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Resveratrol and exercise to treat functional limitations in late life: Design of a randomized controlled trial

Andrew S. Layne, Lisa M. Krehbiel, Robert T. Mankowski, Stephen D. Anton, Christiaan Leeuwenburgh, Marco Pahor, Bhanuprasad Sandesara, Samuel S. Wu, Thomas W. Buford*

University of Florida, Gainesville, FL, USA

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ABSTRACT

Skeletal muscle mitochondrial function declines with age and is a key factor in the maintenance of physical function among older adults. Research studies from animals and humans have consistently demonstrated that exercise improves skeletal muscle mitochondrial function in early and middle adulthood. However, mitochondrial adaptations to both acute and chronic exercise are attenuated in late life. Thus, there is an important need to identify adjuvant therapies capable of augmenting mitochondrial adaptations to exercise (e.g. improved mitochondrial respiration, muscle mitochondria biogenesis) among older adults. This study is investigating the potential of resveratrol supplementation for this purpose. The objective of this randomized, double-masked pilot trial is to evaluate the efficacy of resveratrol supplementation combined with a comprehensive supervised exercise program exercise for improving physical function among older adults. Moderately functioning, sedentary participants aged ≥60 years will perform 24 sessions (2 day/wk for 12 weeks) of center-based walking and resistance training and are randomly assigned to receive either (1) 500 mg/day resveratrol (2) 1000 mg/day resveratrol or (3) placebo. Study dependent outcomes include changes in 1) knee extensor strength, 2) objective measures of physical function (e.g. 4 m walk test, Short Physical Performance Battery), 3) subjective measures of physical function assessed by Late Life Function and Disability Instrument, and 4) skeletal muscle mitochondrial function. This study will provide novel information regarding the therapeutic potential of resveratrol supplementation combined with exercise while also informing about the long-term clinical viability of the intervention by evaluating participant safety and willingness to engage in the intervention.

1. Introduction

The maintenance of one's physical capabilities during older age is an essential part of healthy aging. Declines in physical abilities are associated with not only the onset of disability and the loss of independence but also with increased rates of morbidity and mortality [1–3]. As our group has shown previously, skeletal muscle mitochondrial function—including mitochondrial respiration, oxidative mitochondrial enzyme activity and muscle content of peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1α)–declines with age and is a key factor in the maintenance of physical function among older adults [4,5]. These biological changes have direct implications for the maintenance of key physiologic variables – including skeletal muscle endurance and aerobic fitness – which mediate physical function. Thus, interventions that improve skeletal muscle mitochondrial function hold promise for preserving physical function among seniors.

Research studies from animals and humans have consistently demonstrated that exercise – particularly aerobic exercise – improves skeletal muscle mitochondrial function in early and middle adulthood [6–9]. These changes in muscle mitochondrial function track closely with changes in whole-body aerobic fitness [10]. However, several studies in recent years have indicated that mitochondrial adaptations to both acute and chronic exercise are attenuated in late life [11–14] as are improvements in skeletal muscle oxidative capacity [10]. Thus, age-related mitochondrial

* Corresponding author. Department of Aging and Geriatric Research University of Florida, Gainesville, FL 32611, USA
E-mail address: tbuford@ufl.edu (T.W. Buford).

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impairments do not appear to be completely abated by exercise alone. Accordingly, studies to identify efficacious adjuvants to exercise have the potential to improve older adult's response to exercise interventions.

Resveratrol has received considerable attention as a gene regulator affecting mitochondrial metabolism possibly by activating 5′ adenosine monophosphate-activated protein kinase (AMPK) as well as sirtuin 1 (SIRT1) and SIRT3 [15,16]. These beneficial effects on mitochondrial function have been demonstrated across multiple species – including humans, and have been associated with improvements on a variety of functional tasks and measures of healthspan in preclinical models [15,17–22]. Resveratrol appears to oppose the reductions in mitochondrial function associated with aging largely by affecting the expression of PGC-1α and associated genes. Because several studies using animal models of aging have reported that improvements in physical performance are greater in response to the combination of exercise and resveratrol than from either treatment alone, [19,23–25], we postulated that resveratrol supplementation has significant potential as an exercise adjuvant for preserving function among older adults. This study was designed to begin to test our central hypothesis that, when combined with chronic exercise, resveratrol improves functional outcomes among functionally-limited older adults in a dose-dependent manner. The objective of this randomized pilot trial is to refine and finalize elements critical to conducting a future, fully-powered randomized, controlled trial to definitively test our central hypothesis.

2. Methods

2.1. Study design/methods

This study is a three-arm, randomized, double-masked pilot trial to evaluate the safety and efficacy of combining orally-ingested resveratrol with physical exercise for improvement of physical function among older adults at risk for becoming disabled. The study design allows for the assessment of which dosage/placebo, when coupled with exercise, improves skeletal muscle mitochondrial function, skeletal muscle function, walking speed, lower-extremity function, self-assessed physical function, or self-assessed health status. Following study entry, participants are randomly assigned to receive resveratrol supplementation at 500 mg/day, 1000 mg/day, or placebo. In addition to taking the study supplement, all participants are asked to participate in the center-based multi-model exercise intervention (Fig. 1). Participant safety is overseen by a comprehensive study team—including the principal investigator, study physician, study staff, and an appointed Data and Safety Monitoring Board. The study was registered at www.clinicaltrials.gov prior to participant recruitment (NCT02523274), and all participants provide written informed consent based on documents approved by a university Institutional Review Board.

2.2. Participants

The study team is recruiting up to 60 (n = 20/group) sedentary older men and women ≥65 years of age with objective signs of functional limitations. Inclusion criteria include a long-distance (400 m) corridor walk test time of >290 s indicating functional limitations and moderate to low aerobic fitness, [1], and a sedentary lifestyle defined as <150 min/wk of moderate physical activity as assessed by the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire [26].

Persons currently consuming a resveratrol supplement, with absolute contraindications to exercise training, [27], or with other medical conditions that would preclude safe participation are excluded.

2.3. Screening, randomization and masking

Interested individuals initially complete a pre-screening interview by phone. Participants deemed eligible based on the pre-screening are invited to an in-person screening visit. During this visit, potential participants are first asked to give their informed consent and are then screened for study entry criteria. Initial screening procedures include a review of their medical history, physical activity habits, medication use, cognitive function (assessed by the Mini Mental State Exam), [28], and a physical exam performed by a study physician. The study physician reviews collected information relevant to potential participant's health and makes a recommendation on each individual's suitability to participate in this trial.

Participants are then asked to complete the long-distance corridor walk test to evaluate functional status and aerobic fitness. If all study entry criteria are met, participants return to the clinic research center for baseline assessments prior to randomization. During this visit, participants are asked to complete validated study questionnaires, including the Late-Life Disability Instrument [29] and provide a fasting blood sample for evaluation of clinical safety lab values. Participants also complete the Short Physical Performance Battery (SPPB), a 6-minute walk test, and assessments of muscle strength. Finally, the study coordinator provides participants with a wearable physical activity monitor and dietary intake form to objectively evaluate baseline physical activity and dietary habits. Staff members then assign the participant using permuted block randomization stratified by age (i.e 65–75, >75 years) and gender. Participants who agree to participate in the muscle biopsy procedure are scheduled for a separate visit prior to initiation of study interventions.

2.4. Muscle biopsy

Willing participants undergo a percutaneous skeletal muscle biopsy as previously described [30]. Samples are collected under 2% lidocaine local anesthetic using a six-gauge needle with suction applied. Samples are snap frozen in liquid nitrogen and stored at −80 °C for later analysis. Participants currently taking anti-platelet or anti-coagulant medications, with conditions which reduce wound healing, or with a known allergy to lidocaine are excluded from the biopsy procedure.

2.5. Assessments

Study outcomes include measures of walking speed, lower-extremity function, exercise capacity, skeletal muscle strength, self-assessed physical function, and skeletal muscle mitochondrial function as described below. Physical function assessments will be assessed at baseline, week 6 and week 12, while mitochondrial function will be assessed at baseline and week 12 (Table 1).

2.5.1. Walking speed

Walking speed is assessed by asking the participants to walk at their usual pace over a 4 m course. Participants are instructed to stand with both feet touching the starting line and to start walking after a specific verbal command. Timing begins when the command is given, and the time needed to complete the entire distance is recorded. The faster of two walks is used. The reliability of the 4 m walk test is excellent – with an intraclass correlation coefficient (ICC) > 0.9 [31].