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Influence of enhanced bioavailable curcumin on obesity-associated cardiovascular disease risk factors and arterial function: A double-blinded, randomized, controlled trial

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ABSTRACT

Objectives: This study aimed to determine whether an enhanced bioavailable curcumin formulation, CurQfen®, would improve circulating cardiovascular disease–related blood biomarkers and arterial function in young (age 18–35 y), obese (body mass index ≥ 30.0 kg/m^2) men.
Methods: This double-blinded, placebo-controlled trial evaluated 22 men. The participants were matched based on body mass index and randomized to the intervention (curcumin formulated with fenugreek soluble fiber, for enhanced absorption) or control (fenugreek soluble fiber) group for 12 wk at 500 mg/d without dietary modification or exercise. Blood samples and endothelial function measures were acquired at 0 and 12 wk, and blood samples were analyzed for cardiovascular disease–related blood biomarkers. Furthermore, central (aortic) blood pressure and augmentation index were monitored at 0, 4, 8, and 12 wk.
Results: After 12 wk of intervention, homocysteine levels were lower (curcumin before: 12.22 ± 2.29 μg/mL, after: 8.62 ± 1.02 μg/mL versus placebo before: 9.45 ± 0.84 μg/mL, after: 11.84 ± 1.63 μg/mL; $P = 0.04$) and high-density lipoprotein levels were higher (curcumin before: 40.77 ± 5.37 mg/dL, after: 54.56 ± 11.72 mg/dL versus placebo before: 61.20 ± 5.76 mg/dL, after: 48.82 ± 5.49 mg/dL; $P = 0.04$) in the curcumin group relative to the placebo group. However, there was no significant difference in changes between the circulating concentrations of glucose, insulin, leptin, adiponectin, or oxidative stress biomarkers in the curcumin group compared with the placebo group ($P > 0.05$). No changes were found with endothelial function, augmentation index, or central blood pressure in the curcumin group compared with the placebo group ($P > 0.05$).
Conclusions: Our data provide evidence for an enhanced bioavailable curcumin to improve homocysteine and high-density lipoprotein concentrations, which may promote favorable cardiovascular health in young, obese men. Improvements in endothelial function or blood pressure were not observed with curcumin supplementation, thus further investigation is warranted.

Introduction

The global rise in obesity is associated with an increase in morbidity and mortality owing to cardiovascular disease (CVD), which remains the primary cause of death in the United States [1]. Obesity accelerates both CVD-related morbidity and mortality [2–4] in part through impaired metabolism, which results in alterations to blood biomarkers of glucose and cholesterol homeostasis [2], modifications in adipokine balance of adiponectin and leptin [2,4], elevated homocysteine [4–6], and increased oxidative stress [4]. The unfavorable changes in these circulating blood biomarkers enhance CVD risk by impairing arterial function and hemodynamics.

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Decrements in arterial function through endothelial dysfunction and increased blood pressure (BP), particularly central (or aortic) BP, are two key factors associated with increased CVD risk with obesity. Thus, elucidating novel interventions to modify obesity-induced metabolic dysfunction that leads to impaired arterial health has important clinical implications to reduce CVD events.

Nutraceutical foods, or foods with known health-promoting benefits, have been identified as potential interventions for CVD because of their lipid-lowering effects [7], amelioration of metabolic syndrome components [8], and improvements in vascular function and arterial BP [8]. Curcumin (1,7-bis-[4-hydroxy-3-methoxy- phenyl]-1,6-heptadiene-3,5-dione), which is the active ingredient in the Asian-Indian spice turmeric, is an emerging nutraceutical food that is believed to have numerous health benefits [9]. In particular, curcumin has shown promise to favorably modulate CVD risk factors by lowering cholesterol and reducing oxidative stress and inflammation [10–13]. Curcumin also improves indices of arterial health by enhancing endothelial function [10,14–17], reducing central BP [17], and decreasing augmentation index (AIx) scores (measure of arterial stiffness) [18]. In addition, we have shown that curcumin improves aortic stiffness (another aspect of arterial health) in obese men with increased baseline stiffness [19]. Although previous studies have indicated a significant potential for curcumin to improve CVD-related blood biomarkers and arterial health in preclinical models and in middle-aged and older adults, whether curcumin is an effective strategy to reduce CVD risk in an obese population remains unknown.

The purpose of this study was to examine the effects of an increased bioavailable curcumin formulation [20] on obesity-associated CVD risk factors that would be related to improvements in arterial function. We hypothesized that curcumin would ameliorate CVD-related blood biomarkers, which would be related to improved endothelial function, and central BP in young, apparently healthy men. To test this hypothesis, a 12-wk, placebo-controlled, double-blinded, randomized clinical trial was conducted in young, obese men to evaluate the efficacy of a curcumin intervention (curcumin formulated with soluble fenugreek fiber) to improve CVD-associated blood biomarkers and indices of arterial health compared with placebo treatment (soluble fenugreek fiber only).

Methods

Study design

The University of Kentucky's institutional review board approved all procedures before the commencement of the study, which conformed to the World Medical Association's Declaration of Helsinki. Before participation in the study, written consent was obtained from all participants. This was a 12-wk, double-blinded, placebo-controlled study that examined the effects of an enhanced bioavailable curcumin formulation on the cardiovascular health of young, obese men. Previously, we reported the effects of curcumin on aortic stiffness in this same cohort of obese men [19].

Subjects were matched based on body mass index (BMI) and randomly assigned to the curcumin or placebo group. Testing was conducted in the Exercise Physiology Laboratory in a quiet, thermoneutral room at the University of Kentucky. Endothelial function testing and blood draws occurred at 0 and 12 wk, and central pressure and AIx scores were measured at 0, 4, 8, and 12 wk. Supplements were administered for 12 wk based on group assignment, and subjects were instructed to take one supplement per day at the same time each day. Visits to the laboratory occurred after a minimum of a 4-h fast from food, caffeine, and non-water beverages. Figure 1 displays the study design and includes the measures taken during each visit. Upon enrollment in the study, participants were instructed not to change any major lifestyle factors, including dietary and physical activity habits.

Participants

This study included 22 young, obese men. All men were prescreened before their initial visit to determine whether sex, age, BMI, and current medication status were in conjunction with the inclusion and exclusion criteria. At the time of the initial visit, men were screened further with a self-reported health history questionnaire, resting 12-lead electrocardiogram, and the CAGE Substance Abuse Screening Tool [21]. The inclusion criteria included male sex, age 18 to 35 y, and obesity status (BMI $\geq$ 30.0 kg/m^2). The exclusion criteria included hypertension (systolic blood pressure [SBP] $\geq$ 140 mmHg or diastolic blood pressure [DBP] $\geq$ 90 mmHg), previous myocardial infarction, current medication, CVD, diabetes mellitus, pulmonary disease, renal disease, human immunodeficiency virus, hypercholesterolemia, hyperglycemia, or alcohol dependence or abuse.

Materials

The curcumin and placebo supplements were prepared as previously described [20]. Briefly, 193.0 mg of curcuminoids in the form of 81.8% curcumin, 15.3% demethoxycurcumin, and 2.8% bisdemethoxycurcumin were infused into 60% soluble fiber from fenugreek to improve bioavailability. The intervention was a total of 500 mg, and the placebo supplement was comprised of equal parts of soluble fiber from fenugreek. The placebo pills were identical in size and shape to the intervention pills.

Blood biomarkers

All blood samples were taken by trained staff at University of Kentucky's Center for Clinical and Translational Sciences. Serum insulin, leptin, adiponectin, total antioxidant capacity, high-density lipoprotein (HDL), very low-density or low-density lipoprotein, plasma glucose, and homocysteine were determined at 0 and 12 wk (human insulin enzyme-linked immunosorbent assay [ELISA], human leptin ELISA, human adiponectin ELISA, oxiselect total antioxidant capacity assay, HDL and very low- or low-density lipoprotein cholesterol assay, glucose assay [Colorimetric], and homocysteine ELISA; Cell Biolabs, Inc., San Diego, CA). All procedures and analyses were performed according to the manufacturer's specifications, and samples were stored at −80°C before performing the assays.

Endothelial function

Endothelial function was determined by the Endo-PAT 2000 (Itamar Medical, Ltd., Caesarea, Israel) based on previously described methods [22]. All measures were taken by a single trained investigator. Briefly, the Endo-PAT 2000 uses pulse volume amplitude to determine endothelium-dependent vasodilation. Finger-probe plethysmography was employed to measure pulse volume amplitude of the peripheral arteries. After lying supine in a rested position for at least 10 min, a resting BP measure was taken with a standard manual cuff and recorded in the Endo-PAT software. Subjects were instructed to remain still and in a relaxed position for the duration of the testing.

Finger probes were placed on the index fingers of both hands, and 5 min of baseline arterial pulse wave data were collected after inflation of the probes. Then, the BP cuff was inflated to 200 mmHg on the test arm and maintained for 5 min to ensure full occlusion of the brachial artery while pulse wave data were recorded. After 5 min of occlusion, the BP cuff was deflated, and 5 min of postocclusion data were acquired. Reactive hyperemia index (RHI) scores were determined with software as the post-to-preocclusion

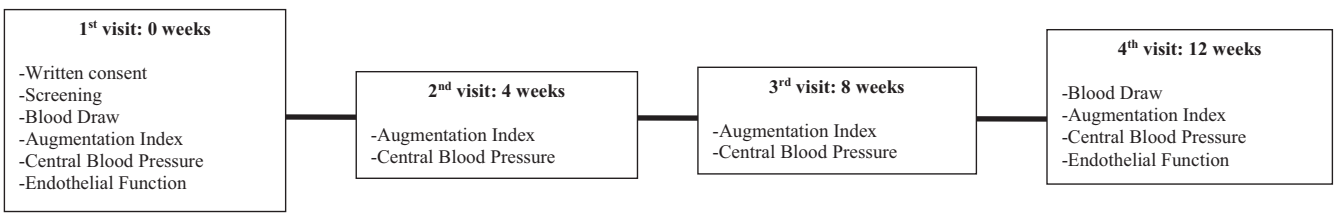

Fig. 1. Timeline of Visits and Associated Measures.

ratio of the recorded data of the test arm divided by the post-to-preocclusion ratio of the recorded data of the control arm.

Augmentation index and central BP measures

Augmentation index and central BP measures were determined with the Sphygmocor system (Sphygmocor; AtCor Medical, Sydney, Australia) as previously described in detail [23]. Measurements were taken after subjects rested in a supine position for a minimum of 10 min. Before testing, BP measurements were taken manually with a sphygmomanometer and recorded in the Sphygmocor software. Applanation tonometry at the radial artery was used to obtain pulse wave measures, and the system software produced and recorded peripheral waveforms. A validated, generalized, transfer function [24] was used to generate a central arterial waveform, which was used to determine AIx scores and central BP, including both SBP and DBP measures. Augmentation index was defined as the difference between the first and second peaks, calculated as a percentage of the central pulse pressure (PP). The Sphygmocor reported measures for AIx and AIx normalized for a heart rate of 75 bpm (AIx_{75}), as is commonly expressed in the literature because of the influence of heart rate on AIx. Central PP was calculated with the Sphygmocor by subtracting central DBP from SBP. Central mean arterial pressure (MAP) was determined as:

$$MAP = (2 \times DBP + SBP) / 3.$$

Statistical analysis

Baseline comparisons between the intervention and placebo groups were analyzed with paired sample *t* tests. The effects of the treatment over time were analyzed with a multilevel regression model, using a random effect to capture BMI-matched pairs and an unstructured covariance matrix to capture repeated measures. The Kenward and Roger method was utilized to estimate degrees of freedom [25]. Insulin levels were not normally distributed at baseline, so log-transformed versions of these quantities were employed in a sensitivity analysis. Data are presented as means ± standard error, except for retention and compliance data, which are presented as percentages. A *P*-value of < 0.05 was considered statistically significant. All statistical analyses were completed with SAS, version 9.4 (SAS System for Windows; SAS Institute Inc., Cary, NC).

Results

The baseline anthropometric characteristics of the 22 men in this study were reported previously [19]. No baseline differences were detected between the curcumin and placebo groups. The present study had a 100.0% retention rate, and no adverse events were reported in the intervention or control groups. Supplement compliance between the groups did not differ ($P = 0.520$), and overall compliance was 96.74%.

Blood biomarkers for CVD risk are reported in Table 1. At baseline, HDL was significantly lower in the curcumin compared with the placebo group ($P = 0.03$). No other baseline differences in blood biomarkers were noted. After 12 wk of intervention, plasma homocysteine concentrations were significantly reduced in the curcumin group compared with the placebo group (before: 12.22 ± 2.29 μg/mL, after: 8.62 ± 1.02 μg/mL versus before: 9.45 ± 0.84 μg/mL, after: 11.84 ± 1.63 μg/mL, respectively; $P = 0.04$; group-by-time interaction). In addition, serum HDL concentrations were elevated in the curcumin group at 12 wk compared with the placebo group (before: 40.77 ± 5.37 μg/mL, after: 54.56 ± 11.72 μg/mL versus before: 61.20 ± 5.76 μg/mL, after: 48.82 ± 5.49 mg/dL, respectively; $P = 0.04$; group-by-time interaction). No differences between the groups were noted in other blood markers ($P > 0.05$; group-by-time interaction). Log-transformed versions of plasma insulin concentrations did not alter the conclusions regarding statistical significance in the sensitivity analysis.

The changes in arterial function are presented in Table 2. From baseline to 12 wk, no significant difference was found between the change in endothelial function of the curcumin group, measured by RHI, when compared with the control group ($P = 0.67$). Furthermore, AIx and AIx_{75} were unchanged in the intervention versus placebo groups ($P = 0.18$ and 0.75, respectively). All measures of central pressure remained unchanged, including SBP ($P = 0.45$), DBP ($P = 0.27$), PP ($P = 0.24$), and MAP ($P = 0.23$).

Discussion

To our knowledge, this is the first study to consider the effects of curcumin on CVD-related blood biomarkers, endothelial function, central BP, and AIx of young, obese men without dietary restrictions or prescribed exercise. The current findings demonstrate that an enhanced bioavailable formulation of curcumin improves homocysteine and HDL concentrations in young, obese men relative to a placebo group despite non-significant changes in endothelial function or BP. A significant improvement in aortic stiffness was also evident among the same population, as reported earlier [19]. The favorable

Table 1
Change in cardiovascular disease-related blood biomarkers in curcumin and placebo groups (n = 10 per group, except where noted)

	Group	0 wk	12 wk	*P*-value
Glucose (mg/dL)	**Placebo**	93.91 ± 2.86*	93.82 ± 3.30*	
	Curcumin	92.91 ± 3.99*	95.82 ± 4.41*	0.54
Insulin (mIU/L)	**Placebo**	26.86 ± 18.14	7.64 ± 0.60	
	Curcumin	18.46 ± 8.45	41.71 ± 19.36	0.14
Homocysteine (μg/mL)	**Placebo**	9.45 ± 0.84	11.84 ± 1.63	
	Curcumin	12.22 ± 2.29	8.62 ± 1.02	0.04†
Leptin (ng/mL)	**Placebo**	433.91 ± 101.1	470.15 ± 130.27	
	Curcumin	464.78 ± 111.98	473.95 ± 82.82	0.86
Adiponectin (μg/mL)	**Placebo**	2.10 ± 0.47	1.70 ± 0.24	
	Curcumin	2.35 ± 0.56	1.98 ± 0.37	0.95
Total antioxidant capacity – UAE (mM)	**Placebo**	4.44 ± 0.23	4.55 ± 0.23	
	Curcumin	4.09 ± 0.48	4.52 ± 0.37	0.38
Total antioxidant capacity – CRE (μM)	**Placebo**	9719 ± 506	9970 ± 499	
	Curcumin	8956 ± 1051	9885 ± 806	0.38
High-density lipoprotein (mg/dL)	**Placebo**	61.20 ± 5.76‡	48.82 ± 5.49	
	Curcumin	40.77 ± 5.37§	54.56 ± 11.72§	0.04†
Low-/very low-density lipoprotein (mg/dL)	**Placebo**	139.83 ± 20.27	86.38 ± 14.26	
	Curcumin	129.73 ± 18.76§	103.08 ± 14.92§	0.10

CRE, copper-reducing equivalent; UAE, uric acid equivalent.
Values are means ± standard error.
*n = 11.
†$P < 0.05$; group by time interaction.
‡$P < 0.05$; baseline comparison.
§n = 9.

Table 2
Change in endothelial function and indices of central blood pressure (n = 11 per group, except where noted)

	Group	0 wk	4 wk	8 wk	12 wk	*P*-value
RHI	**Placebo**	2.08 ± 0.16	n/a	n/a	1.90 ± 0.15	
	Curcumin	2.02 ± 0.16*	n/a	n/a	1.99 ± 0.22	0.67
AIx (%)	**Placebo**	7.55 ± 3.06	−0.36 ± 2.88	0.60 ± 3.45*	0.82 ± 3.43	
	Curcumin	−0.64 ± 3.59	−3.55 ± 3.91	1.45 ± 2.50	3.82 ± 2.90	0.18
AIx$_{75}$ (%)	**Placebo**	−5.00 ± 3.18	−8.55 ± 3.01	−5.60 ± 3.25*	−5.45 ± 3.57	
	Curcumin	−9.45 ± 4.08	−9.64 ± 4.32	−6.64 ± 3.13	−4.18 ± 3.18	0.75
Central SBP (mmHg)	**Placebo**	109.18 ± 1.84	106.82 ± 2.07	108.40 ± 2.09*	107.45 ± 1.72	
	Curcumin	105.64 ± 2.14	106.45 ± 2.13	105.00 ± 2.31	104.73 ± 2.34	0.45
Central DBP (mmHg)	**Placebo**	82.18 ± 1.69	79.73 ± 1.94	81.30 ± 1.75*	80.27 ± 1.56	
	Curcumin	77.64 ± 2.71	80.00 ± 2.18	79.82 ± 2.22	79.36 ± 2.47	0.27
Central PP (mmHg)	**Placebo**	27.00 ± 1.46	27.09 ± 1.96	27.10 ± 1.83*	27.18 ± 1.10	
	Curcumin	28.00 ± 1.86	26.45 ± 1.48	25.18 ± 1.30	25.36 ± 1.87	0.24
Central MAP (mmHg)	**Placebo**	91.18 ± 1.60	88.76 ± 1.75	90.33 ± 1.66*	89.33 ± 1.53	
	Curcumin	86.97 ± 1.47	88.82 ± 2.05	88.21 ± 2.16	87.82 ± 2.26	0.23

AIx, augmentation index; AIx$_{75}$, augmentation index corrected for heart rate of 75; DBP, diastolic blood pressure; MAP, mean arterial pressure; n/a, not available; PP, pulse pressure; RHI, reactive hyperemia index; SBP, systolic blood pressure.
P-values represent group by time interaction. Values are means ± standard error.
*n = 10.

response in CVD-related blood biomarkers may be indicative of an enhanced cardiovascular risk profile, independent of improvements in endothelial function, central BP, and AIx.

Obesity is associated with elevated homocysteine levels when compared with normal weight counterparts [26]. For the first time, we have demonstrated that curcumin reduces homocysteine concentrations by 3.6 μg/mL, or a 29.5% decrease, in obese men. Elevated homocysteine is associated with increased morbidity and mortality independent of traditional risk factors for CVD [27–31]. Notably, adding homocysteine to the risk profile has been shown to improve risk predictions by 12.9% and 18.3% in the Multi-Ethnic Study of Atherosclerosis (MESA) and National Health and Nutrition Examination Survey (NHANES) cohorts, respectively [27]. In contrast, reductions in homocysteine concentrations are associated with a reduced risk for ischemic heart disease and stroke [32,33]. Specifically, a 25% reduction in homocysteine is associated with a reduction in ischemic heart disease risk by 11% to 16% and a reduction in stroke risk by 19% to 24% [33]. Thus, the reduction of homocysteine concentrations with curcumin supplementation has important clinical implications for lowering obesity-related CVD risk.

Although the enhanced curcumin formulation lowered homocysteine in this cohort of obese men, the mechanisms by which this occurred are less clear. Increased plasma homocysteine is a result of complex metabolic processes, which are associated with lower amounts of betaine [34]. As such, betaine supplementation reduces homocysteine concentrations in patients with CVD [34]. Curcumin supplementation has been shown to increase betaine concentrations in a high-fat-fed rodent model [35], which suggests that curcumin may increase betaine to lower homocysteine in the current investigation. Further studies to assess the influence of curcumin on betaine concentrations to reduce obesity-associated homocysteine should be conducted to provide greater insight.

Our findings suggest that curcumin increases HDL cholesterol, which is corroborated by the results from previous studies in healthy subjects [11,36] and individuals with metabolic syndrome [7]. To our knowledge, this is the first study to extend this finding by demonstrating an effect of curcumin to increase HDL cholesterol in obese men. The inverse association between HDL and the incidence of coronary heart disease (CHD), whereby low levels of HDL are associated with CHD [37] and mortality [38], is widely accepted. The cardioprotective nature of HDL is such that a 1 mg/dL incremental increase in HDL is associated with a 2% to 3% reduction in CHD risk [39]. In the present study, we noted a 13.8 mg/dL increase (33.8%) in HDL with curcumin supplementation. The curcumin-related improvements of HDL in a cohort of obese men suggest the potential for CHD risk reduction with curcumin.

A lack of demonstrable improvement in endothelial function was an unexpected finding given previous improvements in endothelial function with curcumin supplementation in prior investigations [14–16]. A probable explanation for the discrepancy between improvements in endothelial function in previous studies [14–16] and the lack of improvement in obesity-associated endothelial function in the present study is likely methodological. In the aforementioned studies, flow-mediated dilation (FMD) and forearm blood flow responses to acetylcholine (FBF$_{ach}$) were used to determine endothelial function with a curcumin intervention [14–16]. In the current investigation, RHI measured by peripheral arterial tonometry assessed endothelial function. RHI independently predicts cardiovascular events [40], but previous work suggests that this assessment may be measuring more complex mechanisms, such as the role of the sympathetic nervous system [41], rather than strictly NO-dependent vasodilation [42]. Therefore, future studies should consider whether this enhanced bioavailable formulation of curcumin improves obesity-associated endothelial function by using alternative techniques.

Our findings showing a lack of effect for curcumin to improve AIx and central BP are consistent with the results of previous studies in postmenopausal women [18] and middle-aged and older adults [16]. However, the combination of exercise and curcumin has been shown to improve AIx$_{75}$ and central SBP in postmenopausal women, whereas exercise or curcumin alone did not [18]. Therefore, improvements in AIx$_{75}$ and central BP may be dependent on the combination of exercise and curcumin supplementation, and further investigations are warranted.

As with all studies, there are limitations with the current investigation that should be noted. For instance, the present cohort of young, obese men was a relatively homogenous group with near-normal arterial function compared with previously published literature. In addition, physical activity was not monitored throughout the study, and greater physical activity or cardiorespiratory fitness may have influenced the findings. Furthermore, this study was designed as a pilot study to determine whether curcumin could influence obesity-associated endothelial function measured by RHI and elucidate potential mechanisms that influenced endothelial function. Oliver et al. recently found a significant benefit of curcumin to improve endothelial function, as quantified by FMD, using a sample of 59 young healthy individuals [15]. If the benefit of circumin on FMD is at least as strong among young obese men as those among young healthy individuals,

then a larger sample size than ours of about 40 persons for a two-arm study (Oliver et al. had a three-arm study) may suffice to establish the benefit of curcumin on FMD among young, obese men. Thus, future studies to assess the effects of curcumin should include a larger sample size or prescribe and assess physical activity behaviors.

Conclusions

An enhanced bioavailable formulation of curcumin, CurQfen®, ameliorated homocysteine and improved HDL concentrations in young, obese men. However, improvements in endothelial function, assessed by RHI, were not significant. Improvements in CVD-related blood biomarkers are suggestive of enhanced cardiovascular health, but further work is required to explore the influence of curcumin, with and without exercise, on endothelial function and central BP. Curcumin has shown potential as a strategy to lower obesity-related CVD risk, but requires further investigation.

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