Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: a randomized controlled trial☆

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Abstract

Curcumin is a phytocompound found in the root of turmeric, a common herbal ingredient in many Asian cuisines. The compound contains anti-inflammatory activity, which is mediated through an up-regulation of adiponectin and reduction of leptin. Consumption of curcumin was shown to prevent some deteriorative conditions caused by inflammation, such as ulcerative colitis, rheumatoid arthritis and esophagitis, and so on. Inflammation-associated cardiovascular conditions such as atherosclerosis are common in diabetes patients. The anti-inflammation effect of curcumin might be beneficial to prevent such condition in these patients. We aim to evaluate an antiatherosclerosis effect of curcumin in diabetes patients. Effects of curcumin on risk factors for atherosclerosis were investigated in a 6-month randomized, double-blinded and placebo-controlled clinical trial that included subjects diagnosed with type 2 diabetes. An atherosclerosis parameter, the pulse wave velocity, and other metabolic parameters in patients treated with placebo and curcumin were compared. Our results showed that curcumin intervention significantly reduced pulse wave velocity, increased level of serum adiponectin and decreased level of leptin. These results are associated with reduced levels of homeostasis model assessment-insulin resistance, triglyceride, uric acid, visceral fat and total body fat. In summary, a 6-month curcumin intervention in type 2 diabetic population lowered the atherogenic risks. In addition, the extract helped to improve relevant metabolic profiles in this high-risk population.
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1. Introduction

Type 2 diabetes mellitus (T2DM) is a cluster of abnormal metabolic conditions that is primarily composed of insulin resistance (IR). Other associated metabolic conditions are abdominal obesity, dyslipidemia, hyperuricemia, high blood pressure and cardiovascular complications. Recent findings indicated that T2DM/IR is not only associated with cardiovascular conditions but also is a driver for atherogenesis [1,2]. Marfella et al. [3] pointed out that inflammation often found in T2DM patients is likely the cause of the diabetes-associated atherosclerosis. Circulating markers of inflammation, as well as monocyte gene expression of proinflammatory mediators, are elevated in type 2 diabetes [4,5]. In addition, a balanced level between a proinflammatory cytokine, leptin and an anti-inflammatory cytokine, adiponectin is often disrupted in T2DM patients; specifically, leptin is up-regulated, while adiponectin is down-regulated [6–8]. The imbalanced levels of these inflammatory-regulating adipocytokines are shown to contribute to the atherosclerosis [9]. It is believed that adiponectin induction, or leptin suppression, in general, should reduce a risk for atherosclerotic diseases in type 2 diabetes patients [10,11]. Other metabolic parameters, known to promote atherogenesis, commonly coexist in the T2DM patients. Such conditions are abdominal obesity [visceral fat (VF) and total body fat (TBF)] [12,13], dyslipidemia [(high triglyceride and low high-density lipoprotein cholesterol (HDL-C)] [14,15] and high uric acid [16,17].

Curcumin is a principal curcuminoid compound found in turmeric (Curcuma longa Linn.), a popular spice in Asian cuisine. It is widely consumed and believed to be beneficial for human health [18]. Curcumin extract was shown, in animal models [19–23] and in human [24], to contain positive effects on several metabolic syndromes. It was also shown to contain anti-inflammation [25], antioxidative stress

activities and reduce aortic fatty streak development in rabbits [26]. In addition, daily treatment of curcumin extract can decrease significantly the low-density lipoprotein (LDL) and apoB levels and increase the HDL and apoA in healthy subjects [27]. Due to these positive indications, a trial in human patients of curcumin treatment for prevention of arteriosclerosis has been proposed.

In this study, we aim to study an efficacy and safety of curcumin extract as an intervention agent for reducing the risks for atherogenesis in T2DM, by conducting an evidence-based, double-blind, placebo-controlled clinical trial to access the possibility of using curcumin as an intervention agent for such condition.

2. Subjects and methods

2.1. Subject screening

This simple randomized, double-blinded, placebo-controlled trial with parallel design was conducted at HRH Princess Maha Chakri Sirindhorn Medical Center of Srinakharinwirot University, Nakornnayok, Thailand. Two hundred forty patients with type 2 diabetes were selected by inclusion and exclusion criteria (for the trial profile and consort information, see Online Supplemental Material in Figure 1). The subjects were enrolled in a 9-month-long study. Nutritionists educated all subjects by having the participants to attend a one-on-one consultation, to perform the same pattern of diet and exercise through course of this study after the enrollment (during a 3-month period before the randomization). Standard lifestyle and diet recommendations were provided for all subjects in written form after understanding in educated program from nutritionists. Because all the subjects were recruited from the same geological background with a very similar ethnicity, we assumed that the type of the dietary intake is not dissimilar. To avoid any interference from other medications, during the recruitment process, we excluded all of patients who were taking any other medicines, as indicated in the exclusion criteria. Only type 2 diabetic subjects at the age of ≥35 years, the typical age range in which T2DM normally develops, were included in this study. Type 2 diabetes was diagnosed following the American Diabetes Association (ADA) practice guidelines [28,29]. Briefly, subjects who fit into at least one of these three criteria were included: subjects with a fasting plasma glucose (FPG) ≥126 mg/dl, an oral glucose tolerance test (OGTT) plasma glucose at 2 h post-glucose load (OGTT at 2 h) ≥200 mg/dl and a glycated hemoglobin (HbA1c) ≥6.5%. Diagnosis of type 2 diabetes was confirmed by second repeating tests of all of the above-listed criteria on a different day.

Subjects diagnosed with prediabetes conditions according to the new ADA guidelines [28] were excluded from the study (subjects who are positive for one of these following criteria: FPG between 100 and 124 mg/dl, OGTT at 2 h between 140 and 199 mg/dl, and HbA1c range from 5.7% to 6.4%). The following subjects were also excluded from the study: subjects receiving oral antidiabetes (biguanide, thiazolidinediones and dipeptidyl peptide-4 inhibitors) or insulin injection; subjects receiving antiplatelet drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, fenofibrate, atorvastatin, rosuvastatin and fluvastatin; subjects with serum creatinine ≥2.0 mg/dl or dialysis; subjects with liver enzyme alanine aminotransferase (ALT) ≥3 folds of upper limit of normal value range; subjects receiving other herbal medicine; subjects with secondary causes of hyperglycemia (receiving steroid or with pancreatic cancer); subjects with acute infections or chronic inflammatory diseases (cancer, rheumatoid arthritis); and subjects with a gall bladder disease or history of cholecystectomy. This study (clinical trial registration no. NCT01052597) was approved by the Ethic Committee of Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand (serial number: SWUEC 30/2550) in accordance with the Declaration of Helsinki and to the guideline by the Consolidated Standards of Reporting Trials (CONSORTs) [30]. Participants were informed and gave their consent before enrollment.

2.2. Randomization procedures

After steps of screening, consenting, and diet and lifestyle training, all subjects were randomly assigned to either the curcumin-treated group (intervention condition) or the placebo-treated group (control condition) using a fixed randomization scheme with assignment based on computer-generated random numbers performed by an independent researcher. The allocation scheme was sealed in opaque and consecutively numbered envelopes. Envelopes were opened sequentially by an independent person. The participants were informed that two types of interventions were being compared.

2.3. The intervention

All participants were instructed to take three capsules with blinded labels of either curcumin or placebo twice a day (total of six capsules per day) for 6 months continuously. Each curcumin capsule has curcuminoid content of 250 mg. Each placebo capsule contains 250 mg of starch. Patients were asked to bring all capsules back when having follow-up visits at 3 and 6 months for assessing their compliance. Numbers of capsules taken by the subjects were recorded in Online Supplemental Material in Table 1.

2.4. Preparation of curcuminoids capsules

Curcumin and identical placebo capsules were manufactured by the Government Pharmaceutical Organization of Thailand. Dried rhizomes of turmeric (C. longa Linn.) grown in Kanchanaburi province, Thailand, were ground into powder. The turmeric powder was extracted with ethanol and evaporated at low pressure to obtain ethanol extract in the form of semisolid containing oleoresin and curcuminoids. Oleoresin was then removed to yield curcuminoid extract (total curcuminoids content is between 75% and 85%). The peak ratio of curcumin: demethoxycurcumin and bisdemethoxycurcumin in the extract was determined by high-performance thin-layer chromatography. The extract (calculated for 250 mg of curcuminoids) was capsulated under the Good Manufacturing Procedures standard. Fingerprints of the extract and a detailed analysis of the chemical composition of the preparation in the extract are shown in Online Supplemental Material in Fig. 2.

2.5. Study outcomes

The primary outcome of the antiatherogenic activities was assessed by an average pulse wave velocity (PWV) in the curcumin-treated group and the placebo group. In addition, the changes in the level of anti-inflammatory adipocytokines (increased adiponectin or decreased leptin) were also recorded. Other parameters assessed included IR (HOMA-IR), triglyceride and uric acid levels, and abdominal obesity (VF and TBF).

Indications of adverse effects of curcumin were monitored by elevated creatinine ≥1.2 mg/dl and aspartate aminotransferase (AST)/ALT ≥3 times of the upper limit of normal value range, and any symptoms of patient complaints were recorded [29].

2.6. Data collection and measurement methods

Measurements were performed at the baseline and during the 3 and 6-month visits. We recorded demographic data at the baseline; the researchers administered a questionnaire and measured the medical history, medication, body weight, body height, waist circumference (WC) and vital sign status. The abdominal obesity indicated by WC was measured by a tape in the direction of the horizontal plane, midway between the inferior margin of the wrist and the superior border of the iliac crest [31]. Abdominal obesity indicated by TBF and VF was determined by bioelectrical impedance analysis (body fat analyzer: OMRON HBF-362), and was then analyzed for body fat level and VF level, respectively [32]. Blood was collected at 8:00 AM from the antecubital vein with the patient in the recumbent position, after an overnight fast. Plasma samples for assays of insulin, adiponectin and leptin were frozen and stored at −70°c until the analyses of hormones were performed. FPG, HbA1c, total cholesterol, triglyceride, LDL cholesterol (LDL-C) and HDL-C levels were measured according to the standard procedures. Plasma insulin, adiponectin and leptin concentrations were determined using the radioimmunoassay kits (Millipore, St. Charles, MI, USA). The signals were detected by a gamma scintillation counter calibrated for 125 iodine measurement. HOMA-IR was calculated to assess change in IR [33,34]. PWV was used as an indicator for the arterial stiffness [35,36]. PWV was measured by Colin Medical Technology (VP-1000) and analyzed by pulse wave diagnosis results [37]. Peripheral PWV (baPWV) represented by volume waveforms for the brachium and ankle and was measured using a VP-1000 pulse wave analyzer (Colin Medical Technology), as previously described [38]. In brief, the PWV measurement system recorded electrocardiogram, phonocardiogram and three-pulse waves from the brachial and dorsalis pedis arteries. Pressure pulse sensors were used to measure pulse waves. Amplifier, filter and isolation circuits were used to detect accurate signals. The intersecting tangent algorithm, using the least square mean method, was adapted to determine up stroke points. Regional PWV values, brachial and dorsalis pedis were calculated automatically after collecting 10 s of data. For baPWV, brachial–dorsalis pedis transit time and PWV were calculated from the brachial–dorsalis pedis path length divided by transit time. Path length was estimated from the linear distance from the sternal notch to the dorsalis pedis artery at the point of applanation.

2.7. Sample size

The sample size was statistically calculated to obtain a power of 80%, with an alpha error of .05. In order to demonstrate an effect in levels of PWV levels, consisting of a 60-cm/s reduction with standard deviation of 160 cm/s [39], a sample size of 226 (113 in the curcumin-treated group and 113 in the placebo group) is required. Assuming a 5% loss to follow-up, 238 subjects between the two groups need to be selected. The two groups will be of equal size in order to obtain the greatest statistical power.

2.8. Statistical analysis

Continuous data are presented as the means±SEM, and P<.05 was considered statistically significant. Two-tailed Student's t test was used for baseline comparisons and outcome evaluations between two groups, and between means at baseline and 3 or 6 months. Categorical variables were presented in percent and analyzed using chi-square test. Outcome data were analyzed on an intention-to-treat basis, including all randomized patients in the efficacy and safety analyses, according to their randomized treatment group regardless of the treatment received. These exclude patients who

have not provided baseline information at the first visit on ward. All statistical analyses were performed using the SPSS version 21.0 for Windows.

3. Results

A flowchart of the trial (CONSORT information) is presented in Online Supplemental Material in Figure 1. A total of 240 subjects were initially enrolled in the study. The baseline characteristics of 240 subjects, who were randomly allocated into the two groups were indistinguishable and presented in Table 1. Average duration of T2DM from both groups was similar (mean=6.34 years in curcumin and 6.01 years in placebo group; Table 1) All parameters at the baseline between placebo-treated group and curcumin-treated group were not statistically different.

3.1. Curcumin treatment improved PWV, increased adiponectin and decreased leptin

PWV in curcumin group was significantly lower than that in placebo group at P<.001 (Table 2; Fig. 1A and B). Levels of adipocytokines such as adiponectin and leptin in both groups were investigated. Six-month curcumin intervention significantly elevated levels of adiponectin and lowered leptin levels (Table 2; Fig. 1C and D).

3.2. Assessments of metabolic parameters related to atherogenic risks

In the curcumin-treated group, IR (HOMA-IR), metabolic profiles (triglyceride and uric acid) and abdominal obesity (VF and TBF) were significantly lower than those in the placebo group (Table 2; Fig. 2A–D). Although not statistically significant, indicators for obesity, such as

Table 1
Baseline characteristics of subjects in the curcumin-treated and placebo-treated group

Variables	Curcumin, mean (standard error) (n=107)	Placebo, mean (standard error) (n=106)	P-value (unpaired t test)
Sex			
Male, no. (%)	50 (46.7)	47 (44.3)	.73[a]
Female, no. (%)	57 (53.3)	59 (55.7)	
Age (y)	59.16 (1.067)	59.58 (1.04)	.78
Systolic blood pressure (mm Hg)	128.9 (1.5)	127.7 (1.6)	.95
Diastolic blood pressure (mm Hg)	75.1 (1.0)	73.9 (1.2)	.44
WC (cm)	90.68 (1.2)	90.21 (1)	.76
BMI (kg/m²)	27.09 (0.52)	26.84 (0.42)	.71
Total cholesterol (mg/dl)	199.43 (4.36)	195.88 (4.29)	.56
LDL-C (mg/dl)	117.86 (3.49)	113.49 (3.23)	.36
Triglyceride (mg/dl)	158.24 (9.84)	166.94 (9.85)	.53
HDL-C (mg/dl)	49.76 (1.04)	49.24 (1.27)	.75
Uric acid (mg/dl)	6.09 (0.17)	6.29 (0.18)	.41
Creatinine (mg/dl)	1.15 (0.06)	1.07 (0.04)	.27
AST (U/l)	24.61 (0.93)	24.53 (0.98)	.45
ALT (U/l)	41.56 (1.34)	41.91 (1.35)	.30
HbA1C (%)	7.1 (0.12)	6.97 (0.11)	.28
FPG (mg/dl)	143.83 (3.51)	139.07 (3.51)	.34
Duration of diabetes mellitus (y)	6.34 (0.59)	6.01 (0.55)	.68
History of smoking, no. (%)			.61[b]
Nonsmoker	73 (70.2)	78 (73.6)	
Smoker	6 (5.8)	8 (7.5)	
Ex-smoker	25 (24.0)	20 (18.9)	
History of dyslipidemia, no. (%)	66 (65.3)	56 (54.4)	.11[a]
History of hypertension, no. (%)	74 (69.8)	73 (68.9)	.88[a]
History of coronary arterial disease, no. (%)	6 (5.7)	6 (5.7)	1.0[a]
History of cerebrovascular disease, no. (%)	1 (1.0)	3 (2.9)	.62[b]
Diabetic nephropathy, no. (%)	20 (19.0)	28 (26.4)	.20[a]
Diabetic retinopathy, no. (%)	33 (31.1)	34 (32.1)	.88[a]
Diabetic peripheral neuropathy, no. (%)	20 (18.9)	20 (18.9)	1.0[a]

[a] Chi-square.
[b] Fisher exact test.

body mass index (BMI), and abdominal obesity/WC appeared to be lower in the curcumin-treated group (Table 2, Fig. 2E; Online Supplemental Material in Table 2).

LDL-C and total cholesterol in curcumin-treated group showed a lower trend, whereas HDL-C in curcumin group showed a higher trend, when compared to those in placebo group (Online Supplemental Material in Table 2).

3.3. Adverse effects and compliance

To monitor possible adverse effects of curcumin intervention, we determined body weight, blood pressure (systolic/diastolic blood pressure), kidney function (creatinine) and liver functions (AST and ALT) (Online Supplemental Material in Tables 2 and 3). We found no significant differences in the means of systolic/diastolic blood pressure, levels of creatinine and AST between the curcumin-treated and the placebo-treated group. In the curcumin-treated group, the level of ALT was significantly lower than that in the placebo-treated group (P=.026; Online Supplemental Material in Table 3). During the course of our study, none of the subject newly developed CAD or any sign of edema (data not shown). A few subjects from the curcumin-treated group reported minor symptoms such as hot flash (one subject), constipation (two subjects) and nausea (one subject). A few patients from the placebo-treated group also reported some minor symptoms such as hot flash (one subject), constipation (one subject), vertigo (one subject) and itching (one subject). Of note, none in the curcumin-treated group showed any hypoglycemia symptoms.

Interestingly, at the last follow-up visit (6 months after intervention), we noticed slight reductions of mean body weight, BMI, WC, lipid profiles (total cholesterol, LDL-C) and blood glucose profiles (FPG and HbA1c) and a slight increase of HDL-C from the group of patients treated with curcumin. We did not see such patterns from the placebo-treated group (Online Supplemental Material in Table 2). All together, these results indicated that curcumin extract can be used for intervention, at least for a period of 6 months, without any serious unwanted effect. Of note, at each follow-up visit, we counted numbers of remaining capsules brought to us by subjects for patients' compliance. Numbers of the capsule consumed by subjects from both groups were very comparable (Online Supplemental Material in Table 1). In the curcumin group, the capsules were taken by average of 5.2 (SD=0.2) and 4.7 (SD=0.1), while in the placebo group, the capsules were taken by an average of 5.1 (SD=0.2) and 4.3 (SD=0.2) in the 3 and 6 months, respectively. Therefore, the effects observed by us were not a result of different level of compliance between two groups.

4. Discussion

Atherosclerosis is a condition that may eventually result in many serious cardiovascular conditions. T2DM patients are especially prone to develop atherosclerosis, due to elevated level of inflammation, and abnormal metabolic profiles, commonly found in these patients. In an attempt to find a safe, well-tolerated and easily available intervention agent to prevent atherosclerosis in the type 2 diabetes patients, we tested a potential candidate, ethanol-extracted curcumin. We evaluated PWV as a primary parameter to assess the risk of atherosclerosis and found that curcumin explicitly and significantly reduced PWV. PWV is a well-accepted surrogate marker used for assessing atherosclerosis status and for following up of atherogenic treatments [40]. PWV indicates arterial stiffness, a reflection of endothelial dysfunction and a major risk for atherosclerosis [35,37,41]. We also examined other parameters that increase the atherosclerosis risk such as IR, dyslipidemia (high triglyceride), abdominal obesity (VF and TBF) and high uric acid [1,12,13,15,16]. HOMA-IR clinically represents IR [33,34]. HOMA-IR has been shown to strongly correlate with the atherosclerosis in T2DM with metabolic

Table 2
Means and ranges of parameters related to atherogenic risks (PWV, adiponectin, leptin, HOMA-IR, triglyceride, uric acid, VF, TBF, WC) from curcumin-treated and placebo-treated group at the baseline and each visit

Parameters	Baseline visit		3-mo visit		6-mo visit	
	Curcumin	Placebo	Curcumin	Placebo	Curcumin	Placebo
PWV Rt (cm/s)	1728.69 (1120–4513)	1726.42 (1107–3067)	1587.46 (1000–4100)	1727.91 * (1115–3067)	1494 (900–4000)	1727.07*** (1112–3067)
PWV Lt (cm/s)	1752.32 (1082–5526)	1764.9 (1044–4976)	1604.89 (1020–5120)	1766.27* (1044–4976)	1511.43 (920–5020)	1765.58*** (1044–4976)
Adiponectin (ng/ml)	9.24 (1.3–34.6)	9.91 (1.7–49.5)	17.61 (7.9–45)	9.09*** (1.7–49.5)	23.91 (7.9–51)	9.28*** (1.7–49.5)
Leptin (ng/ml)	17.38 (1.2–55.5)	16.92 (1.8–85.3)	9.28 (1–31.6)	17.88*** (3.3–85.3	5.8 (0.8–27.9)	17.19*** (1.8–85.3)
HOMA-IR	6.12 (2–24.1)	5.63 (1.4–14.9)	4.05 (1.2–13.8)	5.92*** (1.4–14.9	2.75 (0.9–10.9)	5.66*** (1.4–14.4)
Triglyceride (mg/dl)	158.24 (40–532)	166.94 (51–626)	(114.27 (37–372)	167.24*** (51–626)	82.98 (30–372)	166.87*** (51–626)
Uric acid (mg/dl)	6.09 (2.90–11.30)	6.29 (3.20–12.60)	5.02 (2.00–9.00)	6.44*** (3.20–12.60)	3.29 (1.20–7.50)	6.34*** (3.20–12.60)
VF (%)	13.56 (3–34)	12.49 (3–29)	12.23 (2–33)	12.65 (3–29)	10.55 (2–29)	12.6* (3–29)
TBF (%)	31.99 (15.7–68.4)	30.88 (13.8–45.3)	29.53 (14–64)	31.23 (13.8–45.3)	26.82 (12–58)	31.07*** (13.8–45.3)
Waist circumference (cm)	90.7 (64.0–128.0)	90.2 (59.0–114.5)	89.5 (64.0–126.0)	90.7 (59.0–115.0)	88.2 (64.0–124.0)	90.4 (59.0–115.0)

Unpaired t test statistical analysis was used to compare outcomes at 3 and 6 months between the curcumin and placebo groups. Parameters at baseline between the curcumin and placebo groups were not statistically significant, at P<.05.
* P<.05.
*** P<.001.

syndrome [1,2]. In our study, we found that curcumin treatment improved all of these indicative metabolic profiles. Curcumin treatment has been demonstrated, in vitro and in vivo animal models, to elevate an anti-inflammatory cytokine (adiponectin) and to decrease a proinflammatory cytokine (leptin) [21,42]. Levels of both cytokines have been shown to be major contributors for the development of atherosclerosis. Either lowered level of adiponectin or heighten level of leptin within the context of T2DM results in an

elevated risks of atherosclerotic diseases [10,11,43,44]. Inflammatory reactions mediated by these adipocytokines play a major role in the forming of the plaques inside of arterial wall, which will be the seed for the atherosclerosis. We found that a 6-month curcumin treatment resulted in both significant induction of adiponectin and decrease of leptin in patients with T2DM. These findings along with the other improved metabolic profile (HOMA-IR, triglyceride, visceral/TBF and serum uric acid) may contribute to the reduced PWV observed in
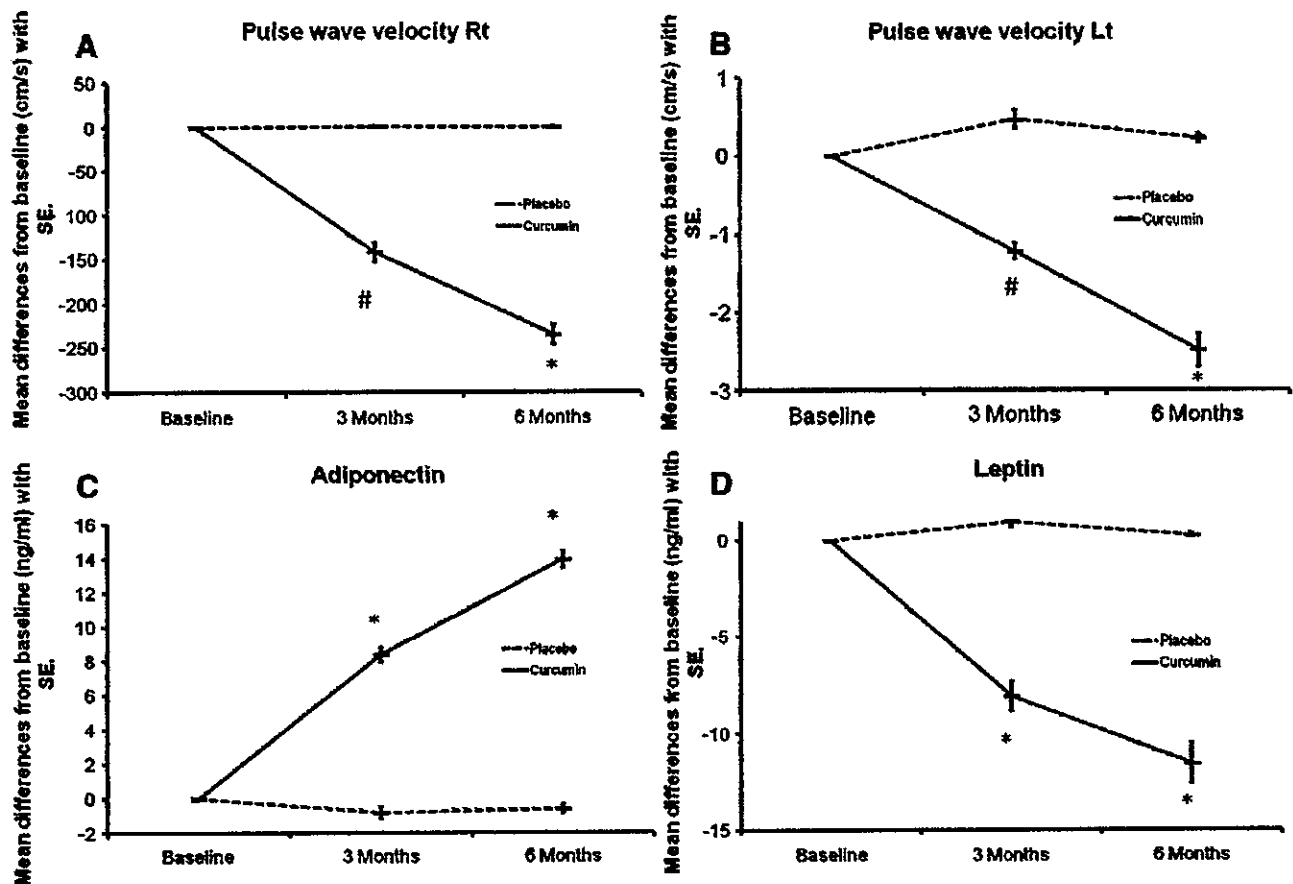

Fig. 1. Mean differences from baseline to 3- and 6-month visits with SEM for PWV Rt and Lt, adiponectin and leptin for the placebo and the control groups. Statistical significances are indicated as follows: #P=.01, *P<.001. Statistical tests were performed for the comparisons of end point at each visit between the two groups. All the parameters including PWV Rt (A), PWV Lt (B), adiponectin (C) and leptin (D) show statistical significance at P<.001, except for the 3-month visit of PWV Rt and Lt.

A HOMA-IR

B Triglyceride

C Visceral fat
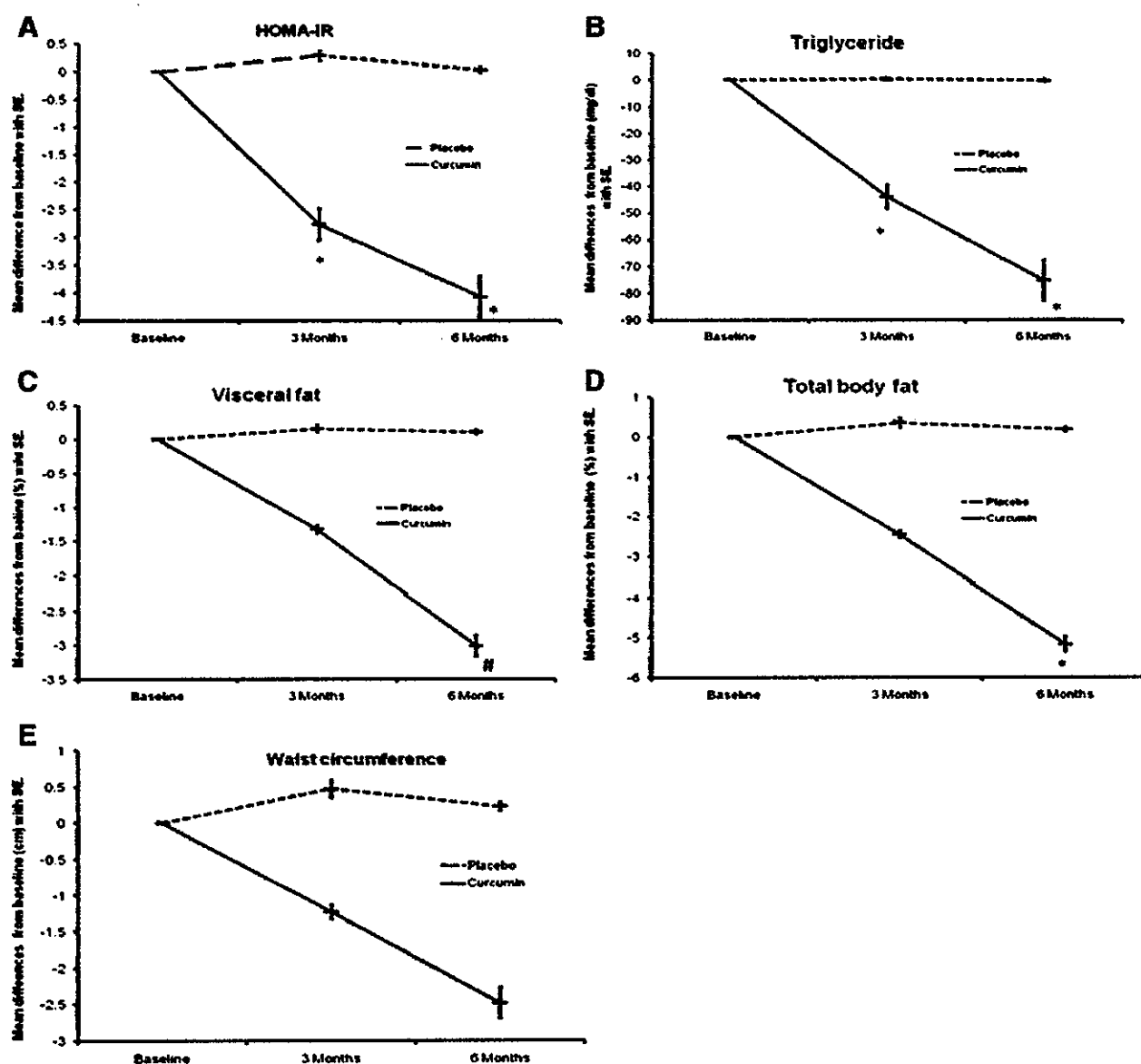
D Total body fat

E Waist circumference

Fig. 2. Mean differences from baseline to 3- and 6-month visits with SEM for HOMA-IR, triglyceride, VF, TBF and WC for the placebo and the control groups. Statistical significances are indicated as follows: *P=.01, *P<.001. Statistical tests were performed for the comparisons of end point at each visit between the two groups. Differences of means between the curcumin and placebo groups at 3- and 6-month visits were statistically significant at P<.01 for HOMA-IR (A) and triglyceride (B), while VF (C) and TBF (D) showed statistically significant only at 6-month visit.

T2DM patients treated with curcumin. Although not statistically significant, curcumin intervention also tended to decrease BMI, WC, LDL-C, total cholesterol and to increase HDL-C. Abdominal obesity reflects the amount of adipose tissues in the body. Adipose tissue is a major secretor of adipocytokines, especially adiponectin and leptin [9,44]. Previous in vivo studies reported that curcumin may have antiobesity effects [20,21]. Curcumin treatment can reduce body weight and amount of adipose tissue. Curcumin treatment also reduces hyperglycemia and IR in a mouse model of obesity fed with high-fat diet [19] and a mouse model of diabesity [21]. In accordance to these previous findings, our results showed that the curcumin treatment reduced the amount of adipose tissue in the T2DM patients. When compared to the placebo group, curcumin-treated patients appeared to have decreased abdominal obesity, indicated by less VF, and TBF. Although not significant statistically, patients treated with curcumin for 6 months also showed a trend of having lower WC, body

weight and BMI. Whether or not these trends help to reduce the atherosclerosis risks, we do not know. Of note, we did not observe any reduction on obesity or fat tissue in the placebo-treated group. It is also not clear if the overall reduction of the amount of adipose tissue in the body contributes to the reduction of the adipose tissue-generated cytokine such as leptin and the changes of some metabolic profiles that are associated with the amount of adipose tissue, such as IR, triglyceride and uric acid [43,45]. It has been shown that the number of adipose-associated macrophage that secrets inflammatory cytokines is reduced upon loss of body fat content in mice. This was proposed to ameliorate many of the inflammatory consequences of obesity in murine obesity models [21,42]. Interestingly, in this study, a 6-month curcumin intervention was sufficient to produce a significant loss in the fat contents in the curcumin-treated group. This finding supports the notion that the loss of body fat and adipose-associated macrophage, at least partly, contributed to the reduction of

the inflammatory related atherogenesis we observed here. Six-month curcumin treatment may also demonstrated some antidiabetic activities. Curcumin treatment appeared to slightly lower FPG, HbA1c, total cholesterol and LDL-C and to slightly elevate HDL-C, when compared to the parameters from measured at the baseline (Online Supplemental Material in Table 2). However, these results did still not yet meet the level of statistical requirement.

To be able to clearly demonstrate efficacy and safety of a plant-based intervention agent, it has been recommended that the agent should be vigorously and carefully tested in a well-controlled, large-scale trial, before the public can be assured of the proper use of the agent [46]. In our observation, we found beneficial effects of a 6-month treatment of curcumin on antiatherogenic risks in type 2 diabetes population. We also demonstrated that 6-months curcumin intervention was well tolerated, with a very few adverse effects. We did not find any significant differences in parameters such as blood pressure, kidney function (creatinine) and liver function (AST and ALT) between the curcumin and placebo groups (Online Supplemental Material in Table 2 and 3). During the period of the trial, we observed an increase of average ALT in the placebo-treated group. This might be a result of hepatic damage often observed in the T2DM patients. Interestingly, the ALT levels in the T2DM patients treated with curcumin remained unchanged throughout the study (Online Supplemental Material in Table 3).

This study was performed in Thai population from a small province in central Thailand. The population shares virtually similar cultural and ethnic background. Even so, high intervariability of physical activity and diet among the population may exist and affect the study. In order to address this issue, we designed a parallel study with a large number of subjects with randomized, double-blinded, placebo-controlled trial. In addition, all subjects were reminded by the nutritionists for remaining in the same pattern of daily diet and exercise. The reminder was given repeatedly in each visit of appointment through the course of this study. In conclusion, we found from a double-blind, placebo-controlled clinical trial that a 6-month intervention of curcumin yielded in a lower PWV and a better overall metabolic profile in T2DM patients, indicating lower arteriosclerosis risks in T2DM patients. In addition, 6-month use of curcumin extract as an intervention agent in T2DM patients only showed a few detected undesirable effects. Despite losing some body weight and WC, all of the subjects treated with curcumin appeared to be healthy. Because of its benefits and safety, we propose that curcumin extract may be used as antiarteriosclerosis in type 2 diabetes population.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jnutbio.2013.09.013.

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