Curcumin Supplementation Ameliorated Vascular Dysfunction and Antioxidant Status in High Sucrose, High Fat Fed Rats

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Curcumin Supplementation Ameliorated Vascular Dysfunction and Antioxidant Status in High Sucrose, High Fat Fed Rats

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Abstract

Vascular endothelial dysfunction is a potential risk factor for cardiovascular diseases. This study evaluated the effect of curcumin on vascular dysfunction relative factors using rats fed on high sucrose, high fat (HSF) diet. The experiment was conducted in two animal feeding stages. In the first feeding phase, male Sprague-Dawley rats were randomly divided into two groups: control group (n=8) was fed on AIN-93G diet and HSF group (n=24) was fed on HSF diet for 8 weeks to induce obese status. In the second feeding phase lasting 4 weeks, HSF group was further randomly subdivided into three subgroups: O group (n=8) continued feeding on HSF diet; OA group (n=8) had HSF diet replaced with AIN-93G diet; and OC group (n=8) was fed on HSF diet supplemented with curcumin (300mg/kg body weight/day). After 8 weeks, HSF diet significantly elevated levels of AST, ALT, insulin, HOMA-IR, LDL-C, Hcy, CRP, VCAM-1 and ICAM-1, but significantly reduced levels of NO and HDL-C. After dietary intervention, OA and OC groups exhibited significantly lower levels of AST, ALT, HOMA-IR, cholesterol, LDL-C, Hcy, CRP, VCAM-1 and ICAM-1, and higher levels of NO and CAT activity compared to those of O group. SOD, CAT and GPx activities were increased in OA group. CAT levels were enhanced in OC group. In conclusion, this study showed curcumin supplementation and dietary replacement can inhibit HSF diet-induced vascular dysfunction potentially through enhanced NO production and antioxidant enzymes activities, thereby leading to suppressed inflammation and oxidative damage in the vascular endothelium.

Key words: curcumin, high sucrose high fat diet, homocysteine, nitric oxide, vascular endothelial dysfunction.
Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; CAT, catalase; CRP, C-reactive protein; GPx, glutathione peroxidase; GR, glutathione reductase; Hcy, homocysteine; HDL-C, high density lipoprotein-cholesterol; HOMA-IR, homeostatic model assessment-insulin resistance; ICAM-1, intercellular adhesion molecule-1; LDL-C, low density lipoprotein-cholesterol; NO, nitric oxide; ROS, reactive oxygen species; SOD, superoxide dismutase; TG, triglycerides; VCAM-1, vascular cell adhesion molecule-1.

Introduction

Vascular endothelium is the primary regulator of blood vessels homeostasis in both healthy and diseased states. Through local production of nitric oxide (NO), vascular endothelium regulates permeability, vascular tone, coagulation, vascular inflammation, and inhibits smooth muscle cell proliferation of blood vessels (Moncada et al. 1991; Toda et al. 2011). Endothelial dysfunction is increased in atherosclerotic conditions such as coronary heart and peripheral artery disease, and thus is considered an independent predictor of cardiovascular events. Endothelial dysfunction is associated with the initial step of atherosclerosis through reduced bioavailability of NO (Ruberg et al. 2002). In vivo studies have revealed synergistic interactions among obesity, insulin resistance, chronic oxidative stress and inflammation towards development and subsequent advancement of endothelial dysfunction events (Raghaven et al. 2014; Campbell and Fleenor, 2017). Chronic oxidative injury and inflammation are among the critical factors that contribute to vascular endothelial dysfunction (Ballou and Lozanski 1992; Libby et al. 2002). Majority of reactive oxygen species (ROS) in the vascular endothelium originate from blood and various cell categories such as endothelial cells, vascular smooth muscle cells and mononuclear cells. As a protective mechanism, the in vivo antioxidant enzyme system comprises superoxide dismutase (SOD), which rapidly
dismutates superoxide anion $\text{O}_2^-$ to $\text{H}_2\text{O}_2$, and subsequently, $\text{H}_2\text{O}_2$ is eliminated by glutathione peroxidase (GPx) and catalase (CAT) (Marín et al. 2013). Previous in vivo studies have reported a negative correlation between levels of NO, antioxidant enzymes activities and vascular endothelial dysfunction (Ruberg et al. 2002; Rodriguez-Manas et al. 2009).

Dyslipidemia is a key feature of obesity and is widely recognized as a major risk factor for vascular dysfunction. Several studies have shown strong positive correlation between total cholesterol (TC) / high density lipoprotein-cholesterol (HDL-C) ratio, low density lipoprotein-cholesterol (LDL-C) / HDL-C ratio, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), malondialdehyde (MDA) levels and vascular endothelial dysfunction (Libby et al. 2002; Majithiya and Balaraman, 2006; Wan Ahmad et al. 2015).

Hyperhomocysteinemia is associated with impairment of vascular function, thus is considered a potential risk factor for cardiovascular disorders. Homocysteine (Hcy) is metabolized by remethylation to methionine or by transulfuration to cysteine. An elevated homocysteine level may arise from an altered enzyme activity in the transulfuration and remethylation pathways (Sharma et al. 2013). The major target of increased Hcy is vascular endothelium where it impacts on structural endothelial injury.

Curcumin is a major ingredient of turmeric (Curcuma longa), which is commonly used as a spice and food-colouring condiment. Curcumin comprises polyphenol compounds that exhibit antioxidant and anti-inflammatory properties (Bengmark et al. 2006; Wongeakin et al. 2014). The effect of curcumin on varied vascular related disorders has been reported by several authors. Curcumin alleviated diabetic
cardiomyopathy and oxidative stress in diabetic rats (Rungseesantivanon et al. 2010; Yu et al. 2012). Campbell et al. (2017) observed curcumin de-stiffened arteries in young, obese men with higher aortic stiffness. Moreover, curcumin improved endothelial function of postmenopausal women and young healthy subjects, potentially through enhanced flow-mediated dilation, suppressed inflammation and oxidative stress (Akazawa et al. 2012; Sugawara et al. 2012; Oliver et al. 2016). However, Nieman et al. (2012) reported turmeric supplement failed to alter inflammation, oxidative stress, or arterial stiffness in overweight/obese women.

The purpose of this study was to investigate the effects of curcumin as a functional ingredient on vascular dysfunction and further examine the underlying potential risk factors including serum lipid profile, Hey, C-reactive protein (CRP), soluble adhesion molecules (VCAM-1 and ICAM-1), NO levels, antioxidant enzyme activities and vascular oxidative damage status using obese rat model induced through high sucrose, high fat diet.

**Materials and Methods**

**Animals**

Thirty-two male Sprague-Dawley rats aged 6 weeks and weighing 250 ± 20 g were purchased from the BioLASCO Taiwan Co., Ltd. (Taipei, Taiwan). The rats were individually housed in polycarbonate cages with stainless steel lid in an air-conditioned room (23 ± 2 °C, 65 ± 5 % relatively humidity) with a 12-hour light-dark cycle and free access to standard chow diet (Labdiet® 5001, Land O’Lake Inc., USA) and water for one week before experiment. All animal experimental procedures complied with published guidelines (Kilkenny et al. 2010; Schulz et al. 2010) and were approved by
the Institutional Animal Care and Use Committee of Taipei Medical University (Taipei, Taiwan).

**Diets and experimental groups**

The experiment was conducted in two animal feeding stages. In the first feeding phase, male Sprague-Dawley rats were randomly divided into two groups: control (C) group (n=8) was fed on AIN-93G diet and HSF group (n=24) was fed on HSF diet for 8 weeks to induce obese status. In the second feeding phase lasting 4 weeks, HSF group was further randomly (using lot and cage numbers) subdivided into three subgroups: O group (n=8) continued feeding on HSF diet; OA group (n=8) had HSF diet replaced with AIN-93G diet; and OC group (n=8) was fed on HSF diet supplemented with curcumin (300mg/kg body weight (BW) /day) as formulated by Rungseesantivanon et al. (2010). Fasting blood samples were collected from tail vein after 8 and 12 weeks for analysis of vascular function-related serum biochemical parameters. After 12 weeks of feeding, animals were sacrificed and abdominal aorta samples obtained for analysis of vascular oxidative damage and antioxidant enzyme activities. The HSF diet was prepared on the basis through modification of AIN-93G diet for rodents (Avogaro et al. 2005; La Favor et al. 2013), and contained (per kg): 340g sucrose, 10g cholesterol and 200g lard and 4.73 kcal/g gross energy (Table 1). The gross energy of the control AIN-93G diet was 3.95 kcal/g.

**Serum biochemistry assays**

Blood samples (2 mL) were drawn from the tail vein of the rats and centrifuged (2500×g for 10 min., 4 °C) to obtain serum. Separated serum was stored at -70 °C until
Alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, TC, HDL-C, LDL-C, and triglycerides (TG) were measured using an automatic analyzer (ADVIA 1800, Dimension RXL, SIEMENS, Germany). Hcy was measured using chemiluminescence method (ADVIA Centaur CP Immunoassay System, SIEMENS, Germany). Insulin (Merckodia AB, Sweden) and CRP levels (Novus Biologicals, USA) were measured using respective ELISA kits. NO level was measured with commercial Nitrate/Nitrite colorimetric assay kit (Cayman Chemical, USA). ICAM-1 and VCAM-1 levels were measured using Quantikine® ELISA kits (R&D System, Inc., USA). Homeostasis model assessment insulin resistance (HOMA-IR) ratio was calculated as follows: HOMA-IR = glucose (mmol/L) × insulin (µIU/mL) / 22.5.

Evaluation of antioxidant enzymes activities and malondialdehyde levels in the abdominal aorta

Abdominal aorta was carefully excised and cleaned to remove abdominal fat and adherent connective tissues, and cut into 4-5 mm rings for biochemical determinations. Abdominal aorta tissue samples were homogenized in 0.1 M potassium phosphate buffer (PBS, pH 7.4) with a homogenizer (Qiagen® Tissuelyser II, Germany). The mixture was centrifuged (10000×g, 10 min., 4 °C) and the collected supernatant was stored at −70 °C for further analysis. Prior to analysis of MDA levels and activities of antioxidant enzymes (SOD, glutathione reductase (GR), CAT and GPx), protein concentration of tissue samples was detected using Pierce® BCA protein assay microreagent system. MDA level was evaluated using thiobarbituric acid reactive substances assay kit (Cayman Chemical, USA). Activities of SOD, GR and GPx were measured using respective commercial kits (RANDOX Laboratories Ltd., UK). CAT
activity was detected by measuring the degradation of H$_2$O$_2$, using the modified spectrophotometric method (Kaplan and Groves, 1972). In brief, an H$_2$O$_2$ substrate (50 mM) was prepared through dilution with 0.05 M KH$_2$PO$_4$ buffer (pH 7.5) in 0.9% NaCl solution. The reaction was initiated by addition of 0.5 mL of H$_2$O$_2$ substrate to one mL of diluted supernatant, and thereafter, decrease of absorbance was recorded for 70 seconds at 240 nm and 37°C, using a spectrophotometer. CAT activities were expressed as µmol H$_2$O$_2$ /minute/mg protein.

**Statistical analysis**

All statistical analyses were done using the SPSS statistical software (version 19.0). Results are expressed as the mean ± standard deviation (SD). Mean differences between the parameters were analyzed by a one way analysis of variance (ANOVA) followed by Duncan's multiple-range test for post-hoc comparisons. Differences were considered significant at $p < 0.05$.

**Results**

*Effects of HSF diet and curcumin supplementation on liver damage, lipid profile, insulin resistance and homocysteine*

Liver damage was evaluated through assessment of serum AST and ALT levels. AST activities in O, OA and OC groups increased significantly by 20.0%, 14.2% and 15.5%, respectively, compared to those of C group. ALT activities increased significantly by 76.0%, 56.9%, and 70.8%, respectively (Table 2). TC levels in O, OA and OC groups increased by 29.2%, 19.5% and 11.2%, respectively, but were not statistically
significant (p=0.053). However, TG concentrations were significantly decreased by 25.3%, 25.0% and 25.9%, respectively, compared to those of C group (Table 2).

LDL-C concentrations of O, OA and OC groups increased significantly by 143.7%, 113.6% and 94.0%, respectively. However, the levels of HDL-C were significantly decreased by 41.5%, 38.4% and 43.4%, respectively, compared to those of C group. Furthermore, TC/HDL-C ratios of O, OA and OC groups were significantly higher by 127.3%, 95.9% and 97.2%, respectively, than that of C group. In addition, LDL-C/HDL-C ratios of O, OA and OC groups were significantly higher than those of C group by 326.4%, 244.2% and 238.8%, respectively. Hcy levels of O, OA and OC groups were significantly elevated compared to those of C group by 27.3%, 16.5% and 19.3%, respectively (Table 2). Insulin levels of O, OA and OC groups were significantly increased by 88.5%, 65.4% and 65.4%, respectively, whereas HOMA-IR values were significantly increased by 96.4%, 78.8% and 75.9%, respectively when compared with C group (Table 2). Altogether, these results show 8 weeks of HSF diet feeding successfully induced abnormal serum biochemical parameters (HDL-C, Hcy levels, TC/HDL-C and LDL-C/HDL-C ratios), which are as associated with vascular dysfunction and cardiovascular diseases.

In the second phase of the feeding experiment lasting 4 weeks, AST levels of O, OA and OC groups were significantly higher by 183.1%, 27.7% and 66.4%, respectively, compared to those of C group. However, AST levels in OA and OC groups were significantly decreased by 54.9% and 41.3%, respectively, compared to those of O group (Table 3). ALT levels increased significantly by 581%, 86.3% and 181.5% in O,
OA and OC groups, respectively, compared with C group levels. However, ALT concentrations of OA and OC groups were significantly lower than those of O group by 72.6% and 58.7%, respectively.

TC levels in O, OA and OC groups were significantly increased by 53.9%, 22.7% and 28.7%, respectively, compared to that of C group, but OA and OC groups were significantly decreased by 20.3%, and 16.4%, separately, compared to those of O group. LDL-C concentrations in O, OA and OC groups were significantly higher than those in C group by 193.2%, 88.4% and 116.9%, respectively. However, OA and OC groups were significantly decreased by 35.8% and 26.0%, respectively, compared with O group levels. HDL-C concentrations of O, OA and OC groups were significantly lower than those in C group by 44.1%, 18.6% and 29.7%, respectively. Compared with O group, levels of HDL-C in OA and OC groups were significantly increased by 45.5% and 25.8%, respectively (Table 3).

TC / HDL-C ratios of O, OA and OC groups were significantly higher than those of C group by 174.5%, 52.9% and 87.6%, respectively. TC / HDL-C ratios of OA and OC groups were significantly decreased by 44.3% and 31.6%, respectively, compared to those of O group. LDL-C/HDL-C ratios of O, OA and OC groups were significantly higher than those of C group by 441.5%, 142.5% and 228.5%, respectively, but the ratios in OA and OC groups were significantly decreased by 55.2% and 39.3% respectively, compared with O group levels (Table 3).

Hcy levels in O group were significantly higher than those of C group by 45.1%. However, the levels in OA and OC groups were significantly decreased by 23.4% and 23.1%, respectively, compared to those of O group. Insulin levels of O and OC groups were significantly increased by 272.7% and 125%, respectively, compared to those of C.
group, but the levels in OA and OC groups were significantly decreased by 63.4% and 39.6%, respectively, compared to those of O group. HOMA-IR values of O and OC groups were significantly increased by 289.1% and 135%, respectively, compared to those of C group but the levels in OA and OC groups were significantly decreased by 64.9% and 39.6%, respectively, compared to those of O group (Table 3).

**Effects of HSF diet and curcumin supplementation on serum CRP, NO, ICAM-1 and VCAM-1 levels**

After 8 weeks of HSF diet feeding, CRP concentrations of O, OA and OC groups were significantly higher than the levels in C group by 86.6%, 83.6% and 87.4%, respectively. VCAM-1 levels of O, OA and OC groups were significantly increased by 197.1%, 173.4% and 174.2%, respectively, whereas ICAM-1 levels were significantly increased by 36.3%, 32.2% and 31%, respectively, compared with C group levels. However, NO levels of O, OA and OC groups were significantly lower than those in C group by 56%, 54.5%, 55.4%, respectively (Table 4).

After 4 weeks of intervention feeding, levels of CRP were significantly increased by 88.6%, 58.4% and 61.6% in O, OA and OC groups, respectively, compared with levels of C group. However, CRP levels of OA and OC groups were significantly decreased by 16.0% and 14.3%, respectively, compared to those of O group (Table 4). ICAM-1 concentrations in O, OA and OC groups were significantly higher than those of C group by 31%, 16.6% and 15.8% respectively, whereas levels in OA and OC groups were significantly decreased by 11% and 11.6%, respectively, compared to those of O group. VCAM-1 concentrations were significantly higher than those in C group by 197.3%, 63.9% and 132.5%, respectively, whereas the levels of OA and OC groups were
significantly decreased by 44.9% and 21.8%, respectively, compared to those of O group. NO levels of O, OA and OC groups were significantly lower than those in C group by 79.6%, 42.5% and 55.3%, respectively. NO levels in OA and OC groups were significantly increased by 181.3% and 118.7%, separately, compared to O group levels (Table 4).

*Effects of HSF diet and curcumin supplementation on vascular MDA levels and antioxidant enzymes activities*

After 12 weeks, MDA levels of O, OA and OC groups were significantly increased by 928%, 639% and 707%, respectively, compared to C group (Table 5). Although not significant when compared with MDA level of O group, those of OA and OC groups were decreased by 28.1% and 21.4%, respectively. Compared to O group, SOD activities of OA and OC groups were increased by 403.7% and 51.9%, respectively, whereas CAT activities of OA and OC groups were significantly increased by 193.6% and 93.6%, respectively (Table 5).

In summary, during first experimental feeding phase lasting 8 weeks, HSF subgroups (O, OA and OC) showed significantly elevated levels of AST, ALT, insulin, HOMA-IR, LDL-C, LDL-C/HDL-C ratios, Hcy, CRP, VCAM-1 and ICAM-1 compared to those in the control group (Table 2). On the other hand, HSF subgroups showed significantly reduced levels of NO, TG and HDL-C compared to those of C group (Table 2). In the second intervention feeding phase lasting 4 weeks, OA and OC groups exhibited significantly lower levels of AST, ALT, insulin, HOMA-IR, TC, LDL-C, LDL-C/HDL-C, Hcy, CRP, VCAM-1, ICAM-1, NO and CAT compared to those of
O group. SOD and GPx activities were significantly increased in OA group compared to those of O group.

**Discussion**

Results from this study showed sustained feeding of HSF diet resulted in reduced vascular endothelial NO production as well as increased levels of atherosclerosis causal factors including serum TC, TC/HDL-C, LDL-C, LDL-C/HDL-C, CRP, Hcy, ICAM-1 and VCAM-1. These biomarkers are potential predictive factors of vascular dysfunction and cardiovascular diseases. Moreover, HSF diet increased vascular oxidative damage (expressed as MDA) as well as decreased activities of vascular antioxidant enzymes. However, the findings of our study show that these effects can be ameliorated by 4 weeks of dietary alteration through replacement of HSF diet or curcumin supplementation as illustrated in Figure 1.

*Effects of HSF diet and curcumin supplementation on liver damage, lipid profile, insulin resistance, homocysteine*

Obesity promotes endothelial dysfunction through various metabolic syndrome disorders such as dyslipidemia and diabetes, which are primary contributors of vascular oxidative stress and inflammation (Van Gaal et al. 2006; Meyrelles et al. 2011; Hirase and Node 2012). In the present study, 8 weeks of HSF diet feeding successfully induced abnormal serum lipid profile indices such as LDL-C, TC/HDL-C and LDL-C/HDL-C ratios, which are as associated with vascular dysfunction and cardiovascular diseases. These biomarkers were reversed upon replacement of HSF diet with control diet (OA) and supplementation with curcumin (OC). Our findings are in agreement with those of Um et al. (2014) who reported 8 weeks of curcumin (0.2 % w/w of diet) supplement
significantly reduced serum levels of TC (-21.5%), TG (-41.2%), and LDL-C (-30.4%), compared with control group levels in a hypercholesterolemic rabbits model. Furthermore, Chuengsamarn et al. (2014) observed substantially reduced pulse wave velocity, leptin, HOMA-IR, TG, uric acid, visceral fat and total body fat and increased serum adiponectin and decreased in type 2 diabetic human subjects after 6 months of curcumin (1500mg/day) dietary intervention. According to a human study by Panahi et al. (2016), curcumin supplementation (1000 mg/day) administered markedly reduced serum levels of TC, LDL-C, TG and uric acid, whereas HDL-C and glucose levels remained unaltered in subjects with nonalcoholic fatty liver disease.

In the present study, HSF diet resulted in substantial increase in Hcy levels in obese rats. This observation is in agreement with those of previous studies that reported abnormal methionine metabolism associated arising from impaired hepatic homocysteine re-methylation, and aberrancy in methyltransferase reactions in high fat high cholesterol diet fed animals (Dahlhoff et al. 2013; Pacana et al. 2015). Antoniades et al. (2009) also reported are substantially elevated serum Hcy levels in patients with vascular diseases compared to levels in normal subjects and concluded that Hcy potentially plays an important role in development of atherosclerotic lesions. In our study, the remarkably higher serum ALT and AST levels of HSF subgroups implied induction of moderate liver damage thereby affecting the hepatic transulfuration and remethylation pathways and resulting in elevated hcy levels.

In the present study, substantially elevated levels of insulin and HOMA-IR values were observed at week 8 after HSF diet feeding. The high insulin levels could explain the non-significant increase in glucose concentration observed during current study. In a combined obesity and insulin-resistant states, the ultimate atherogenic events depend on
two primary insulin activation pathways: (i) Insulin activation of insulin receptor substrate / phosphatidylinositol-3-kinase / Akt (IRS/PI3K/Akt) pathway results in mostly antiatherogenic actions, as this pathway induces activation of endothelial NO synthase (eNOS) by using a Ca\(^{2+}\)-independent mechanism requiring phosphorylation of eNOS by Akt at Ser\(^{1179}\) (Montagnani et al. 2001). Insulin activation of eNOS can produce NO that enhances smooth muscle vasodilatation and blood flow (King et al. 2016). (ii) In contrast, insulin activation of the Grb/Shc/MAPK pathway mediates proatherogenic actions through the expressions of endothelin-1 and plasminogen activator inhibitor-1, which trigger the migration and proliferation of contractile cells. Due to the high levels of insulin required for MAPK activation, insulin resistance selectively inhibit insulin antiatherogenic actions via the IRS/PI3K/Akt pathway and enhance proatherogenic events. This hypothesis could explain the correlation of hyperinsulinemia with increased risk for atherosclerosis (Montagnani et al. 2001; King et al. 2016). In summary, both the previous and present studies indicate curcumin has potential of inhibiting dyslipidemia, insulin resistance and Hcy related risk factors of atherosclerosis.

**Effects of HSF diet and curcumin supplementation on serum CRP, NO, ICAM-1 and VCAM-1 levels**

The findings of our study indicate dietary pattern alteration (OA) or curcumin (OC) interventions could ameliorate inflammation (CRP), cell adhesion (ICAM-1 and VCAM-1) and NO production after HSF diet feeding and consequently promote vascular function. According to Tietge (2014), reduced NO and enhanced vascular oxidation and inflammation are the major hallmarks of initiation and progression of
atherosclerosis. Production of superoxide from eNOS promote vascular dysfunction through depressed NO bioavailability and increased oxidative stress (Channon, 2004). Furthermore, Hcy can initiate an inflammatory response in vascular smooth muscle cells by stimulating CRP production, through NR1 subunit of N-methyl-d-aspartate receptor – ROS – ERK1/2 / p38 – NF-κB signal pathway (Pang et al. 2014).

Hcy plays an important role in the early stages of the atherogenic process by decreasing NO availability, stimulating activation of NF-κB and consequently increasing expression of ICAM-1 (Zhang et al. 2004). Moreover, elevated expression of ICAM-1 increases reactivation, adhesion and metastasis of white blood cells and macrophages during induction of atherosclerosis (Porsch-Oezcuerman et al. 1999). In our study, HSF diet replacement with control diet (OA) and curcumin supplementation (OC) substantially suppressed CRP, ICAM-1 and VCAM-1 levels. This finding is in agreement with that of Um et al. (2014) who reported 8 weeks of curcumin (0.2 % w/w of diet) intervention markedly inhibited the expressions of ICAM-1, VCAM-1 and CRP in hypercholesterolemic rabbits. Furthermore, Wongeakin et al. (2014) reported curcumin supplementation (300 mg/kg BW) remarkably decreased ICAM-1 expression and reduced the number of leukocyte-endothelium interactions in a diabetes-induced endothelial dysfunction model. Altogether, the results of the present and previous studies demonstrate curcumin can confer a protective effect against atherosclerosis, and endothelial dysfunction potentially by decreasing inflammation and soluble adhesion molecules.
Effects of HSF diet and curcumin supplementation on vascular MDA levels and antioxidant enzymes activities

Results of the present study showed dietary pattern alteration (OA) or curcumin supplementation (OC) markedly increased activities of vascular antioxidant enzymes (SOD, GPx and CAT), in OA and OC groups. These findings indicate that dietary pattern alteration or curcumin treatment could protect blood vessel against lipid peroxidation and inflammation induced by HSF diet feeding. Previous in vivo studies have shown that long-term intake of high sucrose, or high fat diet or combined diet can induce NADPH oxidase / mitochondrial-mediated superoxide production as well as depletion of glutathione and activities of antioxidant enzymes (SOD and CAT) (Diniz et al. 2006; Feillet-Coudray et al. 2009; Lima et al. 2016). In addition, Hcy can stimulate NADPH oxidase-mediated superoxide and peroxynitrite production leading to endothelial dysfunction in high-methionine diet fed rats (Edirimanne et al. 2007). Chronically higher levels of Hcy could decrease NO production and inhibit expression of GPx and SOD, leading to production of free radicals and oxidative stress (Nonaka et al. 2001).

In our study, 4 weeks of HSF diet replacement (OA) and curcumin (OC) reversed the reduced levels of CAT experienced during HSF diet feeding. SOD and GPx activities were only enhanced in OA group when compared to O group. Naik et al. (2011) investigated liver and heart tissues in CCl₄ induced liver injury and isoproterenol induced cardiac necrosis models and observed elevated serum AST and ALT activities, lipid peroxidation, and decreased GPx and SOD activities. However, curcumin doses (200, 400 mg/kg BW) treatment substantially reversed these biochemical changes in the
animal models. Yu et al. (2012) reported 16 weeks of 200 mg/kg BW curcumin supplementation markedly decreased serum MDA levels and inhibited the expression of NADPH oxidase in the heart of experimental diabetic rats. Using a neonatal rat cardiomyocytes culture, Yu et al. (2016) found that curcumin (10 µM) attenuated high glucose-induced cardiomyocyte apoptosis by inhibiting NADPH oxidase-mediated oxidative stress probably via PI3K/Akt-related signaling pathway. A study on type 2 diabetic patients, showed 8 weeks of curcumin supplementation (300 mg/day) improved vascular endothelial function alongside reductions in MDA, inflammatory cytokines (IL-6 and TNF-α) (Usharani et al. 2008).

In summary, results of the present study showed that curcumin intervention might have protective effects on vascular damage through reduced ROS production and enhanced antioxidant enzymes activities. According to Panahi et al. (2016), curcumin supplementation (1000 mg/day) was found to be safe and well tolerated by human subjects with Non-alcoholic liver disease. Nevertheless, in view of the current study, prior to application to human interventions, further safety studies are required to determine the acceptable dosages for specific human physiological states including obesity.

As a limitation in the current study, despite randomly (using lot and cage numbers) assigning the rats to the respective experimental groups (O, OA, OC) after 8 weeks of HSF diet feeding, O group generally showed higher trends of some biochemical parameters compared to OA and OC group levels. We, however, performed post hoc statistical mean comparisons and confirmed the differences as non-significant. We attribute the observed trend to inherent biological factors during the experimental period.
For further studies, we suggest a longer intervention period beyond 4 weeks to rule out possible effect of the group differences.

**Conclusion**

As illustrated in Fig. 1, OA and OC groups exhibited significantly lower levels of AST, ALT, insulin, HOMA-IR, cholesterol, LDL-C, LDL-C/HDL-C, Hey, CRP, VCAM-1, ICAM-1, NO and CAT compared to those of O group. SOD and GPx activities were significantly increased in OA group compared to those of O group. Our study shows that dietary pattern alteration or curcumin supplementation could protect against vascular damage through decreased dyslipidemia, inflammation and vascular oxidative damage in HSF diet fed rats.

**Conflict of interest statement**

The authors report that no conflicts of interest exist.

**Acknowledgement**

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Table 1. Components of control (AIN-93G) and HSF diets

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<td>Casein</td>
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<td>174</td>
</tr>
<tr>
<td>L-Cystine</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>70</td>
<td>34</td>
</tr>
<tr>
<td>Lard</td>
<td>0</td>
<td>200</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Choline Bitartrate</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>AIN-93 Mineral Mix</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>AIN-93 Vitamin Mix</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Cellulose</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Percentage of energy (%)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>HSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td>63.8</td>
<td>40.8</td>
</tr>
<tr>
<td>Fat</td>
<td>15.9</td>
<td>44.5</td>
</tr>
<tr>
<td>Protein</td>
<td>20.3</td>
<td>14.7</td>
</tr>
</tbody>
</table>

C: Control diet (AIN-93G); HSF diet: high sucrose, high fat diet.
Table 2. Serum biochemical parameters of the rats after 8 weeks of HSF diet feeding\(^1,2\)

<table>
<thead>
<tr>
<th>Items \ Groups</th>
<th>C</th>
<th>O</th>
<th>OA</th>
<th>OC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (U/L)</td>
<td>165.9 ± 19.6(^a)</td>
<td>199.0 ± 26.7(^b)</td>
<td>189.5 ± 7.7(^b)</td>
<td>191.6 ± 15.0(^b)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>34.6 ± 6.6(^a)</td>
<td>60.9 ± 9.6(^b)</td>
<td>54.3 ± 9.5(^b)</td>
<td>59.1 ± 6.4(^b)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>154.0 ± 16.0</td>
<td>160.1 ± 16.1</td>
<td>168.3 ± 15.5</td>
<td>164.8 ± 10.4</td>
</tr>
<tr>
<td>Insulin (µIU/mL)</td>
<td>12.54 ± 2.09(^a)</td>
<td>23.67 ± 5.50(^b)</td>
<td>20.65 ± 3.02(^b)</td>
<td>20.75 ± 4.63(^b)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.77 ± 0.94(^a)</td>
<td>9.37 ± 2.48(^b)</td>
<td>8.53 ± 1.07(^b)</td>
<td>8.39 ± 1.71(^b)</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>105.4 ± 28.3(^b)</td>
<td>78.8 ± 20.2(^a)</td>
<td>79.0 ± 16.9(^a)</td>
<td>78.1 ± 8.8(^a)</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>56.9 ± 7.5(^a)</td>
<td>73.5 ± 15.8(^a)</td>
<td>68.0 ± 13.0(^a)</td>
<td>63.3 ± 8.6(^a)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>15.9 ± 2.0(^b)</td>
<td>9.3 ± 1.4(^a)</td>
<td>9.8 ± 1.6(^a)</td>
<td>9.0 ± 1.1(^a)</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>19.9 ± 8.5(^a)</td>
<td>48.5 ± 16.0(^b)</td>
<td>42.5 ± 9.7(^b)</td>
<td>38.6 ± 8.1(^b)</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>1.29 ± 0.65(^a)</td>
<td>5.50 ± 2.46(^b)</td>
<td>4.44 ± 1.21(^b)</td>
<td>4.37± 1.17(^b)</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>3.62 ± 0.58(^a)</td>
<td>8.23 ± 2.65(^b)</td>
<td>7.09 ± 1.60(^b)</td>
<td>7.14 ± 1.46(^b)</td>
</tr>
<tr>
<td>Hcy (µmol/L)</td>
<td>7.15 ± 0.90(^a)</td>
<td>9.10 ± 1.20(^b)</td>
<td>8.33 ± 1.24(^b)</td>
<td>8.53 ± 1.15(^b)</td>
</tr>
</tbody>
</table>

\(^1\)Values are means ± SD, n=8. \(^2\)Values in the same row with the different letter superscripts indicate a significant change between groups (p < 0.05). The experiment was conducted in two animal feeding stages for a total period of 12 weeks. In the first feeding stage lasting 8 weeks, 32 male Sprague Dawley rats were randomly divided into two groups: C group (n=8) fed on AIN-93G diet and HSF group (n=24) fed on HSF diet in order to induce obesity status. In the second intervention feeding stage lasting 4 weeks, the HSF group was further randomly subdivided into three subgroups: O group (n=8) continued feeding on HSF diet; OA group (n=8) HSF diet replaced with AIN-93G diet; OC group (n=8) HSF diet supplemented with curcumin (300mg/kg BW/day).
Table 3. Serum biochemical parameters of the rats at the end of experiment 1, 2

<table>
<thead>
<tr>
<th>Items \ Groups</th>
<th>C</th>
<th>O</th>
<th>OA</th>
<th>OC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (U/L)</td>
<td>181.6 ± 5.8a</td>
<td>514.3 ± 51.6c</td>
<td>232.0 ± 4.9ab</td>
<td>302.1 ± 0.4b</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>33.6 ± 4.5a</td>
<td>228.8 ± 51.7c</td>
<td>62.6 ± 12.5a</td>
<td>94.6 ± 31.4b</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>153.0 ± 18.6a</td>
<td>165.6 ± 21.5a</td>
<td>154.5 ± 11.6a</td>
<td>161.0 ± 12.0a</td>
</tr>
<tr>
<td>Insulin (µIU/mL)</td>
<td>10.61 ± 2.50a</td>
<td>39.64 ± 21.70c</td>
<td>14.39 ± 3.60ab</td>
<td>23.86 ± 9.84b</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.03 ± 1.20a</td>
<td>15.68 ± 7.95c</td>
<td>5.51 ± 1.05ab</td>
<td>9.47 ± 3.83b</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>118.1 ± 4.6c</td>
<td>65.5 ± 6.5a</td>
<td>87.5 ± 13.2b</td>
<td>76.8 ± 11.9ab</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>60.3 ± 12.8a</td>
<td>92.8 ± 20.0c</td>
<td>74.0 ± 7.7b</td>
<td>77.6 ± 9.3b</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>11.8 ± 2.1c</td>
<td>6.6 ± 0.9a</td>
<td>9.6 ± 1.9b</td>
<td>8.3 ± 1.5ab</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>24.9 ± 10.8a</td>
<td>73.0 ± 20.0c</td>
<td>46.9 ± 7.7b</td>
<td>54.0 ± 9.9b</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>2.07 ± 0.72a</td>
<td>11.21 ± 3.23c</td>
<td>5.02 ± 1.22b</td>
<td>6.80 ± 2.22b</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>5.18 ± 0.92a</td>
<td>14.22 ± 3.37c</td>
<td>7.92 ± 1.56b</td>
<td>9.72 ± 2.47b</td>
</tr>
<tr>
<td>Hcy (µmol/L)</td>
<td>7.20 ± 0.75a</td>
<td>10.45 ± 1.12b</td>
<td>8.00 ± 0.94a</td>
<td>8.04 ± 0.64a</td>
</tr>
</tbody>
</table>

1Values are means ± SD, n=8. 2Values in the same row with the different letter superscripts indicate a significant change between groups (p < 0.05). The experiment was conducted in two animal feeding stages for a total period of 12 weeks. In the first feeding stage lasting 8 weeks, 32 male Sprague Dawley rats were randomly divided into two groups: C group (n=8) fed on AIN-93G diet and HSF group (n=24) fed on HSF diet in order to induce obesity status. In the second intervention feeding stage lasting 4 weeks, the HSF group was further randomly subdivided into three subgroups: O group (n=8) continued feeding on HSF diet; OA group (n=8) HSF diet replaced with AIN-93G diet; OC group (n=8) HSF diet supplemented with curcumin (300mg/kg BW/day).
Table 4. Serum CRP, NO, VCAM-1 and ICAM-1 levels of the rats during the 12 weeks of feeding\textsuperscript{1, 2}

<table>
<thead>
<tr>
<th>Items \ Groups</th>
<th>C</th>
<th>O</th>
<th>OA</th>
<th>OC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>After initial 8 weeks of feeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (ng/mL)</td>
<td>14.38 ± 1.27\textsuperscript{a}</td>
<td>26.83 ± 2.40\textsuperscript{b}</td>
<td>26.40 ± 1.69\textsuperscript{b}</td>
<td>26.95 ± 1.35\textsuperscript{b}</td>
</tr>
<tr>
<td>NO (µM)</td>
<td>37.14 ± 7.94\textsuperscript{b}</td>
<td>16.35 ± 1.46\textsuperscript{a}</td>
<td>16.89 ± 2.40\textsuperscript{a}</td>
<td>16.55 ± 1.27\textsuperscript{a}</td>
</tr>
<tr>
<td>VCAM-1 (ng/mL)</td>
<td>48.8 ± 18.2\textsuperscript{a}</td>
<td>145.0 ± 19.8\textsuperscript{b}</td>
<td>133.4 ± 13.2\textsuperscript{b}</td>
<td>137.0 ± 16.4\textsuperscript{b}</td>
</tr>
<tr>
<td>ICAM-1 (ng/mL)</td>
<td>3.42 ± 0.36\textsuperscript{a}</td>
<td>4.66 ± 0.47\textsuperscript{b}</td>
<td>4.52 ± 0.31\textsuperscript{b}</td>
<td>4.48 ± 0.35\textsuperscript{b}</td>
</tr>
<tr>
<td><strong>After 4 weeks of intervention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (ng/mL)</td>
<td>15.56 ± 1.14\textsuperscript{a}</td>
<td>29.35 ± 3.11\textsuperscript{c}</td>
<td>24.65 ± 1.41\textsuperscript{b}</td>
<td>25.14 ± 1.29\textsuperscript{b}</td>
</tr>
<tr>
<td>NO (µM)</td>
<td>31.95 ± 8.71\textsuperscript{c}</td>
<td>6.53 ± 0.55\textsuperscript{a}</td>
<td>18.37 ± 7.00\textsuperscript{b}</td>
<td>14.28 ± 2.99\textsuperscript{b}</td>
</tr>
<tr>
<td>VCAM-1 (ng/mL)</td>
<td>55.1 ± 26.5\textsuperscript{a}</td>
<td>163.8 ± 40.5\textsuperscript{d}</td>
<td>90.3 ± 31.5\textsuperscript{b}</td>
<td>128.1 ± 33.5\textsuperscript{c}</td>
</tr>
<tr>
<td>ICAM-1 (ng/mL)</td>
<td>3.74 ± 0.32\textsuperscript{a}</td>
<td>4.90 ± 0.47\textsuperscript{c}</td>
<td>4.36 ± 0.36\textsuperscript{b}</td>
<td>4.33 ± 0.38\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Values are means ± SD, n=8. \textsuperscript{2}Values in the same row with the different letter superscripts indicate a significant change between groups (p < 0.05). The experiment was conducted in two animal feeding stages for a total period of 12 weeks. In the first feeding stage lasting 8 weeks, 32 male Sprague Dawley rats were randomly divided into two groups: C group (n=8) fed on AIN-93G diet and HSF group (n=24) fed on HSF diet in order to induce obesity status. In the second intervention feeding stage lasting 4 weeks, the HSF group was further randomly subdivided into three subgroups: O group (n=8) continued feeding on HSF diet; OA group (n=8) HSF diet replaced with AIN-93G diet; OC group (n=8) HSF diet supplemented with curcumin (300mg/kg BW/day).
<table>
<thead>
<tr>
<th>Items \ Groups</th>
<th>C</th>
<th>O</th>
<th>OA</th>
<th>OC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA (nmole/mg protein)</td>
<td>47.0 ± 18.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>483.0 ± 187.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>347.2 ± 130.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>379.5 ± 131.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SOD (mU/mg protein)</td>
<td>78.3 ± 21.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>29.7 ± 18.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>149.6 ± 9.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>45.1 ± 13.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>GPx (mU/mg protein)</td>
<td>71.5 ± 28.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>101.1 ± 2.6&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>158.1 ± 42.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>126.2 ± 0.2&lt;sup&gt;bc&lt;/sup&gt;</td>
</tr>
<tr>
<td>GR (mU/mg protein)</td>
<td>17.3 ± 5.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21.1 ± 9.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24.0 ± 6.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21.5 ± 7.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>CAT (µmole/min/mg protein)</td>
<td>23.7 ± 7.3&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>11.0 ± 6.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>32.3 ± 10.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>21.3 ± 9.9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup>Values are means ± SD, n=8. <sup>2</sup>Values in the same row with the different letter superscripts indicate a significant change between groups (p < 0.05). The experiment was conducted in two animal feeding stages for a total period of 12 weeks. In the first feeding stage lasting 8 weeks, 32 male Sprague Dawley rats were randomly divided into two groups: C group (n=8) fed on AIN-93G diet and HSF group (n=24) fed on HSF diet in order to induce obesity status. In the second intervention feeding stage lasting 4 weeks, the HSF group was further randomly subdivided into three subgroups: O group (n=8) continued feeding on HSF diet; OA group (n=8) HSF diet replaced with AIN-93G diet; OC group (n=8) HSF diet supplemented with curcumin (300mg/kg BW/day).
Figure 1. Interactive model on ameliorative effects of curcumin on endothelial dysfunction in obesity state. HSF diet leads to elevated levels of HOMA-IR, LDL-C, Hcy, CRP, VCAM-1 and ICAM-1, but reduces NO and HDL-C levels. Curcumin supplementation or HSF replacement (AIN93 diet) results in suppressed levels of HOMA-IR, LDL-C, Hcy, CRP, VCAM-1, ICAM-1, and higher NO and HDL-C levels, and increased SOD, GPx and CAT activities. The overall effect is protection against vascular endothelial dysfunction associated damage through decreased dyslipidemia, inflammation and vascular oxidative damage.
High fat and high sucrose diet

- ↓ HDL-C
- ↑ LDL-C
- ↑ Homocysteine
- ↑ HOMA-IR
- ↑ CRP
- ↑ VCAM-1
- ↑ ICAM-1
- ↑ ROS

Obesity state

- Antioxidant enzymes activities
- ↓ CRP
- ↓ Homocysteine
- ↓ LDL-C
- ↓ HDL-C
- ↓ HOMA-IR
- ↑ NO

Cucurmin supplementation or refeed AIN93 diet

Heart & Vessels Damage

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