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Lipid-Lowering Effects of Curcumin in Patients with Metabolic Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial

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Human studies of curcumin extract on lipid-lowering effect have not been completely investigated and have had controversy results. This study tested the effect of daily curcumin extract for 12 weeks on weight, glucose, and lipid profiles in patients with metabolic syndrome. Sixty-five patients were randomized into two groups; 33 patients taking curcumin extract capsule (630 mg thrice daily) and 32 patients taking a placebo capsule thrice daily for 12 weeks. At 12 weeks after the curcumin extract consumption, the level of high-density lipoprotein cholesterol (HDL-C) significantly increased from 40.96 ± 8.59 to 43.76 ± 2.79 mg/dL ($p < 0.05$), and the level of low-density lipoprotein cholesterol (LDL) was significantly reduced (120.55 ± 36.81 to 106.51 ± 25.02 mg/dL, $p < 0.05$). The triglyceride-lowering effect, a reduction of 65 mg/dL, was also found in this study. In subgroups analysis, the consumption of curcumin may have a lowering cholesterol effect in male patients and an increasing HDL-C effect in female patients, both of which result in a decrease of T-Chol/HDL-C ratio. The intake of the curcumin extract of 1890 mg/day for 12 weeks was associated with lipid-lowering effect but did not improve weight and glucose homeostasis in the patients with metabolic syndrome. Daily curcumin consumption may be an alternative choice to modify cholesterol-related parameters, especially in metabolic syndrome patients.

Keywords: curcumin; lipid-lowering effect; metabolic syndrome.

INTRODUCTION

The use of herbal medicine as a pharmacologic modality in preventing human diseases has received a wide attention from several researches. Curcumin is one such herbal medicine that was first discovered from the rhizomes of *Curcuma longa* (turmeric) (Gupta *et al.*, 2012). Curcumin is a polyphenolic molecule that can be extracted from turmeric and belongs to the ginger family (*Zingiberaceae*) (Ammon and Wahl, 1991). Other names for this plant include jiang huang (Chinese). It is considered a common constituent of diet worldwide. For centuries, curcumin has been an important ingredient in Chinese and Indian herbal medicine. Several animal and human studies have reported that curcumin provides multiple positive benefits for health, including antinausea effects, antioxidant effects, antiinflammatory effects, antidiabetic properties, and improved lipid parameters (Soni and Kuttan, 1992; Wickenberg *et al.*, 2010; Irving *et al.*, 2011; Shehzad *et al.*, 2011; Chuengsamarn *et al.*, 2012a, 2012b; Ji *et al.*, 2012; Di Lorenzo *et al.*, 2013; Dulbecco and Savarino, 2013)). Animal studies have reported that curcumin might decrease absorption of cholesterol and increase the activity of cholesterol-7α-hydroxylase (Feng *et a*l., 2010; Kim and Kim, 2010). These results hint that curcumin consumption might have cardiovascular benefits, which has allowed curcumin to gain potential in the treatment of such diseases.

Hyperlipidemia is a well-known important modifiable risk factor for atherosclerosis, which causes coronary arterial disease. The risk of developing cardiovascular disease (CVD) is reduced by improving lipid and lipoprotein levels (Rosamond *et al.*, 2008). Low-cost therapeutics such as lifestyle change have shown to improve plasma lipoprotein and lipid profiles and thus reduce CVD (Halverstadt *et al.*, 2007; Kelley and Kelley, 2009).

Several human studies on the use of curcumin indicated that it had a significant lipid-lowering effect and antiinflammatory effect and improved the quality of life in healthy middle-aged people and in patients with hyperlipidemia, obesity, active rheumatoid arthritis, solid tumors, and depressive disorders (Soni and Kuttan,

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1992; Ramirez-Bosca *et al*., 2000; Alwi *et al*., 2008; Pungcharoenkul and Thongnopnua, 2011; Chandran and Goel, 2012; DiSilvestro *et al*., 2012; Madaric *et al*., 2013; Mohammadi *et al*., 2013; Sahebkar *et al*., 2013; Sahebkar *et al*., 2013; Panahi *et al*., 2014; Sahebkar, 2014a, 2014b, 2014c; Sanmukhani *et al*., 2014). However, in another study of non-diabetic patients with coronary artery disease, curcumin use has showed no decrease in their blood lipid or sugar levels (Baum *et al*., 2007). Human clinical trials on curcumin have not been completely investigated and have had controversial results. Therefore, this study tested the effect of daily curcumin extract consumption containing 1890 mg/day for 12 weeks on changes in the selected metabolic parameters and the blood lipid profiles. Secondary endpoints included body weight and body mass index in the metabolic syndrome patients.

MATERIALS AND METHODS

Study population. This study was conducted from January 2011 to December 2011 on metabolic syndrome patients in Chung Shan Medical University Hospital (CSMUH) who have had stable medical treatment(s) for at least 6 months prior to study enrollment. The inclusion criteria were patients who have metabolic syndrome, defined according to the US National Cholesterol Education Program Adult Treatment Panel III (2001) as requiring at least three of the following: (1) systolic blood pressure ≧130 mmHg or diastolic blood pressure ≧85 mmHg or treatment of previously diagnosed hypertension; (2) fasting plasma glucose (FPG) ≧110 mg/dL; (3) triglycerides (TG) ≧150 mg/dL; (4) high-density lipoprotein cholesterol (HDL-C) <40 mg/dL for men and <50 mg/dL for women; and (5) waist circumference >90 cm for men and >80 cm for women in Asian populations. The exclusion criteria were chronic illnesses, such as history of myocardial infarction, severe hypertension, endocrine-associated obesity, thyroid pathology, biliary tract disease, pregnancy or breastfeeding, use of sex hormones, cerebrovascular disease, and cancer, and failure to sign an informed consent. All enrolled participants gave written informed consent prior to the commencement of study.

Study design. Using a randomized, double-blind, placebo-controlled design, this pilot study sought to test the hypothesis that the daily curcumin extract consumption as compared with the placebo for a period of 12 weeks would result in significant improvements in metabolic parameters and body weight reductions. The participants were randomized to receive either a curcumin extract or placebo capsule for 12 weeks. Randomization was completed using a table of random numbers, independent of study personnel, at the CSMUH. The investigators and participants were blinded to the capsule compositions until all participants had completed the trial and data analysis was underway.

Materials. The curcumin was produced under supervision according to the standard processing procedure of pharmaceutical materials (Now Health Group, Incorporated, USA). The analysis of curcumin extract concentration was performed using HPLC method at the laboratory of CSMUH. The determination of the curcumin dosage applied in this study was based on the phase I study by Cheng *et al.* In this study, curcumin extract capsule was administered in a dose of 650 mg three times daily for 12 weeks. Each capsule contained 630 mg curcumin [turmeric (*C. longa*)] extract (95% curcuminoids, including curcumin, demethoxycurcumin, and bisdemethoxycurcumin) and various bulk agents (5%), including rice flour, magnesium stearate, stearic acid silicon dioxide, and hydroxypropyl methylcellulose.

Intervention and adherence. All patients took one capsule with water before each of their three daily meals. Thirty-three participants were assigned to the curcumin extract group, and 32 participants received the placebo only. Specific instructions for curcumin extract preparation were provided by the study coordinator during the initial clinical visit.

Compliance and subjective symptoms (abdominal distension, abdominal pain, diarrhea, retching, increase in flatulence, and allergic symptoms) were monitored during and after in both the curcumin group and the placebo group.

Outcome assessments. *Anthropometrics.* The primary outcomes for this research were changes in body weight and body mass index. All measurements were assessed at baseline, prior to randomization, and again at 12 weeks post-treatment.

Metabolic parameters. The FPG, hemoglobin A1c (HbA1c), and lipids, including total cholesterol (T-Chol), HDL-C, LDL cholesterol (LDL-C), TG, very LDL (VLDL), non-HDL-C, and T-Chol/HDL-C ratio, were measured at baseline (prior to curcumin intervention) and at 12 weeks. VLDL was calculated by TG (mg/dL)/5. This formula is valid only when TG are ≤400 mg/dL, and therefore, three participants do not have VLDL data because of this limitation in curcumin group.

Statistical analysis. Baseline measurement values for the anthropometric and lipid profiles were subtracted from follow-up values to produce measurement of change. Independent Student *t*-tests were performed to examine the differences in demographic and clinical characteristics and then performed at 12 weeks to determine the changes in anthropometric measurement and metabolic parameters between the curcumin extract and placebo groups. The significance of changes from baseline to 12 weeks within the group was tested with paired *t*-tests. The final analyses were made by per-protocol analysis. The alpha level considered significant was set at $p < 0.05$. All statistical analyses were performed using SPSS 15.0 (Statistical Program for the Social Sciences, Version 15.0, Chicago, IL).

RESULTS

Study attrition

A total of 65 patients were enrolled: 33 were randomized to the curcumin extract group and 32 to the placebo group, as shown in Fig. 1. In curcumin extract group, two participants were excluded from the final analysis because of poor compliance, and one because of side effects. In the placebo group, one lost follow-up, and one was excluded because of poor compliance. Analyses were collected from those who completed 12-week anthropometric, clinical, and demographic data.

Demographic and clinical characteristics

The demographic and clinical characteristics of the study population at baseline are presented in Table 1. Overall, the participants consisted of a mean age of 59.3 ± 12.0 years, body weight of 78.90 ± 14.2 kg, BMI 30.06 ± 4.12 kg/m^2, T-Chol 187.41 ± 38.11 mg/dL, TG 193.91 ± 150.41 mg/dL, LDL-C 114.01 ± 31.37 mg/dL, and HDL-C 41.23 ± 10.11 mg/dL. There were no significant differences in demographic characteristics between the two groups.

Table 1. Baseline demographics and clinical characteristics

	Curcumin group (n = 33)	Placebo group (n = 32)
Age (years)	59.03 ± 10.10	59.61 ± 14.09
Male	12 (36)	17 (53)
Height (cm)	161.91 ± 7.12	163.22 ± 7.12
Weight (kg)	80.70 ± 12.94	76.96 ± 15.45
BMI (kg/m^2)	30.61 ± 4.15	28.78 ± 4.88
TG (mg/dL)	177.11 ± 83.69	153.42 ± 80.40
T-Chol (mg/dL)	195.63 ± 41.84	178.60 ± 33.32
FPG (mg/dL)	113.73 ± 19.28	116.10 ± 24.29
HDL-C (mg/dL)	40.70 ± 8.57	41.84 ± 11.80
LDL-C (mg/dL)	120.26 ± 36.20	107.32 ± 24.08
T-Chol/HDL-C	4.87 ± 1.05	4.60 ± 1.26
Non-HDL-C	154.14 ± 39.026	144.23 ± 38.34
VLDL (mg/dL)	33.59 ± 16.23	37.77 ± 15.87
HbA1c (%)	6.32 ± 0.89	6.38 ± 1.04

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; T-Chol, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein cholesterol.
Data are expressed as mean ± SD, and number with percentage in parenthesis.
VLDL was calculated by triglycerides (mg/dL)/5.

Metabolic parameters

Overall, there were significant improvements in blood lipid values in the curcumin extract group. The triglyceride, T-Chol, LDL-C, non-HDL-C, and T-Chol/HDL-C ratio levels were significantly decreased only in the curcumin extract group between baseline and at 12 weeks (all $p < 0.05$), as shown in Tables 2 and 3. Furthermore, the HDL-C level increased significantly in the curcumin extract group compared with the placebo group ($p < 0.05$). In the placebo group, there was an insignificant reduction in non-HDL level and T-Chol/HDL ratio after 12 weeks. There were insignificant changes from baseline in VLDL in both groups. There was a reduction of 28.8%, 9.8%, 11.64% in TG, T-Chol, and LDL-C in the curcumin extract group, respectively (all $p < 0.05$ within group before and after), versus 9.28%, 6.9%, 3.99% in TG, T-Chol, and LDL-C in the placebo group, respectively (all $p > 0.05$ within group before and after). There was also an increase of 6.18%

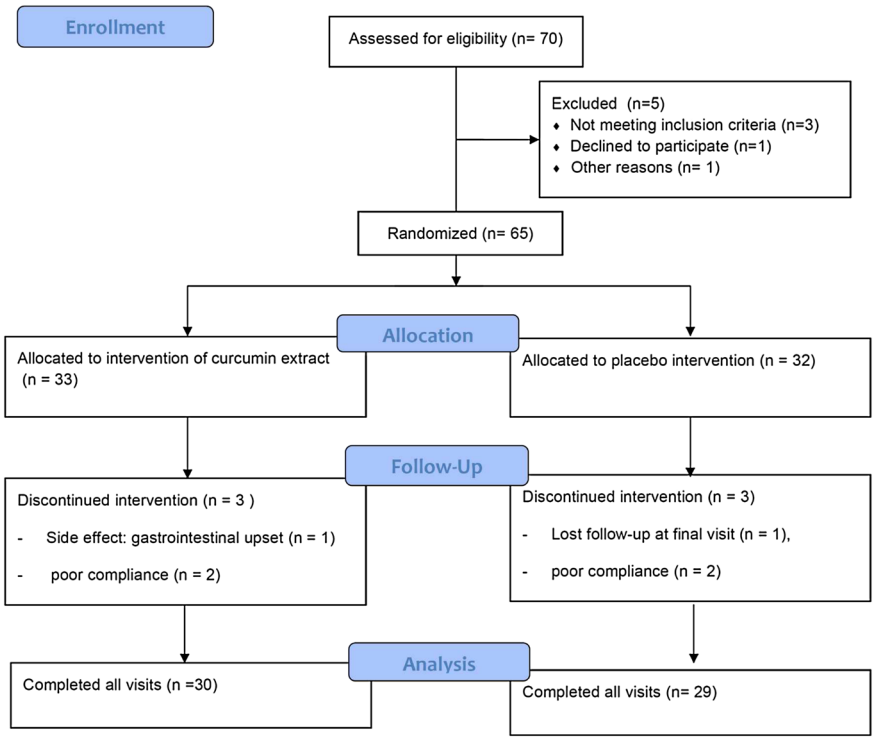

Figure 1. Patient allocation flow diagram.

Table 2. Body composition and chemistry biomarker measures after treatment

	Baseline	3 months	± SEM	*p*-value
Curcumin group				
Weight (kg)	80.46 ± 13.10	80.46 ± 12.97	−.000 ± .49	1.000
BMI (kg/m^2)	34.17 ± 5.54	33.70 ± 5.15	−0.01 ± 0.18	0.929
TG (mg/dL)	226.10 ± 64.99	160.79 ± 75.46	−65.31 ± 28.36	0.029
T-Chol (mg/dL)	195.10 ± 42.47	175.86 ± 30.63	−19.24 ± 7.26	0.013
FPG (mg/dL)	112.75 ± 18.85	114.82 ± 16.15	2.06 ± 2.77	0.461
HDL-C (mg/dL)	40.96 ± 8.59	43.76 ± 9.54	2.79 ± 1.19	0.027
LDL-C (mg/dL)	120.55 ± 36.81	106.51 ± 25.02	−14.03 ± 1.52	0.011
T-Chol/HDL-C	4.87 ± 1.05	4.13 ± 0.84	−0.74 ± 0.16	0.0001
Non-HDL (mg/dL)	154.13 ± 39.02	132.10 ± 27.78	−22.03 ± 6.94	0.004
VLDL (mg/dL)	33.58 ± 16.23	25.55 ± 22.37	−8.00 ± 4.86	0.111
HbA1c (%)	6.32 ± 0.91	6.20 ± 0.73	0.12 ± 0.82	0.157
Placebo group				
Weight (kg)	75.61 ± 10.49	75.67 ± 10.46	0.05 ± 0.03	0.164
BMI (kg/m^2)	28.78 ± 4.88	28.88 ± 4.88	−0.01 ± 0.39	0.161
TG (mg/dL)	159.46 ± 86.28	144.65 ± 56.06	−14.80 ± 10.25	0.61
T-Chol (mg/dL)	180.07 ± 33.82	167.53 ± 37.60	−12.53 ± 7.34	0.99
FPG (mg/dL)	117.53 ± 27.63	124.32 ± 11.91	6.78 ± 5.61	0.237
HDL-C (mg/dL)	41.50 ± 11.93	40.92 ± 9.47	−0.57 ± 1.61	0.723
LDL-C (mg/dL)	107.03 ± 23.97	102.75 ± 26.76	−4.28 ± 4.22	0.320
T-Chol/HDL-C	4.57 ± 1.24	4.20 ± 1.09	−0.37 ± 0.18	0.51
Non-HDL (mg/dL)	144.22 ± 38.33	124.51 ± 52.72	−19.7 ± 8.01	0.02
VLDL (mg/dL)	37.77 ± 15.87	28.32 ± 14.59	−9.54 ± 6.88	0.18
HbA1c (%)	6.41 ± 1.03	6.56 ± 1.06	0.15 ± 0.76	0.079

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; T-Chol, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein cholesterol.
Data are expressed as mean ± SD, and number with percentage in parenthesis.
VLDL was calculated by triglycerides (mg/dL)/5.

Table 3. Comparing difference (delta) values for each measure parameter

All	Curcumin group	Placebo group	*p*-value
Weight (kg)	−0.000 ± .49	0.05 ± 0.03	0.92
BMI (kg/m^2)	−0.01 ± 0.18	−0.01 ± 0.39	0.97
TG (mg/dL)	−65.31 ± 28.36	−14.80 ± 10.25	0.10
T-Chol (mg/dL)	−19.24 ± 7.26	−12.53 ± 7.34	0.51
FPG (mg/dL)	2.06 ± 2.77	6.78 ± 5.61	0.44
HDL-C (mg/dL)	2.79 ± 1.19	−0.57 ± 1.61	0.26
LDL-C (mg/dL)	−14.03 ± 1.52	−4.28 ± 4.22	0.01
T-Chol/HDL-C	−0.74 ± 0.16	−0.37 ± 0.18	0.12
Non-HDL (mg/dL)	−22.03 ± 6.94	−19.7 ± 8.01	0.82
VLDL (mg/dL)	−8.00 ± 4.86	−9.54 ± 6.88	0.85
HbA1c (%)	0.12 ± 0.82	0.15 ± 0.76	0.94

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; T-Chol, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein cholesterol.
Data are expressed as mean ± SEM.
VLDL was calculated by triglycerides (mg/dL)/5.

and 15.19% in HDL-C and T-Chol/HDL-C ratio in the curcumin group, respectively (all $p < 0.05$ within group before and after), versus 1.37% and 8.09% in HDL-C and T-Chol/HDL-C ratio in the placebo group, respectively ($p = 0.723$ and $p = 0.051$ within group before and after). Because there was no statistical significance between the two groups at baseline, these results at 12 weeks suggested a possible improvement of lipid profile after 12 weeks of curcumin extract consumption.

Further subgroup analysis (Table 4) showed that the male participants in the curcumin extract group experienced a statistically significant reduction in T-Chol, LDL-C, non-HDL-C, and T-Chol/HDL-C ratio after 12 weeks relative to baseline. However, the change in TG and VLDL in the male subgroup was not statistically significant. In the female subgroup, the curcumin extract group resulted in a statistically significant reduction in HDL-C and T-Chol/HDL-C ratio after 12 weeks relative to baseline.

The standard deviation values are relatively high, which may be due to each group being composed of both male genders with significantly different triglyceride level. The variation in triglyceride level was significant even in each gender subgroup.

Overall, there was no significant change in glucose profile from baseline to 12 weeks in both groups. However, in subgroup analyses, there was a trend of HbA1c reduction in curcumin extract group after 12 weeks (from 6.44% to 6.17%, mean decrease of 0.26%, $p = 0.030$).

No obvious improvement in blood glucose levels, except a mild reduction in HbA1c, especially in the female subgroup, was observed.

Anthropometrics

Table 2 shows no significant change in body weight and related anthropometric measurements from baseline to 12 weeks of treatment in the curcumin extract and placebo treatment groups.

Table 4. Body composition and chemistry biomarker measures by gender after treatment

	Baseline	3 months	Δ	*p*-value
Male subgroup				
Curcumin (*n* = 12)				
Weight (kg)	89.27 ± 9.83	88.48 ± 10.04	−0.79 ± 0.64	**0.246**
TG (mg/dL)	276.33 ± 236.23	190.50 ± 91.22	−85.83 ± 57.29	0.162
T-Chol (mg/dL)	198.16 ± 54.10	171.00 ± 29.93	−27.16 ± 12.52	0.053
FPG (mg/dL)	117.33 ± 15.39	118.25 ± 16.07	0.91 ± 4.63	0.847
HDL-C (mg/dL)	37.66 ± 8.30	39.50 ± 7.16	1.83 ± 1.96	0.371
LDL-C (mg/dL)	121.50 ± 34.03	105.08 ± 22.07	−16.41 ± 7.33	0.047
VLDL (mg/dL)	39.00 ± 28.91	26.41 ± 14.23	−12.58 ± 8.86	0.184
Non-HDL-C	160.50 ± 49.07	131.50 ± 26.25	−29.00 ± 12.34	0.039
T-Chol/HDL-C	5.31 ± 1.13	4.37 ± 0.66	−0.94 ± 0.33	0.016
HbA1c (%)	6.15 ± 0.80	6.24 ± 0.84	0.08 ± 0.10	0.429
Placebo (*n* = 17)				
Weight (kg)	75.53 ± 11.10	75.53 ± 11.09	−0.00	1.000
TG (mg/dL)	169.05 ± 96.33	142.11 ± 38.52	−26.94 ± 14.27	0.077
T-Chol (mg/dL)	174.82 ± 38.21	159.35 ± 35.41	−15.47 ± 11.58	0.200
FPG (mg/dL)	118.41 ± 28.30	120.35 ± 23.46	1.94 ± 7.31	0.794
HDL-C (mg/dL)	37.88 ± 10.67	37.29 ± 5.75	0.58 ± 2.00	0.772
LDL-C (mg/dL)	103.41 ± 21.21	102.47 ± 25.38	−0.94 ± 5.55	0.868
VLDL (mg/dL)	33.52 ± 25.9	19.58 ± 31.05	−13.94 ± 11.4	0.240
Non-HDL-C	136.94 ± 35.74	122.05 ± 38.22	−14.88 ± 10.64	0.181
T-Chol/HDL-C	4.83 ± 1.27	4.34 ± 1.20	−0.48 ± 0.25	0.067
HbA1c (%)	6.48 ± 1.12	6.52 ± 0.93	0.04 ± 0.09	0.662
Female subgroup				
Curcumin (*n* = 18)				
Weight (kg)	74.25 ± 11.62	74.81 ± 11.96	0.55 ± 0.68	0.429
TG (mg/dL)	190.64 ± 143.77	139.82 ± 55.81	−50.82 ± 27.87	0.087
T-Chol (mg/dL)	192.94 ± 33.67	179.29 ± 31.56	−13.64 ± 8.75	0.139
FPG (mg/dL)	109.53 ± 20.79	112.41 ± 16.25	2.88 ± 3.52	0.425
HDL-C (mg/dL)	43.29 ± 8.24	46.76 ± 10.05	3.47 ± 1.52	0.037
LDL-C (mg/dL)	119.88 ± 39.67	107.53 ± 27.53	−12.35 ± 7.26	0.108
VLDL (mg/dL)	27.74 ± 24.33	25.00 ± 11.31	−4.76 ± 5.55	0.403
Non-HDL-C	149.64 ± 30.94	132.52 ± 29.60	−17.11 ± 8.14	0.052
T-Chol/HDL-C	4.56 ± 0.90	3.96 ± 0.93	0.61 ± 0.16	0..002
HbA1c (%)	6.44 ± 0.98	6.17 ± 0.67	−0.04 ± 0.34	0.030
Placebo (*n* = 12)				
Weight (kg)	67.88 ± 7.73	68.02 ± 7.93	0.13 ± 0.09	0.173
TG (mg/dL)	141.33 ± 64.33	149.44 ± 53.43	8.11 ± 8.95	0.391
T-Chol (mg/dL)	188.18 ± 25.16	180.18 ± 33.90	−8.00 ± 5.93	0.207
FPG (mg/dL)	116.18 ± 18.69	130.45 ± 33.35	14.27 ± 8.65	0.130
HDL-C (mg/dL)	48.33 ± 11.69	47.78 ± 11.56	−0.55 ± 2.88	0.852
LDL-C (mg/dL)	112.63 ± 27.84	103.18 ± 30.04	−0.94 ± 6.49	0.176
VLDL (mg/dL)	42.92 ± 45.68	38.92 ± 35.58	−4.0 ± 6.53	0.551
Non-HDL-C	153.07 ± 40.81	127.50 ± 67.81	−25.57 ± 12.42	0.060
T-Chol/HDL-C	4.09 ± 1.09	3.93 ± 0.84	0.16 ± .23	0.521
HbA1c (%)	6.31 ± .91	6.63 ± 1.26	.031 ± .14	0.051

Data are expressed as mean ± SD, and number with percentage in parenthesis. BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; T-Chol, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein cholesterol.

Data are expressed as mean ± SD, and number with percentage in parenthesis.

VLDL was calculated by triglycerides (mg/dL)/5.

Compliance

Adherence was good throughout the study period. One participant had stomach pain, which occurred 3 days after taking the capsule, and withdrew from the study. Other side effects recorded were mild diarrhea and nausea in two participants in the curcumin extract group.

DISCUSSION

In this double-blind, placebo-controlled trial, consuming curcumin (turmeric root extract) 1890 mg/day significantly alters serum lipid profiles in metabolic syndrome patients. This is consistent to previous reports of cholesterol-lowering effects in animals and humans

(Soni and Kuttan, 1992; Ramirez-Bosca *et al*., 2000; Pungcharoenkul and Thongnopnua, 2011; Hu *et al*., 2013; Sahebkar *et al*., 2013; Zingg *et al*., 2013) but contrary to other reports (Baum *et al*., 2007; Alwi *et al*., 2008).

Although the available reports suggest an overall anti-lipid effect, the results across trials have been inconsistent. The discrepancy between the non-significance and significance of anti-lipid effect of curcumin extract consumption in the previous human studies might be due to different lengths of follow-up period (ranging from 7 days to 6 months), different dosage use (ranging from 20 to 6000 mg/day), and different background diseases of the participants (participants with acute coronary syndrome with LDL >150 mg/dL, patients with cognitive decline, and healthy volunteers (Soni and Kuttan, 1992; Alwi *et al*., 2008; Pungcharoenkul and Thongnopnua, 2011; Baum *et al*., 2007; Sahebkar 2013a).

The effect of curcumin on T-Chol ranged from a reduction of 0.2%5 to 17%, using a dosage of 45 mg, 500 mg, and 4 g. The effect of curcumin on LDL-C ranged from a reduction of 3.4 to 38%, using a dosage of 20 mg and 4 g. The effect of curcumin on HDL-C ranged from an increase of 5.8% to 72.3%, using a dosage of 20 mg and 4 g. Therefore, there was no correlation between dosage of curcumin and lipid-lowering effect. Higher doses (6000 mg) did not reveal any additional anti-lipid effect. The researchers found that using higher doses of up to 4000 and 6000 mg did not demonstrate significant adverse effects (Baum *et al*., 2007; Pungcharoenkul and Thongnopnua, 2011). Our study dosage was determined according to the aforementioned studies; we used a dose of 1890 mg/day and aimed to provide a more profound anti-lipid effect without additional adverse effects. We observed a decrease in T-Chol (9.8%) and LDL-C (11.64%) and an increase of HDL-C (6.18%) with this dosage. In addition, there was also a decrease of non-HDL-C (14.29%) and T-Chol/HDL-C ratio (15.19%).

A reduction of 28.8% off triglyceride-lowering effect was also found in this study. The triglyceride-lowering activity is probably owing to their interaction with multiple targets, including PPAR-α, PPAR-γ, CETP, and lipoprotein lipase, and furthermore, it is thought to be linked to insulin-sensitizing effects and improvements of adipokines and antiinflammatory effects; curcumins are expected to affect both synthesis and catabolism of triglyceride-rich lipoproteins (Sahebkar, 2014a, 2014b, 2014c). This is particularly important because our study participants have metabolic syndrome; with increased risk of insulin resistance and diabetes mellitus, lifestyle changes in combination with supplements are the key to lowering triglyceride levels by standards unattainable by medication (Sahebkar 2013b).

The male participants who consumed curcumin for 12 weeks demonstrated a lipid-lowering effect on cholesterol level, in particular, T-Chol and LDL-C. The T-Chol/HDL ratio decrease was associated with reduction of T-Chol rather than increase of HDL-C. However, in the female curcumin subgroup, the reduction of T-Chol/HDL ratio was associated with increase of HDL-C. This suggests that the consumption of curcumin may have a lowering cholesterol effect in patient with metabolic syndrome in men and an increasing HDL-C effect in women, both of which result in decrease of T-Chol/HDL-C ratio.

These significant changes in lipid profiles of male and female participants may be attributed to an epidemiology survey, which showed that women had higher total and LDL levels (Turnbull *et al*., 2011). Among patients with established CVD, men were more likely to be prescribed a statin for lipid lowering compared with women. Healthcare providers tend to underestimate the magnitude of risk in their female patients (Nguyen *et al*., 2010). However, the exact mechanism remains unknown.

Several bioactive constituents of curcumin, which have been studied in animals, are related with anti-lipid and other metabolic effects. These include tetrahydrocurcumin, ferulic acid, and vanillic acid, all of which are metabolites of curcumin and curminoids diarylheptanoid, demethoxycurcumin, and bisdemethoxycurcumin, desmethoxycurcumin, and bis-desmethoxycurcumin (Wang *et al*., 1997; Pan *et al*., 1999; Ireson *et al*., 2001; Sahebkar, 2014a, 2014b, 2014c). The possible mechanism of modulating anti-lipid effect and the bioactive components mainly responsible for the potential effect include the selective inhibition of 11β-HSD1 (Hu *et al*., 2013), decrease absorption of cholesterol, and increase in the activity of cholesterol-7α-hydroxylase (Kim and Kim, 2010).

Consuming curcumin did not significantly alter FPG and HbA1c concentrations in this double-blind, placebo-controlled trial, contrary to previous reports of glucose-lowering effects in humans (Srinivasan, 1972; Wickenberg *et al*., 2010, 8; Chuengsamarn *et al*., 2012a, 2012b). The first case report was a male patient who had diabetes for 16 years. He ingested 5 g of turmeric powder over a period, after which, his fasting blood glucose decreased from 140 to 70 mg/dL (Srinivasan, 1972). Furthermore, a study that examined the effects of curcumin on postprandial plasma glucose and insulin levels and the glycemic index in healthy participants found that curcumin with 6 g/day, at 15–120 min, might increase postprandial serum insulin levels but has an insignificant effect on plasma glucose levels (Wickenberg *et al*., 2010). More recently, a randomized, double-blind, placebo-controlled clinical trial assessed the efficacy of curcumin in delaying development of type 2 diabetes in the pre-diabetes population. A total of 240 participants were randomly assigned to receive either curcumin (1.5 g/day, 9 months) or placebo capsules. The participants of curcumin-treated group showed a better overall function of β cells, with higher HOMA-β and lower C-peptide levels (Chuengsamarn *et al*., 2012a, 2012b). The daily dosage of previous studies (1500–6000 mg) was higher than the dosage used in this study (1890 mg), and the follow-up periods was also different. These differences could be a possible explanation of our result.

Regarding the safety of curcumin, oral administration has been reported to be safe. Human studies indicate that curcumin can be tolerated in large oral doses, as high as 8000 mg/day, without apparent toxicity (Cheng *et al*., 2001). This is consistent with the findings of this study (100 mg/day). Curcumin does not appear to cause any severe side effects except mild gastrointestinal upset. Taking into consideration the high safety response of curcumin consumption, human trials of curcumin to test effects on other outcomes may be safely conducted. Curcumin appears to be a safe tool for lipid control.

Limitations

As this is a small-sample size and short-duration study, interpretation of the results should be made cautiously because randomization resulted in a high standard deviation in some variables. Although these data are preliminary and only involve a small-sample size, a possible relationship between anti-lipid effect and curcumin consumption is indicated. However, improving the lipid profile does not necessarily mean that curcumin is effective against CVDs. Therefore, further studies are required to demonstrate whether curcumin can have benefits on CVD. Moreover, we could not explain the gender difference effects.

Conclusion

Intake of curcumin 1890 mg/day for 12 weeks was associated with an anti-lipid effect but did not improve weight and glucose homeostasis in the patients with metabolic syndrome. Therefore, daily curcumin consumption may be an alternative choice to modify metabolic-related parameters, especially in metabolic syndrome patients.

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Conflict of Interest

The authors have declared that there is no conflict of interest.

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