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Exercise Accelerates Wound Healing Among Healthy Older Adults: A Preliminary Investigation

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Background. Older adults are likely to experience delayed rates of wound healing, impaired neuroendocrine responsiveness, and increased daily stress. Exercise activity has been shown to have a positive effect on physiological functioning and psychological functioning among older adults. This study evaluated the effect of a 3-month exercise program on wound healing, neuroendocrine function, and perceived stress among healthy older adults.

Methods. Twenty-eight healthy older adults (mean age 61.0 ± 5.5 years) were assigned randomly to an exercise activity group ($n = 13$) or to a nonexercise control group ($n = 15$). One month following baseline randomization, after exercise participants had acclimated to the exercise routine, all participants underwent an experimental wound procedure. Wounds were measured 3 times per week until healed to calculate rate of wound healing. All participants completed assessments of exercise endurance, salivary cortisol, and self-reported stress prior to randomization and at the conclusion of the intervention.

Results. Exercise participants achieved significant improvements in cardiorespiratory fitness, as reflected by increased oxygen consumption (VO_2max) and exercise duration. Wound healing occurred at a significantly faster rate in the exercise group [mean = 29.2 (9.0) days] than in the nonexercise group [38.9 (7.4) days; $p = .012$]. Exercise participants also experienced increased cortisol secretion during stress testing following the intervention. Group differences in wound healing and neuroendocrine responsiveness were found despite low levels of self-reported stress.

Conclusions. A relatively short-term exercise intervention is associated with enhanced rates of wound healing among healthy older adults. Thus, exercise activity may be an important component of health care to promote wound healing.

AMONG older adults, wound healing is delayed and risk of infection during wound healing is elevated (1,2), although age-related changes in wound healing may be due, in part, to comorbid conditions (3). Psychological stress may exacerbate delays in wound healing among healthy older adults, as observed among female caregivers of patients with Alzheimer's disease (4), via impaired epidermal barrier function (5,6) and dysregulated cytokine production (7,8). In addition, older adults may exhibit a reduced capacity for neuroendocrine response to disruptions in homeostasis (9).

Health behaviors appear to have an effect on both immune function and wound healing. Among the most commonly studied health behaviors (e.g., smoking, diet, exercise), physical exercise is especially relevant because of its influence on multiple components of the wound-healing system, including associations with immune and endocrine function (10), as well as its effect on psychological stress (11). Thus, it is important to evaluate the influence of exercise on wound healing, neuroendocrine function, and stress among older adults.

Past studies have demonstrated the feasibility of improving exercise endurance and reducing psychological distress of older adults with a relatively brief (10–12 week) exercise intervention (11,12). Reduced stress, in turn, has been associated with attenuated cortisol levels (13). Thus, there is evidence that physical exercise is a viable intervention to mitigate the negative effects of age and psychological stress in the wound-healing process. However, no prior study has examined the effect of exercise on wound healing in a laboratory experiment with a controlled exercise intervention. This preliminary study evaluated the influence of exercise on wound healing in a randomized controlled investigation. To address one possible mechanism by which exercise may influence wound healing, the study examined changes in stress as measured both by self-report and via salivary cortisol. It was hypothesized that a 3-month program of aerobic exercise, in comparison to a no-treatment control condition, would be associated with: (a) increased cardiopulmonary endurance, (b) significantly faster healing of a dermal wound, (c) lower resting cortisol levels, (d) an enhanced cortisol response to exercise, and (e) lower self-reported stress.

METHODS

Participants

Twenty-eight sedentary older adults [mean age = 61.0 (5.5) years; range: 55–77 years; 68% women] were recruited to participate in this study. The study sample size was based on an effect size from a prior study of wound healing among older adults (4). The randomization procedure was designed to assign two additional participants to the control group to account for higher anticipated attrition from the control condition, as shown in Figure 1. Participants were in good health, with no clinical symptoms or signs of heart disease

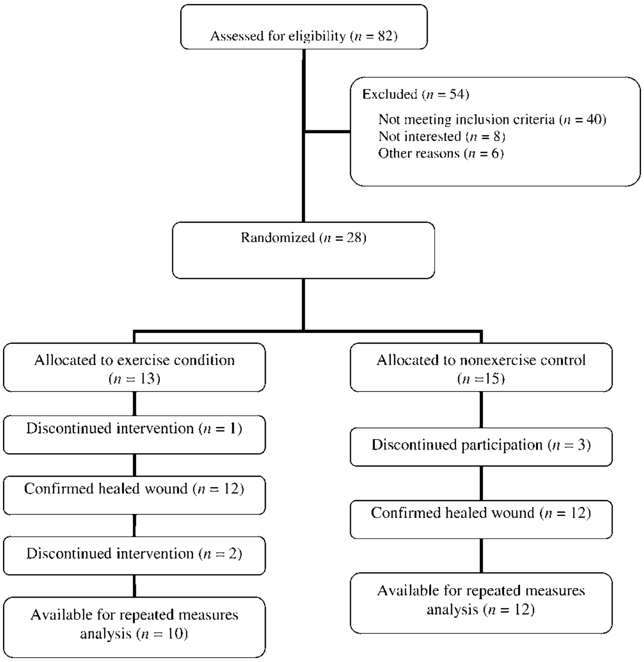

Figure 1. Study profile.

or hypertension and normal resting and exercise electrocardiograms. Sedentary status was defined as not being currently engaged in a program of regular physical exercise and not having engaged in regular exercise for at least 6 months. Potential participants were excluded if there was a history of diabetes, peripheral vascular disease, difficulty with wound healing, immunologically related health problems (e.g., cancer, autoimmune disease, recent surgery), other medical conditions that would limit participation in a regular exercise program (e.g., pulmonary disease, orthopedic problems, major psychiatric illness, or other acute medical problem), or current use of anti-inflammatory medication or medication with immunological consequences. Because data suggest that estrogen-replacement therapy may have a positive effect on wound healing (14), assignment of women using hormone-replacement therapy was balanced across the two conditions.

All participants provided written informed consent. The consent form and all study procedures were approved by the Ohio State University (OSU) Institutional Review Board.

Procedures

Participants completed assessments at baseline and after 3 months. Following the baseline assessment, participants were assigned randomly to either a 3-month program of aerobic exercise or to a nonexercise control group. After 1 month, all participants underwent the experimental wound procedure described below but continued in the assigned condition (exercise or nonexercise) for the remaining 2 months of the intervention, until the 3-month assessment. This schedule provided participants with a 1-month lead-in period of exercise prior to the wound procedure so that wound healing would not be confounded by physiological adaptation associated with initiating a program of regular physical exercise.

Aerobic exercise.—Exercise sessions were conducted 3 days per week for 1 hour each day at the OSU Center for Wellness and Prevention. Based on maximum heart rate (HR) achieved during the baseline exercise test, participants were assigned exercise HR training ranges equivalent to approximately 70% maximum HR. Participants monitored HR via radial pulse and recorded it in daily exercise logs three times during each exercise session. Exercise sessions began with 10 minutes of warm-up floor exercises and stretching, followed by 30 minutes of continuous bicycle ergometry at an intensity sufficient to maintain HR within the assigned training range. Participants then engaged in 15 minutes of brisk walking and/or jogging and arm-strengthening exercise (on an arm ergometer) for 15 minutes. Each exercise session concluded with 5 minutes of cool-down exercises.

Nonexercise control.—Participants randomized to the nonexercise control group did not receive any form of exercise training and were instructed not to change physical activity habits during the 3-month period. Participants in both groups were asked to maintain their regular dietary habits throughout the duration of the study.

Wound procedure.—The wound procedure was conducted at the OSU General Clinical Research Center (GCRC) immediately following the 1-month assessment. All participants underwent a low-risk punch biopsy procedure (15) used in dermatological research. A Miltex Instruments kit (York, PA) was used to create a uniform 3.5-mm wound on the back of the nondominant upper arm. The wound was covered immediately with an adhesive bandage for 24 hours, after which no further bandaging was necessary. A high resolution digital camera (Sony Cyber-Shot, DSC-S50; New York, NY) was used to photograph the wound 1 week after the wound procedure. Thereafter, additional photographs were taken 3 days per week until the wound was no longer visible. For each digital photograph, a standard 5-mm black dot was placed next to the wound as a measurement guide. Participants in both the exercise and nonexercise conditions followed the same schedule of wound-measurement photographs.

Measurement of wounds for all participants was conducted using the following procedure. Each wound photograph was scanned into a computer file, and the wound and dot in each photograph were measured on-screen with Canvas 7 (version 7.0.2, 2000; Deneba Systems, Inc., Miami, FL). Wound size was expressed as the ratio of the wound area to the dot area in each photograph. Each wound was measured by two research assistants who were blind to group assignment. Interscorer reliability was excellent (>98%). Wounds were considered healed when the wound-to-dot ratio was less than 10%.

Assessment Procedure

Participants completed comprehensive assessments of exercise endurance, salivary cortisol, and stress at baseline and at the 3-month assessment. All assessments occurred in the morning with participants in a fasting state.

Exercise endurance.—Participants completed a standard symptom-limited graded exercise treadmill test using a modified Ekelund protocol. Workloads were increased at a rate of approximately 1 metabolic equivalent per minute. Exercise was continued until limited by excessive fatigue and/or shortness of breath. Expired air was collected by mouthpiece for quantification of oxygen consumption (Cardio2; Medgraphics, St. Paul, MN). The electrocardiogram was monitored continuously, and standard limb leads and leads V5 and V6 were recorded initially and after each minute of exercise. Arterial blood pressure was measured by cuff manometry at rest and during each minute of exercise. Exercise training was documented by measuring the duration of the exercise test and maximal oxygen consumption (VO_2max) during exercise.

Cortisol.—Salivary samples were collected, and salivary cortisol was assayed using chemiluminescent techniques (8). In addition, participants provided salivary samples on two separate days (4 times each day) during the week following each assessment to provide an indicator of diurnal variation in cortisol and overall cortisol levels associated with the intervention.

Perceived stress.—The 10-item Perceived Stress Scale (PSS; 16) was used to evaluate the degree to which respondents perceived their lives to be stressful (e.g., unpredictable, uncontrollable). Each item is rated on a 5-point Likert scale, and scores may range from 0 to 40. Prior studies have documented adequate reliability and validity of this measure (17).

Data Analysis

The primary mode of data analysis was repeated-measures analysis of variance (ANOVA) with assessment time (baseline vs 3 months) as a within-subject variable and condition (exercise vs nonexercise) as a between-subject variable. In the presence of a statistically significant Time × Condition interaction, effects of time within condition were evaluated.

Results

One participant dropped out of the exercise condition prior to confirmed healing of the wound, and two additional participants dropped out prior to the 3-month assessment. Thus, wound-healing data were available for 12 of the 13 participants. Among the 10 participants who completed the 3-month assessment, adherence was excellent with a mean number of 36.9 (±1.6) exercise sessions completed.

Among the 15 participants assigned to the nonexercise condition, 3 dropped out before the study was terminated, leaving 12 control participants with wound-healing data and complete baseline and 3-month assessments, as shown in Figure 1.

Table 1. Mean (Standard Deviation) Exercise Endurance, Salivary Cortisol, and Stress in Exercise and Nonexercise Groups

	Exercise ($N = 10$)		Waiting List ($N = 12$)	
Variable	Pretest	Posttest	Pretest	Posttest
VO_2max	24.9 (5.4)	26.6 (5.8)*	23.2 (4.0)	22.1 (4.5)
Exercise time	8.45 (1.39)	10.66 (1.33)†	8.74 (1.40)	8.67 (1.89)
BMI	27.1 (3.2)	26.7 (3.7)	26.5 (3.9)	26.3 (3.7)
Cortisol				
Prestress	0.44 (.78)	0.40 (.33)	0.28 (.21)	0.41 (.20)
Poststress	0.31 (.24)	1.24 (1.30)‡	0.27 (.22)	0.36 (.24)
Perceived stress	10.3 (6.7)	10.9 (6.3)	12.2 (7.4)	12.4 (8.7)

Notes: *Within-group simple time effect, $p < .05$.

†Within-group simple time effect, $p < .001$.

‡Within-group simple time effect from prestress test to poststress test, $p < .05$.

VO_2max = maximum oxygen consumption during stress testing; BMI = body mass index.

Exercise Training/Fitness

Repeated-measures ANOVA of VO_2max revealed a significant Time × Condition interaction [$F(1,20) = 9.23$, $p = .007$], with exercise participants achieving a significant increase in maximal oxygen consumption after 3 months whereas nonexercise participants experienced no change, as shown in Table 1. Similarly, there was a significant Time × Condition interaction for treadmill exercise time [$F(1,20) = 10.99$, $p = .004$], with exercise participants achieving a significant increase in time to maximal performance after 3 months whereas nonexercise participants did not change.

Body mass index was calculated for each participant as weight (in kilograms) divided by height (in meters) squared. As shown in Table 1, body mass index did not change for either group.

Wound Healing

Wound-healing data for one participant in each condition was uninterpretable, leaving wound-healing data for 11 participants in each condition. Consistent with the experimental hypotheses, wounds for participants in the exercise condition healed significantly faster [mean = 29.2 (9.0) days; range 16–38 days] than those for participants in the nonexercise condition [mean = 38.9 (7.4) days; range 29–49 days], as demonstrated by a one-way ANOVA [$F(1,20) = 7.64$, $p = .012$]. The condition effect remained significant when hormone-replacement therapy status was statistically controlled via analysis of covariance. There were no complications or infections during the course of wound healing for either group.

Figure 2 indicates the proportion of participants in each condition with healed wounds in weeks 2–7 following the wound procedure and provides graphic evidence of the more rapid wound-healing rate in the exercise group than in the nonexercise group. As indicated in Figure 2, no participants had healed wounds by week 2, and all participants had healed wounds by week 7. Post hoc chi-square analyses of data for weeks 3–6 indicated that the proportion of participants with healed wounds at week 4 was significantly greater in the exercise condition than in the nonexercise condition [$X^2(1) = 8.25$, $p < .005$].

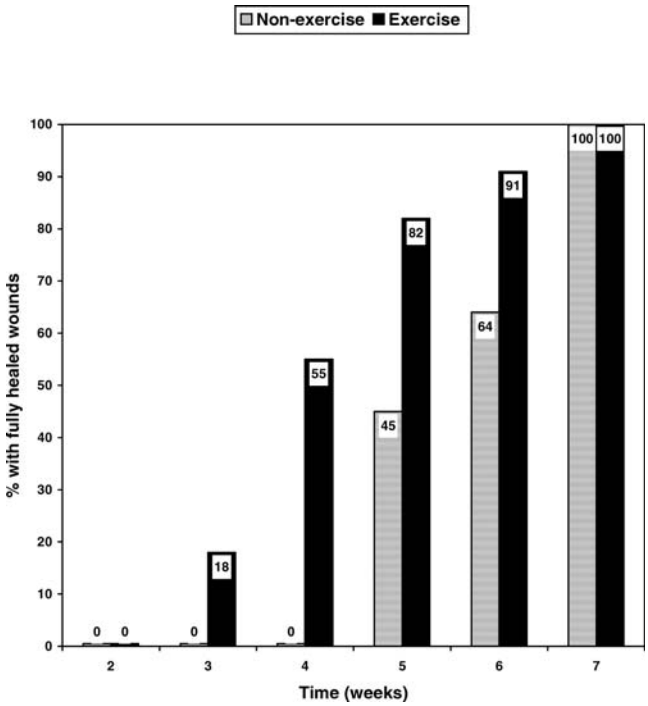

Figure 2. Proportion of participants in each group with fully healed wounds in weeks 2–7 ($n = 22$; $n = 11$ in each group).

Cortisol

Cortisol response to exercise activity was evaluated using a repeated-measures ANOVA, with four levels of time (pre- and poststress testing at both the baseline and 3-month assessments). Results indicated a significant Time $\times$ Condition interaction [$F(3,13) = 6.19$, $p = .008$]. Simple effects testing of change at each stress test session indicated that exercise participants experienced a significant increase in cortisol secretion during the stress test at the 3-month assessment, but cortisol secretion among the nonexercise participants did not change at the 3-month evaluation, as shown in Table 1.

To evaluate the influence of exercise on cortisol secretion, mean daily cortisol readings were summarized by calculating the area under the curve (18). Repeated-measures ANOVA of the area under the curve at baseline and at 3 months revealed no significant interaction effect.

Stress

Repeated-measures ANOVA indicated that self-reported stress (PSS) did not change as a result of the exercise intervention, as shown in Table 1. However, the mean PSS score for this sample (total score mean $= 12.0 \pm 7.8$) at baseline reflected a very low level of overall distress. Thus, it was unlikely that scores would be affected by the exercise intervention.

Discussion

This study demonstrates a beneficial effect of exercise activity on wound-healing rates among healthy older adults. Moreover, exercise was associated with an enhanced neuroendocrine response among the exercise participants. Thus, the data are consistent with the notion that exercise may facilitate wound healing, in part, via neuroendocrine regulation. Although it was hypothesized that exercise would be associated with reductions in resting cortisol levels, the increased responsiveness of cortisol to stress testing following the exercise intervention suggests that exercise contributed to enhanced neuroendocrine responsiveness. Changes in cortisol responsivity, in turn, may be associated with additional neuroendocrine and immune function changes relevant to the wound-healing process. Also, exercise may contribute to blood flow to the skin and increased skin oxygen tension, thereby enhancing wound-healing rates. There was no evidence that changes in cardiopulmonary endurance per se were associated with wound-healing rate (i.e., nonsignificant correlations of change in VO_2max with days until healed), suggesting that other mechanisms associated with exercise may influence wound healing.

This sample of older adults was largely healthy and nondistressed. To conduct this initial randomized study, individuals with medical conditions that might negatively influence wound healing were excluded. Thus, generalizability of the results would be limited to healthy older adults. Further research is required to determine the influence of exercise on wound healing in a wider range of older adults including those reporting greater psychological distress. Among distressed older adults, it is likely that distress would be more likely to moderate the influence of exercise on wound healing. Indeed, prior studies have documented an inverse relationship between stress and physical exercise (19), and an attenuating effect of exercise on stress responses among middle-aged and older adults (20,21). In this nonstressed sample of older adults, neuroendocrine changes were associated with differential rates of wound healing. Further investigation is warranted to evaluate additional mechanisms that may contribute to the observed effect of exercise on wound healing, including exercise-related changes in immunologic function (e.g., proinflammatory cytokines; 10) and neuroendocrine function (e.g., growth hormone, insulin-like growth factor; 22,23).

The results of this study provide evidence for the benefit of physical exercise in the wound-healing process among older adults. The wound-healing rate in the nonexercise group (38.9 days) was nearly identical to that of normal control participants (39.3 days) in prior research on wound healing (4), further indicating that the exercise effect observed in the present study truly represents an enhanced rate of wound healing beyond the norm for this age group. This observed enhancement in the rate of wound healing has not been documented previously. Because exercise can be construed as a controllable form of physical stress, the enhanced rate of wound healing in this study is consistent with prior data indicating that hormonal response (cortisol) to stress may serve to facilitate endogenous immune-function processes in the skin (24). From a practical perspective, the results provide empirical support for the relevance of considering exercise activity as a component of medical care among patients who have sustained dermal wounds or who are recovering from surgical procedures.

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David J. Frid is now with Pfizer, Inc.

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