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Effect of Resveratrol on Walking Performance in Older People With Peripheral Artery Disease

The RESTORE Randomized Clinical Trial

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Key Points

Question

Does resveratrol supplementation (125 mg/d or 500 mg/d) improve the 6-minute walk distance of people 65 years or older with peripheral artery disease at 6 months' follow-up compared with placebo?

Findings

In this pilot randomized clinical trial of 66 participants with peripheral artery disease, those randomized to resveratrol, 125 mg/d, had a statistically significant but not a clinically meaningful improvement in 6-minute walk test results. Those randomized to resveratrol, 500 mg/d, had no improvement in 6-minute walk test results compared with participants randomized to placebo.

Meaning

This study found no consistent evidence that resveratrol supplementation improves walking performance among older patients with peripheral artery disease.

Abstract

Importance

Research shows that resveratrol, a sirtuin activator in red wine, improves exercise endurance and skeletal-muscle oxidative metabolism in animals and may enhance vascular function in humans. Resveratrol supplement sales exceed $30 million annually in the United States, but few data are available regarding its efficacy in humans.

Objective

To determine whether resveratrol, 125 mg/d or 500 mg/d, improves the 6-minute walk performance in patients with peripheral artery disease (PAD).

Design, Setting, and Participants

This parallel-design, double-blind, randomized clinical trial, called Resveratrol to Improve Outcomes in Older People With PAD (RESTORE), was conducted at Northwestern University. Sixty-six participants 65 years or older with PAD were randomized to receive a daily capsule of resveratrol, 125 mg or 500 mg, or placebo for 6 months. Participants were randomized using a randomly permuted block method stratified by baseline 6-minute walk test performance. This trial was conducted between January 1, 2015, and August 5, 2016, and data analyses were performed according to the intention-to-treat concept.

Interventions

Administration of resveratrol, 125 or 500 mg/d, or placebo once daily.

Main Outcomes and Measures

The primary outcome measure was the change in 6-minute walk distance at the 6-month follow-up. One of the secondary outcomes was change in maximal treadmill walking time. Because of the preliminary nature of the trial, the a priori power calculation used a 1-sided test with a significance level of $P < .10$.

Results

The 66 participants were predominantly men (45 [68%]), had a mean (SD) age of 74.4 (6.6) years, and had a mean (SD) ankle brachial index of 0.67 (0.18). Sixty-four (97%) completed follow-up. Six-month mean (SE) changes in 6-minute walk distance were 4.6 (8.1) m for the 125-mg resveratrol group, −12.8 (7.5) m for the 500-mg resveratrol group, and −12.3 (7.9) m for the placebo group ($P = .07$ for the 125-mg resveratrol group vs placebo; $P = .96$ for the 500-mg resveratrol group vs placebo). Six-month mean (SE) changes in maximal treadmill walking time were 0.5 (2.3) minutes for the 125-mg resveratrol group, −0.6 (2.1) minutes for the 500-mg resveratrol group, and 0.4 (2.1) minutes for the placebo group ($P = .18$ for the 125-mg resveratrol group vs placebo; $P = .12$ for the 500-mg resveratrol group vs placebo).

Conclusions and Relevance

The RESTORE trial found no consistent evidence that resveratrol improves walking performance in patients 65 years or older with PAD.

Trial Registration

clinicaltrials.gov Identifier: NCT02246660

Introduction

Resveratrol (3,5,4′-trihydroxy-trans-stilbene), a sirtuin 1 activator derived from red wine, increases mitochondrial activity, improves vascular function, and protects against ischemia reperfusion in preclinical studies on laboratory rats. Preliminary evidence suggests further beneficial effects of this supplement on humans.

Resveratrol to Improve Outcomes in Older People With Peripheral Artery Disease (RESTORE) is a pilot randomized clinical trial designed to gather preliminary evidence on whether resveratrol improves walking performance, vascular function, and skeletal muscle mitochondrial activity in people with lower extremity peripheral artery disease (PAD). Because recent evidence suggests that lower resveratrol doses may be more effective than higher doses, this study used a lower dose (125 mg) and a higher dose (500 mg), hypothesizing that each dose would improve both outcomes more than placebo would.

Methods

RESTORE was a parallel-design, double-blind, randomized clinical trial conducted at Northwestern University, Chicago, Illinois, between January 1, 2015, and August 5, 2016. Recruitment of participants ended when the desired sample size was achieved. Participants were randomized to resveratrol, 125 mg/d; resveratrol, 500 mg/d; or placebo (Figure). The Institutional Review Board of Northwestern University approved the study protocol (available in the Supplement). All participants gave written informed consent.

Inclusion and Exclusion Criteria

The inclusion criteria were age 65 years or older and presence of PAD (ie, an ankle brachial index <0.90, medical record–documented lower extremity revascularization, or noninvasive vascular laboratory test results consistent with PAD).

Potential participants who had below-knee or above-knee amputation, were confined to a wheelchair, used a walking aid, had a walking impairment for a reason other than PAD, had considerable visual or hearing impairment, or required dialysis were excluded. Also excluded were individuals who had lung disease requiring oxygen, had substantial liver disease, or, in the past 3 months, had a major cardiovascular event, major surgery, or endovascular revascularization. Those with a Mini-Mental State Examination score lower than 23 were excluded, along with those who had planned revascularization or major surgery in the next 6 months, were already participating in another clinical trial, were treated for cancer in the past 2 years (unless their prognosis was excellent), were currently taking or allergic to resveratrol, had a baseline 6-minute walk test result of less than 152.4 m or more than 487.7 m, or did not take at least 80% of daily placebo pills during a 2-week study run-in.

Randomization, Interventions, and Outcomes

Eligible participants were randomized by computer to daily capsules of placebo; resveratrol, 125 mg; or resveratrol, 500 mg (both 98% pure trans-resveratrol; Reserveage Nutrition), by using a randomly permuted block method stratified by baseline 6-minute walk performance.

Change in the 6-minute walk distance between baseline and 6-month follow-up was the primary outcome. Secondary outcomes were changes in maximal and pain-free treadmill walking time, brachial artery flow-mediated dilation (FMD), and calf muscle biopsy measures of peroxisome proliferator–activated receptor γ coactivator 1α, and citrate synthase and cytochrome-c oxidase activities. The brachial artery FMD and the calf muscle biopsy measures were selected because small studies in obese men showed that resveratrol improved endothelium-dependent brachial artery FMD as well as skeletal muscle mitochondrial quantity and activity.

Statistical Power

The sample size calculation was developed a priori, anticipating a 10% dropout. Twenty participants per group provided 70% power to detect a difference of 0.61 SD, representing an approximately 31.5-m change in 6-minute walk distance between each resveratrol group and the placebo group based on a 1-sided, 2-sample t test with a significance level of $P = .10$. The level of statistical significance and 70% power were selected because RESTORE was a pilot study intended to collect preliminary data.

Statistical Analysis

Data analyses were performed according to the intention-to-treat concept. Analyses of variance, χ^2 tests, and the Fisher exact test were used to compare the continuous and categorical characteristics of participants in the 3 groups. Two-sample t tests were used to compare changes between baseline and 6-month follow-up in each outcome between each of the resveratrol groups and the placebo group. Analyses used SAS, version 9.4 (SAS Institute Inc).

Results

Of the 66 participants with PAD who were randomized, 45 (68%) were men, and they had a mean (SD) age of 74.4 (6.6) years and a mean (SD) ankle brachial index of 0.67 (0.18). Sixty-four (97%) completed follow-up testing (Figure). Table 1 provides the characteristics of the randomized participants. Adherence rates by pill count were 93.9% for the 125-mg group, 87.8% for the 500-mg group, and 87.4% for the placebo group.

At the 6-month follow-up, the change in 6-minute walk test results was statistically significant for the comparison between the 125-mg resveratrol and placebo group and between the 125-mg resveratrol and 500-mg resveratrol group when we used a 1-tailed t test and $P < .10$ to define statistical significance; however, the magnitude of change did not achieve a clinically meaningful difference (Table 2). At the 6-month follow-up, there were no changes in maximal or pain-free treadmill walking time or brachial artery FMD between each resveratrol group and the placebo group (Table 2). Participants randomized to the 500-mg resveratrol group achieved greater improvement in calf muscle biopsy–measured cytochrome-c oxidase activity using a 1-tailed test and a significance threshold of $P < .10$ (Table 2). There were no other statistically significant changes in mitochondrial measures between each resveratrol group and the placebo group.

In an exploratory longitudinal measures analysis using 3-month and 6-month follow-up data, mean changes in 6-minute walk results per 3 months were 2.2 (95% CI, −5.7 to 10.1) m in the 125-mg resveratrol group, −5.5 (95% CI, −13.0 to 2.1) m in the 500-mg resveratrol group, and −7.3 (95% CI, −15.3 to 0.6) m in the placebo group ($P = .09$ for the 125-mg resveratrol group vs the placebo group; $P = .74$ for the 500-mg resveratrol group vs the placebo group).

Adverse Events

Seven participants (35%) in the 125-mg resveratrol group, 14 (61%) in the 500-mg resveratrol group, and 10 (48%) in the placebo group reported diarrhea. Seven participants (35%) in the 125-mg resveratrol group, 12 (52%) in the 500-mg resveratrol group, and 3 (14%) in the placebo group reported abdominal pain. One participant randomized to the 500-mg resveratrol group discontinued the drug because of a pruritic exanthem. No serious adverse events were considered attributable to resveratrol therapy.

Discussion

At the 6-month follow-up, participants who received resveratrol, 125 mg/d, achieved 16.9 m greater distance in the 6-minute walk test than those who were given placebo and 17.4 m greater distance than those who were given resveratrol, 500 mg/d. The primary comparison of resveratrol, 125 mg/d, vs placebo achieved statistical significance at the 1-sided significance level of $P < .10$. However, the magnitude of 6-minute walk improvement in the 125-mg resveratrol group compared with the placebo group did not achieve a clinically meaningful change, defined as a difference of 20 m.

At lower doses, previous studies showed that resveratrol therapy reduced ischemic damage, while, at higher doses, it promoted apoptosis. A primate study showed that resveratrol prevented increased arterial stiffness induced by a high-fat diet; this effect was more pronounced at a lower dose (80 mg) than at a higher dose (480 mg). Therefore, we studied both a lower and a higher dose of resveratrol. Although the 125-mg dose achieved statistically greater 6-minute walk improvement than did the 500-mg dose, based on our a priori–defined level of significance, the magnitude of improvement did not achieve a clinically meaningful difference. Furthermore, our secondary outcomes did not show a benefit for treatment with resveratrol, 125 mg/d.

There are several potential explanations for our results. First, resveratrol at a 125-mg dose may not have been sufficiently low to achieve benefit. Second, mitochondrial impairment and endothelial function may be too severely impaired in people with established PAD for resveratrol to induce a response. Third, treatment with resveratrol may not improve tissue perfusion in severe atherosclerosis, preventing potential effects on mitochondria. Fourth, a longer therapy duration may be needed.

Limitations

Our study had some limitations. First, these results are generalizable only to patients with PAD who meet our inclusion criteria. Second, although we planned to measure changes in skeletal muscle sirtuin 1, we were unable to detect sirtuin 1 in muscle specimens.

Conclusions

Without additional evidence, these findings do not support prescribing resveratrol to improve walking performance in people 65 years or older with PAD.

Notes

Supplement.

Trial Protocol

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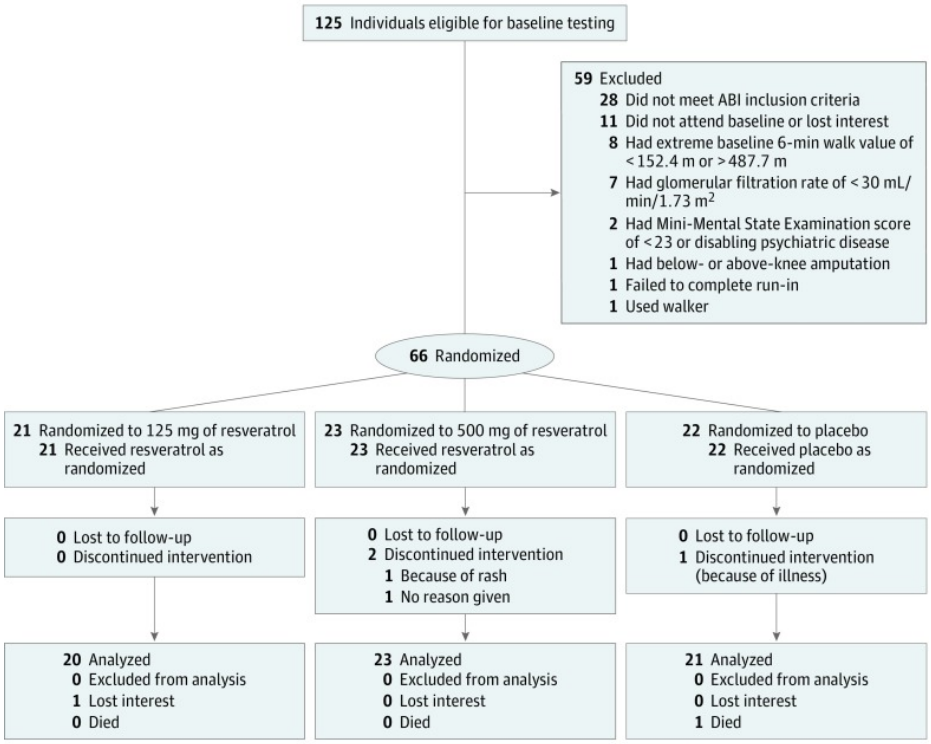
Figures and Tables

Figure.



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CONSORT Flow Diagram

Summary of randomized participants and follow-up rates in the RESTORE randomized clinical trial. ABI indicates ankle brachial index.

Table 1.

Baseline Characteristics of RESTORE Trial Participants According to Group Assignment

Characteristic	Overall (N = 66)	Group Assignment			P Value
		Placebo (n = 22)	Resveratrol, 125 mg/d (n = 21)	Resveratrol, 500 mg/d (n = 23)	
Age, mean (SD), No. (%), y	74.4 (6.6)	74.1 (6.1)	73.6 (6.6)	75.6 (7.3)	.59
Ankle brachial index, mean (SD)	0.67 (0.18)	0.63 (0.13)	0.68 (0.15)	0.69 (0.23)	.48
Male, No. (%)	45 (68)	15 (68)	13 (62)	17 (74)	.69
African American, No. (%)	33 (50)	11 (50)	14 (67)	8 (35)	.11
Current smoker, No. (%)	14 (21)	5 (23)	5 (24)	4 (17)	.87
Former smoker, No. (%)	42 (64)	15 (68)	14 (67)	13 (57)	.68
BMI, mean (SD)	29.9 (5.3)	31.2 (4.8)	28.9 (5.4)	29.6 (5.5)	.35
Myocardial infarction, No. (%)	2 (3)	0	1 (5)	1 (4)	.76
Heart failure, No. (%)	6 (9)	4 (18)	2 (10)	0	.09
Stroke, No. (%)	9 (14)	0	6 (29)	3 (13)	.02
Angina, No. (%)	7 (11)	4 (18)	1 (5)	2 (9)	.38
Pulmonary disease, No. (%)	10 (15)	2 (9)	3 (14)	5 (22)	.53
Cancer, No. (%)	17 (26)	5 (23)	3 (14)	9 (39)	.16
Diabetes, No. (%)	26 (39)	14 (64)	5 (24)	7 (30)	.02
Intermittent claudication, No. (%)	17 (26)	7 (32)	6 (29)	4 (17)	.51
Exertional leg symptoms not consistent with classical intermittent claudication, No. (%)	37 (56)	11 (50)	12 (57)	14 (61)	.76
Asymptomatic, No. (%)[a]	12 (18)	4 (18)	3 (14)	5 (22)	.92
6-min Walk distance, mean (SD), m	360 (63)	354 (70)	370 (65)	357 (58)	.83
Total treadmill distance, mean (SD), m	488.4 (255.9)	443.3 (242.4)	492.8 (261.2)	529.4 (268.6)	.54
Treadmill distance at onset of leg symptom, mean (SD), m	239.1 (168.5)	218.0 (147.3)	226.6 (123.4)	271.1 (217.7)	.56
Cilostazol use, No. (%)	4 (6)	2 (9)	1 (5)	1 (4)	.84
Pentoxifylline use, No. (%)	3 (5)	1 (5)	2 (10)	0	.20
Antiplatelet therapy use, No. (%)	52 (79)	16 (63)	19 (90)	17 (74)	.29
Statin use, No. (%)	47 (71)	17 (77)	16 (76)	14 (61)	.40
Reported walking for exercise ≥3 times/wk, No. (%)	19 (29)	6 (27)	4 (19)	9 (39)	.33

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Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); RESTORE, Resveratrol to Improve Outcomes in Older People with Peripheral Artery Disease Trial.

[a]Ten of the 12 participants who reported no exertional leg symptoms by questionnaire developed exertional leg symptoms during either the 6-minute walk test or the baseline treadmill test.

Table 2.

Six-Month Changes in Walking Performance, Brachial Artery Flow-Mediated Dilation, and Calf Muscle Measures in Response to Resveratrol Therapy in Patients With Peripheral Artery Disease

Group	No. of Participants[a]	Value, Mean (SD)		Difference (95% CI)		P Value		
		Baseline	6 mo	Within Group	Compared With Placebo	Compared With Placebo	Compared With Resveratrol, 125 mg/d	Overall
6-min Walk distance, m								
Placebo	21	353.8 (70.4)	341.5 (85.2)	−12.3 (−28.1 to 3.5)	Reference	Reference	.07[b] .14[c]	.22
Resveratrol, 125 mg/d	20	369.7 (64.9)	374.4 63.9)	4.6 (−11.5 to 20.8)	16.9 (−5.7 to 39.5)	.07[b] .14[c]	Reference	
Resveratrol, 500 mg/d	23	357.4 (57.7)	344.6 (55.3)	−12.8 (−27.8 to 2.3)	−0.5 (−22.3 to 21.3)	.97	.06[b] .12[c]	
Maximal treadmill walking time, min								
Placebo	20	8.7 (4.5)	9.1 (4.8)	0.4 (−0.6 to 1.4)	Reference	Reference	.18	.24
Resveratrol, 125 mg/d	20	9.5 (4.7)	8.9 (3.9)	−0.5 (−1.5 to 0.4)	−0.9 (−2.3 to 0.4)	.18	Reference	
Resveratrol, 500 mg/d	22	10.1 (5.2)	9.5 (4.7)	−0.6 (−1.6 to 0.3)	−1.0 (−2.4 to 0.3)	.12	.87	
Pain-free treadmill walking time, min								
Placebo	19	4.3 (2.8)	4.6 (3.0)	0.3 (−0.8 to 1.5)	Reference	Reference	.74	.65
Resveratrol, 125 mg/d	16	4.4 (2.3)	5.0 (2.2)	0.6 (−0.6 to 1.8)	0.3 (−1.4 to 1.9)	.74	Reference	
Resveratrol, 500 mg/d	18	5.3 (4.4)	5.2 (2.9)	−0.1 (−1.3 to 1.0)	−0.5 (−2.1 to 1.1)	.55	.37	
Brachial artery FMD, %								
Placebo	19	5.6 (3.3)	6.0 (2.5)	0.4 (−0.9 to 1.6)	Reference	Reference	.7	.75
Resveratrol, 125 mg/d	19	5.9 (3.9)	5.9 (3.2)	0.0 (−1.3 to 1.3)	−0.3 (−2.2 to 1.4)	.7	Reference	
Resveratrol, 500 mg/d	21	5.6 (3.3)	5.4 (2.5)	−0.3 (−1.5 to 0.9)	−0.7 (−2.4 to 1.1)	.45	.73	
Calf skeletal muscle COX activity, relative %								
Placebo	7	125.0 (63.2)	99.7 (71.5)	−25.3 (−73.6 to 23.0)	Reference	Reference	.42[b] .84[c]	.22
Resveratrol, 125 mg/d	11	87.3 (61.1)	67.9 (42.9)	−19.4 (−57.9 to 19.1)	5.9 (−55.9 to 67.7)	.42[b] .84[c]	Reference	
Resveratrol, 500 mg/d	7	84.9 (36.7)	112.5 (67.4)	27.6 (−20.7 to 76.0)	52.9 (−15.4 to 121.2)	.06[b] .12[c]	.13	
Calf skeletal muscle citrate synthase activity, relative %								
Placebo	7	110.1 (7.5)	125.9 (30.7)	15.8 (−4.2 to 35.8)	Reference	Reference	.1	.18
Resveratrol, 125 mg/d	11	111.0 (16.0)	105.4 (13.3)	−5.6 (−21.6 to 10.3)	−21.4 (−47.0 to 4.1)	.1	Reference	
Resveratrol, 500 mg/d	7	105.8 (12.1)	118.2 (12.0)	12.4 (−7.6 to 32.4)	−3.4 (−31.6 to 24.9)	.81	.157	
Peroxisome proliferative–activated receptor γ coactivator 1α, normalized value, AU								
Placebo	8	1.5 (1.7)	0.6 (0.7)	−0.9 (−4.5 to 2.7)	Reference	Reference	.73	.37
Resveratrol, 125 mg/d	11	0.4 (0.5)	0.3 (0.4)	0.05 (−3.1 to 3.0)	0.8 (−3.9 to 5.5)	.73	Reference	
Resveratrol, 500 mg/d	8	3.7 (9.3)	0.4 (0.4)	−3.3 (−6.9 to 0.3)	−2.4 (−7.5 to 2.7)	.33	.17	

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Abbreviations: AU, arbitrary units; COX, cytochrome-c oxidase; FMD, flow-mediated dilation.

[a]Thirty-seven of 66 participants (56%) underwent a calf muscle biopsy at baseline, and 27 (73%) of these completed a follow-up biopsy.
[b]P value is based on the a priori method using a 1-tailed test with significance level threshold <.10.
[c]P value is based on a 2-tailed test.