Diabetic women are poor responders to exercise rehabilitation in the treatment of claudication

Andrew W. Gardner, PhD,[a,b] Donald E. Parker, PhD,[c] Polly S. Montgomery, MS,[a] and **Steve M. Blevins, MD,[d]** *Oklahoma City, Okla*

Background: **It is not clear whether subgroups of patients with peripheral artery disease (PAD) and claudication respond more favorably to exercise rehabilitation than others. We determined whether sex and diabetes were factors associated with the response to exercise rehabilitation in patients with claudication.**

Methods: **Eighty patients were randomized to home-based and supervised exercise programs, and 60 finished with complete exercise intervention data. Exercise consisted of intermittent walking to near maximal claudication pain for 3 months. Primary outcome measures included claudication onset time (COT) and peak walking time. Patients were partitioned into diabetic and nondiabetic groups and then further partitioned by sex to form four groups.**

Results: **Overall, exercise adherence was high (84%), and there was no significant difference ($P > .05$) in the amount of exercise completed among the four groups. All groups had significant improvements ($P < .05$) in COT and peak walking time after exercise rehabilitation, except for diabetic women ($P > .05$). Only 37% of women with diabetes had an increase in COT compared with 100% of men with diabetes ($P < .01$), and their risk ratio for nonresponse was 9.2 ($P < .0001$).**

Conclusions: **Women with PAD and claudication, particularly those with diabetes, represent a vulnerable subgroup of patients who respond poorly to a program of exercise rehabilitation. Diabetic women with PAD and claudication may need a greater dose of exercise or another intervention separate from or in combination with exercise to elicit improvements in claudication measures that are similar to nondiabetic women and to diabetic and nondiabetic men. (J Vasc Surg 2014;59:1036-43.)**

Peripheral artery disease (PAD) is prevalent in 8 million Americans[1] and is associated with high health economic costs and high rates of morbidity and mortality similar to coronary heart disease and ischemic stroke.[2,3] Although the prevalence of PAD in women is similar to men at all ages, the burden of PAD, defined as the total number of individuals who have PAD, is greater in women.[4] These numbers are especially impressive given that women are less likely to report symptoms than men,[5] particularly those characteristic of classic intermittent claudication.[6] Once becoming symptomatic, women have a twofold higher mortality rate,[7] a more functionally dependent lifestyle,[5,8] shorter distances to the onset of claudication pain and to maximal pain,[9] and more impaired oxygen saturation of the calf muscle during ambulation than men.[10] More severe impairments in claudication and in calf muscle oxygen saturation in women with PAD may make them particularly vulnerable for progressively worse lower extremity function when these limitations are combined with comorbid conditions that impair microcirculation, such as diabetes.[11,12]

Supervised exercise programs are efficacious for clinical management of claudication[13-16] and have been given a class IA recommendation by the American College of Cardiology and the American Heart Association.[17] Although treatment of claudication with exercise rehabilitation is well documented, whether subgroups of PAD patients respond more favorably than others is not clear. For example, there is a paucity of data on the efficacy of exercise rehabilitation in women who have PAD and claudication, because only a small percentage (27%) of eligible patients in 32 previous randomized exercise trials have been women.[4] Furthermore, comparing sex-specific responses to exercise has not been addressed. Diabetes is another example in which there is conflicting and surprisingly little data on the efficacy of exercise rehabilitation. One recent study found that claudication distances did not improve in PAD patients with diabetes after 6 months of exercise,[18] whereas another recent report found that diabetic patients improved to a similar extent compared with nondiabetic patients.[19]

To address the dearth of information on the potential influences of sex and diabetes on responses to an exercise program, we conducted a follow-up analysis to our recently published[20] prospective, randomized controlled exercise

From the Reynolds Oklahoma Center on Aging, Donald W. Reynolds Department of Geriatric Medicine, University of Oklahoma Health Sciences Center (OUHSC)[a]; the Veterans Affairs Medical Center[b]; and the Department of Biostatistics and Epidemiology[c] and the General Internal Medicine Section, Department of Medicine,[d] OUHSC.

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Reprint request: Andrew W. Gardner, PhD, OUHSC, Donald W. Reynolds Department of Geriatric Medicine, 1122 NE 13th St, O'Donoghue Research Building, Ste 1200, Oklahoma City, OK 73117 (e-mail: andrew-gardner@ouhsc.edu).

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trial in PAD patients with intermittent claudication. The primary aim of the current study was to determine whether sex and diabetes were factors associated with the response to exercise rehabilitation in patients with claudication. Secondary aims were to determine whether the amount of exercise completed during intervention was different according to sex and diabetes status, whether the amount of exercise completed was associated with the change scores of claudication onset time (COT) and peak walking time (PWT), and to determine the characteristics of patients who do not respond to exercise intervention. Our primary hypothesis was that women would experience less improvement in the primary outcome measures of COT and PWT, that the presence of diabetes would blunt the improvement in the primary outcomes, and that the effect of diabetes would be greater in women than in men.

METHODS

The procedures used in this study were approved by the University of Oklahoma Health Sciences Center (HSC) Institutional Review Board.

Patients

Recruitment. Patients participated at the General Clinical Research Center (GCRC), University of Oklahoma Health Sciences Center (HSC) from September 2004 to April 2007. Patients were recruited by HSC vascular clinic referrals and by newspaper advertisements. Written informed consent was obtained from each patient before investigation.

Screening. Patients who had claudication secondary to vascular insufficiency were included if they met the following criteria: (1) a history of any type of exertional leg pain, (2) ambulation during a graded treadmill test limited by leg pain consistent with claudication,[21] and (3) an ankle-brachial index (ABI) $\leq$0.90 at rest[17] or an ABI $\leq$0.73 after exercise.[22] Patients were excluded for the following conditions: (1) absence of PAD (ABI >0.90 at rest and ABI >0.73 after exercise), (2) inability to obtain an ABI measure due to noncompressible vessels, (3) asymptomatic PAD determined from the medical history and verified during the graded treadmill test, (4) use of cilostazol or pentoxifylline initiated $\leq$3 months before investigation, (5) exercise tolerance limited by any disease process other than PAD, (6) active cancer, (7) end-stage renal disease defined as stage 5 chronic kidney disease, (8) abnormal liver function, and (9) randomization into the usual care control group.

As shown in our previous report,[20] 80 patients were randomized to the home-based exercise program (n = 40) or to the supervised exercise program (n = 40), and 60 patients completed both the exercise training programs (n = 29) and the post-tests (n = 31). The remaining 20 patients were not included in our primary analyses because 14 made personal decisions to discontinue, 4 were medically excluded because of experiencing a stroke, myocardial infarction, leg revascularization, and hernia surgery during the study, and 2 were excluded because they had incomplete exercise training data.

Exercise interventions

Home-based exercise rehabilitation program. Exercise sessions in our home-based exercise program were rigorously quantified with a StepWatch3 step activity monitor (Orthoinnovations Inc, Oklahoma City, Okla) to accurately record the duration and cadence of ambulation. The home-based exercise program was designed to be as similar to the supervised exercise program as possible, and we were indeed successful in matching the exercise volume and exercise compliance of the two programs.[20] The home-based exercise program consisted of 3 months of intermittent walking to near maximal claudication pain 3 days per week at a self-selected pace. Walking duration began at 20 minutes for the first 2 weeks and progressively increased 5 minutes biweekly until a total of 45 minutes of walking was accomplished during the final 2 weeks of the program.

Patients were given a step activity monitor and were instructed to wear it on the right ankle during each exercise session and then to remove the monitor at the completion of each session. They also received an exercise logbook to record their walking sessions. Patients returned their step activity monitors and logbooks to the research staff at the end of week 1, 2, 4, 6, 8, 10, and 12 of the program, and data from the monitor were downloaded. During these brief 15-minute meetings, patients discussed their progress with an exercise physiologist, were given feedback about the data from the step activity monitor, and were given new instructions regarding changes in exercise duration. Patients did not perform any exercise in our facility during these meetings with the research staff.

Supervised exercise rehabilitation program. The supervised program was designed to elicit increases in COT and PWT according to our previous studies.[13,20,23,24] This standardized program consisted of 3 months of supervised, intermittent treadmill walking, 3 days per week at a speed of approximately 2 mph. Walking duration began at 15 minutes for the first 2 weeks of the program, and progressively increased by 5 minutes biweekly until 40 minutes of walking was accomplished during the final 2 weeks of the program. Patients exercised at a relatively low intensity by walking at a grade equal to 40% of the final workload from the baseline maximal treadmill test. Patients walked to the point of near maximal claudication pain, at which point they stopped to relieve their leg pain. Patients then repeated the intermittent walking and rest periods until the prescribed total number of minutes of exercise was attained for the training session. During each exercise session, patients wore a step activity monitor on the right ankle to quantify the cadence and time of ambulation. Patients in the supervised program were not given advice or instructions to perform additional exercise away from our research center.

Measurements

Medical history and physical examination. Patients arrived in the morning fasted, but were permitted to take