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# The Effect of Curcumin Supplementation on Pulse Wave Velocity in Patients with Metabolic Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial

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**Abstract**

Cardiovascular disease is a leading cause of death in many societies. Arterial stiffness is an initial sign of structural and functional changes in the arterial wall. Pulse wave velocity (PWV) is the gold standard for non-invasive evaluation of aortic stiffness and a modifiable cardiovascular risk factor. Curcumin is a major component of turmeric with known anti-inflammatory and anti-oxidative effects. Since

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arterial stiffness is affected by inflammation and oxidative stress, it may be improved by curcumin supplementation. The purpose of this clinical trial was to investigate the potential effects of curcumin on improving arterial stiffness in patients with metabolic syndrome. This placebo-controlled, double-blind, randomized clinical trial was conducted among metabolic syndrome patients. Sixty-six eligible individuals were randomly assigned to active intervention or control groups. The active intervention group received curcumin supplement at a dose of 500 mg daily for 12 weeks, whereas the control group received placebo capsule. Physical activity, daily dietary energy intake, anthropometric body composition, and biochemical hemodynamic and arterial stiffness parameters were evaluated at baseline and at the end of the study. Body weight decreased significantly in the curcumin group compared to placebo. Also, curcumin intervention improved PWV, which remained significant after adjustment for potential confounding factors ($p = 0.011$). The current clinical trial demonstrated that daily intake of 500 mg of curcumin for 12 weeks can lead to the improvement of arterial stiffness and weight management among subjects with metabolic syndrome.

**Keywords**

Arterial stiffness · Vascular stiffness · Vascular aging · Arterial aging · Pulse wave velocity · Augmentation index · Curcuminoid · Curcumin · Turmeric · Metabolic syndrome · Obesity

## 1.1 Introduction

Cardiovascular disease (CVD) is the most prevalent cause of death in the world [1]. Arterial stiffness, specifically aortic stiffness, is a primary sign of structural and functional changes in arterial walls and is a predictor of cardiovascular events [2, 3]. Arterial stiffness explains the reduced ability of an artery in dilation and constriction in response to pressure alterations [4]. Collagen and elastin are two important proteins in the arterial wall and any imbalance between them, such as caused by inflammation or increased luminal pressure, results in increased collagen, reduced elastin and subsequently enhanced stiffness of arterial wall [5, 6].

Various methods, both invasive and noninvasive, have been accepted to assess arterial resilience. Pulse wave velocity (PWV) and wave reflection are two noninvasive methodologies for vascular stiffness assessment [7, 8]. Augmentation pressure (AP) and augmentation index (AIX) are measures of pulse wave reflection and evaluated using the pulse wave analysis (PWA) technique [9]. Large elastic artery stiffness and systemic arterial stiffness are evaluated through aortic PWV and wave reflection, respectively [10]. Aortic PWV, as the 'gold-standard' measurement of arterial stiffness, has been determined by carotid-femoral PWV (cf-PWV) [2, 11]. Also, AIX can demonstrate the CVD risks independently of peripheral pressures, as shown in a recent meta-analysis [12].

Several situations can reduce vascular elasticity such as aging, central obesity, smoking, diabetes, hypertension, inflammation disease, metabolic syndrome and genetic factors [8, 13]. Metabolic syndrome is one of the major causes of CVD, and has been described as one of the main public health global challenges [14, 15]. According to the International Diabetes Federation (IDF) definition, metabolic syndrome can be diagnosed with central obesity and the existence of two or more other clinical features that include elevated blood pressure, increased levels of triglyceride and fasting plasma glucose, and reduced HDL-cholesterol concentrations [16, 17]. Lifestyle modifications, such as improved dietary habits, can have a favorable effect on vascular stiffness [18]. Turmeric is a source of an orange-yellow pigment polyphenolic compound called curcumin [1,7-bis-(4-hydroxy-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione] [19]. Curcumin has been reported to have many beneficial effects on health [20–28]. It has been shown that curcumin can

induce nitric oxide production and reduce oxidative stress and inflammation in animal and in vitro models of vascular-related disorders [29–32]. A recent preclinical study in young and older male mice showed that 4 weeks of curcumin supplementation resulted in improved endothelial function and arterial stiffness by enhancement of nitric oxide bioavailability and reduced oxidative stress [33].

The purpose of this study was to test the hypothesis that 12 weeks of curcumin supplementation would lead to improved arterial stiffness indices in metabolic syndrome patients.

## 1.2 Methods

This randomized, double-blinded, placebo-controlled clinical trial with parallel design was conducted at the Persian cohort center of Imam Reza hospital, Mashhad, Iran. In this trial, 200 new cases of metabolic syndrome were assessed using inclusion and exclusion criteria. Of these cases, 66 individuals aged 30–60 years met the IDF criteria [17] and were incorporated into this 12 week study (Fig. 1.1). Exclusion criteria were the following: pregnancy; lactation; smoking; drug abuse; use of statins, contraceptive pills, analgesic, antidiabetic, antiplatelet, or anti-inflammatory drugs; consumption of antioxidants, multivitamins, multivitamin-mineral or herbal supplements 3 months before starting the study; and a history of diabetes, kidney failure, cancer, gallstones, calcium oxalate stones, autoimmune, biliary or obstructive diseases.

This investigation was approved by the Ethics Committee of Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran (serial no. IR.MUMS.MEDICAL.REC.1397.452), in accordance with the Declaration of Helsinki. In addition, this study was registered on Iranian Registry of Clinical Trials website (clinical trial registration no. IRCT20180619040151N2). At the beginning of the study, the nature, side effects, and advantages of the study were illustrated to volunteers and their written informed consent was obtained. All measurements were done at the Persian cohort center of Imam Reza hospital after 12 h fasting (water allowed) and > 24 h refrainment from physical activity.

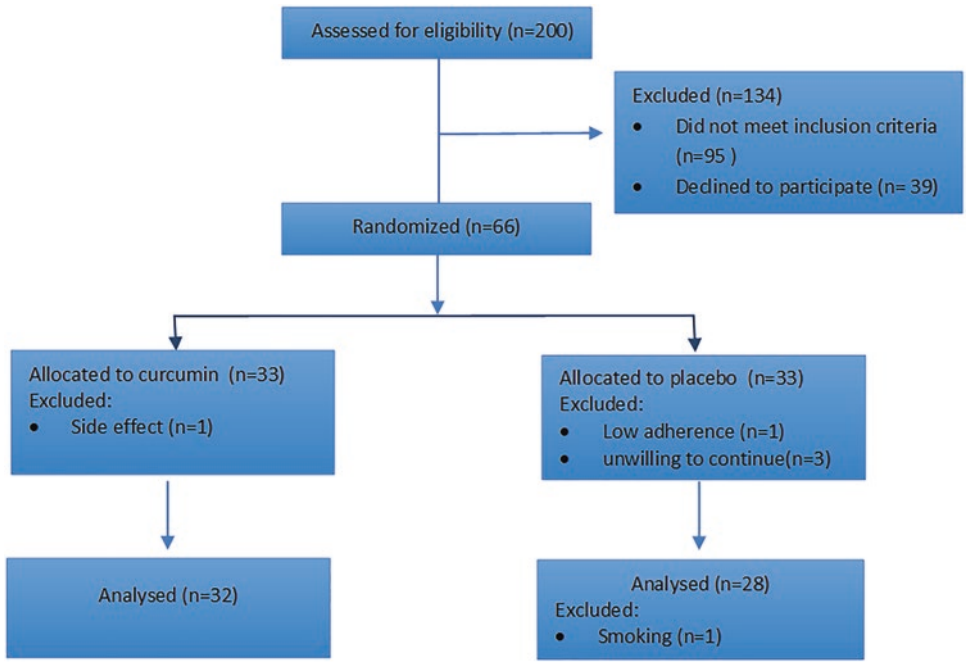


**Fig. 1.1** Flow diagram of study

### 1.2.1 Randomization Procedure

After conducting the screening and consent steps, the randomization procedure was performed using a stratified permuted block scheme, in which the stratification was based on age and gender. Subsequently, all participants were randomly allocated to either the curcumin or the placebo group.

### 1.2.2 Interventions

Curcumin [500 mg (95% total curcuminoids), provided by Karen Pharma and Food Supplement Company] or placebo capsules [500 mg of lactose, provided by the Faculty of Pharmacy, Mashhad University of Medical Sciences] were taken by the participants once per day with the midday meal. Every four weeks during the trial, in-person check-in visits were implemented to change the intervention capsules and evaluate participant compliance by survey and pill count. Additionally, tolerability and side effects of the interventions were assessed during these check-in visits.

### 1.2.3 Dietary and Physical Activity Assessment

Average daily dietary energy intake was evaluated by two-day dietary recall at baseline and at week 12. Dietary recall data were analyzed by Nutritionist IV software (N-Squared Computing, Salem, OR, USA). Also Physical activity was estimated by the long version of International Physical Activity Questionnaire (IPAQ) at baseline and week 12.

### 1.2.4 Anthropometric and Body Composition Assessment

Anthropometric and body composition measures were taken with subjects wearing light-weight clothing with no shoes on. Standing height was measured to the nearest 0.5 cm using a wall-mounted stadiometer. Waist, hip, wrist and neck circumferences were determined by a tension-gated tape at baseline and week 12. Waist circumference was measured to the nearest 0.5 cm at the midway of the distance between the lower rib margin and the iliac crest at the end of a gentle expiration and in the direction of the horizontal plane. Hip circumference was measured to the nearest 0.5 cm around the widest portion of the gluteal area in standing position [34]. Wrist circumference (WrC) was measured around the bony prominences of the radial and ulnar styloids [35]. Neck circumference (NC) was measured at the midpoint of the neck or just below the laryngeal prominence (‘Adam’s apple’) ‘in men with an obvious Adams apple, while the tape was placed vertically [34]. WrC and NC measures were taken to the nearest 0.1 cm. Also, weight and body composition parameters were determined via a bioelectrical impedance body composition analyzer (InBody 770, Biospace Co., Ltd. Seoul, South Korea). To decrease examiner-related errors, all the measurements executed by the same person.

### 1.2.5 Laboratory Parameters

Blood samples were collected from the antecubital vein after 12 h overnight fasting at baseline (0 weeks) and at the end of 12 weeks intervention. Serum concentrations of fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured using the BT1500 chemistry analyser (Biotecnica Instruments S.p.A., Rome, Italy).

### 1.2.6 Blood Pressure and Arterial Stiffness Measurements

Brachial and aortic blood pressure, aortic pulse pressure (PP), mean arterial pressure (MAP,) heart rate (HR), AIX, AIX75, AP, and arterial age measurements were obtained after the participants had rested in a supine posture for at least 10 min in a calm, thermoneutral room. Measurements were obtained with the SphygmoCor XCEL System

(Sphygmocor; AtCor Medical, Sydney, Australia) by a trained physician. After PWA, cf-PWV was measured for assessment of aortic stiffness using the SphygmoCor XCEL System.

### 1.2.7 Statistical Analyses

The sample size was statistically calculated to achieve a power of 90 according to change in AIX75 in the Sugawara [36] investigation. Statistical analysis was performed using SPSS 16. Assessment of data normality was performed using the One-Sample Kolmogorov-Smirnov test. In addition, histogram plots were evaluated visually, and it was observed that data distribution for normality was acceptable. Finally, linear regression was used to confirm the final results.

## 1.3 Results

A total of 66 metabolic syndrome patients were initially enrolled in the study but five placebo group participants (one smoking, three unwilling to continue, one adherence less than 80%) and one curcumin group participant (reflux side effect) did not complete the study (Fig. 1.1). The baseline characteristics of the final 60 study participants, who were randomly assigned into the two treatment arms, are shown in Table 1.1. None of the participant characteristics were significantly different between the two groups at base-

**Table 1.1** Subject characteristics in curcumin and placebo intervention

| | Curcumin | | Placebo | |
|---|---|---|---|---|
| Variables | Week 0 | Week 12 | Week 0 | Week 12 |
| Sex[a] | | | | |
| Male (%) | 43.8 | – | 53.6 | – |
| Female (%) | 56.2 | | 46.4 | |
| Age (year) | 42.84 ± 6.25 | – | 44.43 ± 5.92 | – |
| Physical activity [b] (MET/min/wk) | 826.5(300–1829) | 573(316–1267) | 688.5(352–1160) | 495(233–1449) |
| Energy intake (kcal/day) | 2120.36 ± 501.91 | 2042.02 ± 549.22 | 2057.4 ± 583.15 | 2172.43 ± 575.44 |
| Weight (kg) | 80.09 ± 9.67 | 79.55 ± 9.71 | 79.34 ± 12.39 | 79.77 ± 12.81 |
| Waist circumference (cm) | 97.15 ± 7.46 | 96.25 ± 8.06 | 100.13 ± 11.46 | 100.16 ± 11.86 |
| Neck circumference (cm) | 37.63 ± 2.67 | 37.55 ± 2.67 | 38.3 ± 3.84 | 38.45 ± 3.88 |
| Waist to hip ratio | 0.89 ± 0.05[c] | 0.89 ± 0.05 | 0.94 ± 0.07 | 0.94 ± 0.07* |
| Waist to height ratio | 0.58 ± 0.05 | 0.57 ± 0.05 | 0.6 ± 0.06 | 0.6 ± 0.07 |
| Body mass index ($kg/m^2$) | 28.87 ± 3.65 | 28.7 ± 3.86 | 29.16 ± 4.06 | 29.3 ± 4.06 |
| A body shape index ($m^{11/6}\ kg^{-2/3}$) | 0.08 ± 0.003[c] | 0.079 ± 0.004 | 0.082 ± 0.004 | 0.082 ± 0.004* |
| Protein (kg) | 9.94 ± 1.71 | 9.98 ± 1.71 | 10.02 ± 1.96 | 10.11 ± 2.07 |
| Skeletal muscle mass (kg) | 28.06 ± 5.13 | 28.08 ± 5.16 | 28.26 ± 5.94 | 28.48 ± 6.27 |
| Fat mass (kg) | 36.68 ± 8.21 | 36.22 ± 8.55 | 35.9 ± 6.35 | 35.87 ± 6.74 |
| Visceral fat area($cm^2$) | 143.72 ± 45.23 | 140.7 ± 47.04 | 135.18 ± 37.43 | 135.41 ± 39.1 |
| FPG (mg/dl) | 101.13 ± 10.96 | 94.28 ± 12.8** | 99.04 ± 12.64 | 96.28 ± 17.25 |
| TC(mg/dl) | 180.56 ± 39.01 | 175.22 ± 41.93 | 181.71 ± 37.57 | 178.79 ± 42.92 |
| TG (mg/dl) | 163.25 ± 52.45 | 148.97 ± 59.87 | 189.46 ± 87.21 | 164.11 ± 77.01 |
| HDL-C (mg/dl) | 46.13 ± 10.66 | 44.16 ± 9.62 | 44.11 ± 8.82 | 43.89 ± 9.79 |
| LDL-C (mg/dl) | 101.79 ± 29.56 | 102.42 ± 32.28 | 99.71 ± 31.41 | 102.07 ± 35.89 |
| AST (U/l) | 22.25 ± 9.36 | 18.22 ± 9.73** | 22.57 ± 7.9 | 19.54 ± 8.68** |
| ALT (U/l) | 28.84 ± 13.69 | 23.69 ± 12.59** | 28.18 ± 13.91 | 24.54 ± 13.46** |

Values are means±SD. *FPG* fasting plasma glucose, *TC* total cholesterol, *TG* triglyceride, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

*$P < 0.05$, between groups after 12 weeks of intervention

**$P < 0.05$, compared to baseline

[a]Chi-square

[b]Mann- Whitney test, values are medians ± interquartile range

[c] $P < 0.05$, compared to placebo at baseline

line (all $P > 0.5$), except for waist to hip (WHR) ratio and A Body Shape Index (ABSI), which were both higher in the control group ($P < 0.05$). In the current study, energy intake and physical activity did not change in either the curcumin and placebo groups compared to baseline.

### 1.3.1 The Effect of Curcumin on and Anthropometric, Body Composition, and Serological Tests

The effects of curcumin supplementation on anthropometric, body composition and biochemical tests are presented in Table 1.1 and Table 1.2. After 12 weeks of intervention, a statistically significant reduction in mean body weight was observed in the curcumin compared to the placebo group but body composition and other anthropometric parameters showed no significant changes. A decreasing trend was observed in anthropometric and body composition parameters, including waist circumference, neck circumference, body mass index (BMI), and visceral fat area after curcumin treatment relative to placebo. In both groups, liver enzymea (ALT and AST) were decreased significantly but there was no significant difference between the groups.

### 1.3.2 The Effect of Curcumin on Arterial stiffness and Hemodynamic Parameters

Table 1.3 indicates that there was no difference between the groups in vascular stiffness and hemodynamic parameters at the baseline of the study. As shown in Table 1.4, a significant reduction in PWV was observed following 12 weeks of curcumin intervention compared to placebo. Also, it was shown that after adjusting for confounding factors including age, gender, change in physical activity and energy intake by regression, the curcumin treatment significantly reduced aortic PWV, relative to placebo (Table 1.5). Finally, brachial and aortic systolic blood pressure (SBP) was reduced but totally hemodynamic parameters were not significantly improved with curcumin consumption compared to placebo.

**Table 1.2** Changes in anthropometric, body composition parameters, and serological tests during the intervention

| Variables | Curcumin | Placebo | P- value* |
|---|---|---|---|
| Weight (kg) | −0.53 ± 2.07 | 0.42 ± 1.5 | 0.04 |
| Waist circumference (cm) | −0.9 ± 2.51 | 0.02 ± 2.15 | 0.13 |
| Neck circumference (cm) | −0.07 ± 0.54 | 0.15 ± 0.64 | 0.14 |
| Waist to hip ratio | −0.003 ± 0.01 | −0.0007 ± 0.01 | 0.62 |
| Waist to height ratio | −0.005 ± 0.01 | 0.0005 ± 0.01 | 0.11 |
| Body mass index (kg/m$^2$) | −0.17 ± 0.75 | 0.13 ± 0.52 | 0.07 |
| A body shape index (m$^{11/6}$ kg$^{-2/3}$) | −0.0004 ± 0.001 | −0.0003 ± 0.001 | 0.72 |
| Protein (kg) | 0.03 ± 0.18 | 0.08 ± 0.33 | 0.49 |
| Skeletal muscle mass (kg) | 0.01 ± 0.5 | 0.21 ± 0.9 | 0.29 |
| Fat mass (kg) | −0.45 ± 1.77 | −0.02 ± 1.84 | 0.36 |
| Visceral fat area(cm$^2$) | −3.01 ± 12.39 | 0.23 ± 10.67 | 0.28 |
| FPG (mg/dl) | −6.84 ± 14.08 | −2.82 ± 33.53 | 0.29 |
| TC(mg/dl) | −5.34 ± 23.41 | −2.92 ± 6.33 | 0.74 |
| TG (mg/dl) | −14.28 ± 43.41 | −25.35 ± 65.66 | 0.43 |
| HDL-C (mg/dl) | −3.12 ± 6.11 | −0.21 ± 8.81 | 0.13 |
| LDL-C (mg/dl) | 0.63 ± 17.9 | 2.35 ± 29.08 | 0.78 |
| AST (U/l) | −4.03 ± 5.08 | −3.03 ± 6.51 | 0.5 |
| ALT (U/l) | −5.15 ± 7.26 | −3.64 ± 7.63 | 0.43 |

Values are means±SD
*Between groups

**Table 1.3** Cardiovascular parameters before and after intervention

| | Curcumin | | Placebo | |
|---|---|---|---|---|
| Variables | Week 0 | Week 12 | Week 0 | Week 12 |
| Aortic SBP (mmHg) | 108.44 ± 9.05 | 105.97 ± 7.22* | 109.36 ± 10.65 | 108.11 ± 11.25 |
| Aortic DBP (mmHg) | 74.5 ± 7.04 | 73.44 ± 5.66 | 76.57 ± 8.25 | 76.18 ± 10.22 |
| Aortic PP (mmHg) | 33.94 ± 5.29 | 32.53 ± 5.22 | 32.79 ± 5.1 | 31.93 ± 3.99 |
| Aortic MAP (mmHg) | 88 ± 8.23 | 86.47 ± 6.05 | 70.18 ± 7.66 | 69 ± 6.6 |
| HR (beats /min) | 69.69 ± 9.28 | 68.31 ± 5.64 | 70.18 ± 7.66 | 69 ± 6.6 |
| Aortic AP | 9.91 ± 5.14 | 9.78 ± 4.64 | 9.29 ± 3.75 | 8.86 ± 3.07 |
| Aortic AIX | 28.25 ± 11.75 | 29.38 ± 11.71 | 27.79 ± 9.35 | 27.32 ± 7.5 |
| Aortic AIX75 | 25.75 ± 12.68 | 26.19 ± 12.16 | 25.54 ± 9.98 | 24.36 ± 7.73 |
| Brachial SBP (mmHg) | 118.13 ± 9.54 | 114 ± 53 ± 7.83* | 118.75 ± 12.01 | 117.11 ± 12.23 |
| Brachial DBP (mmHg) | 73.75 ± 6.91 | 72.63 ± 5.71 | 75.86 ± 7.82 | 75.5 ± 9.92 |
| Arterial age(year) | 52.59 ± 18.82 | 51.53 ± 17.3 | 51.89 ± 16.45 | 48.54 ± 11.35 |
| Cf-PWV(m/s) | 7.60 ± 1.43 | 6.67 ± 0.97** | 7.43 ± 1.74 | 7.11 ± 2.03 |

Values are means±SD. SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, MAP: mean arterial pressure, HR: heart rate, AP; augmentation pressure, AIX; augmentation index, AIX75; augmentation index normalized to a HR of 75 bpm, cf-PWV; carotid to femoral pulse wave velocity

*$P < 0.05$, compared to baseline

**$P < 0.001$, compared to baseline

**Table 1.4** Differences of Cardiovascular parameters during the intervention

| Variables | Curcumin | Placebo | P-value* |
|---|---|---|---|
| Aortic SBP (mmHg) | −2.46 ± 6.81 | −1.25 ± 6.94 | 0.49 |
| Aortic DBP (mmHg) | −1.06 ± 6.04 | −0.30 ± 5.92 | 0.66 |
| Aortic PP (mmHg) | −1.4 ± 4.99 | −0.85 ± 4.36 | 0.65 |
| Aortic MAP (mmHg) | −1.53 ± 6.23 | −0.85 ± 6.24 | 0.67 |
| HR (beats /min) | −1.37 ± 9.07 | −1.17 ± 8 | 0.93 |
| Aortic AP | −0.12 ± 4.29 | −0.42 ± 3.24 | 0.76 |
| Aortic AIX | 1.12 ± 9.34 | −0.46 ± 7.2 | 0.46 |
| Aortic AIX75 | 0.43 ± 9.83 | −1.17 ± 7.89 | 0.49 |
| Brachial SBP (mmHg) | −3.59 ± 6.96 | −1.64 ± 7.69 | 0.3 |
| Brachial DBP (mmHg) | −1.12 ± 6 | −0.35 ± 5.78 | 0.61 |
| Arterial age(year) | −1.06 ± 18.31 | −3.35 ± 14.62 | 0.59 |
| Cf-PWV(m/s) | −1.09 ± 0.83 | −0.43 ± 1.24 | 0.03 |

Values are means±SD

*Between groups

**Table 1.5** Linear regression to adjust for confounding factors on PWV change

| Variables | B | Std. error | Beta | P value |
|---|---|---|---|---|
| Δ energy intake | −0.001 | 0.001 | −0.314 | 0.053 |
| Δ physical activity | 0.00006 | 0.00007 | 0.119 | 0.431 |
| Group | 0.84 | 0.319 | 0.39 | 0.011 |
| Gender | 0.547 | 0.307 | 0.251 | 0.082 |
| Age | 0.018 | 0.026 | 0.098 | 0.484 |

Δ after – before

## 1.4 Discussion

The present investigation demonstrated that 12 weeks of regular ingestion of curcumin supplement ameliorated aortic stiffness in metabolic syndrome patients. We assessed PWV as a principal marker of large arteries stiffness and observed that curcumin supplementation significantly reduced PWV. Analysis of potential sex differences did not show any significant improvement in arterial stiffness parameters in women who received curcumin intervention. Initial evidence in a preclinical study performed by Fleenor et al. [33] demonstrated that dietary curcumin supplementation improves age-related large elastic artery stiffness by nitric oxide bioavailability restoration, oxidative stress reduction and normalization of collagen I and advanced glycation end products (AGES) deposition in the arterial wall.

This finding is consistent with research showing that arterial stiffness (PWV or carotid arterial compliance) significantly improves after several weeks to months of curcumin treatment [20, 37, 38]. However, two studies reported that curcumin ingestion does not affect PWV [36, 39]. A recent study conducted by Campbell et al. demonstrated that only subjects with a higher baseline value of aortic PWV (arterial stiffness) responded to curcumin supplementation. In the present investigation, the mean age of patients receiving curcumin was 44 years old and the mean baseline cf-PWV value was 7.6 m/s. However, the mean cf-PWV for healthy 40–49 year-old subjects was found to be 7.2 m/s [40]. This suggests that there may be differences in the measured mean baseline cf-PWV across different studies.

We found that the reflection wave indices (aortic AP, AIX, and AIX75) were not affected by the curcumin intervention. In agreement with this finding, Sugawara et al. [36] found that curcumin significantly decreased aortic AIX75 only when combined with exercise training. AIX is a complicated variable that shows the stiffness of smaller muscular arteries as well as microvascular density, number and location of terminal arterioles that give rise to reflected waves, the velocity of the pressure wave, and the pattern of left ventricular ejection. In addition, in contrast to PWV, AIX is influenced by gender and anthropometric measurements [41].

Today lifestyle modification is the main strategy for prevention of CVD, and weight management is a key factor in this objective. For this objective, curcumin has been reported to have beneficial effects on obesity management [42–45]. A preclinical study suggested that curcumin has antiobesity effects through downregulating the expression of peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer binding protein α, which are key transcription factors in adipogenesis and lipogenesis [46]. This results in suppression of adipocyte differentiation, fatty acid esterification, and adipokine-induced angiogenesis in adipose tissue, and induction of fatty acid oxidation and increased apoptosis of adipocytes. In humans, 10 weeks of curcumin supplementation significantly decreased mean body weight in overweight type 2 diabetes patients [42]. consistent with this finding, we observed that 12 weeks of curcumin ingestion significantly decreased body weight compared to the placebo group. Although not statistically significant, the curcumin intervention also tended to decrease WC, NC, BMI, and visceral fat area, while these parameters had an increasing trend in the placebo group.

Metabolic syndrome is a serious health condition of impaired glucose tolerance and, consequently, elevation of fasting plasma glucose is one of its criteria. Many animal studies have demonstrated that curcumin anti-inflammatory and antioxidant activities may be responsible, at least in part, for its anti-hyperglycemic effects [47–49]. Studies in humans have been inconsistent as some have confirmed the curcumin anti-hyperglycemic effect [42, 43, 50], and others have found no effect [51, 52]. In our study, FPG did not significantly change with curcumin supplementation compared to placebo. Also, we did not observe any significant changes in lipid profiles between the groups. Many preclinical studies have found that curcumin reduces serum cholesterol levels via upregulating the expression of hepatic LDL receptors, inhibition of LDL oxidation, enhancement of cholesterol excretion by increasing bile acid secretion, and suppressing

the expression of genes involved in cholesterol biosynthesis [53, 54]. Furthermore, a recent animal study showed that curcumin reduced serum TG concentrations through inhibition of sterol regulatory element-binding protein 1 (SREBP-1c), liver X receptor alpha (LXR-α), and the target lipogenic enzymes fatty acid synthase and acetyl CoA carboxylase [55]. To our knowledge and according to literature review, curcumin should be consumed in higher doses or in a higher efficacy form (nano-formulation or in combination with an adjuvant) to influence FPG and lipid profiles.

Since the liver is the main organ for drug metabolism and elimination, it should be considered that hepatotoxic reactions may take place there in the present study. Such drug-induced hepatotoxicity manifestations are various, ranging from a mild elevation of liver enzymes to fatal hepatic failure [56]. During the present clinical trial, liver function was not affected by the interventions, as determined by the lack of effect on ALT and AST, which are commonly used as biomarkers of liver damage.

This study was limited by its short-term duration of follow-up that precluded the possibility of assessing hard cardiovascular endpoints. Furthermore, although the mean baseline cf-PWV values of participants were modestly elevated, not all participants had high PWV. The inability to present a mechanistic view for the beneficial effects of curcumin on vascular aging was another limitation of this study.

## 1.5 Conclusions

In the present study, we observed the favorable effects of 12 weeks of curcumin supplementation on arterial stiffness and weight control. We also demonstrated that curcumin intake for 12 weeks was well tolerated. Further trials are warranted to confirm the present findings in target populations with elevated arterial stiffness.

**Conflict of Interest** None of the authors had declarations of interest to publish.

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