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Curcumin ingestion and exercise training improve vascular endothelial function in postmenopausal women

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Abbreviations

FMD; flow-mediated dilation

$\dot{V}O_{2peak}$; peak oxygen consumption

HDL cholesterol; high-density lipoprotein cholesterol

LDL cholesterol; low-density lipoprotein cholesterol

NO; nitric oxide

TNF-α; tumor necrosis factor-alpha

Abstract

Vascular endothelial function is declines with aging and is associated with an increased risk of cardiovascular disease. Lifestyle modification, particularly aerobic exercise and dietary adjustment, has a favorable effect on vascular aging. Curcumin, is a major component of turmeric, with known anti-inflammatory and anti-oxidative effects. We investigated the effects of curcumin ingestion and aerobic exercise training on flow-mediated dilation as an indicator endothelial function in postmenopausal women. A total of 32 postmenopausal women were assigned to 3 groups: control, exercise, and curcumin groups. The curcumin group ingested curcumin orally for 8 weeks. The exercise group underwent moderate aerobic exercise training for 8 weeks. Before and after each intervention, flow-mediated dilation was measured. No difference in baseline flow-mediated dilation or other key dependent variables were detected among the groups. Flow-mediated dilation increased significantly and equally in the curcumin and exercise groups, whereas no changes were observed in the control group. Our results indicated that curcumin ingestion and aerobic exercise training can increase flow-mediated dilation in postmenopausal women, suggesting that both can potentially improve the age-related decline in endothelial function.

Key Words: flow-mediated dilation, turmeric, physical activity, lifestyle modification, menopause, women

1. Introduction

Arterial endothelial dysfunction has been associated with cardiovascular morbidity and mortality [1]. Flow-mediated dilation (FMD), which is an index of endothelial function [2], is progressively impaired with age [3,4]. In women, the age-associated decline in endothelial function is enhanced during menopause because of the estrogen deficiency [5,6], and postmenopausal women are at a higher risk of cardiovascular disease [7]. Thus, slowing the decline of endothelial function in postmenopausal women could have potential health benefits. We and other groups have reported that aerobic exercise training enhances endothelial function [8-10]. Lifestyle modification is a desirable way to prevent or treat endothelial dysfunction without the need for pharmaceutical intervention.

Vascular inflammation and oxidative stress play important roles in development of vascular endothelial dysfunction and cardiovascular disease [11]. Previous studies have demonstrated that increased production of pro-inflammatory cytokines and reactive oxygen species in the aging vessel results in endothelial dysfunction [12,13]. Therefore, following an anti-inflammatory or anti-oxidative diet may help counteract the effects of aging on blood vessel. Curcumin, a polyphenol molecule extracted from turmeric, is a commonly used spice and a yellow pigment. Curcumin regulate biochemical and molecular pathway by modulating several molecular targets including transcription factors, cytokines, enzymes, and genes regulating cell proliferation and apoptosis [14-16]. In addition to the anti-inflammatory and anti-oxidative effects of curcumin [17,18], is has been associated with the protection against cardiovascular disease [19]. However, the effect of curcumin on endothelial function remains unclear.

We hypothesized that, similar to exercise, curcumin ingestion could improve endothelial function. The objective of the present study was to determine the effect of curcumin ingestion and the effect of exercise training on endothelial function. We therefore

investigated endothelial function as measured by the FMD in postmenopausal women before and after 8 weeks of curcumin ingestion or exercise training intervention.

2. Methods and materials

2.1 Subjects A total of 32 healthy, sedentary postmenopausal women (amenorrhea for at least 2 years) participated in the study. Subjects were assigned to one of the following intervention groups: control group (n = 10), curcumin group (n = 11), and exercise training group (n = 11). Subjects were nonsmokers, nonobese, and free of cardiovascular disease as assessed by medical history. None of the subjects were taking cardiovascular-acting medications or hormone replacement therapy. All potential risks and associated with the study were explained to the subjects, and they gave their written informed consent for participation in the study. All procedures were reviewed and approved by the ethical committee of the University of Tsukuba.

2.2 Experimental protocol All experiments were performed in the morning after a 12-h overnight fast. Subjects abstained from alcohol and caffeine for at least 12 h and did not exercise for at least 24 h before beginning the experiment to avoid the potential acute effects of exercise. Measurements were taken in a quiet, temperature-controlled room (24–26°C). After a resting period of at least 20 min, FMD, arterial blood pressure, and blood biochemistry were determined. After these measurements, peak oxygen consumption ($\dot{V}O_{2peak}$) was measured during incremental cycle ergometer exercise.

2.3 Curcumin ingestion Subjects in the curcumin group ingested 6 pills (150 mg total) of curcumin per day [20,21], which supplies 25 mg of highly absorptive curcumin dispersed with colloidal nanoparticles (Theracurmin; Theravalues Corporation, Tokyo) [22]. Supplementary curcumin was administered orally for 8 weeks. All subjects were instructed

not to alter their dietary habits during the intervention period.

2.4 Exercise training Subjects in the exercise group underwent aerobic exercise training more than 3 days per week (2-3 supervised sessions and additional home-based training) for 8 weeks [23]. Initially, subjects performed cycling and walking 30 min/day at a relatively low intensity (60% of their individually determined maximal heart rate). As their exercise tolerance improved, the intensity and duration of aerobic exercise were increased to 40−60 min/day at an intensity of 70−75 % of the maximal heart rate. Subjects in the control and curcumin groups were instructed not to change their level of physical activity.

2.5 Measurements

2.5.1 *FMD.* Brachial artery FMD was assessed noninvasively by using an ultrasound system (UNEXEF18G, Unex, Nagoya, Japan) as previously described [24]. Briefly, high-resolution ultrasound with a 10 MHz linear array transducer was used to obtain a longitudinal image of the right brachial artery in the cubital region at the baseline and then continuously from 30 s prior to 2 min or more after the release of suprasystolic pressure (50 mmHg above systolic blood pressure) maintained for 5 minutes of the right forearm. The diameter at the same point of the artery was monitored continuously, and the maximal dilatation after deflation was recorded. FMD was calculated as the percentage change in brachial artery diameter in response to the forearm reactive hyperemic stimulus. FMD was calculated as follows:

(Maximal diameter – baseline diameter) × 100/baseline diameter

2.5.2 *Arterial blood pressure.* Arterial blood pressure and heart rate at rest were determined in the supine position using an automated device (formPWV/ABI, Colin Medical Technology, Komaki, Japan) [23].

2.5.3 *Blood chemistry.* A blood sample was collected from the antecubital vein after overnight fasting. Serum of cholesterol and triglyceride and plasma of glucose were determined using standard enzymatic techniques [25].

2.5.4 *Peak oxygen consumption.* $\dot{V}O_{2peak}$ was measured during incremental cycle ergometer exercise by using online computer-assisted circuit spirometry (AE280, Minato Medical Science, Osaka, Japan) as we previously reported [23]. All subjects underwent an incremental exercise test (2 min at 40 W, followed by 20 W increases every 2 min) until volitional exhaustion. $\dot{V}O_{2peak}$ was defined as the highest $\dot{V}O_2$ recorded during the test. Heart rate and rating of perceived exertion were recorded throughout the exercise.

2.6 Statistical analyses. The effects of each intervention on the outcomes measured were determined by repeated measures analysis of variance. If a significant effect was detected, specific mean comparisons were performed to determine the significance of each intervention. In the case of a significant F-value, a post-hoc test (Bonferroni test) was used to identify significant differences among mean values. All data are reported as means ± SD. Statistical significance was set a priori at $P < 0.05$ for all comparisons.

3. Results

The compliance/adherence to curcumin ingestion in the curcumin group was 97.6 ± 2.8%. No adverse effects of curcumin were reported. In the exercise training group, the average frequency and duration of the exercise training was 4.5 ± 1.4 days/week and 48 ± 23 min/day. There were no drop-outs in either group.

Table 1 shows the baseline characteristics of the study participants. There were no group differences in age, height, body weight, body mass index, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, glucose, or $\dot{V}O_{2peak}$ between the groups at the start of the study. HDL cholesterol levels increased significantly in the exercise group ($P < 0.05$). There were no significant changes in body weight, body mass index, total cholesterol, LDL cholesterol, triglyceride and glucose levels in any of the groups. $\dot{V}O_{2peak}$ in the exercise group increased significantly after the intervention ($P < 0.05$).

3.1 Heart rate and blood pressure

As shown in Table 2, no statistically significant differences in the baseline hemodynamic parameters at rest were detected among the groups before the intervention. After 8 weeks of intervention, systolic blood pressure decreased in the exercise and curcumin groups ($P < 0.05$). Heart rate and diastolic blood pressure did not change in any of the groups.

3.2 FMD

No significant difference in the baseline FMD was detected among the groups (Fig. 1). After 8 weeks of intervention, FMD increased significantly in the exercise and curcumin groups, whereas no significant change in FMD was detected in the control group. The change in FMD was significantly greater in the exercise and the curcumin groups than in the control group (Fig. 2). The differences in FMD changes between the exercise and curcumin groups were not statistically significant (Fig. 2).

4. Discussion

The present study showed that regular ingestion of curcumin or regular aerobic

exercise training significantly improved endothelial function. The magnitude of improvement in endothelial function to the same extent, suggesting that curcumin may prevent the age-associated decline in endothelial function in postmenopausal women.

Curcumin, a polyphenolic derivative of turmeric, is widely cultivated in Asia and is commonly used as a spice to add flavor and yellow, coloring to food. Curcumin is known to anti-inflammatory and anti-oxidant effects in addition to acting as an anti-carciogenic and neuroprotective agent [26-28]. Recent studies have reported a beneficial effect of curcumin on the cardiovascular system, suggesting its potential as a therapeutic agent for the treatment of cardiovascular disease and endothelial dysfunction [19]. In this study, we showed an improvement in endothelial function after 8 weeks of the curcumin ingestion in postmenopausal women. The magnitude of the improvement achieved by curcumin treatment was comparable to that obtained with exercise. Therefore, regular ingestion of curcumin could be a preventive measure against cardiovascular disease in postmenopausal women. Furthermore, our results suggest that curcumin may be a potential alternative treatment for patients who are unable to exercise.

Our hypothesis that curcumin ingestion may improve endothelial function in a similar manner as exercise was proven in the present study, as shown in the significant and comparable increase in FMD after 8 weeks of curcumin ingestion and exercise training. Regular aerobic exercise improves enhanced endothelial function, which has been associated with increased nitric oxide (NO) bioavailability [9,29]. Therefore, the exercise-induced endothelial function improvement in our study could have been mediated by an increase in NO bioavailability. However, the mechanism responsible for the curcumin ingestion induced improvement in endothelial function is unclear. Curcumin exerts anti-inflammatory and anti-oxidative effects by inhibiting tumor necrosis factor-alpha (TNF-α) [30], suggesting that its effect on endothelial function may be mediated by the suppression of inflammation and/or

oxidative stress via downregulation of TNF-α. However, TNF-α levels were mot assessed in this study. Further studies are warranted to clarify the mechanism undeerlying the effect of curcumin on endothelial function.

In our previous study, we investigated the effect of exercise training and curcumin ingestion on central arterial hemodynamics, i.e., wave reflection and central blood pressure [21]. Wave reflection and central blood pressure did not improve with exercise training alone or curcumin ingestion alone, whereas these parameters improved in response to the combination of exercise training with curcumin ingestion. However, in the present study, we investigated the effect of curcumin on endothelial function as measured by FMD, and demonstrated for the first time that curcumin ingestion alone increased FMD, similar to the effect of exercise demonstrated previously. The effect of the combination of exercise training with curcumin ingestion on vascular endothelial function were not assessed in this study and should be addressed in future studies in comparison to the effect of each agent alone.

The present study had some limitations. First, this study was conducted with a small sample size in each group. However, the power calculation indicated that the number of subjects was sufficient to establish statistical significance. Furthermore, this study focused only on postmenopausal women. Thus, the findings of this study cannot be generalized to other populations, such as men and young women. Second, the present study measured only FMD as an index of endothelial function. We did not measure any biomarkers of inflammation and oxidative stress, plasma curcumin concentration, or endothelial function using different indexs. Further studies are needed to clarify the mechanism underlying the effect of curcumin on vascular endothelial function. Third, analysis of the baseline characteristics of the participants and the baseline FMD suggest that the subjects in the exercise group showed overall better before the start of the study. Although there were no

significant differences in any of the variables among the groups before the intervention, small differences in baseline values might have biased the results.

In conclusion, we examined the effect of curcumin ingestion and exercise training on endothelial function in postmenopausal women and found that regular curcumin ingestion and exercise improve endothelial function. These findings suggest that curcumin could be developed as a therapeutic strategy for the treatment of cardiovascular disease similar to exercise training in postmenopausal women.

5. Acknowledgments

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Figure legends

Figure 1. FMD before and after intervention. Data are expressed as means ± SD. *P < 0.05 before vs. after intervention.

Figure 2. Changes in FMD in response to intervention. Data are expressed as means ± SD. *P < 0.05 vs. control group.

Table1. Baseline characteristics of subjects

	Control (n = 10)		Exercise (n = 11)		Curcumin (n = 11)		P		
	Before	After	Before	After	Before	After	Group	Time	Time×Group
Age, years	64 ± 6		59 ± 5		60 ± 6		NS		
Height, cm	154 ± 6		154 ± 4		155 ± 8		NS		
Weight, kg	51 ± 2	51 ± 2	54 ± 2	54 ± 2	54 ± 3	54 ± 3	NS	NS	NS
BMI, kg/m	21.5 ± 1.0	21.6 ± 1.0	22.7 ± 1.0	22.6 ± 1.0	22.5 ± 1.0	22.7 ± 1.0	NS	NS	NS
Total Cholesterol, mmol/l	6.1 ± 0.5	6.3 ± 0.5	5.4 ± 0.6	5.7 ± 0.6	6.3 ± 0.7	6.6 ± 0.5	NS	0.005	NS
HDL Cholesterol, mmol/l	1.7 ± 0.4	1.7 ± 0.3	1.7 ± 0.3	1.9 ± 0.3*	1.6 ± 0.5	1.7 ± 0.5	NS	0.010	NS
LDL Cholesterol, mmol/l	3.8 ± 0.6	3.9 ± 0.4	3.2 ± 0.4	3.5 ± 0.6	3.8 ± 0.7	4.0 ± 0.7	NS	0.027	NS
Triglyceride, mmol/l	1.4 ± 0.6	1.3 ± 0.4	1.0 ± 0.6	0.9 ± 0.4	1.9 ± 0.9	1.7 ± 0.1	NS	NS	NS
Glucose, mmol/l	5.3 ± 0.4	5.3 ± 0.4	4.9 ± 0.4	4.9 ± 0.3	5.1 ± 1.1	5.4 ± 1.6	NS	NS	NS
$\dot{V}O_{2peak}$, ml/kg/min	22.9 ± 1.4	22.5 ± 1.1	25.3 ± 1.2	27.3 ± 1.2*	21.9 ± 0.7	21.9 ± 0.8	NS	NS	0.024

Values are means ± SD. BMI; body mass index, HDL Cholesterol; high-density lipoprotein cholesterol, LDL Cholesterol; low-density lipoprotein cholesterol, $\dot{V}O_{2peak}$; peak oxygen consumption.

*P < 0.05 vs. before intervention. A main time and group effect overall by repeated-measures ANOVA.

Table 2. Hemodynamics parameter before and after intervention.

	Control (n = 10)		Exercise (n = 11)		Curcumin (n = 11)		P value		
	Before	After	Before	After	Before	After	Group	Time	Time×Group
Heart rate, beats/min	62 ± 6	64 ± 11	61 ± 6	57 ± 5	61 ± 8	59 ± 7	NS	NS	NS
SBP, mmHg	112 ± 12	113 ± 11	112 ± 10	107 ± 10*	122 ± 17	116 ± 15*	NS	0.003	0.025
DBP mmHg	69 ± 5	69 ± 6	71 ± 8	69 ± 9	72 ± 12	69 ± 11	NS	NS	NS

Values are means ± SD. SBP; systolic blood pressure, DBP; diastolic blood pressure

*P < 0.05 vs. before intervention. A main time and group effect overall by repeated-measures ANOVA.

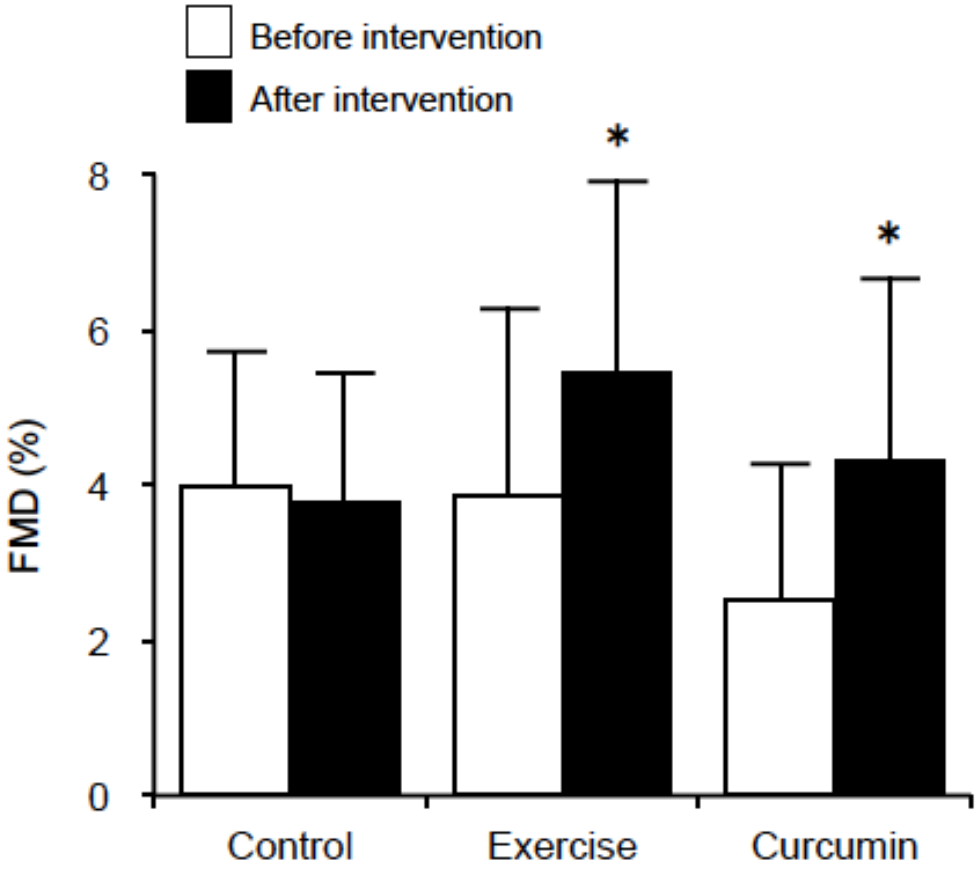

Figure 1. FMD before and after intervention. Data are expressed as means ± SD. *P < 0.05 before vs. after intervention.

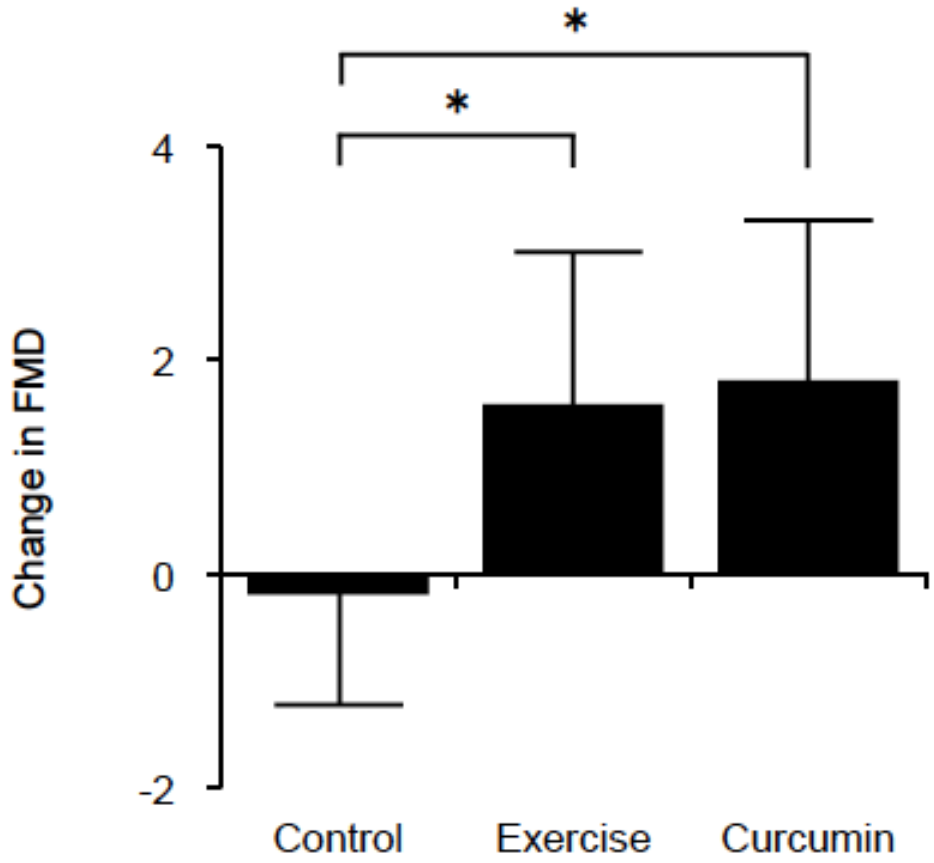

Figure 2. Changes in FMD in response to intervention. Data are expressed as means ± SD. *P < 0.05 vs. control group.