary k-statistic for validity of 0.58 (95% CI 0.52, 0.64).[23]

Stage of Readiness to Engage in Exercise

The Patient-Centered Assessment and Counseling for Exercise (PACE) score was used to identify a participant's readiness for exercise. To obtain a PACE score, a participant chose one of eight graded statements that best described his/her current level of and interest in physical exercise [24, 25] We assessed a participant's PACE score at baseline and 6 weeks; we employed these assessments to tailor each intervention to each patient's respective stage of readiness.

Outcomes

The primary outcome was the three-month change in walking distance, as measured by the 6-minute walk test (6MWT). The 6MWT provides information on a patients' ability to walk in the community. The test is conducted by placing two cones 100 feet apart in a marked hallway and instructing patients to walk as many laps around the cones as possible. Patients were permitted to stop walking during the test; however, time was recorded during the rest period. We recorded time and distance to onset of leg discomfort and total feet walked. In a prior study involving 64 patients with PAD, the reliability coefficient for distance during 6-minute walk tests performed one week apart was 0.94 with a coefficient of variation of 11.7%.[26]

Secondary outcomes included weight loss, quality of life, exercise behaviors, and dietary habits. For weight loss, we used a standardized scale to measure body weight. For health-related quality of life, we used the validated Vascular Quality of Life Questionnaire (VascuQuol Score).[27] The intraclass (reliability) coefficient for the VascuQuol was 0.94 (CI > 90%), and Cronbach α ranged between .7 and .9, indicating good internal consistency within the five domains. The VascuQol total score has a correlation with the Fontaine classification of disease severity [28] of $r = –0.79$ ($P < .001$) and with treadmill walking distances of $r = 0.36$ ($P < .05$). For self-reported physical activity, we used the validated Stanford Patient Education Research Center Exercise Behavior Survey.[29, 30] The Exercise Behavior Survey retest reliability scores between 0.56-0.72. We employed the Fat-Related Diet Habits Questionnaire[31] to assess basic consumption as well as healthier choices, such as substitution of low-calorie or low-fat food alternatives. We modified the survey to a 3.9 reading level. The Fat-Related Diet Habits Questionnaire has high test-retest and internal consistency reliabilities and correlations with percent of calories from fat ranging from 0.34 to 0.57 ($P < .01$). The correlation of the sum of the five scales with percent of

calories from fat is 0.68 (P< .001) and, in multiple regression models, the multiple R2 using all factors to predict percent of calories from fat was 0.47. All outcomes were measured at baseline and 3 months.

Study Flow

Screening

We pre-screened potential participants via phone. The pre-screen assessment captured (1) physical activity readiness (Physical Activity Readiness Questionnaire [PAR-Q]) - the PAR-Q was used to identify conditions which would preclude participation in the study[32], and (2) leg symptoms (San Diego Claudication Questionnaire).[33] Based on eligibility criteria, we scheduled candidates for an in-person visit.

Baseline In-person Visit and Randomization

After obtaining informed consent, a blinded assessor measured individuals' ABI, weight and height. We referred eligible candidates to graded submaximal treadmill testing, as per American College of Cardiology guidelines.

Upon completion of treadmill testing and without evidence of coronary ischemia, participants completed questionnaires to assess quality of life, exercise behaviors, and dietary habits. We then randomly assigned participants to the App or MI. We used a random number generator to blindly assign patients to one of the two groups.

Analysis Plan

We used Wilcoxon rank-sum test to analyze the primary outcome of change in 6-minute walking distance at three months within the MI and App groups, and to compare the changes between the groups with adjustment for baseline (difference in difference). We used this same method for other outcomes. For comparing participants' baseline characteristics between the MI and App groups, we used Wilcoxon test for continuous measurements and Fisher's test for dichotomous measurements. We use R version 4.03 (R Foundation for Statistical Computing) for all data analyses.

Thirteen participants per group were required to provide 80% power at a0.05 error level and to detect a difference between the two groups of 50 meters walking distance change.